

1 DR. NERENSTONE: Could you identify  
2 yourself?

3 MR. BARKER: Kerry Barker, statistics,  
4 Pharmacia. So this is just a smooth scatter plot  
5 so there's no real modeling. This is just a way of  
6 looking at a scatter plot that's smooth. The  
7 endpoints on both the left and the right are fairly  
8 small. We actually have done a logistic regression  
9 on the 0-1 and the slope is basically zero. We're  
10 not statistically different from zero. So the key  
11 point on this one is that performance status 2 is  
12 higher, that shape of that curve is obviously  
13 random noise. It's not -- we don't believe that's  
14 what the age effect is for performance status 2.  
15 It's basically just random scatter. The key there  
16 is that the 0-1 is lower than the 2 and that there  
17 is no age effect after you adjust for performance  
18 status.

19 DR. NERENSTONE: Dr. Extermann?

20 DR. EXTERMANN: We speak about age, and I  
21 would like to make a cautionary comment. The  
22 patients that we speak of age in these studies is  
23 65 to 75. In above 75 you had exactly 19 patients.  
24 By the way, it's also true for the meta-analysis  
25 from Sargent is that in meta-analysis you had

1 exactly 23 patients above the age of 80. So we are  
2 speaking of very young elderly patients and if  
3 there is any geriatrician in this room they are  
4 probably laughing at us because they define aged as  
5 85 plus. But I'm somewhere in between. So I think  
6 we need to keep that in mind when we make any  
7 recommendation about older patients is that the  
8 data provided for the study are limited especially  
9 in the absence of detailed data on comorbidity.

10 DR. GOLDBERG: I wonder if I could make a  
11 comment to that. Goldberg from Mayo Clinic. I was  
12 the second author on the Sargent study. We at  
13 NCCTG have looked at age and prediction of benefit  
14 and toxicity in the adjuvant setting. In addition  
15 we've looked at it in the advanced disease setting  
16 and patients entered in 5-FU/leucovorin studies and  
17 Dr. Balducci chaired a session at ASCO last year  
18 where this was discussed. What we found in that  
19 was older patients with advanced disease did have a  
20 slightly higher rate of grade 3-4 toxicity but  
21 equal potential benefit from 5-FU/leucovorin based  
22 therapies and that really performance score, not  
23 how old a person is, is the most important measure  
24 of this. And as an advocate for the graying  
25 Americans, as one who is graying himself, I would

1 say that I think we ought to allow physicians and  
2 patients to make choices based on performance score  
3 as much data as can be brought to bear to the  
4 situation and not say that arbitrarily you're not a  
5 candidate for Saltz if you're 75 or you're not a  
6 candidate for Saltz if you're 78 or 83 or 91 or  
7 whatever. So I think if you were going to put  
8 something in the package insert, it might say that  
9 patients who are of advanced age may have greater  
10 comorbidities and comorbidities can predict for  
11 greater toxicity as a caution but not as a cut-off.

12 DR. EXTERMANN: I definitely agree with  
13 that.

14 DR. SALTZ: I think you bring up an  
15 important point that we all define age differently.  
16 I personally use a rigorous criteria of 20 years  
17 older than whatever age I am. But I think that  
18 it's really important again to emphasize that as we  
19 talk about these age issues, performance status  
20 issues and so on they are applicable to all  
21 oncology patients and virtually all chemotherapy  
22 treatments that we're talking about. Again, we're  
23 looking at small numbers on the end of the curve  
24 and interpreting them because we're all seeing what  
25 we already know, that we're all concerned that

1 frail, elderly patients aren't going to tolerate  
2 chemotherapy as well as the unfit ones. Again, we  
3 have to be careful about how to codify that and I  
4 would emphasize and reinforce what Dr. Goldberg  
5 said that we have to rely on clinical judgement.  
6 We have to -- we can all be cautionary to each  
7 other, ultimately it's the clinician looking at the  
8 patient that's going to have to make decisions.

9 DR. NERENSTONE: We have time for two more  
10 brief questions. Dr. George?

11 MR. GEORGE: Mine will be brief because I  
12 got in line -- now I'm a little late saying what  
13 I'm going to say but it had to do with the I think  
14 we're over-interpreting things here especially with  
15 respect to the endpoints of the early mortality.  
16 The number of events is small and so the -- and the  
17 total number of patients is small so that things  
18 like these models fitting with large numbers of  
19 variables in them is just liable to be confusing  
20 and certainly looking at some of these things that  
21 even the sponsor said were not reasonable to look  
22 at. So I think we have to be careful with this  
23 with respect to just what the data are.

24 DR. NERENSTONE: Dr. Taylor?

25 DR. TAYLOR: I think Dr. Balducci hit on

1 something that we really haven't talked about and  
2 that is the distance issue. I'm not sure I expect  
3 you to have this data but I think that one of the  
4 important things is how far away the patient is  
5 from the treating physician because the treating  
6 physician most frequently is familiar with the  
7 toxicities and they're the one or their nurse is  
8 the one that's called about the diarrhea it's much  
9 more likely to be taken seriously as opposed to the  
10 patient who goes back out into a small town, at  
11 least in my state and has a primary care physician  
12 that we've tried to train about the toxicities of  
13 the drug whose nurse may just think he has the flu  
14 and may not address the symptoms as seriously. So  
15 I think that some of the familiarity as Dr. Saltz  
16 has said with the toxicities is important in  
17 managing those toxicities. So do you have any  
18 information about distant from the treating  
19 physician?

20 DR. MILLER: It's a fascinating concept.  
21 Unfortunately, I must say we don't. I mean again I  
22 think that the idea of enhancing supportive care  
23 and enhancing education of ancillary treating  
24 physicians about the prospect of infection is  
25 particularly important in this circumstance so that

1 a coverage can be instituted early, as well as the  
2 bases for the recommendation for fluoroquinolones  
3 so the patient has a prescription available and can  
4 start to take that if they're running into trouble  
5 with protracted diarrhea and not wait. That was  
6 the policy that had been instituted in Study V303.  
7 It was not clarified in Study 0038. There was some  
8 fluoroquinolone use in Study 0038 but it was  
9 primarily for prophylactics and neutropenic fever,  
10 not as a specific therapy of complicated diarrhea.  
11 So that might be something that might help in that  
12 regard.

13 DR. NERENSTONE: Thank you very much.  
14 We'll take a break right now. Please be back at  
15 10:30.

16 [Recess.]

17 DR. NERENSTONE: Dr. Chico is going to  
18 present for the FDA. Excuse me, we have some  
19 letters that need to be read.

20 MS. SOMERS: There's been a slight change  
21 of plan. I'll be reading two of the letters from  
22 the public. I'm not going to read the letter from  
23 the NCCTG because it's been pretty thoroughly  
24 covered by the sponsor and I'm not going to read  
25 the letter with the illegible signature. This

1 letter is from Peter Goyton and it was written at  
2 the request of Pharmacia.

3 I understand that there is a current  
4 review underway that may modify or change the  
5 delivery mechanism of CPT-11 used in the treatment  
6 of colon cancer. I am obviously not a medical  
7 professional, and am writing to you because I  
8 wanted to share my experiences with CPT-11. I will  
9 leave the determination of the effectiveness of  
10 this drug to the medical professionals. My primary  
11 interest in this matter is that I would like to  
12 insure that this and any other appropriate  
13 treatment be administered in a way that allows  
14 patients to live as normal a life as possible,  
15 while keeping the costs of the administration of  
16 this drug as low as possible.

17 I was diagnosed with rectal/colon cancer  
18 four years ago and underwent radiation and 5-FU  
19 treatment prior to a resection. I then was treated  
20 with 5-FU even though there was no detectable  
21 cancer in my lymph nodes or body. The disease  
22 metastasized to my liver, and a year later I had a  
23 liver resection. One year later I again had a  
24 liver resection for an identical problem. During  
25 these two cycles I was treated with CPT-11 and 5-

1 FU, and the second time with CPT-11 and Xeloda.  
2 Both treatment programs lasted about six months,  
3 and all of my treatments have been on an outpatient  
4 basis.

5           During this time I was for the most part  
6 able to maintain pretty much a normal life. I  
7 worked, played, and continued to enjoy the things  
8 in life I value. I did suffer the usual side  
9 effects, such as diarrhea, nausea, hair and weight  
10 loss, etcetera. I was at times also incredibly  
11 tired. These side effects were not pleasant, to  
12 say the least. Enough said. But working with my  
13 doctors and nurses, and knowing that each of my  
14 cycles had a beginning, a middle, and an end, and a  
15 short period to allow my body to recover, I  
16 tolerated the treatment as well as could be  
17 expected.

18           The past four years have been the most  
19 difficult and challenging years of my life, and  
20 also the best. Please call me if I can be of  
21 assistance. Peter Goyton.

22           And the other one is from the Cancer  
23 Research Foundation of America. The Cancer  
24 Research Foundation of America, founder of the  
25 National Colorectal Cancer Awareness Month, has

1 been recently made aware of the current review of  
2 irinotecan and 5-FU/leucovorin which we believe to  
3 be the standard of care in the first-line treatment  
4 of advanced colorectal cancer. We recognize that  
5 the Saltz bolus regimen is used in more than 95  
6 percent of patients who received this combination  
7 therapy. In fact, an estimated 100,000 patients  
8 have been treated with the Saltz regimen in the  
9 U.S. and an estimated 60 percent of all advanced  
10 colorectal patients received this course of  
11 treatment as first-line therapy.

12 We are aware that the information from two  
13 U.S. cooperative group trials suggest the  
14 possibility of an increase in early mortality  
15 associated with the use of Saltz irinotecan and 5-  
16 FU/leucovorin bolus regimen. We note that in  
17 assessing the number of deaths, investigators from  
18 the two cooperative group studies used a new  
19 statistic, the mortality rate based on all deaths  
20 of any cause occurring within 60 days from start of  
21 therapy. Because the method of determining  
22 mortality rates was new, placing these results in  
23 context with past clinical trial data was  
24 difficult.

25 We have been informed that to ensure an

1 appropriate comparison of the mortality rates, a  
2 comprehensive review of data from additional 5-  
3 FU/leucovorin, irinotecan registrational and  
4 competitive studies was conducted. It is our  
5 understanding that results showed that there were  
6 no statistically significant differences in  
7 mortality rates between treatment arms of those  
8 deaths that occurred within the first 60 days of  
9 treatment.

10 We believe that the Saltz regimen of  
11 irinotecan and 5-FU/leucovorin have a well-  
12 documented safety profile and has demonstrated no  
13 increase in the risk of early death. With  
14 appropriate patient selection and supportive care,  
15 the regimen can safely treat those with advanced  
16 colorectal cancer, extending life while maintaining  
17 quality of life. Considering the risk ratio of  
18 risk to benefit, it should be retained as a viable  
19 treatment option.

20 As the organization has spearheaded the  
21 creation and implementation of the National  
22 Colorectal Cancer Awareness Month, in collaboration  
23 with more than 40 partner organizations, we at the  
24 Cancer Research Foundation believe that physicians  
25 and patients should have access to as many

1 treatment options for management of their disease  
2 as is proven to be safe and effective. We urge  
3 that the Saltz regimen be maintained, so that  
4 colorectal cancer patients can continue to receive  
5 the survival benefit it offers.

6           And they have a statement here. It says I  
7 am familiar with the bolus irinotecan, 5-  
8 FU/leucovorin regimen, Saltz, and believe it has  
9 demonstrated significant survival benefit and as  
10 such should remain an appropriate treatment option  
11 for suitable first-line patients with metastatic  
12 colorectal cancer.

13           Signed by Coalition of National Cancer  
14 Groups, Cooperative Groups, Colon Cancer Alliance,  
15 Colorectal Cancer Association of Canada, Minnesota  
16 Colon and Rectal Foundation, National Colorectal  
17 Cancer Research Alliance, Interamerican College of  
18 Physicians and Surgeons, James E. Olson Foundation,  
19 Society of Gastroenterology Nurses Associates and  
20 The Better Health Foundation. And again, both of  
21 these letters are in everybody's folders here.

22           DR. NERENSTONE: Thank you, Karen. Dr.  
23 Chico?

24                           **FDA Presentation**

25           DR. CHICO: Thank you. Good morning,

1 ladies and gentlemen. A disproportionate number of  
2 early deaths on the bolus irinotecan arm or the  
3 Saltz regimen arms of two cooperative group studies  
4 lead to a re-evaluation of the safety of this  
5 regimen that was approved in April, 2000. Prompt  
6 action was necessary but had to be based on  
7 evidence. This required a comprehensive review of  
8 clinical data in three parts: a thorough  
9 evaluation of the early deaths from the cooperative  
10 group trials; a reanalysis of the clinical trials  
11 that were the basis for approval; and information  
12 from ongoing studies that was reviewed by the  
13 sponsor but was not submitted to the FDA.

14           The purpose of this advisory committee  
15 meeting today is primarily for information of the  
16 public while we critically evaluate the  
17 observations of early deaths in the cooperative  
18 group trials in light of more extensive and mature  
19 data sets from the licensing and other ongoing  
20 studies and considered the most appropriate  
21 regulatory action. I'd like to first clarify the  
22 definitions of the different combinations of  
23 regimens that will be discussed.

24           The Saltz regimen is a combination of  
25 irinotecan and 5-FU given as a bolus injection

1 weekly for four weeks, with two weeks interval  
2 between cycles. This is one of the two regimens  
3 approved in the United States for first-line  
4 treatment of advanced colorectal cancer. This  
5 regimen was used in the patients who died early in  
6 the cooperative group trials and will be the focus  
7 of our discussion. I will be referring to this  
8 regimen during the rest of presentation as the  
9 bolus IFL regimen.

10           The Douillard regimen is a combination of  
11 irinotecan and 5-FU/leucovorin with 5-FU given as a  
12 continuous infusion for two days every two weeks.  
13 This is also approved in the United States for the  
14 same indication as the bolus IFL regimen. I will  
15 be referring to the schedule as the continuous  
16 infusion IFL regimen.

17           The Mayo Clinic and the Roswell Park  
18 regimens are two bolus regimens of 5-FU and  
19 leucovorin and I will be referring to them as bolus  
20 5-FU while the de Gramont regimen will be referred  
21 to as the continuous infusion 5-FU regimen.  
22 Theradex organized a panel funded by Pharmacia to  
23 review the records of patients who died early in  
24 the cooperative group trials. The results of that  
25 review and the recommendations of the panel were

1 published in the JCO in September of this year.

2 The documents that the panel reviewed were  
3 sent to Pharmacia and the FDA concurrently.

4 Therefore, there are three independent groups that  
5 reviewed the records of the 29 patients who died in  
6 the bolus IFL arms of these studies. It was  
7 important to place the deaths from the cooperative  
8 group trials in perspective with the early deaths  
9 and the overall safety data from the randomized  
10 control trials that were the basis for the approval  
11 of Camptosar in combination with 5-FU/leucovorin  
12 for the first-line treatment of colorectal  
13 carcinoma. Pharmacia and the FDA performed each  
14 analysis independently.

15 Another important source of information  
16 are from ongoing studies and the marketing analysis  
17 that the sponsor just presented. Again, the  
18 primary data was not formally submitted to the FDA  
19 for review but nevertheless we believe it is an  
20 important component of the committee's evaluation.  
21 The FDA review is divided into the following  
22 sections: review of early deaths from the NCCTG  
23 and CALGB studies; review of early deaths from the  
24 clinical trials 0038 and V303; and the re-analysis  
25 of safety in the clinical trials 0038 and V303.

1           The hospital and outpatient records of 29  
2 patients treated with the bolus IFL regimen were  
3 reviewed. The median age of the patients treated  
4 with the bolus IFL regimen was 69. There's a  
5 slight preponderance of patients greater than 65  
6 years old. There are more females and most of the  
7 patients had a Karnofsky performance status of 0-1  
8 at baseline. 11 patients had a history of  
9 cardiovascular problems that were well-controlled  
10 during study and treatment. These 11 patients have  
11 prior histories of one or a combination of  
12 hypertension, coronary artery disease, coronary  
13 artery bypass grafts, myocardial infarction or deep  
14 venous thrombosis.

15           There were four potential protocol  
16 violations at entry. One patient had an unresolved  
17 gastrointestinal infection and one patient had a  
18 baseline performance status of three.

19           Most patients who died early experienced a  
20 combination of gastrointestinal and hematologic  
21 infection syndromes. This finding points out that  
22 a combination of these two syndromes are  
23 exceedingly dangerous and should not be ignored.  
24 Management of these toxicities, especially when  
25 they occur in combination should be aggressive,

1 incorporating drugs for both prophylaxis and  
2 symptom management. Fatal vascular events were  
3 also identified but a number of these patients also  
4 experienced symptoms of other syndromes.

5           The interrelationships of these events  
6 might be evaluated better with complete safety data  
7 from these trials. The median time to grade 3  
8 event in the patients who experienced early deaths  
9 in these trials was about two weeks. The rapid  
10 onset of profound toxicity has prompted suggestions  
11 for lowering the starting dose by 20 percent, that  
12 is from 125 to 100 milligrams per meter squared of  
13 Camptosar and modifying the administration of  
14 treatment. The impact of these changes on either  
15 safety or efficacy of the bolus IFL regimen can  
16 only be a matter of speculation with no supportive  
17 clinical data.

18           Before I move onto the review of the  
19 licensing trials I would like to first make a point  
20 on the different ways by which death has been  
21 analyzed. The analysis of early deaths in the  
22 cooperative group trials and the sponsored-  
23 presentation of data from ongoing studies focused  
24 on deaths that occurred within the first 60 days of  
25 starting treatment. The analysis performed during

1 the MDA review for Camptosar and the information  
2 available in the product label are on deaths within  
3 30 days of drug administration obtained from the  
4 entire data base. Describing deaths that occurred  
5 within the first 60 days of study limits the data  
6 set to a relatively small window but gives a  
7 perspective on the degree of acute toxicity  
8 associated with treatment.

9 This analysis is convenient for interim  
10 looks at safety in ongoing studies but exposes only  
11 a subset population who were enrolled early in the  
12 study. An attempt at determining the causality and  
13 relatedness of death the study drug was made by the  
14 panel who evaluated these patients. The FDA,  
15 however, prefers not to establish subjective  
16 interpretation of causality because of the bias-  
17 introduced interpretation of clinical trials.

18 An analysis of deaths that occurred within  
19 30 days of last drug administration uses a more  
20 comprehensive data base that includes all treatment  
21 cycles. Since the total number of patients is  
22 known and the overall toxicity rates can be  
23 determined from the complete and mature data, the  
24 temporal relationship to such treatment implies the  
25 role of treatment in the death and removes the

1 potential bias inserted by allowing investigators  
2 or the sponsor to judge causality. This was the  
3 analysis presented in the licensing studies for  
4 Camptosar.

5 Dr. Chico continuing: Deaths in patients  
6 with metastatic disease from the NCCTG cooperative  
7 group trial were compared to the deaths in the  
8 licensing trials. The rates of deaths within 60  
9 days of starting treatment in the bolus IFL regimen  
10 arm of Study 0038 and the continuous infusion IFL  
11 regimen arm of Study V303 were similar to the  
12 corresponding control arms. The rate of death  
13 within 60 days of starting therapy in the bolus IFL  
14 regimen arm of licensing trial 0038 is actually  
15 higher than observed on the bolus irinotecan  
16 regimen arms of the NCCTG trial.

17 The rate of deaths within 30 days of  
18 treatment reported in the Camptosar product label  
19 was nine percent in the bolus IFL regimen arm of  
20 Study 0038 and four percent in the continuous  
21 infusion IFL arm of Study V303. Again, these  
22 percentages are higher than the rates presented as  
23 deaths within 60 days of starting treatment in  
24 these studies. In the CALGB study using bolus IFL  
25 for adjuvant treatment deaths were also

1 disproportionately higher compared to the control  
2 bolus 5-FU Roswell Park arm but as might be  
3 expected relatively lower compared to the licensing  
4 trial in patients with metastatic disease.

5           It is important to place the deaths from  
6 the cooperative group trials in perspective with  
7 the deaths in the randomized control trials that  
8 were the basis for approval of Camptosar because  
9 these large randomized trials have complete safety  
10 data bases that permit analysis of safety in the  
11 context of a mature data set. This permitted  
12 evaluation of patient characteristics that might  
13 increase the risk of death or severe toxicity.

14           The safety data base could also be  
15 analyzed to explore questions based on the review  
16 of early deaths in the cooperative group trials.  
17 In the safety profile the approved continuous  
18 infusional IFL could be reassessed in light of the  
19 findings from the cooperative group trials.

20           Like the cooperative group trial deaths  
21 where the median age of patients was 69 the median  
22 age of patients who died in the bolus IFL arm of  
23 trial 0038 was 61. There is a slight preponderance  
24 of females among the early deaths in the  
25 cooperative group trials but a predominance of

1 males in the licensing trial. The performance  
2 status of patients at study entry was usually 1 or  
3 better. Only data on performance status is  
4 consistent but seems hard to believe that patients  
5 with better baseline performance status would do  
6 worse. Characteristics that placed patients at  
7 higher risk for early death with the bolus IFL  
8 regimen cannot be clearly identified using subset  
9 analyses of this type and should be placed within  
10 the context of full patient population enrolled in  
11 the study.

12           This table with selected characteristics  
13 of patients enrolled in the IFL arms of each of the  
14 two licensing studies is being shown to illustrate  
15 two important points. First, there are differences  
16 in the distribution of patients across studies,  
17 especially in patients with performance status of  
18 2, patient sites of primary tumor, prior adjuvant  
19 therapy and prior radiation therapy, for these  
20 reasons comparisons across study populations should  
21 be approached with caution. Secondly, 85 to 95  
22 percent of the patients enrolled in the studies had  
23 a baseline performance status of 0 to 1, offering  
24 an explanation to the preponderance of deaths  
25 within 60 days in this subgroup.

1           In patients enrolled in the bolus IFL arm  
2 of Study 0038 there are a 192 out of 225, or 85  
3 percent, with baseline performance status of 0 to  
4 1, and 33, or 15 percent, with a baseline  
5 performance status of 2. The distribution of  
6 baseline performance status in the 5-FU arm is  
7 similar to the bolus IFL arm. The deaths within 60  
8 days of starting treatment and the deaths within 30  
9 days of last treatment distributed according to  
10 baseline performance status would show that  
11 patients with performance status 2 died at a  
12 disproportionately higher rate compared to those  
13 patients with a baseline performance status of 0 to  
14 1.

15           In the case, for example, of the deaths  
16 within 60 days of bolus IFL, eight out of 33, or 24  
17 percent, with performance status 2 versus seven out  
18 of 192, or four percent, with performance status of  
19 0 to 1. But within patients of the same  
20 performance status group the deaths are similar  
21 between the study arms.

22           It is also important to understand the  
23 prospects for tumor control and survival benefit in  
24 this group but important to bear in mind that these  
25 are subset analyses. The median time to tumor

1 progression and survival of patients with baseline  
2 performance status 2 are lower compared to those  
3 with baseline performance status of 0 to 1,, but  
4 the results are similar between treatment arms in  
5 each subgroup.

6           With these findings regarding the efficacy  
7 and safety of the IFL regimens in patients with  
8 baseline performance status of 2 compared to those  
9 with performance status of 0 to 1 Pharmacia is  
10 proposing to exclude treatment of patients with  
11 baseline performance status of 3 or 4 only. We  
12 would emphasize that patients with performance  
13 status 2 experience significantly greater toxicity  
14 with significantly lowered efficacy compared to  
15 patients with baseline performance status of 0 to  
16 1. Considering the results of the analysis of  
17 early deaths and reanalysis of licensing trials it  
18 seems appropriate to ask the question of whether  
19 treatment with the bolus IFL should be limited to  
20 patients with performance status greater than or  
21 equal to 2 or should it be limited only to patients  
22 with performance status greater than or equal to  
23 three. After hearing the sponsor's presentation  
24 should there be a limiting age in other baseline  
25 characteristics?

1           The median time to death in the bolus IFL  
2 regimen arm of the cooperative group studies was  
3 similar to the median time to death in the bolus  
4 IFL arm of the licensing trial which is 28 days. A  
5 combination of GI and hematologic syndromes was  
6 observed in most patients who died shortly after  
7 starting treatment but both in the cooperative  
8 group studies and Study 0038. This trend across  
9 studies supports the need for heightened awareness  
10 of the risk associated with the simultaneous  
11 occurrence of gastrointestinal and hematologic  
12 syndromes.

13           The sponsor submitted to the agency in  
14 September a proposal to change the label according  
15 to most of the independent panels' recommendations  
16 on heightened supportive care in patient  
17 monitoring. They propose starting a seven-day  
18 course of fluoroquinolone antibiotics for diarrhea  
19 that is persistent for more than 24 hours, fever  
20 accompanying diarrhea and for absolute neutrophil  
21 counts of less than 500. And also proposal that  
22 practitioners should consider giving GCSF for grade  
23 2 or greater neutropenia. Weekly assessment during  
24 the first cycle of therapy and a CBC and  
25 deferential count within 48 hours prior to

1 treatment are measures being proposed for closer  
2 patient monitoring.

3           The sponsor is proposing a number of  
4 changes in the dose modifications in the label.  
5 Currently, treatment may continue in the face of  
6 grade 2 diarrhea and the sponsor is proposing to  
7 hold treatment until resolution. For grade 3  
8 diarrhea the proposal is to hold treatment until  
9 resolution to grade 1 instead of grade 2 as  
10 currently written in the label. For all subsequent  
11 treatments the patients would have to be free of  
12 diarrhea for at least 24 hours.

13           Whether these changes could appreciably  
14 affect the safety and efficacy of the bolus IFL  
15 regimen should be discussed. But more important to  
16 consider is that these safety concerns for the  
17 bolus IFL have led to other more aggressive dose  
18 modifications like those adopted by the NCCTG in  
19 their trial. These changes include reducing the  
20 assigned dose by 20 percent and changes in dose  
21 modification, incorporating treatment interruption  
22 for grade 2 toxicity, two level dose reductions for  
23 grade 3 toxicity that are not present in the  
24 guidelines for administering the bolus IFL in the  
25 product label. We have concerns whether this more

1 aggressive dose modification would retain the  
2 modest median survival advantage of 2.2 months in  
3 the survival of the approved bolus IFL schedule.

4           Such unstudied modifications have the  
5 potential to adversely affect the therapeutic index  
6 of the bolus IFL regimen and has also led to a  
7 question of whether the bolus IFL regimen should  
8 still be appropriately used as a control arm in  
9 ongoing and future studies in first-line treatment  
10 of colorectal cancer. In the most recent meeting  
11 of the chairmen of the GI committees of the  
12 cooperative groups the continuous infusion IFL  
13 regimen was favored as the most appropriate choice  
14 as control arm in future studies for adjuvant  
15 trials. Although both schedules are approved the  
16 implication of a potential change in the practice  
17 of treatment in this disease favoring another  
18 schedule made it necessary to quickly evaluate the  
19 relative safety profiles of the two approved  
20 regimens.

21           No direct comparisons exist between the  
22 bolus and infusional IFL and cross study  
23 comparisons should be approached with caution due  
24 to differences between study populations.  
25 Nevertheless, this remains the only data available.

1 The data in this table presented here were  
2 collected by the sponsor from the licensing trials.  
3 A majority of the patients required reductions in  
4 both the Camptosar and 5-FU doses of Study 0038.  
5 There is a sharp drop of about 27 percent in the  
6 proportion of patients treated with full doses of  
7 the bolus IFL regimen between the second and third  
8 week of the first cycle. Only 47 percent of  
9 patients received full-dose therapy by the second  
10 cycle.

11 In Study V303 there was a more gradual  
12 decline in the proportion of patients treated at  
13 full doses in both treatment arms. More than 85  
14 percent of patients received full doses during the  
15 second cycle. The much higher proportion of  
16 patients treated with full dose in this study  
17 compared to Study 0038 may indicate better patient  
18 tolerance of the higher biweekly dose of IFL  
19 utilized in this study.

20 The overall incidence of first-cycle and  
21 all cycle grade 3 and 4 diarrhea and neutropenia,  
22 neutropenic fever and infections were higher on the  
23 bolus IFL regimen compared to the continuous IFL  
24 regimen. This continuation due to adverse events  
25 and hospitalizations were also numerically higher

1 in the first cycle and all cycles with bolus IFL  
2 regimen compared to the continuous IFL regimen.  
3 Please note again that these are cross study  
4 comparisons and the difference is in the  
5 distribution of baseline patient characteristics  
6 may account for the perceived differences.

7           This table shows the survival advantage  
8 associated with the IFL regimens for which  
9 irinotecan was approved as a component of first-  
10 line treatment of metastatic colorectal cancer.  
11 The bolus IFL and infusional IFL regimens were  
12 associated with a 2.2 and 3.3 months median  
13 survival advantage respectively. We would like to  
14 caution that arbitrary changes in the doses and  
15 treatment schedules may alter the modest efficacy  
16 albeit statistically significant survival advantage  
17 from the IFL treatment.

18           This slide shows studies that were  
19 included in the meta-analysis comparing bolus 5-FU  
20 and continuous infusion 5-FU published in the  
21 January, 1998 issue of the JCO. The purpose is to  
22 show that there has been extensive experience in  
23 the use of continuous infusion of 5-FU in the U.S.  
24 over the past 25 years. This outpatient experience  
25 with 5-FU infusion schedules using portable

1 infusion pumps and end-line catheter lasted for  
2 multiple weeks in some cases. Although approved in  
3 the United States the relative experience with the  
4 continuous infusion IFL regimen is limited to  
5 compared to its widespread use in the European  
6 trials and clinical practice.

7           In this meta-analysis the administration  
8 of 5-FU by continuous infusion showed a  
9 statistically significant increase in survival in  
10 favor of the continuous infusion 5-FU schedules.  
11 However, the magnitude of benefit was small and the  
12 contribution of leucovorin was not considered. In  
13 contrast the difference in response rates were  
14 highly statistically significant and grade 3-4  
15 hematologic toxicity seems to be lower in the  
16 infusional regimens.

17           The incidence of deaths within 60 days of  
18 starting treatment is higher in the bolus IFL arm  
19 of Study 0038 compared to the continuous infusion  
20 arm of Study V303. However, the incidence within  
21 studies among treatment arms are very similar. The  
22 approval of irinotecan for first-line treatment of  
23 colorectal cancer was in part due to an acceptable  
24 safety profile after addition of irinotecan to the  
25 corresponding 5-FU/leucovorin control arms. The

1 differences in toxicity profile cross-study between  
2 bolus and infusional IFL, however, raises the  
3 question of whether the schedule of the  
4 corresponding 5-FU component may make a major  
5 contribution to the differences in toxicity.

6           After the presentation of the clinical  
7 data on the IFL regimens we would like for the  
8 committee to consider and discuss the following  
9 actions. If the committee believes that the  
10 currently approved bolus IFL is safe and  
11 efficacious without any change in the label, the  
12 potential action could be no action. However,  
13 there could be minor changes to the label as  
14 proposed by the sponsor which served to amend  
15 supportive care, patient monitoring and minor dose  
16 modifications. Whether these could significantly  
17 the safety and efficacy profile the bolus IFL is a  
18 matter of discussion as posed in our questions to  
19 you.

20           The third potential action might be  
21 considered as major changes in the label. We  
22 believe that this would require that prospective  
23 studies be done to establish the effect on the  
24 safety and efficacy of the regimen. The concern of  
25 this action, however, would be that potential for

1 patients in the community to be treated with a  
2 regimen that may be inferior to the approved bolus  
3 IFL regimen while the studies are ongoing.

4           If there is a significant safety concern  
5 with the labeled regimen and a serious efficacy  
6 concern with the major modifications of the  
7 regimen, another possibility would be removal of  
8 the bolus IFL regimen from the product label until  
9 results of perspective studies become available.  
10 The continuous infusion IFL or the Douillard  
11 regimen would remain the product label for first-  
12 line treatment of metastatic colorectal cancer.  
13 Thank you very much.

14           DR. NERENSTONE: Thank you. I'd like to  
15 open the floor for questions from the committee. I  
16 want to remind the committee this is really sort of  
17 questions rather than discussion. Let's wait to  
18 get into the discussion until after specific  
19 questions about the FDA presentation. Yes, Dr.  
20 Sledge?

21                           **Questions from the Committee**

22           DR. SLEDGE: A couple questions. First,  
23 if I'm hearing you correctly in essence you agree  
24 with the company's presentation; is that a safe  
25 statement?

1 DR. CHICO: Most of their points, yes.

2 DR. SLEDGE: Second, if I'm hearing you  
3 correctly, the FDA's take on this is that the  
4 problem isn't CPT-11 it's fluorouracil and how we  
5 administer it?

6 DR. CHICO: That could be thought of if  
7 you looked at it, that could be one possible  
8 explanation.

9 DR. SLEDGE: So are you asking us to  
10 change the label for CPT-11 or for fluorouracil?

11 DR. CHICO: Approval for CPT-11 is in  
12 combination with 5-FU/leucovorin.

13 DR. EXTERMANN: If I read correctly your  
14 data, most if not all deaths in certain studies  
15 occurred within the first 60 days?

16 DR. CHICO: Right.

17 DR. EXTERMANN: We also have seen that  
18 even a performance status of 2 was a risk factor.  
19 So my question is what percentage of the patients  
20 with performance status of 2 need a dose reduction?

21 DR. CHICO: There were only 33 patients in  
22 Study 0038 with performance status of 2 and it's  
23 really going to subsets of subsets when we do this,  
24 although the sponsor might have that data.

25 DR. MILLER: I can just comment that the

1 most predictive factor for receiving a lower dose  
2 was performance status. That's for a need for dose  
3 attenuation, PS 2.

4 DR. EXTERMANN: I think it would be  
5 important to know if every single patient with a  
6 performance status of 2 could not achieve a full  
7 dose for cycle.

8 DR. MILLER: I don't know that data  
9 offhand. I just know that as a risk factor that  
10 was the primary risk factor for dose reductions in  
11 the first-cycle.

12 DR. NERENSTONE: Dr. Lippman?

13 DR. LIPPMAN: I'd like to follow up again  
14 on the performance status 2 issue. Avoiding cross  
15 study comparisons it seems like the cleanest study  
16 to look at that would be the 0038 Study. It had a  
17 lower rate of prior treatment 5-FU and radiotherapy  
18 and had the largest percentage of performance  
19 status 2, 15 percent of patients. Based on the two  
20 slides used you showed on the licensing trials, the  
21 second performance status in terms of death and in  
22 terms of survival in your view of looking at these  
23 data very careful at all the aspects can you think  
24 of any compelling reason to not look at the  
25 performance status 2 patients differently?

1           We know it's a subset analysis but this is  
2 really a safety issue. They clearly did  
3 differently in terms of death and obviously had  
4 worse survival. So I think when we're talking  
5 about cut-offs and we spent the morning -- we spend  
6 the early period talking about PS as being the key  
7 factor it seems as though there's a major  
8 difference at performance status 2, which if we're  
9 talking about modifying or suggesting to physicians  
10 how to use this, it seems pretty obvious to me that  
11 performance status 2 is different. Am I missing  
12 something? Is there other data in other analyses  
13 you've done that would suggest that PS 2 should be  
14 included or at least should not have a very strong  
15 recommendation in terms of the safety and benefit?

16           DR. CHICO: Actually that's the question  
17 that we posed to you, whether these patients should  
18 be quite categorically excluded or not because just  
19 recommending caution in these patients is a very  
20 unclear recommendation and we'd like more guidance  
21 about that.

22           DR. LIPPMAN: Right, but again, the data  
23 you showed seemed pretty convincing to me. Is  
24 there in terms of your dissecting all the other,  
25 even the cross study comparisons that maybe you

1 didn't present, is there any other data we're  
2 missing that would suggest that the PS 2 patients  
3 might benefit from this?

4 DR. CHICO: That's the data from the  
5 licensing trials and from the deaths in the  
6 cooperative group trials which point to these  
7 patients not fully benefiting as much as patients  
8 with baseline of 0 to 2 as far as safety and  
9 efficacy from this regimen.

10 DR. NERENSTONE: Just to follow up on that  
11 from Dr. Lippman's point. If you do look at the  
12 performance status 2 patients, they did poorly  
13 whether or not they got irinotecan. They did  
14 poorly on leucovorin, 5-FU alone as well.

15 DR. LIPPMAN: No question. And that gets  
16 at George's point. I mean clearly they divorce.  
17 Now if we need to go back and do a labeling issue  
18 for 5-FU/leucovorin I don't know but what's on the  
19 table now is this regimen and they clearly behaved  
20 differently.

21 DR. NERENSTONE: Dr. George?

22 MR. GEORGE: I have a question that will  
23 be I'm sure hard for you to answer but any change  
24 at all in the treatment could potentially affect  
25 the outcome. So do you have any notion of what you

1 help us in our discussion about the difference  
2 between major and minor changes?

3 DR. CHICO: The minor changes we're  
4 referring to is what the sponsor has proposed.  
5 Basically, from the September 10th submission which  
6 basically which is to treat through grade 2  
7 diarrhea during the cycle but then not retreat  
8 patients until they have 0 or grade 1 diarrhea on  
9 the next cycle. Major changes are those which I  
10 presented as changes that were affected by the  
11 NCCTG in their modification of their trial where  
12 they're starting out with a lower dose of CPT-11  
13 plus having more aggressive or dose modification  
14 criteria for patients where they have two dose  
15 reductions in patients who have grade 3 diarrhea  
16 and where they hold treatment for patients with  
17 grade 2 diarrhea and reduced by one level.

18 MR. GEORGE: My only comment about that  
19 was those are two specific examples of major and  
20 minor but there are other things. I just wondered  
21 if you had any other comments on that?

22 DR. CHICO: Those changes as far as  
23 supportive care and closer patient monitoring; is  
24 that what you're referring to?

25 MR. GEORGE: Right. In our discussion,

1 we'll come up with this later, we'll be talking  
2 about it but I guess there are other things other  
3 than what the sponsor proposed and what NCCTG did.

4 DR. CHICO: Would you please be more  
5 specific?

6 MR. GEORGE: We'll discuss it.

7 DR. NERENSTONE: Dr. Grem?

8 DR. GREM: For the performance status 2  
9 patients --

10 DR. NERENSTONE: Please speak more into  
11 the microphone.

12 DR. GREM: I'm sorry. It looked like in  
13 the North American trial of bolus IFL that only  
14 about half of the patients actually received full  
15 dose at the start of cycle two and we know that the  
16 proportion of patients with PS 2 wasn't that great.  
17 It was, I don't know, maybe about a third of the  
18 patients. So it looks like most everybody needed a  
19 dose reduction at the start of cycle two and it's  
20 possible that the PS 2 patients needed more than  
21 just the one dose reduction. They may also have  
22 not been able to be treated on time or they may  
23 have dropped out after one cycle. So having that  
24 kind of information would be helpful because it  
25 might suggest that a lot of them were dropping out

1 because of significant treatment delays and  
2 profound dose reductions that maybe in that  
3 category of patients it would be prudent to dose  
4 reduce them for their first cycle. Observe them  
5 and if it turns out they happen to fly they can be  
6 dose escalated cycle two rather than just excluding  
7 all PS 2 patients because even though the PS 2  
8 patients did poorly, it looked like in both of  
9 those studies there was still some benefit. I  
10 don't know if it's significant but if you look at  
11 the time to treatment progression and survival, it  
12 did look like it was a little bit longer in the  
13 patients who got the irinotecan. So to arbitrarily  
14 exclude all PS 2 patients from therapy, that may be  
15 extreme.

16 DR. BALDUCCI: I just wanted to second  
17 that.

18 DR. NERENSTONE: Other questions for Dr.  
19 Chico? Dr. Brawley?

20 DR. BRAWLEY: Dr. Chico, thank you for  
21 your presentation. Can I just ask one  
22 clarification? Am I correct that, and I realize  
23 I'm comparing two different studies here, am I  
24 correct that patients who got infusional therapy  
25 generally had a lower mortality than patients who

1 were given the bolus therapy? And also, secondly,  
2 am I correct that there were more PS 2 patients on  
3 the bolus therapies?

4 DR. CHICO: You're correct on both points.  
5 Patients who were given infusional IFL therapy had  
6 lower death rates when you look at 60 days and 30  
7 days from last treatment but, of course, between  
8 treatment arms the deaths were similar. And you're  
9 also correct in your second point.

10 DR. NERENSTONE: Dr. Takimoto?

11 DR. TAKIMOTO: Just another clarification.  
12 My understanding is that the sponsor has withdrawn  
13 the proposal to change the label that you described  
14 up there?

15 DR. CHICO: That was not submitted to us  
16 formally. That was presented to us when they came  
17 to the FDA orally but was not submitted in writing.  
18 Although if you look closely at what they've  
19 retained, which is not treating patients if they  
20 have grade 1 diarrhea, that's essentially saying  
21 that we're not going to treat through grade 2  
22 diarrhea. Although let me say then that also that  
23 within a treatment cycle they're proposing that for  
24 patients who have grade 2 diarrhea that we still  
25 continue to treat them.

1 DR. PAZDUR: Even if the company is not  
2 presenting this, the reason why we included this in  
3 the discussion is we would like to have these  
4 points discussed because they have been bandied  
5 about the community and have appeared in the JCO  
6 article, some of them. So even though there is not  
7 a formal presentation, at one time the company did  
8 present this in writing to the FDA and  
9 nevertheless, we would like a discussion of these  
10 points and that's why they're presented here.

11 DR. NERENSTONE: Just a point of  
12 clarification, Dr. Chico, the two studies that are  
13 being compared that everyone says really can't be  
14 compared, the infusional versus the bolus, these  
15 were also done, the bolus was done completely in  
16 the United States and the infusional study was done  
17 completely in Europe. I think that makes  
18 comparison even more fraught with difficulties  
19 because of the way people practice, what people  
20 call performance status 2 patients, supportive care  
21 issues, who they put on investigative bias, that  
22 kind of thing. So it's not even that it was done  
23 in the U.S., both studies, there are really even  
24 more differences than just the way the chemotherapy  
25 was given.

1 DR. CHICO: Absolutely.

2 DR. NERENSTONE: Dr. Temple?

3 DR. TEMPLE: I don't want to put words in  
4 his mouth, but I think Dr. George was suggesting  
5 that as soon as you leave the regimens you've  
6 studies and start modifying you're in totally  
7 uncharted territories. I just wonder if you think  
8 we might be reassured by the fact that the  
9 contribution of CPT-11 was the same in two  
10 different continents with two very different  
11 fluorouracil regimens to which it was added? Does  
12 that in any way suggest that at least modifications  
13 of fluorouracil might not be as troublesome as you  
14 think with respect to the contribution of CPT-11?  
15 Do you have a view on that?

16 DR. CHICO: No.

17 [Laughter.]

18 DR. NERENSTONE: And you don't want to  
19 expand on that. Other questions for Dr. Chico?

20 Thank you very much.

21 I think what we should do now is go to the  
22 discussion. Are there comments that people would  
23 like to have before we look at the questions? We  
24 could discuss the questions. Are there any other -  
25 - Dr. George?

1 MR. GEORGE: A quick comment. I would  
2 just like to publicly state that I think what the  
3 cooperative groups did was actually quite good in  
4 the context of what they knew, when they did it.  
5 It's why we're here I guess and it's caused us some  
6 grief and discussions of this. So some of the  
7 presentation sort of led to an implied criticism I  
8 think that I wanted to state for myself I think  
9 they did a good job and I think they were right on  
10 top of things and that was a benefit to the  
11 patients on the studies.

12 **Committee Discussion and Vote**

13 DR. NERENSTONE: No other further general  
14 comments? Then why don't we go to the questions?  
15 I believe that everyone has them in front of you.  
16 The first one is significance of the early deaths  
17 from the cooperative group trials and implications  
18 with Camptosar product label. There are two  
19 approved Camptosar 5-FU/leucovorin regimens for the  
20 first-line treatment of metastatic colorectal  
21 cancer. As we've talked about the bolus regimen  
22 and continuous infusion regimen. As summarized in  
23 the table a higher early death rate associated with  
24 the bolus regimen in two cooperative group trials  
25 relative to the control arms resulted in clinical

1 holds of the trial.

2           The NCCTG trial was reopened with a  
3 modified bolus regimen with reduced starting doses  
4 of Camptosar and 5-FU and more aggressive dose  
5 modifications for toxicity. The CALGB trial was  
6 closed to accrual since its original accrual goal  
7 had been reached. In contrast, in licensing study  
8 0038 the early death rate associated with this  
9 bolus IFL regimen was similar to the 5-  
10 FU/leucovorin control arm or the Mayo Clinic  
11 schedule. Then they have the table. So does the  
12 available evidence in the cooperative group trial  
13 and the licensing trial support removal of the  
14 currently approved bolus IFL regimen from the  
15 Camptosar product label? The infusional IFL  
16 schedule would remain even if we decided to pull  
17 the bolus regimen. Discussion? Dr. Carpenter?

18           DR. CARPENTER: I think it's helpful to  
19 have all these presentations to make a distinction  
20 between what early on appeared to be a big  
21 difference and what in retrospect probably did not  
22 turn out to be a big difference from previously  
23 observed death rates. I think I would speak  
24 strongly for retention of the bolus schedule as an  
25 option with no real evidence that it's any more

1 dangerous than it originally was thought to be in  
2 the licensing studies.

3 DR. NERENSTONE: Other comments? Dr.  
4 Krook?

5 DR. KROOK: I would agree with that.  
6 Having been involved with this I believe that what  
7 has occurred is that a concern of the first two  
8 months of treatment has been brought to the  
9 attention of people, or of investigators should I  
10 say and going back and looking at a repeat  
11 definition. So if I had a vote, I would favor the  
12 no-vote. Pardon me, I would favor that it stay  
13 there.

14 DR. NERENSTONE: The question is for  
15 removal of the currently approved bolus regimen.  
16 So should it be taken out? Other comments? Dr.  
17 Brawley?

18 DR. BRAWLEY: Very briefly. I do a lot of  
19 health practices research and I'd like to point out  
20 that there are a number of hospitals in the United  
21 States in a number of places where cancer is  
22 treated where infusional therapies are still not  
23 available, the machinery is just not available,  
24 especially in poorer hospitals. So bolus therapy  
25 is all that they currently have.

1 DR. NERENSTONE: Dr. Temple?

2 DR. TEMPLE: One could also recommend that  
3 one be considered preferable if available so with  
4 respect to that last question. Could you all make  
5 it clear what you think the deficiencies in data  
6 are that don't allow you to conclude, for example,  
7 that the Saltz regimen is toxic? For example, you  
8 might think, well, one's in one country, one's in  
9 another. Just some clarification of exactly why  
10 you don't think say the six or seven percent  
11 mortality in 0038 is worse than the two percent  
12 mortality in V303 or why one shouldn't think that  
13 just so we understand the reasoning.

14 DR. NERENSTONE: Dr. Sledge?

15 DR. SLEDGE: I think the simple answer to  
16 that is that they're not head-to-head comparisons.  
17 We don't accept head-to-head comparison -- lack --  
18 without head-to-head comparisons even within the  
19 same cooperative group we're not comfortable making  
20 comparisons.

21 DR. TEMPLE: You might think NCCTG is a  
22 sort of direct comparison but, of course, it's not.

23 DR. SLEDGE: But it's not.

24 DR. TEMPLE: It's not simple.

25 DR. SLEDGE: It's not. The patients who

1 went into these trials were different patients  
2 treated by different physicians on different  
3 continents with different supportive care measures.  
4 To expect them to be comparable results I think is  
5 expecting too much of the data sets. Now I think  
6 it's a reasonable hypothesis that infusional  
7 fluorouracil might be safer than bolus fluorouracil  
8 but I don't think any of us around the table  
9 hopefully consider it a tested hypothesis.

10 DR. NERENSTONE: Dr. Krook?

11 DR. KROOK: I guess what I'd like to  
12 comment on to answer Bob's question, I think that  
13 the north central without knowing it put a new  
14 definition in and then this group which we saw here  
15 today went back and looked and had to be  
16 recalculated by Pharmacia. When we look at that, I  
17 think that that early death rate has probably  
18 always been there and it's probably been in the  
19 community because what we have done by doing that  
20 is remove and we'd simply say did they die or did  
21 they not die in the first 60 days? That's a hard  
22 fact like age is. Performance status for  
23 physicians, we can move the performance status from  
24 1.4 to 1.6 and then round but again we were dealing  
25 with a hard definition that all deaths. I think

1 that's why the committee that had the article in  
2 the JCO basically went back and tried to attribute  
3 these to what, and as you read that -- and there  
4 was an increased death rate in the arm we're  
5 talking, the IFL versus the other two arms. Now if  
6 the other two arms had been as high, we may not be  
7 here.

8 DR. NERENSTONE: Dr. Blayney?

9 DR. BLAYNEY: Yes. To speak to Dr.  
10 Temple's point, I think page 70 of the sponsor  
11 presentation is persuasive to me. What it sounds  
12 like is that a new metric was introduced and as a  
13 result of this early reporting system that we heard  
14 described earlier for NCCTG that in my experience  
15 with industry trials is in place any way, that is  
16 if somebody's in the hospital we need to notify IRB  
17 sponsor, etcetera right away so that early warning  
18 system when it was, sounds like when it was  
19 introduced and activated in the NCCTG led to this  
20 new metric and then going back and reanalyzing the  
21 data showed that it looked to be right across the  
22 board about the same. And its post-marketing  
23 practice study that they did is also useful  
24 information, in my view.

25 DR. NERENSTONE: Dr. Albain?

1 DR. ALBAIN: I think that we've heard data  
2 many of us that were on ODAC heard when we  
3 recommended approval with these pivotal trials the  
4 data has not changed. Its' just a different way of  
5 looking at it and also points out how toxic just  
6 simple 5-FU can be as used in this country in many  
7 settings still without the addition of CPT-11.

8 DR. NERENSTONE: Dr. George?

9 MR. GEORGE: On the newer studies the  
10 ones, the group studies we don't have the follow up  
11 yet either for enough follow up to know the longer  
12 term results. That was influence with me. So I  
13 think it's just the level of evidence doesn't raise  
14 -- it's not to the point to remove something from a  
15 label based on this. That's my take.

16 DR. NERENSTONE: I want to echo those  
17 sentiments. I'm not sure, Dr. Temple, perhaps you  
18 realize how much of a big deal it is to go from a  
19 bolus to an infusional set up. Yes, there are  
20 large institutions which have continued to use  
21 infusional but out in the community it's very hard,  
22 not because the doctors don't accept it, because  
23 the patients don't accept it. I think you're  
24 trying to fix something that isn't broke. So I  
25 think you have to be careful and I think the weight

1 of evidence has really had to be a preponderance to  
2 raise our concerns that there is such a safety  
3 issue that we need to really reanalyze, and I think  
4 the question is really not going to be the  
5 Camptosar but reanalyze the leucovorin 5-FU data  
6 which you know is a morass to begin with. But it  
7 hasn't -- this data hasn't raised that level for me  
8 at least.

9 DR. TEMPLE: But the question really is  
10 about the fluorouracil, leucovorin, not the  
11 Camptosar at all. This question doesn't go to the  
12 CPT-11. But what I hear you generally saying is  
13 that there's a hypothesis there that some of the  
14 trials suggest a greater early mortality. If you  
15 really believed it was true, you'd be nervous but  
16 you don't think the case is made yet.

17 DR. NERENSTONE: Dr. Lippman?

18 DR. LIPPMAN: I think you said exactly  
19 what I was going to say because the way you phrased  
20 the question is tell us why you don't think that  
21 the bolus is more toxic. That's a hard question to  
22 answer. I personally believe it is. Based on all  
23 the data that I've seen I would think that the  
24 higher therapeutic index in terms of benefit and  
25 toxicity would be with the continuous infusion but

1 as Dr. Sledge mentioned we just don't have the data  
2 here in a head-to-head comparison. So in my view  
3 it hasn't risen to the point of making a change.

4 DR. TEMPLE: Would you, if you were asked,  
5 be urging cooperative groups or some other body to  
6 actually do a head-to-head on CPT-11 given with  
7 various regimens? Would anybody do that? Is it  
8 enough of a hypothesis so that we should be urging  
9 anybody to do it?

10 DR. NERENSTONE: That would have to be a  
11 very large trial because you're talking about a  
12 toxicity reduction trial. So you're talking about  
13 tying up a lot of resources for a lot of time  
14 without any thought that you're going to move  
15 treatment of metastatic colon cancer forward.

16 DR. TEMPLE: Okay, but if the difference  
17 were real, if the difference in the two  
18 registration studies were real, a five percent  
19 difference in early mortality, you'd be worried  
20 about that, if you believed it, right?

21 DR. NERENSTONE: Dr. Blayney?

22 DR. BLAYNEY: But I think the N9741 has an  
23 arm that does not have 5-FU/leucovorin in it. It's  
24 as I read it CPT-11, oxaliplatin. If that is  
25 useful and hope we be able to move way from 5-

1 FU/leucovorin and maybe generate some momentum and  
2 get over the ethical hurdle of removing 5-  
3 FU/leucovorin from our treatment.

4 DR. TEMPLE: But if we're saying that  
5 suggests you think that the higher levels of early  
6 mortality probably do have to do with the  
7 fluorouracil, leucovorin and the regimen it's given  
8 in, which is why you want to get away from it.  
9 That seems reasonable but...

10 DR. BLAYNEY: I think one of the reasons  
11 to get away with it is the data is so muddy and in  
12 an era of modern clinical trials we should be able  
13 to answer those questions but right now I would  
14 think our ethical hurdle is to removing 5-  
15 FU/leucovorin because it has been used for so long.

16 DR. NERENSTONE: Dr. Lippman?

17 DR. LIPPMAN: This reminds me in some way  
18 of -- this is what I view a classic study of  
19 lymphoma, large cell lymphoma with CHOP versus the  
20 third and fourth generations, there was a time  
21 where if you used CHOP it would have been  
22 unethical, you would have lost lawsuits because it  
23 was felt to be inferior to these newer third and  
24 fourth generation regimens. It just points out  
25 that it's hard to go back and ask these important

1 questions. We'd like to think and take sort of a  
2 self-fulfilling prophecy that we're making advances  
3 and we don't want to go back. So I don't know if  
4 it's practical, this disease, to ask that question  
5 but I think it's a very valid hypothesis that I  
6 think would be useful to answer in the 5-FU  
7 question.

8 DR. NERENSTONE: Dr. Grem?

9 DR. GREM: Let's not forget that the North  
10 American trial that was done, the CPT-11 by itself  
11 was maybe -- it was no better than 5-FU/leucovorin,  
12 may have been a little bit worse and it was clear  
13 that it was the combination of CPT-11, 5-  
14 FU/leucovorin that led to the improvement in  
15 survival. So I don't think you can just say let's  
16 get away from it because that implies that there is  
17 at least some clinical synergism or clinical  
18 benefit from the combination. So right now what  
19 we're talking about before us is really changing  
20 the label and the indications for the combination.  
21 I don't know that you can single out one of the  
22 drugs alone.

23 DR. TEMPLE: The striking thing about the  
24 registration trial is that the mortality seems to  
25 go, of course, it's different studies, different

1 environments and all that, but it doesn't seem to  
2 have much to do with whether there is CPT-11 added  
3 or not, it seems to be the same in the two  
4 treatments whether or not the CPT-11 is there and  
5 the CPT-11 then adds survival. So it at least is  
6 compatible with the idea that one fluorouracil  
7 regimen is more toxic. But what I hear -- that  
8 discussion was very helpful. I think it answers  
9 the question I posed. You think for various  
10 reasons the cross study comparisons aren't reliable  
11 enough to take an action on and there are major  
12 inconveniences associated with that action if it's  
13 not well supported.

14 DR. NERENSTONE: Dr. Temple, do you take  
15 any solace in the fact that, although it's a very  
16 unscientific review of non-protocol treated  
17 patients the mortality was not worse, in fact, it  
18 looked like the trend was less, with the  
19 implication that we worry about more mortality as  
20 our treatments are disseminated through the  
21 community and that does not look like that's  
22 happening but, in fact, that with good physician  
23 education that maybe paying more attention to the  
24 preventable mortality with physician education we  
25 could even get that mortality down below what we've

1 seen in the trials, and is that reassuring?

2 DR. TEMPLE: Yes, it is, although it  
3 raises the question that Steve raised. Are they  
4 now getting you down below the regimen that worked?  
5 Again, I take reassurance from the fact that CPT-11  
6 seems to work whatever you add it to, which is sort  
7 of good, but then you don't know whether you're  
8 losing effectiveness of fluorouracil, leucovorin by  
9 changing the regimen. It sounds like it would be  
10 extremely hard to get anybody interested in finding  
11 out.

12 DR. NERENSTONE: If there are no more  
13 comments then let's vote. The first question, do  
14 we think that we should support removal of the  
15 currently approved bolus regimen from the Camptosar  
16 product label? We have to go around the room  
17 individually to record the vote. Dr. Redman, if  
18 you'd like to start?

19 DR. REDMAN: No.

20 DR. GREM: No.

21 MS. FORMAN: No.

22 DR. ALBAIN: No.

23 MR. GEORGE: No.

24 DR. BALDUCCI: No.

25 DR. LIPPMAN: No.

1 DR. EXTERMANN: No.

2 DR. SLEDGE: No.

3 DR. NERENSTONE: No.

4 DR. TAYLOR: No.

5 DR. KROOK: No.

6 DR. TAKIMOTO: No.

7 DR. CARPENTER: No.

8 DR. BLAYNEY: No.

9 DR. NERENSTONE: The result is 15 no, zero  
10 yes. Does the available evidence from the  
11 cooperative group in licensing trials support  
12 modification of the dose or schedule of the bolus  
13 IFL regimen? Discussion?

14 DR. EXTERMANN: I think there is a piece  
15 of data that is available but that we couldn't get  
16 which is what happens to the performance 2  
17 patients.

18 DR. NERENSTONE: Do you want to repeat  
19 that, Dr. Extermann?

20 DR. EXTERMANN: Yes. There is a piece of  
21 information that is available in the data but that  
22 we didn't get in detail is what happened to the  
23 dose with which we treated the performance two  
24 patients that we -- because the question is whether  
25 we recommend these patients to be treated initially

1 with the lower dose or not, for example. I think  
2 it's an important question. Should we exclude  
3 them? Should we treat them at the lower initial  
4 dose or should we just leave it to the judgement of  
5 the clinician?

6 DR. NERENSTONE: Dr. Albain?

7 DR. ALBAIN: Yes. Madam Chair, I was  
8 going to ask if we could perhaps separate out two  
9 different issues here. One is the dose, the  
10 starting dose issue. Then the second is dose  
11 modifications for toxicity, although that's in the  
12 label question three. But I think we've been  
13 mixing that discussion a bit and I would feel very  
14 strongly that we have not heard evidence to justify  
15 a recommendation in the label to lower the starting  
16 dose in the broad population. The PS 2 group is  
17 another group as she's just pointed out. I think  
18 that there are different ways we can discuss this  
19 question and how to vote would depend on which dose  
20 issue you're raising.

21 DR. NERENSTONE: I would interpret this as  
22 saying a dose modification for the starting dose.  
23 Do we think that we should be telling on the  
24 product label that the dose should be changed from  
25 what was originally FDA approved at the beginning,

1 so starting dose?

2 DR. PAZDUR: Let's ask both questions,  
3 because I think Kathy brought it up and I think  
4 when we wrote that question we had two things in  
5 mind. So let's ask the starting dose first and  
6 then a question about dose modification so there's  
7 really two separate questions.

8 DR. NERENSTONE: So let's just keep it now  
9 right now for starting dose. Dr. Lippman?

10 DR. LIPPMAN: I'd just like to underscore  
11 what Dr. Extermann said. We've had a lot of mixing  
12 of PS 2 and trying to hypothesize what, in fact,  
13 happened to those patients. Based on what we were  
14 presented I think I would leave that out. I have  
15 strong feelings about the PS 2 issue. If I had  
16 more information on the PS 2 and dose we could  
17 handle that question, but at this point I'm looking  
18 at those as very different issues.

19 DR. NERENSTONE: Further discussion? So  
20 the question is should we change the starting dose  
21 and schedule of the bolus IFL regimen? Dr. Redman,  
22 you did such a good job, would you start?

23 DR. REDMAN: No.

24 DR. GREM: If you're referring to all  
25 patients across the board, the answer -- my vote

1 would be no.

2 MS. FORMAN: I wanted to add that caveat  
3 too. It's no but I think later on we may address  
4 it as to how it's labeled.

5 DR. ALBAIN: No.

6 MR. GEORGE: No.

7 DR. BALDUCCI: No.

8 DR. LIPPMAN: No.

9 DR. EXTERMANN: Again with the same caveat  
10 as a general no, but reserving my opinion on how it  
11 should be labeled.

12 DR. SLEDGE: No.

13 DR. NERENSTONE: No.

14 DR. TAYLOR: No.

15 DR. KROOK: No.

16 DR. TAKIMOTO: No.

17 DR. CARPENTER: No.

18 DR. BLAYNEY: No.

19 DR. NERENSTONE: Fifteen no, zero yes.

20 DR. PAZDUR: With the caveat under  
21 consideration the fact that some people had  
22 reservations about the fate of the performance  
23 status 2 patients. Would people recommend a  
24 reduction in a subgroup, for example, performance  
25 status 2 patients even with a starting dose, even

1 without any clinical trial information  
2 prospectively identified, prospectively performed?

3 DR. NERENSTONE: Any discussion? I'm  
4 going to weigh in for a minute? I think that there  
5 I feel that you should not tie the clinician's  
6 hands. I think that what perhaps what we should do  
7 is put the warning in the discussion about untoward  
8 toxicity has been associated with poor performance  
9 status patients and leave it up to the  
10 discrimination of the treating physician as to the  
11 appropriate dose. I think that I am very concerned  
12 that efficacy is going to be compromised and I  
13 think as you said we just don't have the data.  
14 There are not that many patients. But certainly  
15 again physician awareness that performance status  
16 could be a problem need to be advised.

17 DR. PAZDUR: But I think that's especially  
18 important because as was pointed out before  
19 performance status can be a rather moving target  
20 here. What your performance status 2 is may be my  
21 3, might be my 1, etcetera. So I think that there  
22 can be a high degree of subjectivity even in the  
23 data we collect with regards to this.

24 DR. NERENSTONE: Dr. George?

25 MR. GEORGE: You scooped some of what I

1 was going to say that I'd just repeat again that  
2 any change like that starting dose that we've  
3 talked about in particular subgroups can very well  
4 affect the efficacy in ways we're not going to  
5 know. So it seems very risky to put that kind of  
6 change in. However, I do think it's a good -- the  
7 idea of education on the safety issues and some  
8 kind of statement in there about that is one I  
9 would support.

10 DR. NERENSTONE: Dr. Grem?

11 DR. GREM: Just in terms I fully agree  
12 that you don't want to mandate that all patients  
13 with performance status since that's a subjective  
14 determination should have to be receiving a lower  
15 dose but I think that it might be important as you  
16 were suggesting that in the sort of disclaimers or  
17 information about the warnings that not only are  
18 they at increased risk for toxicity but they're  
19 less likely to benefit. Then it would be at the  
20 discretion of the treating physician and the  
21 patient to take that into account. That might be  
22 one compromise.

23 DR. NERENSTONE: Dr. Extermann?

24 DR. EXTERMANN: Yes, I would like to  
25 branch on what you said that we judge the

1 performance status quite subjectively. There is  
2 one unconscious thing that we've mistaken to  
3 performance status which is also the other diseases  
4 the patients had and that hasn't been analyzed at  
5 all. The other diseases the patient has, the  
6 comorbidities they have, if you have somebody with  
7 five diseases, you are more likely to label that  
8 patient a performance two even if they do the same  
9 thing as somebody who has no other diseases. We  
10 need to separate these issues and analyze them.

11 DR. NERENSTONE: Dr. Lippman?

12 DR. LIPPMAN: The reason it's hard to  
13 answer the question of reducing the dose is  
14 although it may make some degree of common sense,  
15 we don't know how the PS 2 patients did at the  
16 lower dose. It could be that all sort of benefit  
17 toxicity decrease substantially. Survival went  
18 down, toxicity went down a little bit. It's just a  
19 different group. Although there is subjectivity in  
20 the classification it was very consistent, and I  
21 would maintain a lot more objective or consistent  
22 than data we heard yesterday between 2 plus and 1  
23 plus. So I think that I'm very concerned about the  
24 subgroup. I don't know that we remove it from the  
25 label but I think it really should be featured in a

1 very strong recommendation. Then physicians can  
2 interpret whether that means they want to reduce  
3 the dose or not. We just don't know whether that's  
4 going to benefit patients with PS 2.

5 DR. NERENSTONE: Dr. Balducci?

6 DR. BALDUCCI: Mine might be more an  
7 advocate type of talk but I've practiced oncology  
8 for 30 years, the Saltz regimen is the first time  
9 that really has allowed us in the United States at  
10 least to see complete responses in this disease and  
11 prolonged responses in this disease. Although it  
12 is true that patient low function, 2 or more added  
13 increased risk is also true that without treatment  
14 these patients are at the very, very -- have a very  
15 initial mortality, not due to the treatment but due  
16 to the cancer and it's true that at least I have  
17 seen some of these patients that were more than  
18 dead than alive and now we are discussing whether  
19 we should resect their liver metastases or not. So  
20 I think that we have to keep the things in really  
21 in the perspective what is killing the patients is  
22 not the chemotherapy, it's the cancer. I would  
23 really be extremely reluctant and I feel extremely  
24 strongly to guide the clinicians' and the patients'  
25 decisions with the label recommendation. I think

1 that things should be discussed with the patient  
2 but the patient should have that privilege no  
3 matter what his or her performance status is to  
4 decide to forego few weeks of disease for the hope  
5 to get a stable response so that is a small hope.

6 DR. NERENSTONE: Mr. Ohye?

7 MR. OHYE: I'd just like to state that you  
8 have to be reassured by the data that you have from  
9 the community practice in terms of the safety of  
10 the product. I think that underscores how  
11 responsible Pharmacia has been in terms of  
12 educating the physicians.

13 DR. NERENSTONE: Dr. Lippman?

14 DR. LIPPMAN: Just to clarify about the  
15 regimen producing the higher CR rate and response  
16 duration and so on and clearly it's an advance but  
17 again we're talking about the PS 2 patients, and  
18 this small data subset but, in fact, if you look  
19 at, for instance, time to progression was actually  
20 in the PS 2 patients actually slightly higher in  
21 the 5-FU/leucovorin alone. So I don't feel that  
22 we're depriving those patients of a life-changing  
23 regimen. I think it's really the better  
24 performance status patients.

25 DR. NERENSTONE: Dr. Krook?

1 DR. KROOK: In answer to Bob Temple's  
2 question, those physicians who understand what a  
3 performance status of 2 really is won't have a  
4 problem. Physicians who don't understand what a  
5 performance status 2 is are going to be in trouble  
6 no matter what. So the better you define what that  
7 is, the performance status 2 patients that we all  
8 call that, most of us may not treat at full dose.

9 DR. NERENSTONE: Do you want to vote?

10 DR. PAZDUR: No, I don't think so. Let's  
11 move on to the dose modification part of that  
12 question. Remember we were going to divide it up  
13 into two things?

14 DR. NERENSTONE: I thought that was what  
15 we were talking about. Does the available evidence  
16 from the cooperative group then support  
17 modification of -- why don't you state the question  
18 you want answered?

19 DR. PAZDUR: ...licensing trials to  
20 support modification of a dose modification.  
21 Basically what we're after is should there be a  
22 change in the dose modification of the current  
23 label? That leads us to question number two.

24 DR. NERENSTONE: So you really want us to  
25 go to question number two where it's addressed?

1 DR. PAZDUR: Right.

2 DR. NERENSTONE: That is the impact of  
3 modifications on the safety and efficacy of the  
4 bolus irinotecan and 5-FU/leucovorin regimen. The  
5 sponsor has proposed changes in the label to  
6 improve the safety of administration of the bolus  
7 IFL regimen that include recommendations for  
8 heightened supportive care, patient monitoring and  
9 limited dose modification. The changes are  
10 summarized in the table below. Now is that  
11 correct? This is what you want us to look at?

12 DR. PAZDUR: No, these are not the  
13 modifications. These are things that were  
14 submitted or modifications that were submitted at  
15 one time in writing to the agency but are more  
16 comprehensive rather listing of modifications. So  
17 we wanted to discuss them individually. So  
18 basically what I'd like to see is the dose  
19 modifications outlined that dose modifications on  
20 the next page, or page two where it says change  
21 label two, what people's opinions were regarding  
22 that.

23 DR. NERENSTONE: Okay. So the real  
24 question is, what do we think about the proposed  
25 label changes?

1 DR. PAZDUR: Correct. Even though these  
2 are not currently Pharmacia Upjohn.

3 DR. NERENSTONE: Right. Whoever proposed  
4 it. You're proposing them?

5 DR. PAZDUR: We're proposing them.  
6 Somebody.

7 DR. NERENSTONE: Comments from the group?

8 DR. CARPENTER: Why don't we take these in  
9 groups so that we're --

10 DR. PAZDUR: For example, dose  
11 modification --

12 DR. NERENSTONE: We'll start with dose  
13 modification. Dr. Takimoto?

14 DR. TAKIMOTO: Just to reiterate, the dose  
15 modifications for diarrhea my concern was, as  
16 proposed here for patients having grade 2 diarrhea  
17 that are actually within a cycle you would actually  
18 dose reduce but continue to treat. You look at  
19 sort of the third recommendation here, saying  
20 patients must be diarrhea free for 24 hours prior  
21 to re-treatment. I think actually in practice  
22 that's what is being done. That's what is  
23 recommended to be done when you're just giving 5-  
24 FU/leucovorin on a weekly schedule and I think that  
25 would be the sort of best clinical practice. I

1 would certainly support having that as a formal  
2 recommendation in the label.

3 DR. NERENSTONE: Other comments?

4 DR. PAZDUR: Do you want to vote on that  
5 one?

6 DR. NERENSTONE: That's fine.

7 DR. GREM: But it sounds like there's  
8 three separate dose modifications and I'm not sure  
9 --

10 DR. PAZDUR: We'll get to those other ones  
11 then.

12 DR. NERENSTONE: No. Go ahead, Dr. Grem.  
13 Go ahead.

14 DR. GREM: Within the management of  
15 diarrhea I think there's three different  
16 recommendations and I think the committee members  
17 may have different feelings about each of those  
18 modifications. So they might have to be voted on  
19 separately.

20 DR. PAZDUR: That's what I'm suggesting  
21 but Chris already mentioned the point about have to  
22 be diarrhea free for 24 hours is already  
23 incorporated in many people's practices. What do  
24 people think of officially incorporating that into  
25 the label?

1 DR. NERENSTONE: I would agree that that's  
2 best patient management and I would strongly urge  
3 that we do that. Dr. Carpenter?

4 DR. CARPENTER: I support the same.

5 DR. NERENSTONE: Do you want to vote?

6 DR. CARPENTER: Yes.

7 DR. NERENSTONE: So all those in favor  
8 that the package insert, we're going to go around  
9 again, that the patients must be diarrhea free for  
10 24 hours prior to re-treatment.

11 DR. TEMPLE: Can I just ask, Karen, if you  
12 take a hand vote and it's unanimous, is that good  
13 enough? You actually have to --

14 MS. SOMERS: Are we sure --

15 DR. TEMPLE: No, but you can find that out  
16 in about three seconds.

17 MS. SOMERS: We have to have every person  
18 vote in the record. So I guess if it's unanimous  
19 we can -- if it's not unanimous we can go back.

20 DR. TEMPLE: Yes, that's what I was  
21 thinking.

22 DR. GREM: One question I have then is  
23 that so if a person had grade 3 diarrhea and you  
24 pulled and they're diarrhea free now do you still  
25 continue at the same dose next week? So that's

1 sort of a separate --

2 DR. NERENSTONE: I think this is, at a  
3 minimum they must be diarrhea-free for 24 hours and  
4 then there may be other dose reductions but the  
5 bottom line is that you have to be diarrhea free  
6 for 24 hours before you get the next dose of  
7 whatever. So the first question is --

8 DR. LIPPMAN: Stacy, can I just clarify  
9 one thing? So on the other bullets where it says  
10 hold we're really saying we're substituting 24  
11 hours of diarrhea free? No?

12 DR. PAZDUR: We're going to get to those  
13 later. Let's just take bullet number three, vote  
14 on it.

15 DR. NERENSTONE: Dr. Redman?

16 DR. REDMAN: This is just bullet number  
17 three?

18 DR. PAZDUR: Correct.

19 DR. NERENSTONE: Correct. Bullet number  
20 three. Patients must be diarrhea free for 24 hours  
21 prior to re-treatment. Are just going to --

22 DR. PAZDUR: Just do a hand vote.

23 DR. NERENSTONE: One other question?

24 DR. GOLDBERG: Can I make a comment?

25 DR. NERENSTONE: Brief comment.

1 DR. GOLDBERG: The only point I would make  
2 is that many of these patients have part or all of  
3 their colon gone and many of them have diarrhea as  
4 a baseline and, therefore, it would probably be  
5 more practical in the management of these patients  
6 to say return to baseline status.

7 DR. PAZDUR: We'll get to the minutia here  
8 but just the general concept here.

9 DR. GOLDBERG: That's a real question.

10 DR. NERENSTONE: It is. Right. I'm  
11 willing to amend your recommendations because I  
12 think that it's baseline stools per day. So the  
13 question is do we support changing the label that  
14 they must be diarrhea free for 24 hours prior to  
15 re-treatment or return to their baseline stool  
16 function? Everyone in favor, please raise their  
17 hand.

18 [Show of hands.]

19 DR. NERENSTONE: Okay, that is unanimous.  
20 For grade 2 diarrhea neutropenia or abdominal  
21 cramping hold and then dose reduce one level intra-  
22 cycle, then resume treatment at original dose  
23 level. Would you clarify that a little bit? That  
24 means that if they get grade 2 diarrhea you hold  
25 the next week and then you continue to do your four

1 -- do you make up the four treatments or do you  
2 skip that week? You're going to have to clarify it  
3 a little bit.

4 DR. GRIEBEL: That's actually the way --  
5 the way the label is currently written you treat  
6 through grade 2 diarrhea but you dose reduce one  
7 dose level and then when you get to the next  
8 treatment cycle you bump back up to the original  
9 dose level that you started with in the original  
10 cycle. What's different here was actually about  
11 three things. One was the hold issue that we just  
12 voted on and then once you've held until you get to  
13 no diarrhea you resume at one dose level reduction  
14 and then when you get to the next treatment cycle  
15 then you bump back up to the original dose. The  
16 third subtle change is just adding in abdominal  
17 cramping as the same thing as having diarrhea.

18 DR. NERENSTONE: Comments from the group?

19 DR. TEMPLE: I think the only change is to  
20 add the hold from the current label, isn't it?  
21 That's the only difference, you hold until they've  
22 gone 24 hours being better.

23 DR. GRIEBEL: And the abdominal cramping.

24 DR. NERENSTONE: Dr. Lippman?

25 DR. LIPPMAN: That was the point I was

1 making before and that's why I brought it up is are  
2 we now by going on three, which brought it on, that  
3 when hold is in here it means 24 hours at baseline.

4 DR. TEMPLE: So the question here is -- I  
5 mean, three sort of already takes care of that  
6 unless you wanted to make an additional change.  
7 It's the same recommendation with the hold  
8 introduced. Right?

9 DR. GRIEBEL: Correct.

10 DR. NERENSTONE: Would you remind people  
11 exactly what Grade 2 diarrhea is? Do you have  
12 that? Because I want to make sure everybody  
13 understands the exact toxicity because obviously  
14 that's what we're concerned about. We're concerned  
15 about people getting unduly dehydrated because of  
16 the diarrhea.

17 DR. TAKIMOTO: By the common toxicity  
18 criteria, the NCI, the version two, it's 4 to 6  
19 bowel movements above baseline is grade 2.

20 DR. CHICO: That's correct.

21 DR. GREM: That can be while they're  
22 receiving more modal of whatever.

23 DR. CHICO: That's one thing that's a  
24 little bit different about the current situation  
25 than it was back in the days of 5-FU/leucovorin

1 alone where they didn't use aggressive  
2 antidiarrheal therapy.

3 DR. NERENSTONE: I guess my question to  
4 people who use this a lot, or have used it a lot on  
5 treatment what is the likelihood if you have a  
6 grade 2 or 3 diarrhea and you reduce the dose but  
7 you don't run into that same problem where you re-  
8 escalate?

9 DR. GREM: I think the only reason that  
10 that is sometimes put in is it's the attribution  
11 that it's treatment-related diarrhea because the  
12 patient may have had some kind of meal and had a  
13 little bit increase and it qualifies as grade 2 but  
14 you're not exactly sure that it is treatment  
15 related but the prudent thing to do within a cycle  
16 is to hold.

17 DR. NERENSTONE: Other comments? Dr.  
18 Lippman?

19 DR. LIPPMAN: But four to six bowel  
20 movements above baseline would be quite a meal if  
21 that was the case. I mean that really suggests  
22 something's going on.

23 DR. NERENSTONE: Dr. Redman?

24 DR. REDMAN: I have a similar question  
25 that you have and I don't know if anybody's had

1 more experience in using this. When you encounter  
2 grade 2 intra-cycle those reduce and then start the  
3 next cycle at the same dose again does the diarrhea  
4 get less for the same dose of treatment? The sense  
5 is that it would either be the same or worse with  
6 repetitive dosing.

7 DR. NERENSTONE: Dr. Sledge?

8 DR. SLEDGE: It strikes me we're doing a  
9 fair amount of micromanipulation based on zero  
10 data. Is that really what you want from us?

11 DR. PAZDUR: No.

12 DR. NERENSTONE: Dr. Carpenter?

13 DR. CARPENTER: Could we just suggest  
14 something generic instead of a bunch of specific --

15 DR. PAZDUR: Yes, why don't we.

16 DR. CARPENTER: -- unvalidated dose  
17 schedule modifications but that dose reduction  
18 should be that if you hold for diarrhea that the  
19 physician should consider dose reduction and leave  
20 the specifics to judgement?

21 DR. PAZDUR: Why don't we do this? Let me  
22 offer a suggestion. Do you believe that some dose  
23 modifications are in order, correct? We will meet  
24 with the company and discuss this internally with  
25 the company, the specifics so we don't get tied up

1 with the minutia here in the actual management of a  
2 specific patient. So let's go on to the supportive  
3 care aspects and go through them relatively quickly  
4 if we could because I have other questions and I  
5 know we have to move on.

6 DR. NERENSTONE: Right. The supportive  
7 care issue  
8 fluoroquinolone, 7-day course for diarrhea  
9 persisting greater than 24 hours on the loperamide,  
10 fever accompanying the diarrhea and see less than  
11 500 with or without diarrhea or fever. You want  
12 them all as a bundle or you want each one?

13 DR. PAZDUR: All as a bundle.

14 DR. NERENSTONE: Okay. GCSF for greater  
15 than --

16 DR. PAZDUR: In fact, why don't we do  
17 this, why don't we just discuss this rather than  
18 voting on it because here again we'll come back to  
19 the company but let's here your pros and cons,  
20 especially with some of the more perhaps  
21 controversial things like, for example, using GCSF  
22 for grade 2 neutropenia --

23 DR. NERENSTONE: Okay. The others are  
24 antibiotic support with severe diarrhea if they  
25 develop ileus fever, severe neutropenia or

1 hospitalization for IV antibiotics for persistent  
2 diarrhea or fever or ileus despite fluoroquinolone.

3 DR. PAZDUR: So a discussion basically.

4 DR. EXTERMANN: I have a discussion point  
5 about the recommendation of putting GCSF for grade  
6 2 neutropenia in a weekly regimen. There was a  
7 study published in the JNCI a few years ago about  
8 giving GCSF concomitantly with chemotherapy and it  
9 was 5-FU and it was increasing the rate of  
10 neutropenia. The intent was to decrease mucositis.  
11 So I think the concomitant use of GCSF and 5-FU is  
12 not to be recommended because you increase  
13 neutropenia by stimulating perforating cells that  
14 can be hit with chemotherapy.

15 DR. NERENSTONE: Other comments? I guess  
16 I feel this is also getting into micromanagement  
17 but we don't do in any other kinds of things.  
18 Again I think a warning or a discussion of concerns  
19 about the combination of neutropenia with diarrhea  
20 even in the absence of fever would suggest that  
21 antibiotics might be instituted. I agree that GCSF  
22 automatically given I think is a bad idea and  
23 certainly not what the ASCO guidelines recommend.  
24 Hospitalization of patients, it seems like a little  
25 redundant and a little insulting to tell a patient

1 they need to hospitalize patients who are this ill.  
2 They need to be hospitalized, I'm not sure we need  
3 to put it in our guidelines. Dr. Balducci?

4 DR. BALDUCCI: About hospitalization --  
5 and again right now I'm talking about as geriatric  
6 oncology, I really would like personally to see a  
7 mention somewhere that patients should be  
8 hospitalized according to the physician judgement.  
9 The reason why I say that is because I think there  
10 has been a trend in the last few years due to  
11 managed care due to DRGs to hospitalize less and  
12 less. I think that has hurt enormously especially  
13 older individuals who are much less resistant to  
14 dehydration than younger individuals are. So I  
15 really would like to have something that justifies,  
16 something that physicians want to say this is part  
17 of the directions so that they won't have to fight  
18 with the managed care or with case managers and  
19 with all the people who are in between because I  
20 really think that this is one of the reason maybe  
21 why we have seen an excess of death. I have a very  
22 strong feeling about that obviously.

23 DR. NERENSTONE: Can we do that with  
24 suggestions in the warning box rather than making  
25 it a requirement in the drug label?

1 DR. PAZDUR: Here again, these are some of  
2 the specifics we'll discuss with the company.

3 DR. TEMPLE: It sounds like an overall  
4 recommendation for handling these things  
5 aggressively early.

6 DR. BLAYNEY: May I?

7 DR. NERENSTONE: Dr. Blayney?

8 DR. BLAYNEY: In southern California we  
9 have a very high -- we've been dealing with managed  
10 care for a long time and I think that that's, with  
11 all due respect, that's not an issue. If people  
12 are sick, they get hospitalized. But I don't -- I  
13 would worry about mandating hospitalization such  
14 that medical legally some might be liable if a  
15 patient wasn't hospitalized for their own reasons  
16 or could be hydrated at home but it certainly  
17 should be aggressive fluid resuscitation is a  
18 phrase I would encourage you to use in whatever  
19 setting.

20 DR. NERENSTONE: For the next -- Dr.  
21 Lippman?

22 DR. LIPPMAN: I think since in this case  
23 we don't have specific trial data to address these  
24 issues, I think again we run the risk of telling  
25 doctors how to use clinical judgement and practice

1 medicine. So I think that your point, Bob, of just  
2 that these people may need early and aggressive  
3 supportive care may be enough without any  
4 specifics. In other words, if we had trial data on  
5 seven days of fluoroquinolone, that would be  
6 different in this setting but we don't in this  
7 setting.

8 DR. NERENSTONE: Monitoring weekly  
9 assessment during the --

10 DR. PAZDUR: Here again, these are  
11 relatively of these specific things. I guess if  
12 these were adapted we at the FDA in our internal  
13 discussions have been looking at these vis-a-vis  
14 what's said about changes in the schedule and  
15 altering the efficacy would be looked at as  
16 relatively minor changes and perhaps not  
17 constituting a major problem with the efficacy of  
18 the regimen. I just would like to get a vote on  
19 this. If we look at minor dose modifications here,  
20 for example, as proposed here as well as the  
21 supportive care issue. How do people -- hold till  
22 they're better, etcetera, I assume people -- let's  
23 put that to a vote perhaps that if people would  
24 assume that that would impact on the efficacy of  
25 the regimen.

1 DR. NERENSTONE: The dose modifications as  
2 we discussed, which is just holding the dose and  
3 then as written?

4 DR. PAZDUR: Correct.

5 DR. NERENSTONE: Do you want to give the  
6 exact wording of the question?

7 DR. CHICO: The bolus IFL regimen is  
8 associated with a modest survival advantage of  
9 approximately two months compared to a five-day  
10 bolus 5-FU/leucovorin regimen. The sponsor's  
11 proposed labeling change is likely to affect the  
12 efficacy of the bolus IFL regimen.

13 DR. NERENSTONE: You want a vote on that?

14 DR. PAZDUR: Correct.

15 DR. NERENSTONE: Any further discussion?  
16 Dr. Albain?

17 DR. ALBAIN: Yes, it could affect the  
18 efficacy favorably if in fact you limit toxic  
19 deaths so do you mean an adverse effect?

20 DR. PAZDUR: Adverse effect.

21 DR. NERENSTONE: Dr. Sledge?

22 DR. SLEDGE: This question is asking us to  
23 read the mind of God. I mean we don't know.

24 DR. PAZDUR: Here again, it's a matter of  
25 -- no one knows obviously until there's a

1 randomized study that is done but we have to make  
2 some clinical judgement here if we do make changes  
3 in a label that are minor to address safety issues.  
4 How does one see that ultimately affecting the  
5 efficacy of the regimen? Here again, it's a  
6 clinical judgement question.

7 DR. SLEDGE: And because it's a clinical  
8 judgment question it gets down to how much drug can  
9 a patient tolerate. It doesn't matter if in a  
10 thousand patient study you improve survival by two  
11 months if you kill the individual patient. So I  
12 don't even think it's appropriate to try and guess  
13 the answer to this. I mean if you're a practicing  
14 physician you deal with the individual patient.

15 DR. NERENSTONE: Dr. Lippman?

16 DR. LIPPMAN: I hate to disagree, but of  
17 all the kinds of questions we get I feel very  
18 comfortable answering this that they're very  
19 unlikely based on what we know about biology, the  
20 kinds of modifications we're talking about,  
21 preclinical systems. I think it's extremely  
22 unlikely to affect efficacy.

23 DR. NERENSTONE: Dr. Temple?

24 DR. TEMPLE: I guess the thing that  
25 strikes me is that variations of this kind are

1 built into all of the trials anyway. People are  
2 constantly making judgements about how well you  
3 have to be before you resume therapy. So one  
4 question you could ask, admittedly it's impossible  
5 to know as we just said is do these kinds of  
6 changes seem large compared to the kinds of  
7 differences that were already inherent in the  
8 trials. What I guess I hear is not too.

9 DR. NERENSTONE: Do you want to vote on  
10 the question or did you get the sense of the  
11 committee?

12 DR. PAZDUR: I think we get the sense.  
13 And I think really for question number E we already  
14 about dose modifications for proposed ongoing  
15 trials, this was already discussed to our  
16 satisfaction. So we're done.

17 DR. NERENSTONE: Okay, so we're done. I'd  
18 like to thank everyone. We will adjourn now. I  
19 would like us back to start at 1:00 promptly.  
20 There are a lot of concerns about committee members  
21 who have to catch flights so 1:00.

22 [Whereupon, at 12:06 p.m., the meeting was  
23 recessed, to reconvene at 1:00 p.m., this same  
24 day.]

AFTERNOON SESSION

[1:07 p.m.]

**Call to Order and Opening Remarks**

DR. NERENSTONE: Thank you. I'd like to get started for this afternoon's session. First we'd like to have an introduction of the committee because there are new audience for us. So Mr. Ohye, if you'd start again?

MR. OHYE: George Ohye, nominee for industry representative.

DR. REDMAN: Bruce Redman, medical oncologist, University of Michigan Cancer Center.

DR. FINE: Howard Fine, neuro-oncology branch, NIH.

MR. GEORGE: Stephen George, biostatistics, Duke University Medical Center.

DR. BUCKNER: Jan Buckner, medical oncology, Mayo Clinic.

DR. LIPPMAN: Scott Lippman, M.D., Anderson Cancer Center.

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

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

DR. NERENSTONE: Stacy Nerenstone, medical

1 oncology, Hartford Hospital, Hartford.

2 MS. SOMERS: Karen Somers, executive  
3 secretary to the committee, FDA.

4 DR. TAYLOR: Sarah Taylor, medical  
5 oncology, University of Kansas, Kansas City.

6 DR. KELSEN: David Kelsen, medical  
7 oncology, Sloan-Kettering, New York.

8 DR. BRAWLEY: Otis Brawley, medical  
9 oncologist, Emory University in Atlanta.

10 MR. LUSTIG: Craig Lustig, I'm a brain  
11 tumor survival and here as the patient rep.

12 DR. CARPENTER: John Carpenter, medical  
13 oncologist, University of Alabama at Birmingham.

14 DR. BLAYNEY: Doug Blayney, medical  
15 oncologist, Wilshire Oncology Medical Group,  
16 Pasadena.

17 DR. LI: Ning Li, biometrics, FDA.

18 DR. SHAPIRO: Alla Shapiro, medical  
19 reviewer, FDA.

20 DR. MARTIN: Alison Martin, medical  
21 oncology, FDA.

22 DR. PAZDUR: Richard Pazdur, division  
23 director, FDA.

24 DR. TEMPLE: Bob Temple, office director,  
25 FDA.

1                   **Conflict of Interest Statement**

2                   MS. SOMERS: The following announcement  
3 addresses the issue of conflict of interest with  
4 respect to this meeting and is made a part of the  
5 record to preclude even the appearance of such as  
6 this meeting.

7                   Based on the submitted agenda and.  
8 information provided by the participants, the  
9 agency has determined that all reported interest in  
10 firms regulated by the Center for Drug Evaluation  
11 and Research present no potential for a conflict of  
12 interest at this meeting with the following  
13 exceptions. In accordance with 18 USC Section  
14 208(b)(3) full waivers have been granted to George  
15 Sledge, M.D. and Scott Lippman, M.D. A copy of  
16 these waiver statements may be obtained by  
17 submitting a written request to the agency's  
18 freedom of information office, Room 12A30 of the  
19 Parklawn Building.

20                   We would like to note for the record that  
21 George Ohye is participating in this meeting as an  
22 industry representative acting on behalf of  
23 regulated industry. As such he has not been  
24 screened for any conflict of interest. In the  
25 event that the discussions involve any other

1 products or firms not already on the agenda for  
2 which FDA participants have a financial interest,  
3 the participants are aware of the need to exclude  
4 themselves from such involvement and their  
5 exclusion will be noted for the record.

6 With respect to all other participants, we  
7 ask in the interest of fairness that they address  
8 any current or previous financial involvement with  
9 any firm whose product they may wish to comment  
10 upon.

11 Again, I would like to note for the record  
12 that our consumer representative Dr. Jody Pelusi  
13 had to cancel her participation in the meeting at  
14 the last minute and there was no time to replace  
15 her. We are, however, fortunate to have Craig  
16 Lustig as our patient representative to provide  
17 that point of view.

18 And again, please remember to talk into  
19 the microphones. Thank you.

20 DR. NERENSTONE: Now is the open public  
21 hearing portion of our meeting, our afternoon  
22 session. Is there anyone here who had requested or  
23 wants to request to speak?

24 [No response.]

25 DR. NERENSTONE: Okay, thank you.

1           Then I'd like to begin with Guilford  
2   Pharmaceuticals, the NDA 20-637/S016, Gliadel  
3   wafers indicated for use as a treatment to  
4   significantly prolong survival and maintain overall  
5   function, as measured by preservation of Karnofsky  
6   performance status and neurological function in  
7   patients with malignant glioma undergoing primary  
8   and/or recurrent surgical resection.

9           **Sponsor Presentation [Guilford Pharmaceuticals]**

10           MS. PELTIER: Good afternoon. My name is  
11   Louise Peltier. I'm senior director of regulatory  
12   affairs for Guilford Pharmaceuticals. On behalf of  
13   Guilford Pharmaceuticals, we are pleased to have  
14   this opportunity to present an additional  
15   indication for Gliadel wafer.

16           This approval was based upon the results  
17   obtained from three clinical studies. Gliadel  
18   wafer is currently approved by the FDA for use as  
19   an adjunct to surgery to prolong survival in  
20   patients with recurrent glioblastoma multiforme for  
21   whom surgical resection is indicated.

22           Study 8701, a 21-patient multicenter open  
23   label dose escalation trial, study 9115, a 40-  
24   patient multicenter open label Phase III trial, and  
25   study 8802, a 222-patient multicenter randomized

1 double-blind placebo controlled Phase III trial.  
2 Additionally, Gliadel was made available to 349  
3 patients with recurrent malignant glioma under a  
4 treatment protocol during the NDA review and  
5 approval process. This brings the total number of  
6 patients enrolled with recurrent malignant glioma  
7 to 632.

8 We have also completed three clinical  
9 trials with a total enrollment of 294 patients with  
10 newly diagnosed malignant glioma. Study 9003, a  
11 22-patient multicenter open label Phase I/II trial,  
12 study 0190, a 32-patient multicenter, randomized,  
13 double-blind, placebo-controlled Phase II trial,  
14 and study T-301, a 240-patient multicenter,  
15 randomized, double-blind, placebo-controlled Phase  
16 III trial. The total number of all patients  
17 enrolled in these six clinical trials and the  
18 treatment protocol in both recurrent surgery and  
19 newly diagnosed center is 926.

20 Since receiving approval in the U.S.  
21 Gliadel received marketing approvals in Canada for  
22 patients with newly diagnosed or recurrent  
23 malignant glioma, and in 23 countries for patients  
24 undergoing recurrent surgery. This afternoon we  
25 will present the results of a 240-patient Phase III

1 trial, T-301, supporting the proposed new  
2 indication for Gliadel wafer to include the  
3 treatment of patients with newly diagnosed  
4 malignant glioma.

5           The 0190 study was determined by FDA to  
6 have many of the features of an adequate and well-  
7 controlled trial, but was not deemed large enough  
8 to support the labeling for newly diagnosed  
9 patients at the time of our original NDA  
10 submission. Study T-301 was conducted in response  
11 to FDA's request made at the time of the initial  
12 approval for Gliadel for a larger Phase III trial  
13 in the initial surgery setting. We believe study  
14 0190 provides supporting evidence for conclusions  
15 drawn from the T-301 study.

16           The proposed new indication for Gliadel  
17 wafer is for use as a treatment to significantly  
18 prolong and maintain overall function as measured  
19 by preservation of Karnofsky performance status and  
20 neurological function in patients with malignant  
21 glioma undergoing primary and/or recurrent surgical  
22 resection.

23           Our presentation will include a clinical  
24 overview of malignant glioma and the use of Gliadel  
25 wafer by Dr. Allan Hamilton, who is a professor and

1 chairman of the department of neurosurgery at the  
2 University of Arizona School of Medicine. Dr. Dana  
3 Hilt, vice president of clinical research at  
4 Guilford Pharmaceuticals will review the results of  
5 the previous Phase III trial of Gliadel wafer in  
6 primary malignant glioma and present the design of  
7 the Phase III T-301 trial. Dr. Steven Piantadosi,  
8 professor and director of oncology biostatistics at  
9 the Johns Hopkins University School of Medicine  
10 will review the statistical analytical methods and  
11 the statistical issues that have been raised. Dr.  
12 Dana Hilt will then complete the presentation with  
13 a summary of the efficacy and safety results from  
14 the Phase III T-301 trial.

15           Invited guests include Dr. Henry Brem,  
16 Harvey Cushing professor of neurosurgery and  
17 oncology, chairman, department of neurosurgery,  
18 Johns Hopkins University School of Medicine; Dr.  
19 Henry Friedman, professor and director, neuro-  
20 oncology, Duke University School of Medicine; and  
21 Dr. Janet Wittes, the president of Statistics  
22 Collaborative.

23           Additional representatives from Guilford  
24 including Dr. Craig Smith, chief executive officer,  
25 Dr. Ina Bortay, associate director biostatistics,

1 Dr. Valerie Riddle, VP, medical affairs, and Ms.  
2 Francesca Cook, VP, policy and reimbursement  
3 services.

4 At the end of our presentation Dr. Hilt  
5 will be happy to take any questions or refer them  
6 to our presenters or Guilford's invited guests. I  
7 would like to introduce our first speaker, Dr.  
8 Allan Hamilton, professor and chairman, department  
9 of neurosurgery, University of Arizona School of  
10 Medicine. Dr. Hamilton?

11 DR. HAMILTON: Thank you. I'm pleased to  
12 be here and to present an overview of primary  
13 malignant glioma and its treatment. There are  
14 approximately 16,500 patients diagnosed annually  
15 with this illness and the majority, approximately  
16 75 percent of these patients have glioblastoma  
17 multiforme. Patients with a malignant glioma have  
18 a very poor prognosis and approximately 13,000  
19 patients die from this disease each year.

20 Typically, patients present with headache,  
21 seizure, or a new neurologic deficit. The average  
22 age of onset is 55 to 60-years-old. The initial  
23 provisional diagnosis is made after an imaging  
24 study such as a CT or an MRI. While the surgeon  
25 may have a high index of suspicion that the patient

1 has a high grade malignant glioma, the tentative  
2 diagnosis of malignant glioma cannot be confirmed  
3 until pathologic examination has been completed.

4           At the time of initial craniotomy for  
5 tumor biopsy and resection a provisional pathologic  
6 diagnosis is made based on the intraoperative  
7 tissue sample that the neuropathologist examines by  
8 frozen tissue section of squash prep. This allows  
9 the pathologist to inform the surgeon that the  
10 patient likely has a malignant glioma. The exact  
11 histological diagnosis cannot be rendered until the  
12 final pathologic assessment has been completed  
13 which requires fixed tissue examination.  
14 Therefore, the neurosurgeon proceeds with a  
15 provisional diagnosis in the operating room.

16           The treatment that we can offer these  
17 patients is limited and is primarily palliative in  
18 nature. The standard treatment is primary surgical  
19 resection followed by radiotherapy. Complete  
20 resection of high grade tumors is, however,  
21 virtually impossible due to the infiltrative nature  
22 of the lesions. A high percentage of tumors recur  
23 locally within a two centimeter rim of the original  
24 resection site, mostly likely from local tumor  
25 nests of tumor cells that could not be resected.

1                   Radiation therapy after surgery is  
2 designed to treat the remaining unresected tumor.  
3 Some physicians also use systemic chemotherapy with  
4 carmustine, or BCNU, as the most widely studied  
5 agent. Other chemotherapeutic regimens commonly  
6 used include PCV, such as procarmuzine, lomustine,  
7 and vincristine, and temazolamide, although these  
8 therapies have not been conclusively shown to  
9 increase survival in patients with GBM in a  
10 randomized controlled clinical trial.

11                   The standard treatment produces a modest  
12 clinical benefit for patients with glioblastoma  
13 multiforme, the most malignant form of this  
14 disease. The median survival with surgery alone is  
15 four months. With surgical resection followed by  
16 radiotherapy there's a significant improvement in  
17 survival up to approximately nine months. The  
18 addition of IV BCNU may produce a modest  
19 incremental improvement in survival of  
20 approximately of one-half to one month.

21                   In a recent large, randomized prospective  
22 study at 15 MRC centers in the United Kingdom, Brad  
23 and colleagues examined the effect of PCV  
24 chemotherapy when added to surgery and radiotherapy  
25 in the treatments of patients with high grade

1 malignant glioma. Sixty-hundred-seventy-four  
2 patients were enrolled and randomized to either  
3 surgery and radiotherapy, or surgery, radiotherapy  
4 and PCV combination chemotherapy. The treatment  
5 groups were well balanced for the known prognostic  
6 factors affecting survival, and 76 percent of the  
7 patients enrolled had a GBM tumor histology.

8           The median survival for the RT group, the  
9 RT-alone group was 9.5 months versus the 10 months,  
10 or half a month difference, for the surgery,  
11 radiotherapy, and the PCV group. The authors  
12 concluded that PCV chemotherapy did not confer a  
13 treatment benefit in this trial. In addition, this  
14 study points out the likely expected median  
15 survival time of about nine to 10 months in a  
16 population of patients with a high grade malignant  
17 glioma.

18           The median survival time of nine and-a-  
19 half to 10 months contrast to the figure cited in  
20 the FDA briefing document of 13 months for GBM  
21 patients from Shinota, et al. 2001. The Shinota  
22 data represents a surgical case series of only 82  
23 patients at two single institutions in Japan.  
24 Therefore, its relevance to the patient population  
25 in the T-301 study is unclear.

1           In summary, the expected standard therapy  
2 for malignant glioma are palliative in nature.  
3 Advances in the treatment of this disease have been  
4 in small increments. Clearly, additional  
5 treatments are needed for these patients to  
6 increase their survival.

7           There are several prognostic factors which  
8 influence survival in patients with malignant  
9 glioma. These include age, Karnofsky performance  
10 status, and tumor histology with glioblastoma  
11 multiforme having the worst prognosis. Patients  
12 over the age of 60 and patients with a Karnofsky  
13 performance score of 70 or less have a worse  
14 prognosis. Other factors such as the extent of  
15 surgical resection and the size of the tumor are  
16 proposed by some investigators to influence  
17 survival. However, these factors are not  
18 universally accepted as significant prognostic  
19 factors.

20           BCNU is active against malignant glioma  
21 cells both in vitro and in vivo. However, the  
22 limitations of systemic BCNU treatment include the  
23 fact that BCNU is rapidly cleared from the systemic  
24 circulation with a half-life of about 15 minutes.  
25 This short half-life limits the exposure of the

1 tumor cells to BCNU. BCNU dosing is also limited  
2 by systemic toxicities, which can be severe and can  
3 include bone marrow suppression and pulmonary  
4 fibrosis.

5           The Gliadel wafer is a biodegradable  
6 polymer matrix containing BCNU. BCNU is released  
7 from the wafer in a controlled manner, exposing the  
8 residual tumor cells to high local concentrations  
9 of BCNU for two to three weeks. The application of  
10 the Gliadel wafer to the resection surface in the  
11 brain after resection of the glioma tumor  
12 circumvents many of the limitations of systemic  
13 BCNU. Most importantly, it circumvents the  
14 systemic toxicities of BCNU.

15           Importantly also, the clinical use of  
16 Gliadel wafer does not require any additional  
17 surgery. Virtually all patients receive primary  
18 surgical resection for malignant glioma.  
19 Therefore, Gliadel wafers can be simply implanted  
20 at the conclusion of the surgical resection  
21 procedure and do not require any specific  
22 additional surgical intervention.

23           I'm going to show you a video loop here in  
24 the operating room. You'll see the tumor coming  
25 out. Here's the tumor section cavity and the last

1 remnants of tumor being removed. Now you can see  
2 the implants of the Gliadel wafer. You can see  
3 that this is mechanically very easy, and from a  
4 technical point of view and also from a time point  
5 of view in the operating room, really requires no  
6 additional effort or time.

7 Gliadel wafer has been shown to be safe  
8 and prolong survival in the setting of recurrent  
9 glioblastoma multiforme. In the 8802 study there  
10 was a risk reduction of 43 percent compared to  
11 placebo. This effect was statistically  
12 significant. This study led to the present  
13 indications for Gliadel wafer use.

14 The 8802 study was conducted in patients  
15 with recurrent malignant glioma. The primary  
16 endpoint of the study was six-month mortality for  
17 all patients enrolled. As you can see on this  
18 slide, 60 percent of the patients in the Gliadel  
19 arm were still alive at six months compared with  
20 only 47 percent in the placebo arm. The p-value  
21 for this primary analysis is 0.06. There were only  
22 77 patients with tumor types other than GBM, and  
23 only 31 had anaplastic astrocytoma, the second most  
24 common tumor type. Thus, the power of this study  
25 to detect an effect in patients with tumors other

1 than GBM was extremely low.

2           A single previous Phase III study, the  
3 0190 study, has been performed in patients with  
4 primary malignant glioma. The 0190 trial was a 32-  
5 patient trial conducted in Norway and Finland.  
6 After surgical resection of the primary glioma, 16  
7 patients were treated with placebo wafers and 16  
8 patients were treated with Gliadel wafers. All  
9 patients then went on to receive radiotherapy.  
10 There was a significant increase in median survival  
11 in the Gliadel wafer treatment group with a risk  
12 reduction of 63 percent.

13           The clinical experience to date with  
14 Gliadel wafer is significant. More than 6,000  
15 patients have been treated with Gliadel wafers.  
16 Gliadel is generally well tolerated, with attention  
17 by the surgeon to post-op management of cerebral  
18 edema with corticosteroids, a watertight dural  
19 closures to decrease the likelihood of cerebral  
20 spinal fluid leak, and the use of post-operative  
21 anti-convulsant medications.

22           Post-operative use of corticosteroids and  
23 anti-convulsants as well as a securing of a  
24 watertight dural closure are all standards of care  
25 in this patient population regardless of Gliadel

1 wafer use. A package insert for Gliadel calls  
2 attention to the importance of these steps to  
3 reduce the probability of obtaining any adverse  
4 outcome.

5           The rationale for the present T-301 Phase  
6 III study is to confirm the safety and efficacy  
7 results from the smaller 0190 study, the fully  
8 define the safety profile of Gliadel wafer in the  
9 primary glioma clinical setting, and finally, to  
10 determine the extent of clinical benefit on various  
11 clinical endpoints, including the Karnofsky  
12 performance score, neuroperformance measures, and  
13 time to disease progression.

14           I'd now like to introduce Dr. Dana Hilt  
15 who will review the results of the 0190 Phase III  
16 trial in more detail and then go on to present the  
17 design of the T-301 Phase III trial. Thank you.

18           DR. HILT: Thank you, Dr. Hamilton.

19           Two Phase II trials of Gliadel wafer in  
20 primary malignant glioma have been conducted to  
21 date. Before I discuss the results of the T-301  
22 trial I'd like to review the results of the 0190  
23 trial.

24           The 0190 trial was conducted in four  
25 centers in Finland and Norway. Patients with

1 primary malignant glioma underwent surgical  
2 resection and insertion of either placebo or  
3 Gliadel wafers followed by radiotherapy. The pre-  
4 specified primary efficacy endpoints in this trial  
5 were 12-month and 24-month survival. Shown here,  
6 the baseline characteristics of patients enrolled  
7 in the trial in the two treatment groups -- there  
8 were 16 patients per treatment group.

9           Characteristics of the patients were well-  
10 balanced as far as age and median mini-mental  
11 status score. But the Karnofsky performance score,  
12 placebo group was healthier, shown here with a  
13 median Karnofsky score of 90 versus 75 in the  
14 Gliadel wafer treatment group shown here. Now a  
15 Karnofsky score of 90 indicates near normal  
16 function, and Karnofsky score of 75 indicates a  
17 significant decreased level of function although a  
18 patient does maintain some level of independent  
19 functioning.

20           Now there were more patients with GBM  
21 tumor histology in the placebo group versus the  
22 Gliadel group; 16 versus 11 as shown here. Thus,  
23 the prognostic factor of Karnofsky performance  
24 score favors the placebo group while tumor  
25 histology favors the Gliadel group. Therefore, one

1 must account for the imbalance in both of these  
2 factors, not just one factor, when estimating the  
3 treatment effect of Gliadel in this study.

4           Shown here, the Gliadel wafer treatment  
5 produced a significant survival benefit in overall  
6 survival. The medial survival time for the Gliadel  
7 group is 13.4 months versus 9.2 months in the  
8 placebo wafer treated patients with a risk  
9 reduction of 63 percent as shown here. Now in  
10 order to account for the imbalances in the tumor  
11 type, the FDA statistical review of the 0190 study  
12 evaluated the treatment effect of Gliadel wafer in  
13 the subgroup of GBM patients and found a p-value of  
14 0.1.

15           This type of analysis, however, only  
16 accounted for one important prognostic factor:  
17 tumor histology. When one carries out the same  
18 analysis but also accounts for the effects of age  
19 and Karnofsky score, the treatment effect remains  
20 statistically significant at both the 12-month  
21 survival time point and in overall survival.

22           Therefore, the conclusions from the  
23 initial Phase III 0190 efficacy trial of the  
24 Gliadel wafer in conjunction with surgery and  
25 radiotherapy prolonged survival in patients with