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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

58TH MEETING

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Wednesday, September 3, 1998

8:00 a.m.

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FDA

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Isagani Chico, M.D. (a.m.)
Robert Justice, M.D.
Grant Williams, M.D.

C O N T E N T S

C O N T E N T S (continued)

P R O C E E D I N G S

Call to Order and Introductions

DR. DUTCHER: Good morning. Welcome to Day 3. We will go ahead and introduce the members of the committee. Most of us have been here for a few days, but some are new. For those of you in the audience who are new, we will introduce the committee. I am Janice Dutcher from Albert Einstein, medical oncologist.

DR. JUSTICE: Bob Justice, Acting Director, Division of Oncology, FDA.

DR. WILLIAMS: Grant Williams, medical team leader, FDA.

DR. SIMON: Richard Simon, National Cancer Institute.

DR. MARGOLIN: Kim Margolin, City of Hope, Los Angeles.

MS. FORMAN: Sallie Forman, patient representative.

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

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

DR. OZOLS: Bob Ozols, Fox Chase Cancer Center, Philadelphia.

MS. BEAMAN: Carolyn Beaman, consumer advocate,

Sisters Breast Cancer.

DR. DUTCHER: Thank you.

We are now going to read a 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 interests 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.

Dr. Richard Schilsky and Dr. David Johnson are excluded from participating in today's discussion and vote concerning Camptosar. In addition, because of his past involvements with respect to Camptosar, Dr. James Krook will be permitted to participate in the committee's discussions of Camptosar. However, he is excluded from voting and he also is a victim of the Northwest Airline strike, so he is not here.

In addition, we would like to disclose, for the record, that Dr. Robert Ozols' employer, the Fox Chase

Cancer Center, has an interest in Pharmacia & Upjohn which does not constitute a financial interest in the particular matter within the meaning of 18 USC 208 but which could create the appearance of a conflict.

The agency has determined, not withstanding this interest, that the interest in the government in Dr. Ozols' participation outweighs the concern that the integrity of the agency's programs and operations may be questioned. Therefore, Dr. Ozols may participate fully in today's discussion and vote 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. DUTCHER: Thank you.

Open Public Hearing

DR. DUTCHER: We have no one who has requested to speak in advance at the open public hearing. We do have

time, if there is anyone in the audience who has come to speak.

If there is no one, then we will proceed with the sponsor's presentation.

Sponsor's Presentation

Study V301 and V302: Clinical Benefits of Camptosar

DR. MILLER: Good morning.

[Slide.]

My name is Langdon Miller. I am here representing oncology drug development at Pharmacia & Upjohn. I would like to share with you today important efficacy and safety information regarding the use of CPT-11, also known as irinotecan or Camptosar, for use in the therapy of colorectal cancer.

The data I will describe are presented in support of changing the U.S. CPT-11 registration from an accelerated approval status to full regulatory approval.

[Slide.]

Within the presentation today, I would first like to provide you with background information relating to the worldwide development of CPT-11 and its current regulatory status in the United States. In addition, I would like to describe the phase II U.S. and European trials that will be the basis for initial approval.

Thereafter, the primary focus of my remarks will

be in results from two Rhone-Poulenc-Rorer-sponsored phase-III, randomized, controlled clinical trials in patients with previously treated colorectal cancer. These studies directly document the clinical benefits of CPT-11.

[Slide.]

By way of background, it is important to understand that CPT-11 has undergone worldwide clinical development by four independent companies. In Japan, Yakult Honsha and Daiichi have obtained registration of CPT-11 for several tumor types including colorectal cancer. Rhone-Poulenc Rorer has developed the drug in Europe, Asia and Africa primarily for the treatment of colorectal cancer.

Development in the United States has been conducted by Pharmacia & Upjohn and has also focused on the use of CPT-11 as an active agent in the treatment of colorectal cancer.

As a component of CPT-11 licensing, these four companies have agreed to share clinical-trials data. The results of the phase III studies that I will present today have been provided by Rhone-Poulenc Rorer to Pharmacia & Upjohn under this data-sharing agreement.

[Slide.]

On June 14, 1996, Pharmacia & Upjohn received an accelerated or conditional approval from the FDA to market CPT-11. This approval came after documentation that CPT-11

could induce tumor responses. The specific indication for use of CPT-11 was as treatment for patients with metastatic carcinoma of the colon or rectum whose disease had recurred or progressed following first-line 5-FU-based therapy.

[Slide.]

The primary basis for this approval was the conduct of three U.S. studies in which CPT-11 treatment was given in repeated six-week courses comprising weekly and 90-minute infusions for four weeks followed by a two-week rest. The recommended starting dose derived from these trials was 125 mg/m^2.

At the same time, our colleagues in Europe developed a different regime for use in phase II and II trials of CPT-11 as second-line therapy of colorectal cancer. Patients enrolled in these studies were treated with an every-three-week regimen of CPT-11 given at a starting dose of 350 mg/m^2.

[Slide.]

This slide describes the overall results of the U.S. and European experience from these phase II studies juxtaposing the efficacy endpoints observed with the recommended weekly dose and regimen with those seen in two RPR-sponsored studies using the every-three-week starting dose and regimen.

It is evident that very similar intent-to-treat

response rates, median times to tumor progression and one-year survivals were seen with both dose regimens.

[Slide.]

The primary CPT-11-related adverse events and both the U.S. and European phase II experience were diarrhea and neutropenia. Grade 3/4 frequencies of these toxicities were observed at generally analogous levels in both the U.S. and the European trials.

[Slide.]

In summary, these phase II data indicate that administration of CPT-11 with either the weekly or every-three-week schedules results in similar efficacy outcomes and comparable toxicities. The results suggest no evidence of schedule dependency.

[Slide.]

It was these pivotal U.S. results and supporting European data that met the initial requirement for accelerated FDA approval because they demonstrated that CPT-11 has consistent antitumor activity and manageable toxicities in multiple studies conducted in patients with a life-threatening illness for which no effective treatment had existed.

A confirmatory control trial to document CPT-11 clinical benefit in colorectal cancer was required to obtain full approval.

[Slide.]

RPR sponsored two randomized, phase III international trials that directly document CPT-11 benefit in the second-line therapy of colorectal cancer. RPR has shared these data with Pharmacia & Upjohn. Pharmacia & Upjohn proposes that these trials now form the basis for full CPT-11 approval.

I would now like to describe to you the results of the RPR-sponsored trials, V301 and V302.

[Slide.]

Study V301 was a phase II trial that evaluated the benefit of giving CPT-11 versus best supportive care in the second-line therapy of patients with previously treated colorectal cancer. The results of this trial were presented at the ASCO plenary session by Dr. David Cunningham of the Royal Marsden Hospital in the United Kingdom. Dr. Cunningham is here with us today to assist in answering any questions that you may have.

[Slide.]

The trial was a large multicenter effort. The trial was conducted in locations where active second-line chemotherapy of colorectal cancer was not necessarily considered the standard of care. Patients were enrolled between September, 1995 and November, 1996 in eleven countries at 48 study sites.

[Slide.]

Patients were assigned to treatment with CPT-11 plus best supportive care or best supportive care only in a two-to-one randomization. Patients randomized to the CPT-11 arm were to be treated with 350 mg/m^2 of CPT-11.

By amendment to their study after it was under way, patients older than 70 years of age and those with performance status of 2 were to begin treatment with CPT-11 doses of 300 mg/m^2 because it was felt that these patients might better tolerate a somewhat lesser starting dose. Patients in the CPT-11 were permitted to receive additional chemotherapy after cessation of CPT-11 treatment.

Patients assigned to the best supportive care arm could receive antibiotics, analgesics, transfusions, steroids, counseling and other palliative care as needed. These patients were allowed to receive chemotherapy if that was consistent with institutional guidelines for application of supportive care.

[Slide.]

The hypothesis of the study was that the use of CPT-11 would be associated with a 15 percent approval in one-year survival. Differences in survival were to be tested by means of a two-tailed log-rank test. At least 264 patients were required to meet study objectives.

[Slide.]

The primary endpoint of this study was survival. Secondary endpoints included additional measures of clinical benefit, time to first performance status deterioration, time to first weight loss, symptom-free survival, pain-free survival and, also, patient quality of life as measured by the validated EORTC QLQ-C30 questionnaire.

[Slide.]

Patients in both groups were assessed every three weeks up to one year for these endpoints. After one year, information regarding survival was collected.

[Slide.]

To be included in this trial, patients were required to have: histologically proven colorectal cancer; metastatic disease; a WHO performance status of 0, 1 or 2; and no more than two prior 5-FU regimens for metastatic disease.

Patients were to have documented progression of disease either while on 5-FU or within six months after the last 5-FU infection. Adequate organ function was required. Patients were permitted to have had prior radiotherapy.

[Slide.]

Altogether, 279 patients were felt to meet eligibility criteria and were randomized. 198 were assigned to treatment with CPT-11 and 90 were assigned to treatment with best supportive care. Of note, six patients never

received study drug, patients who had been assigned to receive CPT-11. However, these patients are included in all analyses as part of the intent-to-treat study population.

[Slide.]

There was a predominance of males enrolled in both arms of the study. The median ages were similar. The majority of patients had tumor-related symptoms at baseline, both as documented by a performance status of 1 or 2 and as confirmed by specific review of baseline symptoms. Approximately one-tenth of patients in both groups had experienced obvious weight loss prior to enrollment.

Of note, there was a statistically significant difference in performance status between the two groups with patients in the CPT-11 arm having better overall baseline performance status.

[Slide.]

Disease-related characteristics were well-balanced. As might be expected, given the epidemiology of the disease, there was a predominance of primary tumors of the colon. A majority of patients in both groups had metastases to two or more organ sites. The most common site of metastatic disease was the liver.

[Slide.]

Patients were assessed for baseline laboratory parameters with potential predictive value for outcome

including hemoglobin, white blood-cell count and serum values of lactate dehydrogenase, alkaline phosphatase and CEA.

The populations were generally well balanced except that a significantly higher proportion of patients in the best supportive care arm were anemic as defined by a baseline hemoglobin value of less than 11 g/dL. Of note, there was no statistically significant difference in the mean hemoglobin value between these groups.

[Slide.]

With regard to prior local therapies, almost all patients had undergone prior surgery and approximately one-quarter of those in each group had received prior radiation therapy.

[Slide.]

100 percent of the patients had received prior 5-FU-based chemotherapy. The vast majority of patients had received 5-FU in the palliative setting. When documented, bolus and infusional forms of 5-FU had been given in similar proportions. Objective response to prior 5-FU was reported as 23 percent in those patients assigned to CPT-11 and 32 percent in the patients receiving best supportive care.

[Slide.]

Documentation of disease progression prior to study enrollment was present in virtually all patients. The

substantial majority of patients had progressed while actually receiving 5-FU or within six months of the last 5-FU therapy. As a consequence, the median times from the last 5-FU to randomization and from date of progression to randomization were short in both groups.

Of note, a small minority of patients had a rising CEA as their only documentation of disease progression prior to study enrollment. However, this baseline characteristic, as with other prior treatment characteristics, was well-balanced in both the CPT-11 and best supportive care groups.

[Slide.]

Overall, treatment administration while on CPT-11 therapy was excellent with a median dose intensity of 95.8 percent. Of the 1,154 courses of CPT-11 that were administered, only 4.9 percent were reduced and only 13.6 percent were delayed. The median duration of CPT-11 therapy was 4.1 months but ranged as high as 12.6 months.

[Slide.]

With a median follow up of 13 months, median survival was 9.2 months in the CPT-11 group and 6.5 months in the best supportive care group. The one-year survival was 36 percent with CPT-11 and 14 percent in those patients receiving best supportive care.

The difference in overall survival was highly statistically significant with a p-value of 0.0001.

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[Slide.]

This slide shows survival for each of the baseline performance status categories. In each subpopulation of patients, whether the baseline performance status was 0, 1 or 2, CPT-11 treatment was always associated with better survival.

[Slide.]

As planned in the protocol, a multiple regression analysis was performed to evaluate the effect of treatment in the context of assessing the effects of other baseline variables on survival. As shown on this slide, when these baseline characteristics, including performance status and hemoglobin, were taken into account, CPT-11 treatment was still highly significantly associated with approved survival with a p-value of 0.001.

[Slide.]

Additional measures of clinical benefit were secondary endpoints in this study and revealed CPT-11 to be consistently associated with improved outcomes; time until performance status deterioration--

[Slide.]

Time until the occurrence of weight loss greater than 5 percent--

[Slide.]

And time to onset of pain, were all significantly

improved with CPT-11 therapy.

[Slide.]

As expected, the most common grade 3/4 adverse events observed among patients receiving CPT-11 were neutropenia and diarrhea. Neutropenic fever was seen in only 3 percent of patients treated with CPT-11. Vomiting and cholinergic symptoms were more often seen in patients receiving CPT-11.

Of interest, grade 3 asthenia and abdominal pain, events often attributed to CPT-11, were actually equally common in patients receiving best supportive care suggesting that these problems may often be related to the underlying tumor.

Only 5 percent of patients discontinued CPT-11 therapy due to adverse events. The most common such events were diarrhea, asthenia, and nausea and vomiting. Two patients died of events, one patient with grade-4 diarrhea and asthenia and the other with neutropenic sepsis that were considered to be potentially drug-related.

[Slide.]

An additional analysis performed as a component of this study was a formal assessment of quality of life using patient-completed EORTC QLQ-C30 questionnaires. Compliance in completing the quality-of-life questionnaires was excellent at over 70 percent in both arms of the study and

was comparable between the arms of the study.

[Slide.]

Evaluation of the global health-status quality-of-life scale during the study revealed that, on average, CPT-11-treated patients assessed quality of life as being continuously better than did patients receiving best supportive care. And this result was highly statistically significant.

[Slide.]

One method of comparing the two groups was to assess the worst patient quality-of-life score during the study. Such an analysis revealed significantly improved global quality of life in patients receiving CPT-11. All of the QLQ-C30 functional scales favored CPT-11.

Cognitive, social, physical and role functioning were highly significantly improved in the CPT-11-treated patients as depicted by the higher scores on this graph.

[Slide.]

When analyzing symptom scales that are also a part of the EORTC instrument, where, it should be noted, higher scores are worse, patients receiving CPT-11 noted significantly less fatigue, appetite loss, pain, constipation and dyspnea than did patients receiving best supportive care.

Insomnia and nausea and vomiting were not

at.

appreciably different between the groups. As expected, diarrhea was significantly more likely to be noted as a quality-of-life concern with CPT-11 therapy than with best supportive care.

[Slide.]

In conclusion, second-line CPT-11 treatment significantly prolongs survival, controls tumor-related symptoms and improves quality of life. In other words, the results of this important study demonstrate that active anticancer treatment with CPT-11 is a better option than just symptom-directed therapy in patients with previously treated colorectal cancer.

[Slide.]

Next, I would like to describe for you the results of the companion study to V301. Study V302 was a phase-III trial that evaluated the benefit of giving CPT-11 versus infusional 5-FU-based chemotherapy, again as second-line treatment of patients with previously treated colorectal cancer.

The results of this trial were presented at ASCO this year by Dr. Eric Van Cutsem of the University Hospital at Leuven in Belgium. Dr. Van Cutsem is also here with us today to assist in answering your questions.

[Slide.]

As for study V301, this trial was also a large,

multicenter effort. It is important to note that the trial was conducted at different sites from those that were involved in study V301. At these centers, the prevailing philosophy was to routinely provide chemotherapy as a component of a second-line treatment of colorectal cancer. Patients were enrolled between September, 1995 and July, 1996 in eleven countries at 46 study sites.

[Slide.]

Patients participating in V302 were assigned to treatment with CPT-11 or infusional 5-FU in a one-to-one randomization. Patients were stratified by study site and performance status in this trial.

Patients randomized to CPT-11 were to be treated with 350 mg/m^2 of CPT-11. From the beginning of the study, patients older than 70 years of age and those with performance status of 2 were to begin treatment at CPT-11 doses of 300 mg/m^2. Patients in the CPT-11 group were permitted to receive additional chemotherapy after cessation of CPT-11 treatment.

[Slide.]

Patients assigned to receive 5-FU were to be treated with one of three commonly used infusional 5-FU regimens. These are often designated at the DeGramont, Lokich and AIO treatment regimens.

Participating institutions were allowed to select

two of the three regimens for use in the patients treated at that site. This practice allowed treating physicians to choose an on-study 5-FU regimen that was different from that previously used in the same patient before enrollment.

[Slide.]

The hypothesis of the study was that use of CPT-11 would be associated with a 15 percent improvement in one-year survival. Differences in survival were to be tested by means of a two-tailed log rank test. In this study, at least 250 patients were required to meet study objectives.

[Slide.]

The primary endpoint of this study was also survival. Secondary endpoints included additional measures of clinical benefit and also patient quality of life as measured by the EORTC instrument.

[Slide.]

Patients in both groups were assessed every three to five weeks for up to one year depending up on the regimen they were receiving. After one year, information regarding survival was collected.

[Slide.]

The entry requirements for V302 were similar to those for V301 except that patients could have had no more than one prior regimen for metastatic disease whereas in study V301, up to two prior palliative regimes were allowed.

[Slide.]

Altogether, 267 patients met eligibility criteria and were randomized. 133 were assigned to treatment with CPT-11 and 124 to 5-FU. Six patients randomized to receive CPT-11 never received study drug and five patients randomized to receive 5-FU also never received study drug.

As a consequence, 127 patients were actually treated with CPT-11 and 129 patients were treated with 5-FU. As designated in the protocol, these patients who were actually treated with study drug were those included in all of the analyses on the study.

[Slide.]

In study V302, the treatment groups were well-balanced in terms of baseline patient characteristics including gender, median age, WHO performance status, symptom review and prior weight loss before study.

[Slide.]

Disease-related characteristics, including the primary site, number of organs involved, and metastatic sites were also well-balanced.

[Slide.]

Baseline laboratory parameters with potential predictive value for outcome were well-balanced except for the significantly higher proportion of patients in the 5-FU group had the better prognostic parameter of higher white

blood-cell counts.

[Slide.]

Almost all patients had undergone primary surgery and approximately one-fifth in each group had received prior radiation therapy.

[Slide.]

Again, 100 percent of patients in both groups had received prior 5-FU-based chemotherapy. The vast majority of these patients had received 5-FU in the palliative setting, usually with a bolus regimen of 5-FU treatment. Response to 5-FU was similar in the two treatment groups.

[Slide.]

Documentation of disease progression prior to study enrollment was also present in virtually all patients in this study. As in study V301, a small majority of patients had rising CEA as the only evidence of disease progression. Again, all treatment characteristics were quite well-balanced between the two treatment groups.

[Slide.]

Overall CPT-11 treatment administration in study V302, as for study V301, was excellent resulting in a relative median dose intensity of 96 percent. Median relative dose intensity for each of the three 5-FU treatment regimens was universally greater than 80 percent.

The median treatment duration with CPT-11 was

4.2 months, and 5-FU was 2.8 months. This difference was statistically significant.

[Slide.]

With a median follow up of fifteen months, median survival was 10.8 months with CPT-11 and 8.5 months with 5-FU. The one-year survival was 45 percent with CPT-11 and 32 percent with 5-FU. The difference in overall survival when analyzed for the treated population of patients was statistically significant, with a p-value of 0.035.

[Slide.]

A multiple regression analysis was performed to evaluate the effect of treatment in the context of assessing the effects of other baseline variables on survival. As shown on this slide, when these baseline patient characteristics were taken into account, CPT-11 treatment was even more significantly associated with improved survival with a p-value of 0.017.

[Slide.]

Time to tumor progression was also significantly improved with the CPT-11-treated patients as compared to those receiving infusional 5-FU. Respective median times to tumor progression were 4.2 months and 2.9 months for the two groups. A log rank comparison of the time to tumor progression in the two study arms was statistically significant with a p-value of 0.03.

[Slide.]

A trend toward improved pain-free survival was also observed in patients receiving CPT-11, patients on this study, with a p-value of 0.06.

[Slide.]

Again, the most common grade 3/4 adverse events observed among patients receiving CPT-11 were diarrhea and neutropenia. Vomiting and cholinergic symptoms were also more often seen in patients receiving CPT-11. Asthenia and abdominal pain were again distributed similarly between the two groups as had been observed in study V301. Severe mucositis and cutaneous toxicities were infrequent in either arm but were more often associated with 5-FU-based treatment.

10 percent of patients in the CPT-11 group and 6 percent of patients in the 5-FU group discontinued study treatment due to adverse events. The most common reason for discontinuing therapy was diarrhea for both treatment groups. No CPT-11-related deaths were observed. There was one potentially treatment-related death in the 5-FU group. This was attributed to 5-FU-induced diarrhea.

[Slide.]

As in study V301, quality of life in study V302 was also formally assessed with the EORTC QLQ-C30 instrument. Compliance in completing the quality-of-life

questionnaires was good and was well-balanced in the two study arms.

[Slide.]

Evaluation of the global health status quality-of-life scale during the course of the study revealed that, on average, CPT-11-treated patients and 5-FU-treated patients had similar quality of life.

[Slide.]

A comparison of the worst patient quality-of-life score during the study revealed similar global quality of life and functioning during the trial.

[Slide.]

Quality of life symptom parameters were generally similar except that patients receiving CPT-11 noticed significantly more diarrhea and nausea and vomiting than did patients receiving 5-FU.

[Slide.]

In conclusion, the combined results of this study demonstrate that second-line CPT-11 treatment significantly prolongs survival and time to tumor progression when compared to use of intensive second-line infusional 5-FU and that CPT-11 provides this survival benefit with a similar quality of life.

[Slide.]

In final summary, the data presented to you today

document that CPT-11 safely prolongs survival, controls symptoms and provides quality-of-life benefits to patients. These results validate the ODAC and FDA decision of 1996 granting accelerated approval for CPT-11. The positive clinical benefit data from these two well-controlled studies clearly support full approval of CPT-11.

[Slide.]

It is also clear that CPT-11 has consistent activity when given in either a weekly or an every-three-week dosing regimen with similar efficacy outcomes and comparable toxicity profiles. The proposed modifications to the package insert provide documentation of the risk/benefit, dose modifications and supportive care for both of these commonly used regimens.

Inclusion of a description of both treatment schedules is the safest method for enhancing patient and physician flexibility in managing this life-threatening disease.

[Slide.]

Thank you for your attention. My colleagues at Pharmacia & Upjohn and at Rhone-Poulenc Rorer, as well as Dr. Cunningham, Dr. Van Cutsem and I, would be pleased to answer any questions you may have. U.S. investigators with considerable experience in the development of CPT-11, including Drs. Goldberg, Pazdur, Rothenberg and Saltz, are

also present to address your queries.

DR. DUTCHER: Thank you.

Questions from the Committee

DR. DUTCHER: Do we have questions from the committee for the sponsor?

DR. MARGOLIN: I would like you to spend a little bit of time telling us about the diarrhea syndromes that are associated with CPT-11, the early diarrhea, what is called late diarrhea, and whether there is an even later diarrhea such as a mucositis type of effect and whether that has any bearing on optimal schedules for approval or for use.

DR. MILLER: There are two potential forms of diarrhea associated with CPT-11 use. The most common and most clinically significant is a cytotoxic diarrhea, so-called late diarrhea, that occurs consistent with a cytotoxic pattern of injury to the bowel.

[Slide.]

As depicted here, this is basically a plot of frequency of diarrhea by day. Over several courses of therapy, one sees a cytotoxic pattern of injury, in essence.

There is a second form of diarrhea that can be seen with CPT-11 and that is a cholinergic diarrhea. It is actually quite infrequent, at least in a serious form. More commonly, patients have abdominal cramping, diaphoresis, lacrimation as symptoms associated with cholinergic events

with CPT-11.

That is thought to be mediated by CPT-11, the parent drug, itself. High peak levels during infusion during infusion seem to cause this syndrome. It actually has anticholinesterase activity.

DR. MARGOLIN: So would weekly dosing with expected lower peak doses be likely to cause that problem less frequently?

DR. MILLER: Yes; it would. In fact, in looking at the weekly schedules, the cholinergic symptom was not systematically quantified in the early studies. But if one looks at the first day of dosing, for instance, about 22 percent of patients will have some cholinergic syndrome. This rises to closer to 50 to 60 percent with 350 mg/m^2.

Generally, symptoms are mild and it has been found that use of atropine in low doses, either subcutaneously or intravenously, will moderate these symptoms. In practical fact, in studies study V301 and study V302, prophylactic atropine was used, particularly in patients who had had cholinergic symptoms in an early course, and it was found to be quite effective.

In courses where prophylactic atropine was used, the rate of any grade of early diarrhea--again, most of these are low-grade events--fell from 22 percent without prophylaxis to 11 percent with.

at.

DR. MARGOLIN: One last thing on the same theme. This later cytotoxic diarrhea pattern that, I guess--I would like to understand whether that is similar to 5-FU or--I think there was a report recently in the JCO about studying the mechanisms, and there is some secretory aspect of this mechanism. Does it occur earlier? In what ways is it different than what we oncologists think of as fairly typical gut toxicity from some of the drugs we use?

DR. MILLER: It is probably quite comparable to 5-FU-induced diarrhea in terms of its general pathophysiology. Probably 5-FU-induced diarrhea has best been characterized in a paper that was actually published in 1962 where patients underwent routine endoscopy after receiving 5-FU. The pattern of induction of cytotoxic damage to the mucosa was quite consistent and started to come on about day 8 or so, rose and peaked around the second week after treatment, and then fell off.

It is a very similar situation with CPT-11.

MS. FORMAN: Just to follow up on that. In terms of your plans for either labeling or package inserts for patients and doctors, are you going to be able to give some expectation as to what the patient might experience in diarrhea?

DR. MILLER: Yes. We have gone to considerable lengths to try to educate patients, themselves. We have

prepared patient handouts that we have been told are quite appreciated by clinic staff in terms of educating patients. Physicians and nurses have been provided with instructional materials.

The other thing that we have done is to try to encourage provision of loperamide when the patient is first seen. So the patient goes home from the clinic with loperamide to specifically use as therapy for the diarrhea so that they are not at home with just a prescription and no medication to counter the diarrhea.

Early institution of loperamide clearly helps this syndrome with quick application at the first sign of loose stools or an increased frequency in stools. Many patients have slight loose stools but then, actually, don't go on to even develop grade 1 diarrhea and can ameliorate this syndrome quite quickly. It is patients who, perhaps, don't adhere to those guidelines as readily who have some more protracted diarrhea.

DR. SIMON: First, I would like to compliment you or, perhaps, RPR on two really excellently designed and analyzed studies. I think this committee struggles a lot with making decisions in settings where we really don't have good clinical trials. I think these are examples of exemplary clinical trials.

I had a couple of small questions. One, although

I don't think it matters, what were the response rates in the CPT-11 arm?

DR. MILLER: The response rates were not systematically characterized in either trial. They were not characterized at all in study V301. In study V302, the response-rate assessment was according to institutional or the kind of standard of practice outside of the study and so, I think, was really fairly meaningless.

DR. SIMON: The other question was in study V301, did you do any analyses of survival without pain deterioration or survival without performance-status deterioration or survival without quality-of-life deterioration adjusted for the performance status imbalance prior regression, the way you did for--

DR. MILLER: In terms of the quality of life, yes, a look a changes from baseline was performed. Most of the endpoints were still statistically significant. When one looks at global health status and cognitive function, it was significantly better when looking at a change from baseline.

Pain, dyspnea and appetite loss were also significant better in those receiving CPT-11 while diarrhea was less commonly noted in those receiving best supportive care. So the results tended to corroborate, just looking at absolute scores, when one looked at changes from baseline.

DR. SIMON: That is not actually what I meant, but

it does provide--

DR. MILLER: In terms of an adjusted analysis.

DR. SIMON: You could have a time to event where the event is either death or deterioration of score and use a Cox model to adjust for performance status the same way you did on survival.

DR. MILLER: This wasn't done.

DR. OZOLS: I also want to commend you on coming back to the committee and the FDA in a timely manner after accelerated approval. I think that is commendable.

I want to focus a little bit on the poor-performance group of patients in PS2, over-70 patients. That is the group of patients frequently, of course, that don't enter trials but are treated in a community situation. And you dose-reduced on that group of patients.

A couple of questions. Did you see, really, more toxicity in the PS2 and over-70 group of patients? And should you really be dose-reducing in that group of patients?

DR. MILLER: Let me show you some data that may address that point. It is the survival curves.

[Slide.]

Looking at diarrhea, in study V301, the institution of the lower-starting dose level began after the study had started. As a consequence, about 70 percent of

the patients above the age of 70 or with performance status of 2 actually received the 350 mg starting dose. This graph depicts the overall incidence of diarrhea, grades 1, 2, 3 and 4. Here is the grade 3/4. It is split by 65 years of age instead of 70 because that makes it comparable with what we did in the pivotal trials here in the U.S. where the split was at 65.

As you can see, in the first course of treatment, the rate of grade 3/4 diarrhea was about double in the older patients.

[Slide.]

When one looks in study V302 where 90 percent of the patients over the age of 70 and with poor performance status received 300 mg/m^2 , you can see an evening out in the grade 3/4 diarrhea so, perhaps, an indication that this had some positive effect in the early courses where diarrhea is most common.

[Slide.]

The other thing that we looked at was the survival by CPT-11 starting dose in this trial. As you can see, there is no difference whether patients began treatment at 300 or 350 mg/m^2. The same result was observed when one looks at these same data, 300 versus 350 in patients on study V302.

DR. ALBAIN: So, to follow that up, what is your

sense now, in terms of what you would like to recommend for the fit elderly, so to speak? Are you going to recommend the lower dose?

DR. MILLER: At this time, the provisional changes to the package insert recommend that patients with age over 70, performance status of 2, and prior pelvic radiotherapy receive 300 mg/m^2 as the starting dose.

DR. ALBAIN: I guess I still haven't seen the data to convince me that just because someone is over 70, they should start at a lower dose. Might it be the other competing comorbidities that they have, the performance status, for example, or other symptoms?

DR. MILLER: It could well be. There are data from the phase II studies from the original pivotal phase II studies that indicate that age was a significant risk factor for a greater likelihood of diarrhea. In an RPR phase II study, an initial multiple regression analysis showed that that, and poor performance status, were associated with greater toxicities. So there has been this previous evidence that was the basis for use of this lower dose in these trials. Our assumption was that these trials represent the database for use of this regimen and so, therefore, this dose might be recommended.

One other thing that is going on is that we are trying to determine whether there are better ways to predict

toxicity using approaches--looking at CPT-11 metabolism and, perhaps, we can refine our dosing better based on some better predictors.

Dr. Schaff, would you like to comment on that?

DR. SCHAFF: Larry Schaff from Clinical Pharmacokinetics at Pharmacia & Upjohn. I should mention that CPT-11 is metabolized into an active metabolite called SN38. SN38 is approximately a thousand-fold more potent than CPT-11 in in vitro and in vivo tests in terms of cytotoxicity.

SN38 is glucuronidated to an inactive metabolite called SN38 glucuronide and it has recently been shown that the enzyme that is responsible for that conversion is an enzyme called glucuronal transferase and, more specifically, an isoform called UGT1A1.

What is interesting is this particular enzyme is also responsible for glucuronidating bilirubin and, consequently, there is some belief that those individuals who have, let's say, Gilbert's syndrome which have a genetic defect in their ability to glucuronidate bilirubin will also have a deficiency in glucuronidating SN38.

So there are current trials going on now in the United States, at least three of them, which are trying to correlate genotype with phenotype for UGT1A1 and also to see how this relates to CPT-11 toxicity.

There are other studies going on looking at UGT1A1 genotyping in different ethnic groups in order to see whether there are differences in those groups as well.

I should mention with regard to age, we have seen no differences in CPT-11, SN38 or SN38G pharmacokinetics in patients greater than 65 and less than 65.

DR. MARGOLIN: So, as a follow on to that, in your studies that you alluded to in the sponsor packet of first-line therapy, are you also recommending a lower starting dose for elderly patients who don't have, also, the prior history of pelvic radiation or a low PS?

DR. MILLER: By first-line therapy, do you mean--

DR. MARGOLIN: I think there were some studies that were alluded to that are going to go into a future application for first-line CPT-11--

DR. MILLER: Those studies involved a combination--a weekly schedule is being used in those trials. As a consequence, we are not recommending a reduction in older patients there because, since you can modulate the dose week by week, it is very easy to tailor the dose of the patients quite rapidly. We thought that the 350, where you can't do that so readily when you are giving it every three weeks, it might be better to start with 300 and then escalate if a patient tolerated the treatment, particularly given that the treatment outcomes were not different.

DR. ALBAIN: How far has your experience gone since your initial application in terms of which patients with liver abnormalities due to disease can safely tolerate this drug? I know you have the cut points that you describe, but has there been additional experience gathered where it is safe to treat some of these patients, where they might have been excluded from these pivotal trials?

DR. MILLER: Again, I think I would like to ask Dr. Schaff to address that question as he is involved with a trial specifically looking at hepatic dysfunction in patients receiving CPT-11.

DR. SCHAFF: I should mention that this data is very preliminary. We currently have 14 patients on trial. This is a study specifically looking at the pharmacokinetics as well as the phase I study of CPT-11 in four different groups of patients with varying degrees of hepatic dysfunction.

These four groups are looking at dysfunction in terms of altered bilirubin and also in terms of transaminase values.

[Slide.]

This is the preliminary data for the first 12 patients. This is protocol 0017 which is the brown column here. The clearance in the first 12 patients has been 8.7 $L/h/m^2$. If we compare this fact, four other studies in

which the drug was given on the weekly schedule, protocol 6, protocol 37, protocol 32, we see clearance values that are around 13. This particular protocol was a Q three-week phase I protocol.

So you can see, compared to patients that have normal bilirubin levels, these particular patients are showing somewhat of a decrease. We don't have a sufficient database right now to say whether there is going to be a correlation with various degrees of decreases in bilirubin or transaminase values. That study is ongoing.

I should also mention that Rhone-Poulenc Rorer is conducting a similar study with a Q three-week regimen. I believe their database is going to be coming out probably in the next year. There is also a study that is going to be initiated by the CALGB looking at hepatic dysfunction as well.

DR. MARGOLIN: At this time, the package insert doesn't have a specific recommendation other than to say that, really, the drug shouldn't be given to such patients. We are finding that doses of 50 to 60, 75 mg/m^2 may be tolerated but, as Dr. Schaff has pointed out, we need more data.

DR. DUTCHER: Could you just comment--we have the brochure, but could you just comment on the comparability of the toxicities with the two different schedules?

DR. MILLER: Sure.

[Slide.]

This is a depiction of clinically relevant adverse events, grades 1 through 4, here with the weekly treatment administration in 193 patients in the U.S. pivotal trials who received 125 mg/m^2 as the starting dose, and here, in study V301 and study V302.

As you can see, there are generally comparable rates of these major toxicities, diarrhea and neutropenia, nausea and vomiting. Alopecia, about comparable. Cholinergic symptoms, you see the step up a little bit here in study V301.

This only includes first CPT-11 dosing day but, if anything, we would expect it to be maximum there because doses tend to get modulated somewhat after the first day.

[Slide.]

When one looks at grade 3/4 toxicities, here, diarrhea, vomiting, neutropenia. Neutropenia, fever and deaths. The U.S. experience in the 193 patients treated with a weekly dosing regimen. The two phase II studies that are presented in the brochure and then study V301 and study V302 with CPT-11, we see the rates of diarrhea here.

They tend to fall off a little bit in the later phase II experience. In the phase III experience, vomiting roughly comparable, perhaps somewhat less in the later

experience. Neutropenia, generally comparable rates across the schedules.

Neutropenic fever, hasn't been a material problem. We are not recommending, for instance, the use of GCSF since the rates have been so low and toxic deaths have been quite infrequent.

One of the things that we have observed and also RPR has observed is that, in our later phase I experience, in their later phase II and their phase II experience, the rates of grade 3/4 diarrhea seem to have declined somewhat. We think that this is probably largely due to increased experience with use of the drug, a learning-curve phenomenon, more rigid application of the intensive loperamide regimen and better understanding of the dose modification recommendations.

DR. MARGOLIN: I'm sorry; you may have already covered this and it may be in the insert already, but could you just go back to our ability to predict the lowered clearance is probably most closely correlated with some measure of the bilirubin glucuronidation.

This is a unique patient population which, unlike many of our other solid tumors, by the time they get to this therapy, they are highly likely to have abnormal liver function because the vast majority of these patients have liver metastases and they have either elevated

transaminases, often have elevated alkaline phosphatases and sometimes have elevated bilirubins with various patterns.

So is there going to be more clarity on actual guidelines or are we just going to leave it that caution should be exercised in treating these patients with bilirubin over "x" value with this drug?

DR. MILLER: At this junction, without specific data about what dose to give, what starting dose to give, we are basically recommending against treating such patients. Once we have the data from our own study, from the RPR study and we also have been involved in talking to the folks at CALGB about their study, we would propose to change the package insert to reflect that information and give specific guidelines for the correct dose to administer.

We are looking, as is RPR, at different categories of patients in terms of bilirubin-elevated, transaminases elevated, both elevated. So we are trying to characterize that as best we can.

DR. DUTCHER: Any other questions? No other questions? Wow.

Thank you very much.

Can we go ahead with the FDA presentation rather than taking a break an hour early and just move right along?

FDA Presentation

DR. CHICO: Good morning, everyone, members of the

advisory committee, my colleagues at the FDA, ladies and gentlemen.

[Slide.]

Today, I am presenting the clinical review of two pivotal trials for sNDA 20-571 on irinotecan for the treatment of patients with colorectal cancer.

[Slide.]

First I would like to acknowledge the members of the FDA review team. I would like take this opportunity also to thank the applicant for their promptness and cooperation in responding to our information requests during the review process.

[Slide.]

This application seeks approval for CPT-11 for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has progressed or recurred following 5-FU-based chemotherapy. The new proposed dosing schedule is 350 mg/m^2 as a 90-minute intravenous infusion given on day 1 every three weeks. This is the dosing schedule popularly used in Europe and was the dosing schedule used in the pivotal trials.

The U.S. approved schedule is weekly times 4 every six weeks.

[Slide.]

CPT-11 was granted accelerated approval in June of

1996 on the basis of tumor response in 305 patients with colorectal cancer whose disease progressed or recurred following 5-FU. The NDA was submitted on April 22 of 1998 and was given priority designation on the basis of a claim of superiority and survival compared to the corresponding treatment-control arm.

[Slide.]

During accelerated approval of CPT-11 in June, 1996, it was agreed that study 038 would be the confirmatory trial. This was a multicenter, three-arm, phase III trial in patients with previously untreated colorectal carcinoma comparing CPT-11 versus 5-FU leucovorin versus the combination of CPT-11 5-FU leucovorin.

The primary efficacy endpoint of this trial is time to tumor progression. The applicant met with the agency in December, 1997 to propose submitting an NDA to fulfill requirements for accelerated approval to full approval.

At that time, study 038 was nearing completion. However, the applicant proposed submission of two EORTC-conducted studies, study V301 and study V302. These studies were done on patients who have received prior 5-FU and the applicant claimed a significant survival advantage for CPT-11 over the corresponding treatment control arms.

[Slide.]

A total of 535 patients were enrolled in these two large, randomized, non-blinded, multicenter, phase III trials. This is supported by efficacy and safety data from other phase I and phase II trials using the proposed dosing schedule. A summary report on the survival analysis of the original 304 patients was also submitted. A cholinergic-effects report provided more detailed information on the diagnosis and management of cholinergic symptoms from CPT-11.

[Slide.]

Study V301 and study V302 were sponsored by Rhone-Poulenc Rorer and performed in Europe by the EORTC. Patients randomized to the CPT-11 arm received 350 mg/m^2 of CPT-11 as a 90-minute infusion on day 1 every three weeks. Patients enrolled in arm B of study V301 received best supportive care according to institutional standards. These may include antibiotics, analgesics, blood transfusions, corticosteroids, psychotherapy and any other symptomatic therapy including radiation and chemotherapy in a number of study centers.

A 2-to-1 randomization resulted in 189 patients enrolled in arm A and 90 patients in arm B. Patients were stratified by treatment center and randomized centrally. An independent committee of four oncologists was placed as monitors of study V301.

Patients enrolled in arm B of study V302 received one of three widely used infusional 5-FU regimens in Europe. There were similar numbers of patients between treatment arms A and B in study V302.

[Slide.]

Pretreatment characteristics among patients in both studies were generally well balanced. Patients were not stratified by performance status in study V301 and there was a statistically significant difference in the performance-status distribution favoring CPT-11. Fishers Exact Test comparing performance status 0 plus 1 versus performance status 2, however, did not yield statistically significant differences.

[Slide.]

Median time from diagnosis and median time from progression of disease after 5-FU treatment to randomized into the studies was also similar between treatment arms in both studies.

[Slide.]

The primary efficacy endpoint in both studies is a comparison of survival defined as the time from randomization to death. The primary analysis was prospectively defined and performed on the intent-to-treat group. Data on quality of life using the EORTC QLQ-C30 and clinical benefit endpoints such as pain-free survival,

symptom-free survival, survival without weight loss and survival without performance-status deterioration were collected but the statistical analysis plan was retrospectively defined.

Safety and toxicology data were collected and described using the NCI common toxicity criteria.

[Slide.]

Enrollment to study V301 started in November, 1996 and the cutoff date for data analysis was seven months later, in June of 1997 at which time 194, 70 percent, of the patients were dead. The remaining proportion of patients were mostly censored. Note that of the 66 patients censored in the CPT-11 arm, 33 were still alive after one-and-a-half months after the cutoff date.

[Slide.]

The protocol specified the cutoff date for study V302 was March 3, 1997 at which 184 patients, or 69 percent, were dead. Approximate 183 deaths were determined prospectively as needed to show a difference in one-year survival rates for this study. However, in the sponsor's analysis, they used a later cutoff date of July 14, 1997.

[Slide.]

Survival analyses for study V301 by the FDA and applicant agree for study V301. The median survival rate was 9.2 months for patients in the CPT-11 arm and 6.2 months

for the best-supportive-care arm. A log rank test showed the highly statistically significant difference favoring the CPT-11 arm with a p-value of 0.0001. The hazard ratio for best-supportive-care arm versus CPT-11 is 1.75 with a 95 percent confidence interval of 1.31 to 2.36.

[Slide.]

The FDA's analysis of survival for study V302 was based on the data that was submitted by the sponsor with a cutoff date of March 3, 1997. Unlike the sponsor's results, the FDA survival analysis showed borderline significance between CPT-11 and 5-FU using the earlier cutoff date. The median survival was 10.2 months for patients in the CPT-11 arm and 8.4 months for the 5-FU arm.

A log rank test showed a p-value of 0.056 with a hazard ratio between 5-FU versus CPT-11 of 1.32 with a 95 percent confidence interval between 0.991 and 1.77.

[Slide.]

The following table summarizes the differences in analysis of survival for patients in study V302 using different cutoff points during the study. Note that the median survival for patients in the CPT-11 arm was longer by the applicant's analysis using this cutoff date.

[Slide.]

I would like to direct your attention first to the slides in your handouts because these contain more updated

information. 57, or 30 percent, of the patients in the CPT-11 arm received therapy after 5-FU was terminated, 40 of whom received systemic chemotherapy with 5-FU, 5-FU analogues and other experimental therapy.

This is compared to 28 patients, or 31 percent, in arm B. The median survival of the 40 patients who received subsequent chemotherapy was 11.7 months compared to 9.2 months for the whole group of patients in arm A.

[Slide.]

The applicant was requested to perform a survival analysis for study V301 by censoring those patients who received subsequent anticancer therapy at the start of this therapy. This resulted in 87 patients being censored with a medial survival of 9.3 months. For the best-supportive-care arm, this resulted in the censoring of 35 patients with a medial survival of 6.3 months.

However, the log rank test still showed statistically significant differences showing CPT-11 over best supportive care with a p-value of 0.005. These findings were confirmed by the FDA reviewers.

[Slide.]

Patients who were more than 70 years old and those with a performance status of 2 were given 300 mg/m^2 of CPT-11 instead of 350. The doses of CPT-11 on patients who experienced dose-limiting toxicities were likewise

decreased. Assuming no further dose delays or adjustments, the dose intensity of drug for these patients would approximately be 100 mg/m^2 per week.

As such, patients enrolled in the CPT-11 arm were artificially divided into two groups. The dose intensity of CPT-11 in 33 of 189 patients was less than 100 mg/m^2 per week. The median survival for this group was 10.1 months. The median survival for this group in study V302 is 11.6 months.

Adjustment of CPT-11 dose to accommodate certain populations in dose-limiting toxicities is probably not associated with worsening of survival.

[Slide.]

In summary, the analysis of efficacy was well controlled with appropriate censoring of patients for survival. The most impressive result is a finding of consistently significant survival advantage favoring CPT-11 regardless of lower dose intensity or adjustment for subsequent chemotherapy.

[Slide.]

The same is true for the analysis of study V302 which is well controlled with appropriate censoring of patients for survival. Significant survival advantage favored CPT-11 and analysis of dose intensity did not show a significant effect on survival in the lower-dose group.

The FDA review showed less significant survival differences, however, between CPT-11 and 5-FU.

[Slide.]

The following clinical-benefit endpoints were analyzed; pain-free survival, symptom-free survival, survival without weight loss and survival without performance-status deterioration. The major weakness of this analysis is its retrospective nature.

With regard to pain-free survival, only a few patients in either arm were pain-free at baseline and records were obtained retrospectively. Symptom-free survival is very sensitive to the amount of reporting by either the patient or the investigator and a change in weight in these patients may be affected by several uncontrolled factors such as the presence of diarrhea, nausea or vomiting, or intake of certain medications such as diuretics.

These, in addition to unequal follow-up schedules between treatment arms in both studies make the analysis of clinical-benefit endpoint less reliable.

Clinical benefit was also analyzed retrospectively by the applicant in study V302 and no statistically significant differences between treatment arms were found in the analyses of these four clinical-benefit endpoints.

[Slide.]

Performance status, however, was collected prospectively in study V301 and, according to the sponsor's report, 33 percent of patients in arm A with a performance status of 1 or 2 were able to improve compared to patients in arm B. There was also a statistically significant difference not only in the deterioration but also in patients improving their performance status in favor of CPT-11.

These results are consistent with Cox regression analyses of covariates for survival and may truly represent the clinical benefit advantage for the use of CPT-11. These differences, however, were not shown in study V302.

[Slide.]

The quality-of-life instrument used in study V301 and study V302 can be subdivided into fifteen subscales. There were five functional scales, one for global health status and nine symptom subscales which include fatigue, nausea, vomiting, pain, dyspnea, sleep disturbance, appetite loss, constipation and diarrhea.

[Slide.]

Patient compliance during quality-of-life testing in study V301 was good with approximately 70 to 80 percent after week 12. The applicant's analysis showed an advantage for CPT-11 with regard to improvement from baseline in six subscales and comparison from worst scores in ten of the

fifteen subscales.

Diarrhea, on the other hand, was in favor of best supportive care. Similar to the analysis of clinical benefit, the quality-of-life data were prospectively collected but the analysis plan was determined retrospectively. There was also no plan for controlling type 1 error to account for the number of subscales that were considered.

Clinically relevant subscales were not identified and the applicant's analysis assumed random occurrence of missing data.

The FDA statistician performed a longitudinal analysis that divided patients into dropouts and completers to cope with informative dropouts. There were significant differences favoring the best-supportive-care arm with pain in the dropout group and nausea and vomiting in the completer groups.

[Slide.]

Patient compliance during quality-of-life testing in study V302 was also favorable. Similarly, the analysis plan was determined retrospectively. Clinically relevant endpoints were not identified and there was no plan for adjustment for type 1 error for multiple subscales. Also, the analysis assumed random occurrence of missing data.

According to the analysis by the applicant, there

was a significant advantage favoring 5-FU in regard to diarrhea, nausea and vomiting when compared to baseline in worst course. The FDA analysis of physical functioning was also in favor of 5-FU.

[Slide.]

A descriptive analysis of adverse events was performed on the randomized population of both treatment arms according to the NCI common toxicity criteria. The incidence of grade 3 and 4 neutropenia and non-hematologic toxicities such as nausea, vomiting, diarrhea and cholinergic symptoms were significant greater but were expected toxicities from CPT-11.

Grade 3 and 4 leukopenia, and neutropenia and diarrhea, were experienced by 22 percent of the patients, nausea by 14 percent of the patients and vomiting by 14 percent.

Other adverse events with an incidence of greater than 10 percent such as asthenia, neurologic symptoms, pain, abdominal pain and others, are similar in both arms and listed on the bottom half of the chart.

[Slide.]

A descriptive analysis of toxicity was also performed for study V302. More patients in the CPT-11 arm also had severe hematologic toxicities including fever and neutropenia, gastrointestinal toxicities, cholinergic

at.

symptoms, asthenia and alopecia. More patients in the 5-FU arm, however, experienced more mucositis and hand-and-foot syndrome compared to the patients treated with CPT-11.

The incidence of cholinergic symptoms reported by the applicant in the NDA was lower than what was described in other studies including study V301. Incidence was 2 percent for CPT-11.

Since the cholinergic symptoms include one or several of fifteen different symptoms, it was difficult to make an assessment of its true incidence. Instead, atropine use was reviewed which revealed more widespread use of atropine but can be accounted for by the 20 percent incidence reported by the applicant.

Data on the incidence of cholinergic symptoms in study V302 should, therefore, be reexamined.

[Slide.]

A total of eight patients died within 30 days of last treatment with CPT-11. The investigators assessed five of these deaths to be unrelated to drug. The FDA, however, reviewed these deaths and we came up with about three patients whose deaths were most probably, or definitely, related to drug which translates to less than 2 percent.

In study V302, three of 129 patients, or 2 percent, died within 30 days of CPT-11. One patient died within 30 days in the 5-FU arm.

[Slide.]

A total of 1,154 courses of CPT-11 were given to 189 patients in arm A of study V301. 268 courses, or 23 percent, were associated with hospitalizations. These hospitalizations were due to several reasons, the most common of which were diarrhea, fever, nausea and vomiting and pain. There were thirteen courses, or 1 percent, associated with fever and neutropenia.

According to the applicant's analysis, 155, or 13.5 percent, of these hospitalizations were due to adverse events. In arm B, there were 85 episodes of hospitalization for which pain is the most common reasons. For applicants receiving CPT-11, overall, 23 percent of treatment courses were associated with hospitalizations, 13.5 percent due to adverse events.

[Slide.]

In summary, the adverse events reported for CPT-11 were similar to most that have been described and experienced with the approved weekly schedule. As expected, there were higher incidences of neutropenia, fever and neutropenia, nausea, vomiting, diarrhea and cholinergic symptoms associated with CPT-11 but lower incidence of mucositis and no hand-and-foot syndrome as compared to 5-FU.

23 percent of the courses of CPT-11 were associated with hospitalizations regardless of cost. Since

collection of safety data may be dependent on the frequency of patient visits and reporting, the unavoidable imbalance between treatment arms may have biased the results somehow.

[Slide.]

For a drug to be approved for this indication, it is important that a favorable ratio of benefit to risk be established. First, this requires the results from studies that are both adequate and well controlled. In the current application, data from two large randomized and well-controlled studies with the requirements for full approval.

The control arms in each of the studies were well selected, one having a no active treatment, best supportive care in study V301 and the other with an active comparator arm. Patients mostly having 5-FU-resistant disease were carefully selected and balanced between treatment arms in both studies.

[Slide.]

Efficacy could be demonstrated by a significant increment in survival. Regardless of the control arm, CPT-11 consistently showed a statistically significant advantage in overall survival. The method of censoring for survival was appropriate and careful between treatment arms. Survival did not seem to be affected by lower dose intensities of CPT-11 required by certain patient population.

Censoring on the date of subsequent chemotherapy also did not change the survival outcome for patients for study V301.

[Slide.]

Another criterion may be superiority in response rates, time to progression or a believable increment in quality of life. The clinical benefit endpoints were not prospectively defined. Although the quality-of-life tests used in these studies were validated and patient compliance was good, the methods of analysis by the sponsor were determined retrospectively.

The FDA reviewer expressed concerns regarding the lack of control for type 1 errors as a result of multiple subscales and the lack of appropriate adjustments for the non-random nature of missing data. The FDA reviewer proposed different methods of analyses and obtained different results. Further discussion with the applicant are warranted.

[Slide.]

Last but not least, the treatment being considered should also demonstrate a tolerable toxicity profile. Adverse events were well described and expected. The toxicity profile is consistent with those observed in the phase 1 trial submitted as supporting studies and to the weekly FDA approved schedule.

There may be a difference in the severity of some toxicities such as cholinergic symptoms, but the applicant made available additional data to more clearly define, diagnose and manage these symptoms more appropriately.

[Slide.]

One important consideration for discussion was a difference in dosing and schedule between the approved NDA for CPT-11 and the current application. Accelerated approval was based on significant responses in patients enrolled in three open-label, phase II studies who were given weekly injections of CPT-11.

On the other hand, CPT-11 given every three weeks showed a significant survival advantage over the control arms in two large randomized trials. If approved, the applicant's proposed package insert recommends the use of either schedule.

[Slide.]

In summary, the applicant has submitted two large randomized, well-controlled studies which showed a statistically significant improvement in survival compared to both active control arm and no-active-treatment arm. Other efficacy endpoints under clinical benefit and quality of life were less convincing and should be discussed further. Adverse events from the treatment arms were expected, well described and manageable.

Thank you very much.

Questions from the Committee

DR. DUTCHER: Thank you.

Questions for the FDA?

DR. MARGOLIN: Just a small arithmetical question. You stated in one or your later slides that the sponsor claimed that only 13 percent of the hospitalizations in patients on CPT-11 in, I guess, it was in study V301 against best supportive care were due to AEs.

DR. CHICO: Right.

DR. MARGOLIN: There is an excess, however. There are about 1.5 hospitalizations per patient, I believe, in that arm versus 1 per patient in the 90 patients on best supportive care. So do you agree with--it seems that there is an excess beyond what is claimed as AEs, contribution of the drug to reasons for hospitalizations in those patients.

DR. CHICO: The reason why my analysis was on the whole patient population who was hospitalized was because it was very difficult to determine which patients were hospitalized for adverse events or for other reasons.

The most common reasons for hospitalizations are usually multiple. The way I counted it was I just considered the highest grade toxicity as a reason for hospitalization.

DR. MARGOLIN: But I think it is fair to say that

it is correct, that there was 1.5 hospitalizations per patient in CPT-11 and 1 hospitalization per patient on best supportive care.

DR. CHICO: I think you can infer that.

DR. MARGOLIN: You can do with that whatever you want.

DR. SIMON: I wanted to pick up some of your points about quality of life. I certainly agree with you that it is preferable to define--when you have lots of potentia endpoints which you have within quality of life, to define your analysis plan beforehand.

When I read the description of the sponsor's analysis of quality of life, though, it did not look to me as if there was any multiplicity problem, that they had looked at sort of overall, summary--and they had done a multivariate analysis of variance demonstrating that there was an overall effect, highly significant, favoring the CPT-11 arm, and it was only then that they went and started looking at subscores.

I view that as an adequate way of controlling type 1 error. And they also did things like--for example, in study V301, two analyses of global quality of life assigning a score of 0 to missing values of patients who died from their dates of death on was also highly significant favoring CPT-11. I find that a very reassuring

type of analysis.

So I find these analyses of time to deterioration or death, whichever occurs earliest, in a way a preferable way of doing quality-of-life analyses.

DR. CHICO: I agree with your points. However, those results which you mentioned that show statistically significant differences were not available to us during the submission of NDA. The analyses of the subscale results were available to us at that time. These are relatively new analyses that were done.

DR. DUTCHER: Other questions for FDA?

Thank you very much.

DR. CHICO: Thank you.

DR. DUTCHER: Moving right along--we have it figured out by the third day.

Committee Discussion and Vote

DR. DUTCHER: We are at the point of discussion and questions. You have your questions? There are only two as opposed to eight.

We will start. "Two randomized, prospective, multicenter trials in more than 500 patients have examined Camptosar (irinotecan) in colorectal cancer. Study V301 compared irinotecan plus best supportive care to best supportive care alone. Study V302 compared irinotecan to three infusional schedules of 5-FU. There were

statistically significant differences in median survival in favor of irinotecan in both studies.

"The incidence of severe neutropenia, fever and neutropenia, nausea, vomiting, alopecia and cholinergic symptoms were greater with irinotecan than the control arms in both studies while the 5-FU in study V302 had more severe mucositis and hand-and-foot syndrome. These adverse events are well described and are similar to those seen with the weekly schedule approved in the United States.

"The indication sought by the applicant is for the treatment of patients with metastatic carcinoma of the colon or rectum whose disease has progressed or recurred following 5-FU-based chemotherapy. The applicant's recommendation is that irinotecan be administered at a dose of 350 mg/m^2 every three weeks--the regimen in study V301 and study V302) or at a dose of 125 mg/m^2 weekly times four weeks every six weeks, the schedule approved previously based on tumor-response studies."

So the first question is, "Do you agree that Studies V301 and V302 are adequate and well-controlled trials demonstrating the efficacy and safety of irinotecan at 350 mg/m^2 as a 90-minute infusion every three weeks for the treatment of metastatic carcinoma of the colon or rectum whose disease has progressed or recurred following 5-FU-based chemotherapy?"

DR. MARGOLIN: I do. I will also read Dr. Krook's statement. He was the other primary reviewer although, apparently, he was not going to vote. Is that right?

DR. DUTCHER: Right.

DR. MARGOLIN: "I consider study V301 to be well controlled and designed. It was conducted as well as any study in this setting as I believe could have. It has shown that CPT-11 has an advantage in survival (quantity) as well as quality. My only concern in this study was the toxicity in the treated group; i.e., increased hospitalizations.

"Study V302, although a good design, recognizing the difficulties of best supportive care in a randomized trial, is not as significant to me. The three 5-FU arms rather than a single arm make this more complex. I suspect that some crossovers happen and this can affect the endpoint.

"It is my recommendation, based on my review, that CPT-11 be granted full approval for the requested indication." I will just go ahead and read the whole thing. "I am also comfortable that the dosing of every three weeks is similar or equivalent to the weekly dosing."

DR. DUTCHER: Any other comments with respect to question 1?

All those who would vote 'yes' on question 1 please raise your hand.

[Show of hands.]

Seven out of seven. Seven yes, zero no.

Question no. 2 deals with the dosing schedule. "What dosage regimen should be approved: a), approve only the three-week regimen used in the studies demonstrating a survival advantage or, b), approve both the every-three-week regimen used in the studies demonstrating a survival advantage and the initially approved weekly times-4 regimen?"

Any comments? We have heard Dr. Krook's recommendation that both be approved.

DR. OZOLS: The advantage that we heard today, of course, is survival and the survival was with the Q-3-week schedule. I think that is a much more patient-friendly schedule. I would certainly emphasize that schedule to be the preferable schedule for use in this situation.

DR. MARGOLIN: My opinion is that we shouldn't approve only one schedule. My own clinical practice is that, in patients who are fairly ill for whom I might be considering this treatment, for some patients, it is more appropriate to see them every week and to judge their appropriateness for therapy weekly because their performance status is changing, their liver functions may be changing and that may provide you with sort of a rationale for seeing them on a frequent basis.

DR. DUTCHER: I think that we all agree that a survival advantage is the ultimate test of a regimen. I am not in favor of restricting it to one schedule but I think that this data is very compelling in terms of, perhaps, a better schedule.

Other comments? All those who would approve only the every-three-week schedule please raise your hand.

[One hand raised.]

Dr. Ozols; one.

All those who would not restrict it to only the three-week schedule, raise your hand.

[Show of hands.]

Six. So approve both schedules. All those who would approve both schedules?

[Show of hands.]

Six. All those who would not?

[One hand raised.]

One.

Anything else you need from us on this one?

DR. JUSTICE: No.

DR. DUTCHER: Thank you very much, at 9:45.

[Whereupon, at 9:45 a.m., the proceedings were recessed, to be resumed at 11:00 a.m.]

AFTERNOON PROCEEDINGS

[11:00 a.m.]

Open Public Hearing

DR. DUTCHER: We do have some time scheduled for open public hearing but we do not have anyone who has requested an opportunity to speak. Is there anyone in the audience who is requesting this?

If not, then we will proceed with the sponsor's presentation on Photofrin.

Sponsor Presentation

Regulatory History

MS. MANCINI: Thank you. Good morning, Madame Chairman, members of the advisory committee and FDA.

[Slide.]

My name is Alexandra Mancini. I am Vice President of Regulatory Affairs for QLT Phototherapeutics. We are very pleased to be here today to discuss with you our NDA supplement for Photofrin, porfimer sodium, for injection.

[Slide.]

I will begin today's presentations with a brief look at our regulatory history for this application. Dr. Harvey Pass will present the efficacy and safety data from our clinical trials and I will end with a few concluding remarks.

[Slide.]

Also with us this morning are three additional consultants: Dr. Jeffery Wieman, a surgical oncologist; Dr. Seth Rosenthal, a radiation oncologist; and Mr. Louis Tura, our statistician.

[Slide.]

Photofrin was originally approved in December, 1995 for the palliation of obstructing esophageal cancer. In January of this year, it was approved for the third-line treatment of microinvasive non-small-cell lung cancer.

[Slide.]

The supplemental indication we are requesting today is for the reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing non-small-cell lung cancer.

Our original application for this indication, our supplement, was filed in February of 1997 and this committee deliberated on it in September of last year.

[Slide.]

At last year's meeting, this committee voted that these studies were not adequate and well-controlled. There were important concerns raised about the collection of symptom scores in these unblinded trials by the treating physician and about the amount of and imbalance in missing data.

The FDA review had highlighted some putative

study-design flaws and, as well, had commented on the fact that a number of decisions were made post hoc on how to conduct the analyses.

[Slide.]

All of these factors were considered potential sources of bias and, thus, the committee was left with the impression that one could not get clear estimates of the benefit of PDT and, furthermore, that statistical comparisons between PDT and YAG were unreliable.

In addition, the occurrence of some life-threatening adverse events left some members of the committee questioning the overall net benefit of this therapy. After that meeting, we submitted a written response to the FDA addressing the study-design issues and explaining our rationale for our analysis decisions.

We then met with the FDA in October to discuss how to go forward. Two members of the ODAC committee participated in this meeting. Based on our written response, the medical officer concluded that luminal response was a valid response endpoint, that the QLT analyses were fully reasonable but just not fully prespecified, that PDT was at least as good as YAG for producing luminal response in both trials, and he agreed that symptom changes of two or three grade levels were not likely due to investigator bias.

[Slide.]

The FDA's advice at this meeting was that QLT's resubmission should include an analysis of marked symptom improvements to address the concern of potential bias as well as a detailed analysis of all life-threatening adverse events. In addition, at last year's meeting, the ODAC committee suggested that improvement in atelectasis might be helpful as another measure of patient benefit.

[Slide.]

We will be presenting today several new analyses which were all conducted to address your previous concerns. Throughout the presentation, we will be displaying statistical differences based on confidence intervals. This is for information purposes. We wish to emphasize that we are not claiming statistical superiority.

DR. DUTCHER: Excuse me. Before you introduce Dr. Pass, we forgot to read our conflict of interest statement.

MS. MANCINI: Certainly, I will pause for a moment.

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 interests 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.

Kenneth Giddes has been granted a waiver that permits him to participate in all matters concerning Photofrin. A copy of this waiver statement may be obtained by submitting a written request to the FDA's Freedom of Information Office in Room 12A-30 of the Parklawn Building.

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. I apologize to the company for the interruption.

MS. MANCINI: No problem. It gives me a chance to recover my voice.

Sponsor Presentation (continued)

I would now like to introduce Dr. Harvey Pass who will present the efficacy and safety results from our trials including the new analysis we have conducted to address your concerns.

[Slide.]

Dr. Pass is present Aerodigestive Program Director at the Karmanos Cancer Institute and was Chief of Thoracic Oncology at the National Cancer Institute in Bethesda from 1986 to 1996. His interest in PDT began in 1986 and he has extensive experience in endobronchial, skin and intrapleural uses of PDT. He has conducted phase I, II and III trials in PDT and has published extensively on the use of PDT not only clinically but also on benchwork mechanisms.

Efficacy and Safety

DR. PASS: Thank you, Alex. Members of the committee, ladies and gentlemen.

[Slide.]

The majority of patients with non-small-cell lung cancer will present with disease which is incurable by presently available standard therapies. Many of the patients will present with or progress to local disease which will require rapid, effective palliation to maintain the patient's quality of life.

[Slide.]

Patients with partial or total obstructing lesions

of the bronchus can present with a variety of symptoms. This can significantly alter their functional status. Irritating or recalcitrant coughing may not respond to antitussants. Dyspnea from obstruction and resulting atelectasis will not resolve without therapy and hemoptysis can be marginal or massive.

Palliation of these symptoms and signs is clinically important.

[Slide.]

In designing trials to evaluation risks and benefits of new therapies in patients with advanced lung cancer, investigators are challenged by the population's poor performance status and limited survival. Objective quantitation and symptoms palliation is difficult by itself and the duration of benefit can be impacted by toxicities which, in reality, may represent disease progression.

Moreover, for patients with endobronchial disease, proper surveillance of luminal improvement requires repeated bronchoscopies. Despite these difficulties, the aggressive evaluation of innovative endobronchial therapies to increase options in these patients is necessary.

[Slide.]

Photofrin PDT involves the use of light, oxygen and a sensitizer. The sensitizer, Photofrin, is carried in the serum as a complex with lipoproteins and is delivered to

tumor cells and normal cells. The drug is selectively retained by the tumor and its vasculature possibly due to its relation with this lipoprotein.

Since the levels decrease in the normal cells, a temporally related therapeutic index can be reached with favors sparing of the normal tissue when the sensitizer is activated by 630 nanometer red light, usually through an argon pump dye laser.

There are direct and indirect mechanisms for PDT-associated cytotoxicity. Formation of single oxygen in the tumor cells due to the photochemical process is directly toxic to cells in the vasculature. Besides the direct tumor-cell effects, there will be an indirect effect of vascular shutdown causing tumor necrosis.

This occurs very rapidly over a 24- to 48-hour period and will create a local inflammatory response. Repair mechanisms, however, of the tissue then occur and this is usually completed by one month in the studies in which this process has been observed.

[Slide.]

Two open-label, randomized, multicenter studies were conducted in symptomatic patients with advanced lung cancer. P17 was conducted in North America and enrolled 70 patients. P503 in Europe enrolled 141 patients. Both trials used the same study design with neodymium YAG as the

control therapy.

[Slide.]

A single course of PDT consists of an injection with a photosensitizer, Photofrin 2, on day 1 which is followed by activation of the drug with non-thermal red light and possibly, again, on day 5. Debridement of necrotic tissue is performed on day 5. Both studies permitted a maximum of three courses of PDT to be given separated by at least 30 days.

[Slide.]

For YAG therapy, there was unlimited number of courses permitted. For each course, there were no limitations on the energy dose permitted per session or the number of sessions per course. In each course, the YAG position was to treat until desired palliation was achieved or further treatment was deemed futile.

Debridement could be done concurrent with the laser treatment or done at a separate bronchoscopy.

[Slide.]

It was decided to carry out YAG therapy in this fashion to be consistent with clinical practice and to avoid any possibility of undertreatment bias. This definition of YAG allowed it to have the best chance to succeed.

[Slide.]

The different course definitions might have lead

to difficulty in comparing the therapies. A course of YAG therapy could have taken longer to complete because of multiple sessions. Since response was measured from the completion of a course of therapy, this could have been a potential problem. But this did not occur.

The median active treatment period differed by only two days. In fact, PDT took two days longer which is the time from the injection to light therapy. Furthermore, YAG had the potential advantage because of unlimited laser sessions being permitted. This did not occur, also, because the two therapies had an essentially identical number of laser sessions per patient.

[Slide.]

This slide presents the baseline characteristics for all randomized patients and, as such, represents the intent to treat population. Both studies are combined since the patients in the studies were similar with regard to most of these characteristics.

The study population was typical of patients with advanced lung cancer. The majority were men with a median age of 65 and a median Karnofsky performance status of 70. Three-quarters of the patients were clinical stage IIIa disease or worse.

[Slide.]

Asymptomatic patients were not eligible. Most

patients presented with multiple symptoms. Nearly all had dyspnea and cough. Approximately 60 percent had hemoptysis and 60 percent had at least a 90 percent obstruction of the bronchus. The proportion of patients with tumor-associated atelectasis was comparable between the PDT and the YAG group.

[Slide.]

For patients with advanced lung cancer with airway compromised, the most important measures of treatment effects include the quantitative reduction of obstruction as measured by objective tumor response, the resolution of atelectasis and symptom palliation, specifically dyspnea, cough and hemoptysis. All of these endpoints had been specified in the protocols with the exception of atelectasis which was added at the recommendation of the committee last September.

[Slide.]

When does one measure efficacy? Obviously, multiple longitudinal time points should be used. In these studies, efficacy of each therapy was assessed at one week and at months 1, 2, 3 and 6. Many patients did not survive long enough to have month 3 or 6 assessments. In fact, one-third had died by month 3 and half had died by month 6.

[Slide.]

The protocol and statistical plan did not specify

certain aspects of how to conduct the efficacy analyses and some decisions were criticized last September as potentially introducing bias. The analyses were selected to address the most relevant questions for a palliative treatment; namely, how much benefit is obtained from a course of therapy, how quickly is the palliation achieved and how long does the benefit last.

[Slide.]

It was decided to focus on course 1 efficacy outcome since palliation benefit should be rapid and efficient to spare patient discomfort. In reality, almost all patients had their responses in course 1. It was decided to compare efficacy at prespecified time points within course 1.

Week 1 efficacy provides a measure of immediacy of response while later time points will give an indication of the duration of response. In addition, new analyses were performed which looked at efficacy at any time in course 1 to provide analysis which reduces the comparative bias from the imbalance in missing data between the therapies at month 1.

This analysis also provides the upper estimate of response.

[Slide.]

Objective tumor response resulting in increases in

luminal diameter is the most objective evidence of treatment activity. In general, for a single point of obstruction, a larger lumen will provide improved air flow. Complete tumor response was defined as the absence of endoscopically visible tumor. A partial response was defined as a 50 percent or more increase in luminal diameter.

[Slide.]

This slide presents the objective tumor-response for the intent-to-treat population. The two studies are presented side by side. As can be seen in the week 1 results in both studies, both therapies were effective in removing tumor rapidly.

The month 1 results suggest that PDT may have a somewhat longer-lasting response and this pattern is also seen at month 2. But the later time points are complicated by an imbalance between the groups and the amount of missing data in study P503. In study P17, there was no imbalance in missing data at month 1 but still a difference between PDT and YAG is seen.

[Slide.]

The reasons for the missing data at month 1 are seen in this slide. The studies are combined for simplicity. There are several important points to be made. First, with so many missed evaluations, one might consider that the studies were poorly conducted. However, this was

not the case.

The proportion of patients who were still on study but for whom evaluations were missed was 7 percent. Secondly, the reasons, the first four reasons, for the missing evaluations--not treated, too sick and off-study--reinforce how sick these patients were.

In the two studies combined, 23 percent of the PDT group and 28 percent in the YAG were not available for assessment for these reasons. The excess of missing evaluations in the YAG group comes mostly from reasons that suggest YAG failure such as retreatment or intervening therapy, 1 percent for PDT versus 6 percent for YAG, or that the patient requested withdrawal, 1 percent for PDT versus 6 percent for YAG.

In conclusion, the majority of these reasons for missing data suggest palliation failure of either therapy. In the intent-to-treat analyses, missing data are treated as failures which appears to be correct in these studies.

[Slide.]

A number of additional analyses were conducted to try to address concerns about the amount of missing data and the ability to compare the therapies. The most compelling of these analyses was a sensitivity analysis which was essentially a worst-case construct for PDT and a best-case for YAG.

Since more YAG patients were not treated, the analysis was done on treated patients only. Deaths were counted as failures for both groups and other missing data was considered to represent a failure for PDT and a success for YAG.

[Slide.]

Even with the stringent, worst-case assumptions, YAG was not statistically superior to PDT. In fact, the response rates were very similar between the groups. Therefore, the fact that response rates are comparable, even with this worst-case assumption, allows one to conclude that PDT is at least as good as YAG at luminal response at month 1.

[Slide.]

Another new analysis was conducted which counted response attained at any time in course 1. In this analysis, three-quarters of the PDT patients and 50 to 70 percent of the YAG patients obtained a response sometime in the first course. Therefore, one can conclude that both therapies are highly effective at debulking tumor and establishing luminal patency.

We also show the FDA analysis on slide. This analysis counted patients who demonstrated a response at some time after day 18 on the study including a few who had a response after a second course was initiated. The FDA

analysis does not count patients for whom a response was documented solely at week 1.

Therefore, it focuses on durability of response which we agree is an important consideration.

QLT's month 1 analysis, seen here, does the same. One can see that both analyses had the same pattern of response of PDT versus YAG. Each analysis provides useful information. The FDA analysis includes the durability of response and QLT time analysis provides what one might consider to be an upper limit of the estimate of response rates, the proportion of patients who are going to derive clinical benefit. This is a measure of activity for both therapies.

[Slide.]

Luminal response, in and of itself, however, is not considered direct evidence of patient benefit. However, resolution of tumor-associated atelectasis and obstruction could ameliorate the risk of post-obstructive complications and also improve tumor-related symptoms. Each of these potential benefits will now be discussed.

[Slide.]

It is important to note that atelectasis improvement based on the chest X-ray was assessed by staff radiologists and would, therefore, have been less susceptible to potential bias in these studies than symptom

improvement evaluations which were scored by the treating physicians.

As mentioned before, this was not a protocol-specified endpoint.

[Slide.]

In both studies, the rate of improvement was higher in the PDT group. Approximately half of the PDT-treated patients with atelectasis at baseline had documented improvement at some time in the first course. About one-third of the patients had improvement at month 1.

In the YAG group, the rate of improvement was 30 percent in course 1 and 15 to 20 percent showing improvement at month 1. Correlation analyses revealed that approximately half of the patients who had a luminal response achieved improvement in atelectasis.

[Slide.]

For the patient with advanced lung cancer, the relief of symptoms is an important goal. Tumor response and symptom palliation generally go together. However, in some patients, there can be an objective tumor response without symptom relief. Dyspnea and cough may be caused by other pulmonary conditions in addition to the presence of tumor.

Hemoptysis, on the other hand, is a symptom that is clearly tumor related.

[Slide.]

New analyses focused on marked improvements at any time in course 1. Marked improvements were defined as improvements in symptom scores from a baseline of 2 or more grades.

[Slide.]

For example, a two-grade improvement in dyspnea going from grade 3 to grade 1 would mean that a patient who had difficulty walking less than 100 meters on level ground could then climb more than one flight of stairs without difficulty. Recording such an improvement would unlikely occur due to chance or investigator bias.

[Slide.]

Returning to the new analyses, this additional analysis was done for marked improvements at any time in course 1 as previously presented for tumor response and atelectasis improvement.

[Slide.]

These new analyses were conducted for each of the specific symptoms. Additionally, a per-patient approach was taken in which a patient with a two-grade or better improvement in any symptom was considered to have had a clinically significant symptom response.

[Slide.]

This slide shows the proportion of patients who had the ability to improve two or more grades in a

particular symptom. We see here that approximately 60 percent of patients presented with moderate or severe dyspnea or cough meaning that the symptom was at least grade 2 at baseline.

These are the patients who had the ability to show marked improvements. About one-quarter had moderate to severe hemoptysis at baseline. On the other hand, almost all patients had at least one symptom that could be evaluated for substantial improvement.

[Slide.]

The first analyses are for dyspnea improvement. The new analyses of marked improvements in patients who had at least grade-2 dyspnea at baseline are shown here. Marked improvements in dyspnea were seen in approximately 25 percent of these patients at any time in course 1 with either therapy.

The month-1 rates were 20 percent and 7 percent. The original intent-to-treat analyses based on any level of improvement are shown in the first two columns. In comparing the two analyses, it is noteworthy that the pattern of response is similar. At all three time points, the relative pattern between PDT and YAG is the same in both sets of analyses.

It is recognized that the month-1 comparisons are affected by missing data in both analyses, but there is no

evidence of bias favoring PDT by the inclusion of single-grade improvements.

These new analyses of marked improvements were performed because the single-grade improvements were believed to have been potentially influenced by investigator bias. The fact that the new analyses parallel the original analyses should allay that concern and provide confidence that the original analyses were unbiased.

[Slide.]

For cough, fewer patients demonstrated marked improvements compared with dyspnea. Marked improvements at any time in course 1 were noted for 17 percent of the PDT patients and 11 percent of the YAG patients. The rates at month 1 were 13 percent and 5 percent.

Nevertheless, the profile of relative responses was the same based on marked improvements or any improvement, once again confirming the lack in the original analysis.

[Slide.]

Turning to hemoptysis; the rates of marked improvement are the highest of any of the three symptoms. 88 percent of PDT patients with at least grade 1 hemoptysis and 52 percent of the YAG patients had marked improvements during course 1. The month-1 rates were 71 percent and 32 percent.

At every time point, the data suggests that PDT may be providing a better level of improvement than YAG. This is entirely consistent with the known ability of PDT to affect tumor vasculature.

[Slide.]

Up to now, we have focused on the improvement rates for specific symptoms. However, these patients who improve for dyspnea may not improve for cough or hemoptysis. Therefore, it is helpful to summarize the proportion of patients with marked improvement in at least one symptom.

[Slide.]

This slide provides improvement rates at month 1 and at any time in course 1 for the intent-to-treat population. Approximately two-thirds of the PDT patients had a symptomatic improvement at any time in the first course and these improvements were, in fact, marked improvements in half of these patients.

Similarly, at month 1, 55 percent of the PDT patients had some improvement and 30 percent had marked improvement. The same pattern was seen for YAG confirming the assessment of single-grade improvements that were not biased in favor of PDT.

Overall, significant numbers of PDT patients demonstrated marked improvements. Fewer patients in the YAG group had marked improvement at month 1.

[Slide.]

In summary, new efficacy analyses were done to address concerns raised by the committee last year. The new analyses confirmed the conclusions drawn from the original analysis; specifically, PDT is at least as good as YAG and may be better for luminal response, resolution of atelectasis and symptom palliation.

Furthermore, the magnitude of palliation provided by PDT is clinically important.

[Slide.]

We now turn to the analysis of the safety data from these trials. Because adverse events may be reactions to therapy or may be symptoms of disease or related to assessment procedures, temporal association will be used to identify those events truly caused by therapy.

In addition, as adverse events are collected over the entire follow-up period, we will also look at the impact of extent of follow up on the reporting of symptoms of disease and events due to assessment procedures.

[Slide.]

In an attempt to quantify the amount of extra follow up in the PDT group, the number of patient months of follow up were counted. For selected time intervals after the completion of treatment, the number of days of follow up were counted for each patient and these were compiled to

arrive at these numbers.

Patient days were converted to months for convenience in presentation. One can see from the column providing the ratio of the amount of follow up for PDT versus YAG that, in every interval of follow up, there was more follow up in the PDT group.

In the earliest interval, within 30 days, which is the interval most germane for assessing response, there was only a 10 percent longer follow up in the PDT group. The imbalance was most dramatic at the later time intervals.

Overall, there was a one-third longer follow up in the PDT group. Days of follow up are really days at risk for reporting adverse events. The fact that the PDT group had considerably more follow up in the later periods increases the likelihood of reporting events either due to disease progression or concurrent medical conditions.

This difference in follow up should be considered as the safety comparisons are made.

[Slide.]

With respect to the number of study procedures in the two groups, we see that a similar number of treatment courses was administered. More bronchoscopies seemed to be performed in the PDT arm. Further review of the reasons for these bronchoscopies revealed that the imbalance in the number of bronchoscopies was primarily due to follow up

assessment bronchoscopies. This is consistent with the longer follow up shown previously.

[Slide.]

This slide provides a summary of the major safety parameters based on all adverse events in treated patients. Slightly more patients in the PDT group had at least one adverse event. This difference was not statistically significant. More investigation episodes were reported for PDT and this appears to be due to the longer follow up.

Few patients in either group withdrew from the study because of the adverse events. The overall death rate was similar for both groups for both early and late time periods.

[Slide.]

An important subset of adverse events are those considered to be life-threatening. In the presentation a year ago, concerns were raised about a difference between PDT and YAG with regard to life-threatening adverse events. I would like to clarify the misconception that PDT caused more life-threatening adverse events than YAG.

This misconception was undoubtedly because of the way the data were presented to the committee last year.

[Slide.]

This slide reveals that the total number of deaths in the PDT and the YAG group were equivalent. At last

year's presentation, 14 of the PDT deaths and 6 of the YAG deaths had been inappropriately counted as both deaths and life-threatening events.

These double-counted events were already counted in the total number of deaths.

[Slide.]

Last year, the number of life-threatening events for PDT and YAG were listed as 19 and 8, respectively. When you remove the 14 inappropriately double-counted events for PDT and 6 for YAG, the actual number of reversible life-threatening but non-fatal events was 5 for patient and 2 for YAG.

[Slide.]

Of the five patients with life-threatening events for PDT, two experienced these events within 30 days and three at the later time point. Similarly, in the YAG group, one was in the early period and one was in the later time point. The important take-home message from this slide is that the number of deaths and non-fatal life-threatening adverse events was similar for the two groups in both the early and late periods.

We will discuss these events in detail later.

[Slide.]

This slide shows the most commonly occurring adverse events for both therapies. Many of these adverse

events are also symptoms of disease. Statistically significant differences were noted for photosensitivity, dyspnea, bronchitis and the overall category of psychiatric events. Each of these will be discussed briefly.

[Slide.]

All patients who receive Photofrin injections will be photosensitive for four to six weeks. The rate of reaction is a measure of compliance with instructions and precautions. 20 patients had 24 reactions most of which were mild or moderate. Only one severe event occurred.

Based on a large database of patients treated for many indications, photosensitivity reactions are transient, self-limiting sunburn-like reactions occurring on the face and the hands. The period of photosensitivity can be shortened by exposure to ambient light which deactivates the drug in the skin through a photo-bleaching process.

[Slide.]

Dyspnea was not only assessed for efficacy. Investigators were also instructed to record worsening dyspnea as an adverse event. Dyspnea was reported as such in 32 percent of the patients with PDT and 17 percent of the patients with YAG.

The total number of episodes reported was 36 for PDT and 18 for YAG at any time in the follow up. Many of the events, 17 for PDT and 6 for YAG, were reported more

than 30 days after the last treatment procedure and were, therefore, most likely due to disease progression and unlikely due to treatment.

Looking more closely at those events that occurred within 30 days, the slight imbalance between the groups and the number of events was due to events that occurred within the first ten days. These rapid-onset events are consistent with an inflammatory response in the treated area which is expected to be slightly greater in the PDT group because of its mechanism of action.

[Slide.]

The severity of events that occurred within these ten days is shown on this slide. All of the events were moderate or severe for both groups. As dyspnea was a symptom of disease present at baseline in most patients to be recorded as an adverse event, it would need to be getting worse. Thus, it is not surprising to see severe dyspnea in both groups.

[Slide.]

Bronchitis was reported in 11 percent of the PDT patients and 3 percent of the YAG patients. All events except two in the PDT group occurred within 30 days after treatment and are, therefore, possibly due to therapy. Most of these events resolved within ten days on antibiotic therapy.

[Slide.]

Psychiatric events as a category were reported more often for the PDT group although no specific adverse event occurred at a statistically higher rate. Most of the events were insomnia, anxiety, nervousness or agitation. Careful review of the individual event showed that most of these events, 15 out of the 18, were temporally associated with the bronchoscopic examinations.

We have previously seen that more bronchoscopies were performed for follow-up assessment in the PDT group.

[Slide.]

Most of the psychiatric events were mild or moderate. The two severe events were anorexia and confusion occurring in patients who were experiencing rapid disease progression. Based on safety data from all indications, Photofrin has not demonstrated central-nervous-system effects.

[Slide.]

Turning now to survival as a safety measure; this figure shows the Kaplan-Meier survival curves for the combined studies. There was no significant difference in overall survival. The hazard ratio of 0.85 indicates a slightly lower risk of PDT which is probably due to the separation of the curves at the later time points.

The confidence interval on the hazard ratio was

from 0.62 to 1.16 which suggests that the risk of death for PDT is no more than 16 percent worse than that with YAG and may be 38 percent lower.

[Slide.]

We will now turn to the fatal and life-threatening adverse events in more detail. Temporal association provides a way to focus on events that might possibly be due to either of these acute-acting local therapies.

The number of patients who died within 30 days or who could have died within that time was essentially the same for both therapies. We are not saying that 18 percent of the patients in both groups experienced serious complications because of the therapy since not all of these events were due to the therapy.

[Slide.]

A careful review of all of these early events was conducted to determine which were likely due to either therapy. For the early deaths, the treating investigators attributed more early events to PDT than to YAG, 6 versus 1 percent. In considering why this difference happened, I suspect there was bias in these unblinded trials where the investigators were more likely to attribute a complication leading to a death to be related to a new drug than to a procedure that they were familiar with and had done many times.

The potential imbalance, however, was of concern to the sponsor. Therefore, they requested a blinded assessment of the early deaths which was conducted by Dr. Eric Adell, a respected pulmonologist at the Mayo Clinic, who is familiar with both therapies.

In these very ill patients, it is often difficult to determine whether the cause of death was due to treatment, disease progression or concurrent underlying illness. Based on the blinded assessment, 6 percent of the PDT patients and 4 percent of the YAG patients died of possibly treatment-related complications.

There was a 1 percent incidence of non-fatal life-threatening events in both groups.

[Slide.]

The specific early events that were considered to be treatment associated are shown here. Treatment-associated respiratory distress, with or without congestive heart failure, was observed in 4 percent of the PDT patients and 2 percent of the YAG patients. 3 percent of the patients in both groups died of hemoptysis that was probably caused by treatment.

Thus, the relative risk of fatal or life-threatening complications appears to be the same for PDT and YAG, 7 versus 5 percent, and the nature of such events is also the same. It is to be noted that the medical officer

has his own review of these events. I am sure that there will be further discussion of this topic after the presentations.

[Slide.]

These two causes of early associated death, respiratory insufficiency and massive fatal hemoptysis, will be discussed in more detail.

[Slide.]

The term "respiratory insufficiency" is a standard adverse event dictionary term that covers many different types of life-threatening or fatal events such as those listed on this slide.

[Slide.]

Respiratory insufficiency is not a surprising event in lung-cancer patients and is often the manifestation of disease progression. It was reported for 11 percent of the PDT patients and 4 percent of the YAG patients during the entire follow-up period. This difference was not statistically significant.

Using temporal association as a means to focus on those events possibly attributable to therapy, there were 6 patients in the patient and 3 in the YAG group who experienced respiratory insufficiency within 30 days of a treatment procedure.

Events considered to be related to therapy

occurred in 3 percent of PDT patients and 2 percent of YAG patients. Therefore, the two therapies appear to have a similar risk of acute respiratory complications.

[Slide.]

For both PDT and YAG, such reactions are precipitated by the acute inflammatory response in the main airway. The risk is the same for both therapies, 2 to 3 percent. The current package insert warns that PDT should be used with extreme caution for endobronchial tumors in locations where treatment-induced inflammation could obstruct the main airway.

[Slide.]

Fatal hemoptysis in patients with advanced lung cancer can be caused by tumor invasion, treatment-induced necrosis of such invading tumors, or it may be due to instrumentation injury with bronchoscopy or during debridement procedures.

Rates of fatal hemoptysis in the literature vary depending upon the therapy. In autopsy series, the incidence of death due to hemoptysis in untreated patients was 2 to 5 percent. The rate of fatal massive hemoptysis is increased in patients who have had external-beam radiotherapy approximately 8 to 11 percent.

The highest rates of fatal hemoptysis have occurred with brachytherapy. A number of series have

reported incidences greater than 20 percent and the full range reported is from 4 to 50 percent.

These rates vary not only because of the nature of the therapy but also the characteristics of the patients treated. Those who would be candidates for brachytherapy are the patients most similar to those studied with patient and YAG as they are mostly recurrent patients with centrally located endobronchial tumors.

Such patients inherently have a higher risk of this complication because of the proximity of the tumor to major vessels.

[Slide.]

The total incidence of fatal hemoptysis was 10 percent in the PDT group and 5 percent in the YAG group. This difference was not statistically significant. 4 percent of the patients in both groups experienced these events with 30 days of a treatment procedure.

Based on the blinded assessment of early deaths, these events were treatment related in 3 percent of the patients in each group. We believe that these are the only events due to either therapy, but it is important to discuss the late-occurring events as well.

[Slide.]

This slide lists the exact study days when all events of fatal massive hemoptysis occurred. C1, day 5,

means that the patient died in course 1 on day 5 with days counted from the beginning of therapy. The events listed in the top half of the slide reflect those that are within 30 days of a treatment procedure and the bottom half as late-occurring events.

There were six late-occurring events for PDT for FMH. As can be seen from the timing, the six PDT events occurred long after any PDT-induced tumor necrosis would be expected given its mechanism of action.

For three of these six patients, progressive disease was also listed as the cause of death. It is notable that two of these patients benefitted from prolonged survival.

It is important to reemphasize that the overall survival for the two groups was the same.

[Slide.]

In my opinion, the patients who are at greater risk for FMH following PTD therapy and frankly following YAG or brachytherapy are the patients who have central lesions associated with a major pulmonary vessel. The presence of a large extrinsic component of chest X-ray or CT and radiographic evidence of vessel invasion on CT would indicate that that patient would be a high risk.

Cavitation is an added risk factor. A given number of patients presenting with these findings will

develop FMH without any intervention. In these patients, any interventional benefit must be weighed against the risk of this catastrophic complication and the family and the patient should be informed of the possible consequences of therapy.

There is no doubt that there will be a learning curve for new clinicians which demands proper conservative labeling practices.

[Slide.]

In the current package insert, it states, "PDT is contraindicated in patients with tumor eroding into major blood vessels." The following wording is proposed for the warning section. "Patients should be assessed for the possibility that a tumor may be eroding into a blood vessel. Patients at high risk for fatal massive hemoptysis include those with cavitating tumors or those with extrinsic, extensive extrinsic component to the bronchus.

[Slide.]

In conclusion, fatal hemoptysis can be caused by local therapy such as PDT, YAG and brachytherapy. For all these therapies, the event is due to tumor resolution or instrumentation injury when the tumor is invading a pulmonary vessel.

In these trials, PDT and YAG had the same rate of early events and the same rate of associated events.

Patient selection, therefore, is the key to avoidance.

[Slide.]

The overall safety conclusions are as follows. The PDT and the YAG groups had the same median survival, early mortality and early life-threatening adverse events. The rates of associated mortality and life-threatening adverse events and the nature of these events were also similar for the two therapies.

Therefore, PDT and YAG have similar risk levels for significant events. The differences in the safety profile between the two therapies are due to the potential photosensitivity reactions and the potential for a greater inflammatory response within the airway.

These mucositis reactions can lead to transient dyspnea, bronchitis and respiratory distress in approximately 10 percent of these patients.

[Slide.]

Up to now, the assessment of benefit and risk has focused on specific parameters assessed for the whole population. Understanding the net benefit to individual patients is complicated when there are multiple efficacy parameters. If one parameter improves but another three worsens, or there are other important toxicities that occur, then it is hard to say that the patient received any net benefit.

The total clinical context including adverse events is relevant.

[Slide.]

Therefore, QLT evaluated the net benefit and risk for each patient and identified a subset of patients for whom PDT provided clinically important net benefit. This analysis used rigorous efficacy criteria which generally required marked symptom improvement with some measure of durability or durable tumor responses.

The exact criteria have been provided in your background document. This analysis also required that the patients had minimal adverse reactions and did not receive any intervening therapy. Such an approach was very helpful in assessing the palliative benefit of PDT in esophageal cancer.

[Slide.]

A total of 36 patients were identified who achieved clinically important net benefit. The duration of benefit was calculated from the first to the last day of documented benefit and was at least two months. This was a conservative estimate of duration because 23 of these patients were still in response at their last assessment.

[Slide.]

In his review of this analysis, the FDA medical officer agreed that 33 of these 36 patients appeared to have

important net benefit particularly because benefit was demonstrated for more than one measure.

[Slide.]

This slide shows the number of patients with benefit documented with multiple endpoints. Only two of the patients had improvement in just one endpoint. Nine patients had benefits in four to five endpoints. Ten patients had improvements in six or seven parameters. And, all in all, more than half of the patients demonstrated benefit of four or more of these clinically significant endpoints.

[Slide.]

Therefore, based on the original and new analyses, the following conclusions can be made regarding efficacy as demonstrated with PDT in these trials. Tumor response was achieved in 74 percent of patients and the month 1 rate was 55 percent.

Atelectasis improvement was observed in 48 percent of patients who presented with this symptom. The month 1 rate was 30 percent. Marked symptom improvement occurred in 36 percent of patients, 30 percent at one month.

[Slide.]

In patients who presented with moderate to severe symptoms at baseline, the rate of marked improvements at any time was 25 percent for dyspnea, 17 percent for cough and

88 percent for hemoptysis. The month 1 rates, shown here, are similar.

Overall, 42 percent of the patients who had at least one marked symptom at baseline demonstrated a marked improvement with PDT. These rates of improvement clearly demonstrate that clinically important benefit was obtained with PDT.

[Slide.]

The following conclusions define the safety profile of PDT demonstrated in these trials. Photosensitivity reactions occurred in 20 percent of patients. Transient inflammatory reactions occurred in 10 percent. Associated fatal and life-threatening adverse events occurred in 7 percent of patients.

[Slide.]

In numerous efficacy analyses, both the original ones and the new one, PDT consistently demonstrated a higher level of response than YAG. Based on these analyses, one can conclude that PDT is at least as good as YAG and probably better than YAG for removing tumor obstruction, resolving atelectasis and palliating symptoms due to tumor.

PDT has the potential for some additional mild to moderate adverse reactions but these are offset by the somewhat higher efficacy. PDT and YAG for endobronchial obstruction demonstrate comparable therapeutic ratios in

these trials.

[Slide.]

The armamentarium for management of endobronchial obstruction should not be limited and as many options should be available because each have inherent benefits and risks. YAG will rapidly open up airways but may require multiple treatments and does not have the specific oncologic response prolongation seen with PDT.

External-beam radiotherapy takes a longer period of time, requires multiple outpatient treatments and has persistent problems with tumor control and fatal hemoptysis. Endobronchial brachytherapy, although rapid in its response, has the highest incidence of fatal massive hemoptysis, can only be offered at specialized centers and is dose-limited.

PDT, although associated with a risk of early reversible complications as well as a finite risk of fatal massive hemoptysis, can be used as an independent modality or in association before or after other therapies.

Taking all these matters into careful consideration for my patients, I personally think that PDT offers the best combination of risk/benefit for patients with endobronchial obstruction. This is due to its rapid palliative and durable effect, its possibility for retreatment and its acceptable toxicity profile.

This therapy will only improve in the future with

the explosion of technology in light delivery and smarter sensitizers.

Ms. Mancini will make some concluding remarks.

Concluding Remarks

MS. MANCINI: Thank you, Dr. Pass.

[Slide.]

So, where did we leave off last year? A number of concerns were raised last year as noted here. I would like to take a few moments now to go through each of these points and review how we have addressed them.

[Slide.]

Regarding estimates of benefit first, to address the concern about the collection of symptoms in these unblinded trials by the treating physicians, we conducted some analyses of marked symptom improvements as these are unlikely due to investigator bias and they demonstrate clinically relevant improvements.

We conducted some new analyses at any time to give upper estimates of benefit. We recognize that this does not have the duration aspect of benefit built into it, but it does give one the upper estimate of benefit achievable.

The intent-to-treat analyses which we have done give one the lower estimates of response because, in these analyses, responders are only those who have documented response. Patients with missing data are counted as

failures in the intent-to-treat analysis.

The true response rates are at least as good as the intent-to-treat rates. They may have been higher. We also looked at atelectasis resolution to provide an independent corroboration of patient benefit based on the advice of this committee last year.

[Slide.]

We conclude, then, regarding estimates of benefit, that there was no apparent bias in our original analyses. The pattern of response in the new analyses that we did on marked symptom improvement was the same as what we did in the old analyses. The pattern was the same as we saw in the old analyses. Therefore, we believe that this confirms that there was no bias in the original analysis.

We are providing a resubmission both upper and lower bounds on the estimate of benefit from the different approaches we have taken and the analyses of marked symptom improvements have demonstrated that the magnitude of palliation achieved was clinically important. These were not trivial changes and they were achieved in a significant number of patients.

[Slide.]

Statistical comparisons between PDT and YAG were deemed unreliable for the reasons outlined here, and I will go through each of those now.

[Slide.]

Because the analysis plan and the protocol were not as detailed as one would like in today's world--I should preface that by saying these trials were initiated in 1988. Because these plans were not sufficiently detailed, a number of decisions did need to be made post hoc on how to analyze the data with respect to the definitions of response endpoints, analysis time points, some clarification there, and the decision to focus on course 1 analyses.

We believe, though, that we have chosen clinically relevant efficacy measures. We have chosen the palliation of symptoms which was a primary endpoint in the trials to begin with. This is very important for these patients.

We chose objective tumor response which is an important measure of the reduction of obstruction. It was originally a secondary endpoint and we moved it to primary status.

We chose to analyze course 1 time points of week 1 and month 1. This was specified in the protocol. What we did was we actually defined the time windows for those intervals and we believe that focussing on the week 1 and month 1 addresses both the immediacy of response and the duration of response both of which are important questions for a palliative therapy.

These decisions, although post hoc, were not made

after looking at the data for this application. I would like to point out that these exact same approaches were used three years earlier in our submission of our esophageal cancer palliation data.

There was also a potential for bias because of the different treatment schedules. I would like to reiterate that we did deliver PDT and YAG in these protocols according to the standard of clinical practice. Although there was a potential for difference in the way it was delivered, in fact, this did not occur because the number of laser sessions given per patient to deliver therapy was the same for both treatment regimens.

[Slide.]

Statistical comparisons were also challenged because of the imbalance in missing data at the month 1 time point. We did a number of new analyses to address this point. The first one was an evaluable analysis which has been provided in your background although it was not presented today.

This was based only on patients who had assessments of response. Because there was more missing data for YAG, this essentially boosted the YAG response rates more so than it did the PDT response rates relative to the original intent-to-treat analysis. But, even so, the evaluable analysis shows the same pattern relative between

patient and YAG.

[Slide.]

We examined in detail the reasons for missing data and we concluded that counting these patients as palliation failures, as was done in the intent-to-treat analysis, was, in fact, the correct way to handle this missing data.

We also looked at the response at any time in course 1 to provide a comparison in which the bias from the month 1 imbalance was reduced, although we recognize it is not entirely eliminated. The primary motivation for doing this analysis, however, was to address a question raised by this committee last year and that was to get a measure of the activity and why weren't more patients responding when we just emphasized month 1 response rates.

The most compelling of all the analyses we did were the sensitivity analyses which were worst-case constructs for PDT.

Based on the totality of all these analyses, we conclude that the statistical comparisons at month 1 appear to be valid, the PDT is at least as good as YAG and that the PDT benefit appears to last longer. However, recognizing that our analyses were not fully prespecified, we accept the claims of statistical superiority at month 1 of PDT over YAG would not be permitting in labeling.

[Slide.]

Turning now to safety issues, last year, the rate of associated fatal massive hemoptysis and respiratory insufficiency were unclear for some members of the committee. Furthermore, some may have been left with the misconception that PDT caused more life-threatening adverse events than YAG. This was, no doubt, due to the way in which we presented this information to the committee.

In our resubmission, we have conducted a thorough reevaluation of all cases of fatal hemoptysis and respiratory insufficiency including an evaluation of potential prognostic factors. We have corrected our analyses of the life-threatening adverse events basing it now on the worst outcome for each specific event.

Previously, some events had incorrectly been included in both the life-threatening and fatal categories. I want to emphasize that what we are stating is that the exact same event was being counted twice in last-year's presentation.

[Slide.]

Based on the thorough reevaluation of safety, we are confident that we now have accurate estimates of the risks due to PDT and YAG and we have shown that PDT does not cause more life-threatening adverse events than YAG.

[Slide.]

We hope that we have addressed all of your

concerns regarding this supplemental application and that you will agree with our final conclusions which are:

[Slide.]

From a regulatory perspective, we conclude that these studies were adequate and well controlled; that Photofrin PDT provides important clinical benefit in a significant percentage of patients; that the risks associated with Photofrin PDT are understood and appropriate labeling can be written; that the therapeutic ratio is favorable for this indication and--

[Slide.]

Therefore, that Photofrin PDT is indicated for the reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing endobronchial non-small-cell lung cancer.

Thank you. That concludes our presentations.

DR. DUTCHER: Thank you.

Questions from the Committee

Are there questions for the sponsor?

DR. JOHNSON: I think the issue from my perspective that is of importance is the fact that we have demonstrated that there is luminal improvement with this procedure. I am still not convinced that we have seen that the benefits outweigh the risks with this particular procedure.

I am particularly concerned if the committee does recommend approval that we understand the group of patients for whom this process is being recommended. As I went through the briefing document, there was a considerable amount of information about attempts to select individuals who would not be candidates for PDT and individuals in whom toxicities would be considerable.

The exact frequency of FMH is not known and that is particularly concerning. The predisposing factors are not well defined and that is particularly disturbing. It is possibly related to previous irradiation but, by my calculations, I did not concur with that agreement or that particular statement that was made in the document.

Lastly, there was some comment made about the investigator experience. Obviously, that is a major issue. If physicians' experience with this particular procedure is going to have a bearing on FMH, that is especially worrisome.

Then, lastly, in doing my own background review for this particular presentation, I went, once again, to the medical literature and came up with an article which uses Photofrin 2 in a randomized fashion, alone or in combination with palliative irradiation in patients with inoperable obstructive non-small-cell lung cancer. I was wondering if you have any information pertaining to that trial. This

paper was published in 1987.

So that is a lot of questions related to a group of patients.

MS. MANCINI: That is a lot of questions; right. Could I just ask you first on the reference that you are citing who the author was so we can identify the trial.

DR. JOHNSON: Dr. Lamb.

MS. MANCINI: Dr. Steven Lamb; okay.

DR. PASS: Why don't we address the issues of the risk first. If I could have slide 2-140.

[Slide.]

There was a large database in patients treated with PDT from a variety of supportive studies also that the sponsor was able to look at what the risk analysis was. This is demonstrated in this slide. You have raised a couple of issues here which have to do, first of all, with prior radiotherapy.

If you look at the patients who get PDT and then have FMH, yes, there seems to be a higher incidence of FMH with PDT. But if you look at the time period, the events do not occur in the time period that you would expect to be PDT related meaning that the events in these that occurred were late events.

I, in my own opinion, agree with that that the FMH that we are seeing in these trials that are late, as we

tried to show you in the presentation, also, are way out there meaning that they are not close to the actual therapy which is the light and the drug.

The investigator experience situation is also a very important one. We agree that the investigator experience will define who are the patients that are going to be treated because, in our analysis of this, it was seen that the investigators who were not as experienced were putting the patients who were later in their course on the disease and certainly could have a higher risk of FMH and also the patients that had prior radiotherapy which also is a marker for lateness of disease the inexperienced investigator put on the trials.

This is an issue that is already being addressed. There are centers that have already been set up to train people how to do PDT.

DR. ALBAIN: Can I ask a follow up on that slide before you leave it?

MS. MANCINI: Certainly.

DR. ALBAIN: Dr. Pass, in your view, what would these late events be due to? Is it potentially due to scarring eroding into the vessels late? What is your sense? Or is it due to disease progression?

DR. PASS: The scarring phenomenon is one that you don't really see with PDT. When you treat animals and

patients with PDT and you look at the skin and you look at what happens, there is resolution to this and there is minimal scar. So the scarring that is attributable to other therapy such as radiation or endobronchial brachytherapy is a different mechanism and we should not confuse those.

So I think that we need, in my opinion--I do believe that this is, in the majority, progression of disease. If, on trial, you are also doing instrumentations just to assess what is in the bronchus, there are two of those that, on the trial to determine a response, it was temporally related to an assessment bronchoscopy but not to PDT.

So, for the main, you are talking about progression of disease. But, on a trial like this where instrumentation is necessary for response documentation, you can have temporally related events. That is not PDT. That is bronchoscopy. So that is my opinion.

MS. MANCINI: If I can just add further to what Dr. Pass has said. He is referring to--two of the six late occurring PDT events were associated with a bronchoscopic procedure. I would like to go back to Dr. Johnson's--

DR. ALBAIN: Excuse me once more. I'm sorry. Were those procedures ones that were protocol mandated and may not be performed in the usual practice setting?

MS. MANCINI: Yes.

DR. ALBAIN: Or would this be an issue of concern in following these patients out in the community.

MS. MANCINI: These were protocol mandated. These were, like, three-month, four-month assessment follow up bronchs and they would not be done in routine practice. We actually found some events of respiratory insufficiency, late occurring also, linked with late procedures. It is the same phenomenon.

Returning to the question of radiotherapy, I think it is helpful if we get slide 2-143.

[Slide.]

This slide will present the data, the impact of prior radiotherapy also for the YAG group and the same pattern is seen there. In the regression analysis we did looking for risk factors--well, I will just speak to this first. In both the PDT and the YAG groups, the incidence of FMH was higher in patients who have had prior radiotherapy, statistically significant comparing to the no-prior-radiotherapy groups.

There is no statistical difference between PDT and YAG, however. I want to point that out. We believe that the status of prior radiotherapy is really a marker for later disease, more recurrent disease, and the fact is that these patients are going to be, therefore, at higher risk for FMH due to just the presence of the tumor at that point

invading that deeply.

If we could then back to the regression slide 2-140, please.

[Slide.]

I would just like to clarify a little more what we did in this analysis. This was based on our entire database and, in fact, it includes the data that Dr. Johnson is referring to in the publication from Dr. Lamb. We did have three supportive studies that are not discussed today in which PDT was followed by radiotherapy. This was not prior radiotherapy.

But those are in the 182, and I will come back to your later question again. In this analysis, we analyzed for potential prognostic factors on all of the events occurring at any time which was a total of 27 events. And we also looked at the early events believing that the early events are clearly the ones that would possibly be due to PDT; not necessarily due to but possibly due to.

Whereas, the late events, given the mechanism of PDT, there is no known mechanism that we can imagine. In fact, we even get PDT intraarterially. We can show you that data if you would like to know that. We don't see any effects on the vasculature.

So in the early events, which are the ones that might possibly be due to PDT, the only place where there was

a statistical significant was in this investigator experience. As Dr. Pass has pointed out, this appears to be linked to patient selection.

These patients did have more prior therapy. They also were earlier stage of disease. We have patient-characteristic data to share with you if you would like to see it.

The prior radiotherapy was not a significant predictor in the analysis on early events. Therefore, we believe that it is independent of PDT-induced effects. It is a predictor. We agree that it is a predictor for fatal hemoptysis just as it would be a predictor for any subsequent therapy, YAG brachytherapy or no therapy.

DR. JOHNSON: I guess the aspect of that study that would be of interest to me, since one arm received PDT and one received the two therapies together would be, first of all, what were the differences of early FMH in that trial and then what happened to that group of patients that received PDT and subsequently went on to receive external beam or radiation which is generally a little more available to patients at present than PDT.

MS. MANCINI: Yes. If we could go to slide 2-159, please.

[Slide.]

This will be an overview of all of the events that

occurred in those supportive trials, so it won't have the primary trial data merged in. Just to explain the slide a little bit, PDT was to be followed by radiotherapy, external beam. The control arm was radiotherapy in two of the studies.

In one of the three studies, we had a second control arm which was brachytherapy followed by external beam, radio. The incidence, when one looks at these--when we first looked at this data, and I know when Dr. Williams first looked at the data, these numbers jumped out at all of us; 17 percent here versus 8 percent here.

Therefore, we went and looked at these cases in more detail. The first thing that was quite impressive was the fact that a lot of the patients, seven, in fact, died of fatal hemoptysis before they got to the RT, the delivery of RT.

We accept that six of these cases were, in fact, PDT-induced FMH. Of the surviving patients that went on to get RT, the rate of fatal hemoptysis is not different than what we saw in the RT arm. Now, we recognize this is not a perfect comparison and, actually, we have gone to great length in the submission that we have given to Dr. Williams to explain why we believe that this rate is higher here because of what is an additive effect, not a synergistic effect.

These patients here, the first 9 percent, seven patients, did not get any RT. They had died before they got to that point. So we believe that the risks--if there are additional risks, they are additive. There is no synergy between giving PDT and RT.

Is that clear? I'm sorry if I garbled it a bit.

DR. PASS: May I address, if I may, the question of experience again which we raised which is important in the future, also. We are very fortunate to actually have Dr. Jeff Wieman here who is actually one of the crucial leaders in setting up these types of training centers at the Norton Cancer Center in Louisville.

If we could go to slide 272, 277, there is anticipation of the need for this and it has already started because of the esophageal trials.

[Slide.]

Those sort of training programs are a combination of both didactic and hands-on training for individuals who are interested in doing PDT. I would like Dr. Wieman to address his particular program at this point.

DR. WIEMAN: Thank you very much. To give you a little background of our group, we have been working both experimentally in the laboratory and clinically with photodynamic therapy since 1984 and have a relatively large experience, I think, in treating lung disease.

I would like to make just one comment regarding the question of the fatal hemoptysis. Actually, one gets the perception that there is just one mechanism involved and, really, that is erroneous. There is a question of patient selection which, I think, is not terribly difficult to deal with.

But, like any other complex activity, one goes through a training process and has to learn to be sensitive to the human body. The primary problem that we have identified over the years in fatal hemoptysis has not been the massive explosion of blood but just the individual's learning to deal gently with tissues like in any other surgical procedure.

Many of these tumors are fairly fragile and the early experience with instrumentation may not be one of understanding of that. But once one learns to look at these tissues and deal gently with the tumors, then not the precipitous explosive hemoptysis but the continuous volume of blood that can come from abusing a tumor is what causes most of these respiratorily impaired patients to deteriorate.

So a lot of it is really how to touch, feel, or not touch and not feel, these tumors. And it takes time to do that. In order to try and forward this field, we have been involved in the education of many people over the years

and have formalized our activity in the last year or two.

We have a two-day course for numbers of individuals who spend the first day essentially learning in a didactic setting the basic understanding of what photodynamic therapy is both from a drug-related standpoint and from the mechanical or device-related perspective.

We teach them about how to manage the disease process, itself and select the patients for treatment. We then dwell specifically on the means of treating groups of patients with either esophageal disease or with a pulmonary disease and give them the opportunity to ask detailed questions about this type of thing.

Then we delve fairly extensively into so-called dosimetry or how to actually determine the parameters of patient treatment. On the second day, we have live demonstrations. And we bring a selection of varied patients so that the individuals who are anticipating carrying out this particular form of therapy have the opportunity to see us make judgments about these individuals.

And we do try and provide different examples of the disease process in order to give them this opportunity. I think, through doing that and our experience over the years, is once one teaches people who are generally pretty experienced in bronchoscopy or some other endoscopic procedure in this case, the parameters of this particular

type of therapy, that the safety issue becomes one of somewhat less concern.

So experience is helpful.

DR. DUTCHER: Could you just comment on what you think the learning curve is, how many times a person really--I know that in a lot of surgical procedures, there are a certain number of cases before someone is considered proficient. Do you have a feel for that?

DR. WIEMAN: Sure. Again, that is something that people spend months arguing over because there is a different learning curve for every individual. But an experienced endoscopist who has seen these tumors in the past and treated them with other means will learn how to do this over a course of five to ten patients without difficulty.

DR. SCHILSKY: I have a few questions. I am curious. When these studies were designed, what hypothesis was being addressed in the clinical-trial design?

MS. MANCINI: They were designed as superiority trials.

DR. SCHILSKY: I think one of the things that at least I am grappling with is the fact that these are sick patients. The symptoms of the disease and the side effects of the treatment are oftentimes difficult to distinguish. It gets sort of confusing when you think about the fact

that, for example, patients treated with PDT have less dyspnea, but they also have more dyspnea as a side effect.

So I am wondering if you could just help us understand a little bit, at least for those patients who had, say, marked symptom improvement. When did that improvement occur relative to when the treatment was actually administered? How long did it last?

It seems like the side effects might be most likely to occur in the first few days after the treatment when there is an acute inflammatory reaction. So can you give us some sense of when these patients got better and how long did the improvement last.

MS. MANCINI: Yes. Just give us a moment to find a slide for you. The marked improvements did occur rapidly. We are going to try to present our week-1 data for you and I think you will see that the magnitude of improvement at week 1 far outweighs any of the sort of decrease from a transient inflammatory response.

You would like to see the marked--any level of improvement or just marked?

DR. SCHILSKY: I think marked improvement would probably be most informative.

MS. MANCINI: That is provided in your document in the tables. Slide 214?

[Slide.]

This shows the week-1 improvement in the patient population that had--they were in greatest need of palliation. They had the moderate to severe symptom present at baseline. So we see that the level of marked improvement was 15 percent, 18 percent, for the two therapies so they are about the same at week 1.

Any level of improvement was higher, of course, but these are the marked improvements over here.

DR. SCHILSKY: I have another question. You were able to identify a group of patients that you characterized as having clinically important net benefit. You had 36 patients in the PDT group.

MS. MANCINI: Yes.

DR. SCHILSKY: Were you able to identify a similar group of patients in the YAG group? How many patients met those same criteria in the YAG group?

MS. MANCINI: Yes; I can present that data to you. This is slide 345, please.

[Slide.]

We found 23 such patients versus the 36 in the PDT group. The majority of the ones in the YAG group were meeting this criteria because they had durable tumor response not so much because they had clinically important symptom relief.

The median duration using the way we calculated

this was about the same for the two therapies and I do want to emphasize this was an extremely conservative calculation of duration of benefit. It was from documented first-day of benefit to documented last-day of benefit.

If the next assessment was missing or was not in benefit, you went back a visit, so it was very conservative. That is why we put the two-months plus. Also, the fact that 23 of these patients and 20 of these patients were still in response at last assessment.

DR. SCHILSKY: So since these are the patients who seem to have the greatest net benefit from the therapy, can you tell us about the characteristics of those patients? Is there a way to use this analysis to cull out the group of patients who might have the greatest chance of benefitting?

MS. MANCINI: Slide 349, please.

[Slide.]

We looked at the patient characteristics in the subset of patients with this clinically important improvement versus the other patients that did not fit into this category. We did not do statistical testing but these were the trends that we found. The patients who had the higher level of obstruction, there were more in--greater than 90 percent.

They had worse dyspnea at baseline. They also had worse KPS. Some of these patients--they were provided in

your background document. A few of them did demonstrate remarkable improvements in KPS.

DR. PASS: But the intriguing thing about this is that you have to treat the worst patients to be able to mark them as marked improvement. Those are the patients who are going to have the marked obstructions. Those are the patients who may be the sickest. Those are the patients that if you get a transient inflammatory response could have the 10 percent early stuff.

So you have to watch them although they seem to get the best benefit. So to try and cull out what are the characteristics that you can define a set population for this is very difficult and is really going to be based on the experience the investigator and the admonishing of people who have done it before of what you have got to be careful of.

DR. SCHILSKY: One other thing. As someone who does not do these kinds of procedures, I am still trying to grapple with why would you do this as opposed to using the YAG laser. It seems that this takes longer to apply because you have to have 48 hours before you can even do the procedure. It is possible that it may require more bronchoscopies. It takes longer for it to have an effect. As I understand it, you put the laser in there, you burn it out and the lumen is open. Here, you may have to wait a

couple of days for the tissue necrosis to occur.

The patient may be disadvantaged by having to stay out of the light for a period of time and these patients don't live very long on the average. So I am still a little unclear--from the patient's point of view, what is the real benefit here.

DR. PASS: I think that the real benefit to these patients is that it is not the same mechanism as YAG. For these patients, if you look at the durability of the response, and we both agree that these patients have a fixed time point of when you can palliate them.

With YAG what you see, and what is my experience, is that you treat them and then you have to treat them again because at month 1, or a little bit longer than that or earlier than that, they are closing up again. That is because the mechanism is the burning mechanism which you mentioned.

PDT is not a burning mechanism. PDT is a photochemical reaction that then stays around meaning that the effect seems to be more prolonged because it has a direct effect, a direct oncologic effect.

So, yes. But let me address some of the issues you said about the photosensitivity. The photosensitivity issue is, at present, a frustrating one but in the more than 120 patients that I had at the NCI that I gave phototherapy

to, independent of the type, if you tell these patients what to do and you are cautious about that, then your incidence will be lower.

I was doing PDT for a while so I knew how to tell the people what to do and it wasn't new there. These people can live. These people can be in fluorescent lights for eight to twelve hours a day. These people can go out. They can go to a mall. These people at night can take their walks.

These people should not be looked at as hermits. And they are not. We specifically tell them that they need to get out, with caution. So I cannot address, at this time--I am not going to address cost, of course, but, for my money, I also think, believe it or not, that it is an easier procedure.

You are not having to rely upon multiple kinetic movements to do this. If you can do it interstitially. It is one stick. It is ten minutes. That's it. You're back. And then you come back two days later which you would do with YAG also to see whether you need to debride.

So, from a patient perspective, anesthesia time, if there is anesthesia, there are some subtle things that have not been brought out here that I think are to the patient's advantage.

DR. ALBAIN: Just to go back to your clinically

important net benefit. When patients did not qualify for that, was it often due to disease-related issues more often than toxicity issues?

MS. MANCINI: I think that is a very good question to ask. We were very conservative when we did this review because we knew that it was a post-hoc review, it was highly dependent on clinical judgment and that it would be, therefore, severely criticized. So we were very, very careful.

Some of the patients that we did not include because of adverse events we think some of those were truly disease progression adverse events not true toxicities due to the therapy. But we were very conservative in excluding those patients.

So we have come up with 36 in our count, 33 that Dr. Williams agrees with, that had really dramatic improvement here with no or absolutely minimal adverse events. That is not to say they are the only people that improved with the therapy. There were more but we did use very, very rigorous criteria here.

DR. ALBAIN: I was just a bit impressed. These are patients, at least from my read and I wanted to ask Dr. Pass a bit more here about who these patients were at the start. These are patients, obviously, you would not consider candidates for potentially curative

chemoradiotherapy; is that correct? In other words, their symptoms were such that you could not afford to put them into the rigors of such an approach and that you need to immediately deal with the palliative issue locally; is that correct?

DR. PASS: In these trials; that is correct.

DR. ALBAIN: So these patients are incredibly sick patients that are a major challenge for whom standard external-beam approaches are not useful; correct?

DR. PASS: Correct. But you said it.

DR. ALBAIN: Then I had one other question about the 7 percent fatal adverse events. How many of those might be attributed to the learning curve of either patient selection or the gentle handling of tissues that we heard about such that an educational approach could bring that rate down significantly, realizing there would be learning curves on your trial as well.

MS. MANCINI: We do expect that the rate would come down, to address--the 7 percent rate that we are presenting here was based on the trial designs which did mandate certain procedures to occur. Some of those procedures would not occur in clinical practice. I think that as the investigators do get more experience through training programs and their own experience and as the labeling is written appropriately to point out the potential

risks, I think the risk will come down.

It is difficult to be able to say to you exactly what it will come down to.

DR. PASS: I would like to address that even on a more technical term. There are certain tricks that you have to learn which I'm sure Jeff would agree with. When you do the debridement bronchoscopy, this is an avascular necrosis so you biopsy the areas. And you are saying to yourself, "This is great," because it is not bleeding as opposed to if you would have gone without doing the light to treat it, it would have been bleeding at that point of biopsy.

Once you get to the area where it starts to have a little bit of bleeding, you know that you are out of the treatment area for PDT. But investigators who first will do this, who haven't had the proper training of these subtleties, may be a little bit more aggressive and, even when it is bleeding a little bit, go a little further.

These are the things that need to be taught. I think that the experienced investigators have an obligation to do that.

MR. GIDDES: I am a stage 4 lung-cancer survivor so I have a lot of experience with anxiety and so forth. I also have a big database. I call a lot of people around the states. Your anxiety is a lack of education in many of the cases for the patient.

I read also all patients who receive Photofrin will be photosensitive. What is the sponsor going to be doing to educate these patients that they are going to have this problem to prevent the anxiety and so forth, because the doctor probably will not tell them this or they will not communicate this or hear what they say.

MS. MANCINI: We would hope that the physicians would communicate the issue of photosensitivity.

MR. GIDDES: I said the patient may not hear it.

MS. MANCINI: Just one point and then I will let Dr. Pass speak to this as well. Currently, for our approved indications, there are patient information leaflets that are given to patients at the time of treatment that discuss a number of aspects about how to take the proper precautions for photosensitivity and other aspects of treatment.

So there is some printed material that is given to patients.

DR. PASS: I can certainly commiserate with the fact that sometimes physicians don't do the greatest job in talking to patients. I can only talk about my own program at the NCI in which, very early in the record, we were using the patient information leaflets as well as either myself or my nurse clinician spending real time with these people.

Not only that. We would tell the patient what you need to bring before you are going to go home because we

want to have that in-house so that you have your wide-brimmed hat, you have your sunglasses, you have your gloves. It is really a very detailed thing.

It would be as detailed as if you were going to talk about the toxicity of chemotherapies which, certainly, is a standard practice among medical oncologists. So that is the way I approach it.

DR. SCHILSKY: One more question about the potential population of patients who might be candidates for this. My sense is that there is not a lot of these patients likely to be seen in any particular institution in the course of a year. So, again, it relates to the issue of experience, number of procedures, et cetera.

If you took a typical large community hospital or a typical academic medical center, what is your estimate of the number of cases in a year that would be seen that might be candidates for this type of approach?

DR. PASS: I think that, even at the large cancer centers, the number of patients that are going to come in with an acute obstruction that are going to need it is not as many as you think it is.

I would say that a conservative estimate of a busy practice is going to be between 20 and 30 per year. The problem, though, is that if you look at 20 to 30 per year and you are talking 170,000 patients with lung cancer and a

lot of centers, that is going to be a significant number of patients.

So whether YAG can cover all those patients, I am not so sure, especially if you have a therapy that is just as good and is of great interest in an experimental situation at many more centers now than, say, when these studies started.

So I think the utility of the therapy in the future is going to increase. I think it is important that maybe it is important that there be a strict training program and only be at certain places that are going to really be able to follow this carefully so that, then, you are able to make sure of quality control.

DR. SCHILSKY: It is not likely, then, that, even in the busiest places that the average practitioner that might undertake this is going to do more than one or two of these a month.

DR. PASS: I think that is correct. But what we are also talking about is that investigator who may be doing lung may also be doing esophagus. So it is not like the commitment of the center to PDT is going to be limited with indications now to just lung. That very well may be, at least with surgeons, the same investigators. So he may be very busy doing PDT.

DR. SCHILSKY: I suspect that the places that

might do this for lung might well be the places that are already doing it for esophageal cancer since you do have to make a capital investment in the equipment, and so on. It seems that if you have already bought it for esophageal cancer, that it is likely that you will use it for lung cancer.

Can you tell us anything about how many places in the country are already using this for esophageal cancer?

MS. MANCINI: What is the current number? About 80 institutions in the U.S.

DR. SIMON: Maybe I have missed this. How many centers were involved in the PDT and what was the level of experience of the individuals who were doing it in these two studies?

MS. MANCINI: In the U.S. study, there were twenty centers. It was U.S. and Canada; excuse me. In the European trial, there were fifteen centers. The investigators that were chosen, because PDT was the new modality--the investigators were all, primarily, very experienced YAG physicians, knowing how to use the YAG therapy.

There were a few investigators who came into these trials who did have some PDT experience but very few.

DR. OZOLS: I guess for us non-bronchoscopists and non-thoracic oncologists, patient selection is something I

am a little bit unclear about. Is there any group of patients, looking it from the other direction, who you would want to use YAG instead of PDT?

DR. PASS: I think that in the patient who presents with acute bleeding that is salvageable, meaning that it is not massive in the patient--it would be heroic. But the patient who comes in and is coughing up a cupful but it is controllable, his airway is still manageable, that is not for PDT.

You want to have a quick-acting effect. That is the patient you would use for YAG. In the chronic situation, with the non-life-threatening presentation hemoptysis or non-massive hemoptysis, I don't see any difference, really, between indications for YAG and for PDT.

I think the bleeding is the one.

DR. DUTCHER: Ten-minute break and then FDA presentation. Your choices are a break or lunch. A ten-minute break.

[Break.]

FDA Presentation

DR. WILLIAMS: Dr. Dutcher, members of the committee, ladies and gentlemen.

[Slide.]

I am going to present the FDA view of the efficacy supplement for Photofrin for the treatment of patients with

obstructing non-small-cell lung cancer. As you know, a similar presentation was given about a year ago and, after deliberation, the committee recommended non-approval for this indication.

Subsequently, there were meetings between the FDA and QLT which lead to further analyses and further considerations. I believe that several of these analyses are important and that they address several concerns raised by the committee.

In this presentation, I will first review the findings I presented last year and then I will discuss new analyses and considerations which have been submitted to the NDA.

Actually, since I think the company did an excellent job of presenting what happened and what I said last year, I think I will try to skip through some of those slides.

[Slide.]

First, I would like to review the team that reviewed this application. The medical reviewers are presented here, statistical reviewers, device reviewer and the project manager for the additional clinical data that we reviewed.

[Slide.]

I am going to page down through several slides

until I get to--these points were discussed, basically what we presented last year. I think the company did an excellent job of presenting all of our criticisms.

[Slide.]

I would like to stop at this slide, though, which is the pulmonary symptom severity rating scale which was used to evaluate symptoms. I looked back at this more critically because the way that symptoms were obtained from a patient became a very big point with the committee.

One criticism was that there was no detailed prospective plan for getting this information from the patients. But, anyway, here is the scale. Basically, it is a functional scale. It is not just a questionnaire and it is very similar to scales which we use in oncology for evaluating performance status and severity of toxicity.

I believe that this is the sort of thing that a physician would be able to obtain information from a patient in a reliable manner even though, in most quality-of-life-type analyses, we would like to see very specific detailed plan for obtaining such information.

But I do believe that this scale, the one-point change, could easily be due to bias but a two-point change in most cases is a pretty big change, a big functional change, and is unlikely to be recorded by bias or by random chance differently than the two-point change.

So I do think this would be meaningful.

I am going to skip again.

[Slide.]

I would like to go to this slide which, again, is the endpoint the QLT looked at retrospectively to address concerns that patients were having actual clinical benefit. These changes are a two or three-grade improvement in symptoms which are two points for dyspnea and three points for hemoptysis or cough. So you could have had any one of these changes and be called a clinical benefit.

Or a 40 percent improvement in FEV1. I evaluated these changes at one month when I thought would be the most clinically meaningful time when a significant number of patients had such a change.

[Slide.]

Here is the difference at one month. In the QLT analysis, there were 36 PDT patients and 23 YAG patients who appeared to have such benefit. During the initial submission, I had copies of a graphical summary that was provided by the sponsor that had the symptoms, the toxicities, et cetera.

In addition to meeting the criteria specified here, as a physician, my gut level reaction, did I think this patient really benefitted or not. I think they were selected in such a way that it was likely that I would find

that to be case.

I did except for three cases. So, in my initial application, I did a lot of what you might call trashing the study in terms of a comparison of the arms. But my final conclusion was I did think that if you didn't compare the arms and you looked at it just as a sort of single-arm study where missing data really hurts you rather than potentially helps you, then I did think that there was a significant number of patients who did seem to have benefitted.

Again, the sponsor has summarized the findings as we discussed them last year.

In summary, there was a 60 percent luminal response in the analysis I did after day 18. There was a 33 percent incidence of what I thought was clinically important benefit. And I found that the findings were numerically superior to YAG but the statistical comparisons were suspect.

[Slide.]

In terms of safety, there was statistical more photosensitivity, dyspnea, bronchitis and psychiatric adverse events and a non-significant increase in hemoptysis and FMH.

[Slide.]

So you might ask what's new. I was trying to think, what's new? One thing I note is that we are

hungrier. The other is that we are at the other end of the room because I believe last year--but, in addition, there are some new analyses.

So I will go back into the text that I wrote for this talk now. These are the new analyses. For efficacy, there is an analysis which I will label the worst-case scenario for missing data. I believe this supports the claim that Photofrin is at least as good as YAG for opening the lumina of bronchi obstructed by lung cancer.

There is the analysis of two-point improvement in symptoms that seeks to overcome the issues of potential bias and clinical relevance. There is an analysis of improvement in atelectasis which was asked by a committee member. For safety, there is analysis of patient days of follow up suggestion that there may have been a bias against Photofrin in the toxicity reporting.

There is an evaluation of the life-threatening events noting that there were more double reports of death and life-threatening events in the Photofrin arm. And there was analysis of the timing of the occurrence of fatal massive hemoptysis noting that the incidences of early FMH events were similar on the two arms.

[Slide.]

To address the problem of the large amount of missing data or dropouts and the fear that the pattern of

missing data could have been biased, the applicant performed an analysis where the missing data was reassigned in a manner that was extremely biased against Photofrin.

In patients who have been treated and were alive, missing evaluations were counted as successes for YAG and were counted as failures for Photofrin. The results of this analysis yield luminal response rates that are similar for YAG and Photofrin.

This analysis suggests to me that despite the missing data, we can reasonably conclude that Photofrin is at least as good as YAG at opening the lumina of bronchi obstructed by lung cancer.

[Slide.]

The next analysis by QLT evaluated two-point improvements in symptoms on the pulmonary symptom severity scale. The thrust of this analysis was the belief that the two-point improvement would be more meaningful and would be less likely to occur by chance or because of bias than a one-point change.

The result of this analysis demonstrates that 30 percent of patients who received Photofrin had such an improvement at one month after treatment. While the missing data preclude a strict comparison to results with YAG laser therapy, the fact that the numerical results are twice as large for Photofrin as for YAG lends credence to the

assertion that the findings are real rather than due to chance or bias.

So I believe this finding that 30 percent of the patients treated with Photofrin reported a two-point improvement in pulmonary symptoms one month after treatment--I find this to be credible evidence of patient benefit.

[Slide.]

Turning to new analyses of safety, QLT makes the observation that patients on the Photofrin study arms remained on study on an average 33 percent longer than patients on the YAG study arms. Therefore, such patients would be more likely to be observed to have events that might be reported as adverse events.

This seems to be a reasonable argument, especially for the late-occurring events. QLT also notes that while there was a non-significant increase in the incidence of FMH on the Photofrin study arms compared to YAG, the number of patients dying with hemoptysis within 30 days of treatment were similar on the two arms.

[Slide.]

Probably the most troubling finding was the excess in the number of life-threatening events reported by investigators for Photofrin versus YAG, 19 percent versus 8 percent. As discussed by QLT, these events were a constellation of pulmonary findings, the kind of events one

would expect to find in patients with obstructing lung cancer.

If one restricts one's view to the 30 days after treatment, there were 9 percent of such patients with events on Photofrin and 5 percent on YAG. If one were observing a real increase in events which threaten life, I would have expected an increase in deaths occurring soon after treatment.

A puzzling aspect of this application is that, despite an increase in reported life-threatening events on the Photofrin study arms, there was no increase in early deaths. Similarly, if one looks at early deaths and early life-threatening events, the number of patients with either an early death or an early life-threatening event was the same, 18 on each arm.

So there seems to have been more double reporting of deaths and life-threatening events on the Photofrin arm.

[Slide.]

For the 19 reported events on Photofrin and 8 reported events of YAG, I tried to make a retrospective assessment of my own. I found the process very difficult and only felt comfortable attributing three cases on Photofrin and two cases on YAG as definitely associated with treatment. I believe it is difficult to sort out the meaning of the increased reporting of life-threatening

events on the Photofrin arms of the trials and I believe the bottom line is the equal number of early deaths.

[Slide.]

So, in conclusion, I believe that the efficacy of Photofrin at one month is documented by a luminal response rate of over 50 percent, at least as good as that of YAG. There is a two-point improvement in the symptom scale and 30 percent of patients numerically superior to YAG, a 28 percent improvement in atelectasis from baseline which is numerically superior to YAG.

[Slide.]

The toxicity of Photofrin; there was more photosensitivity, psychiatric symptoms, bronchitis and dyspnea reported by investigators. There was a reporting bias against Photofrin, 33 percent more patient days on the Photofrin arm. There was a non-significant increase in hemoptysis and FMH but no increase in early FMH.

There was an increase in reports of life-threatening events but no increase in early deaths and no increase in overall survival.

[Slide.]

So, in my opinion, there appears to be overall benefit and this benefit, I think, outweighs the risk. Compared to YAG, I believe that there is more evidence of benefit but, again, I don't think we could statistically

declare that it is a greater symptom benefit or greater response rate, but, in general, everything trends better for Photofrin.

Similarly, I do believe there is more toxicity and some it is a little hard to exactly find, why should there be more life-threatening events reported on Photofrin. There is certainly a sense that there is more toxicity. However, I do feel that these are two viable treatments and I think they are likely to develop their own niche in the therapeutic community.

So that concludes my presentation. I will be glad to take questions.

DR. DUTCHER: Thank you.

Questions from the Committee

DR. DUTCHER: Are there questions for Dr. Williams from the committee?

DR. SCHILSKY: I don't really have any specific questions, Grant, but I am curious to know your thoughts on I guess this whole issue of operator dependence and risk of toxicity, particularly in view of the fact that it seems to me that these cases are relatively uncommon. So it is unlikely that at any institution any one physician is going to have lots of experience doing them.

How important, from your review of the data, do you think this whole question of operator experience is?

DR. WILLIAMS: I don't have anything beyond what the company has presented to you on that. There is nothing within my review that I could find any more information.

I do note that Ms. Mancini--there was one other point that she wanted to make on this that she didn't, so, if it is okay--

MS. MANCINI: I just wanted to comment that there has been a lot of discussion on the difference in fatal hemoptysis rates in experienced versus inexperienced investigators. I wanted to just reinforce that despite the fact that half of the patients were treated by inexperienced investigators, we saw the same rate of early fatal hemoptysis as was seen in YAG arm. And these were all very experienced YAG users.

So I think that is an important context to look at. There was some confounding of experience with prior radiotherapy used as well. In the patients treated by inexperienced investigators who did not have prior radiotherapy, it was 4 percent hemoptysis. So I think that the two variables are confounded somewhat and the 4 percent hemoptysis rate is not different than the rate seen in the patients treated by experienced physicians.

So I just wanted to bring that point out again. Thank you for giving me a chance.

DR. DUTCHER: Other questions for Dr. Williams?

Thank you.

Committee Discussion and Vote

DR. DUTCHER: We will turn to the questions. Dr. Johnson did leave for the airport but I do have his responses and his comments which, not surprisingly, fill up the space below the question.

The first page and a half; "Two prospective, randomized trials, P503 with 141 patients and P17 with 70 patients, compared photodynamic therapy with Photofrin PDT to YAG laser therapy in patients with obstructing non-small-cell lung cancer. The results of the applicant's analysis of month 1 response rate, the rate of increasing the diameter of the obstructed lumen by at least 50 percent from baseline on days 18 through 45 and the FDA analysis of response are summarized in the table," which you can look at.

"In both trials and by both methods of analysis, the luminal response rate was higher with PDT than with YAG. However, because of the large amount of missing data--i.e., deaths, dropouts, et cetera--strict statistical comparison would not be appropriate.

"The applicant performed a worst-case sensitivity analysis of the missing data. Missed evaluations for PDT were assigned "no response" and missed evaluations for YAG were assigned "response." The results of this evaluation

give similar overall one-month response rates for PDT, 57 percent, and for YAG, 62 percent.

"Collectively, these analyses suggest that PDT with Photofrin produces a luminal response rate one month after treatment that is at least as great as that produced by YAG laser treatment.

"Clinical benefit was evaluated using the pulmonary symptom severity rating scale. Since small improvements on this scale might have been attributed to chance or bias in this open-label trial, the data were evaluated for two-point improvements from baseline values.

"At one month after treatment, 30 percent of the patients on the PDT arms of the trials experienced at least a two-point improvement of at least one pulmonary symptom. 22 percent had a dramatic symptom improvement; two-point increase in dyspnea, three-point increase in hemoptysis; three-point increase in cough; or 40 percent increase in FEV." I presume that means improvement in dyspnea, improvement in hemoptysis, improvement in cough.

"The number with improvement with YAG was about half that with PDT. IN patients with pulmonary atelectasis at baseline, 28 percent on PDT and 19 percent on YAG were reported to have improvement or resolution of atelectasis one month after treatment."

Question no. 1. "The division believes that these

two trials are adequate and well-controlled trials demonstrating the efficacy of Photofrin for treatment of patients with partially or completely obstructing endobronchial non-small-cell lung cancer." That is making a strong statement here.

DR. WILLIAMS: Maybe I should explain it. Dr. Temple has sort of suggested that if we have an opinion, we should express it. So there it is.

DR. DUTCHER: "Does the committee agree with either?"

DR. SCHILSKY: I think that I am persuaded that these trials do demonstrate efficacy for some group of patients. I am not exactly sure who those patients are, quite frankly, but it does seem to be pretty clear that there are some patients who do benefit from this treatment.

I don't know that one can draw a firm conclusion with respect to efficacy of PDT versus efficacy of YAG. But I am also pretty well persuaded that PDT is not likely to be substantially worse than YAG.

So I would answer this question yes.

DR. DUTCHER: Dr. Johnson also answered this question yes.

Are there other comments? All those that would vote yes on question no. 1?

[Show of hands.]

Seven out of seven, yes. Zero, no. Plus Dr. Johnson is eight.

The second question: "The incidences of several toxicities were higher on the PDT arm. Photosensitivity, psychiatric symptoms"--actually, I was looking at that; seem to be related to immediately after bronchoscopy--"bronchitis and dyspnea were significantly more common on PDT. There were more life-threatening events on PDT, 19 versus 8, mostly pulmonary events, predominantly hemoptysis and respiratory insufficiency.

"The rate of fatal massive hemoptysis in the PDT group was about twice that of YAG, 10 percent for PDT and 6 percent for YAG. However, the rate of fatal massive hemoptysis occurring in the first 30 days after treatment was the same, 4 percent for each treatment.

"Despite these findings, there was no difference between the PDT arm and the YAG arm in either survival or the number of deaths within 30 days of a procedure, 16 percent on PDT versus 17 percent on YAG. Furthermore, there appeared to be some bias against PDT in the collection of toxicity data. The incidences of toxicity attributed to PDT may have been inflated relative tc YAG since there were 33 percent more patient days of follow up for PDT than for YAG.

"Similarly, patients who died were more likely to

have a life-threatening event reported on the PDT arm than on the YAG arm. When early life-threatening events and early deaths were combined, there was no difference between the study arms.

"Considering the balance of efficacy and toxicity demonstrated in these trials, should Photofrin be approved for reduction of obstruction and palliation of symptoms in patients with completely or partially obstructing endobronchial non-small-cell lung cancer?"

Before we answer this, Grant, the patients who died were more likely to have been reported on PDT?

DR. WILLIAMS: No. It is just that if a patient died--if a patient had a life-threatening event, what is puzzling to me is it seems like everybody who died should have had a life-threatening event. How did they die if they didn't have a life-threatening event.

DR. DUTCHER: You are saying the double-reporting was greater.

DR. WILLIAMS: Right; exactly.

DR. DUTCHER: Okay. So this is the question of approval. Dr. Schilsky, do you want to start?

DR. SCHILSKY: Sure. I don't have too much to say, actually. I agree with Dr. Williams' characterization of this as a niche therapy. It seems to me that the people, the doctors, most likely to use this are doctors who are

already using this technology for treating esophageal cancer, so those are people who already have some experience with the therapy.

I think the only really unresolved--the two sort of unresolved issues in my mind are it is not exactly clear how you would select patients for this therapy as opposed to YAG, but I don't know that it is ever going to be possible to easily resolve that.

And then there is still the issue of whether or not there really is any increased early risk to these patients. I think as the company and the FDA have delved into the data, I am reasonably satisfied that there is not and that those individuals who use this are likely to gain experience with it and figure out a way of optimally selection patients and optimally applying this therapy.

So when it is all said and done, I guess I would answer this question yes.

DR. ALBAIN: This is a question for you, Dr. Justice, or Dr. Williams, how extensively can the labeling indicate some of these comments that were brought out about extrinsic compression as a high risk? Can you get that into the labeling to further define who these patients are with completely or partially obstructing.

As we have heard, not all such patients should be candidates for this therapy.

DR. WILLIAMS: I think the submitted labeling already has a lot of that in it. Unfortunately, we are not able to identify the subgroup that is not going to get an adverse event and who is going to get benefit, but, to the extent we can, we will certainly put it in the labeling.

DR. DUTCHER: I just want to read Dr. Johnson's comments because he also voted yes. He said, "However, I recommend use only in patients with CT-scan evidence of intrinsic bronchial disease and polyploid lesions. The procedure should not be used in patients with submucosal or peribronchial disease nor should the procedure be used in patients with bronchial stump lesions.

"Caution should be used in patients with prior pneumonectomy or with a main-stem bronchus lesion because of risk for inflammatory reactions caused by PDT."

DR. WILLIAMS: What I would suggest is that we get that and talk--negotiate with the company to make sure appropriate things are included in the labeling.

DR. DUTCHER: Other comments? All those who would vote yes on question no. 2.

[Show of hands.]

DR. DUTCHER: Seven, plus Dr. Johnson is eight. Zero no.

Well, this was quite a day. Thank you so much.

[Whereupon, at 1:30 p.m., the proceedings were adjourned.]

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.

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