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DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

ONCOLOGIC DRUGS ADVISORY COMMITTEE

Sixty-Ninth Meeting

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Thursday, December 6, 2001

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P R O C E E D I N G S**Call to Order and Introduction**

1 DR. NERENSTONE: I'd like to thank
2 everyone for coming this morning. We're going to
3 start by the introduction of the committee. Go
4 around the room and introduce yourselves and where
5 you're from. Mr. Ohye, would you like to start
6 again this morning?

7 MR. OHYE: I'm George Ohye, nominee for
8 industry representative.

9 DR. REDMAN: Bruce Redman, medical
10 oncologist, University of Michigan Medical Center.

11 DR. GREM: Jean Grem, medical oncologist,
12 NCI Navy.

13 MS. FORMAN: Sallie Forman, patient
14 representative.

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

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

19 DR. BALDUCCI: Lodovico Balducci,
20 geriatric oncology, H. Lee Moffitt Cancer Center,
21 Tampa, Florida.

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

1 DR. EXTERMANN: Martine Extermann, medical
2 oncology for the University of South Florida.

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

5 DR. NERENSTONE: Stacy Nerenstone, medical
6 oncology, Hartford Hospital, Hartford.

7 MS. SOMERS: Karen Somers, executive
8 secretary to the committee, FDA.

9 DR. TAYLOR: Sarah Taylor, medical
10 oncology, University of Kansas, Kansas City.

11 DR. KROOK: James Krook, medical oncology,
12 Duluth CCOP, member of CCPG Disease Monitoring
13 Committee.

14 DR. BRAWLEY: Otis Brawley, medical
15 oncologist, Emory University in Atlanta.

16 DR. TAKIMOTO: Chris Takimoto, medical
17 oncologist, University of Texas Health Science
18 Center at San Antonio.

19 DR. CARPENTER: John Carpenter, medical
20 oncologist, University of Alabama in Birmingham.

21 DR. BLAYNEY: Doug Blayney, medical
22 oncologist, Wilshire Oncology Medical Group in
23 Pasadena.

24 DR. CHICO: Isagani Chico, medical
25 reviewer, FDA.

1 DR. GRIEBEL: Donna Griebel, FDA.

2 DR. PAZDUR: Richard Pazdur, division
3 director, FDA.

4 **Conflict of Intrest Statement**

5 MS. SOMERS: The following announcement
6 addresses the issue of conflict of interest with
7 respect to this meeting and is made a part of the
8 record to preclude even the appearance of such at
9 this meeting. Based on the submitted agenda and
10 information provided by the participants the agency
11 has determined that all reported interests in firms
12 regulated by the Center for Drug Evaluation and
13 Research present no potential for a conflict of
14 interest at this meeting with the following
15 exceptions: in accordance with 18 USC 208(b)(3)
16 full waivers have been granted to Douglas Blayney,
17 M.D.; Steven George, Ph.D.; Scott Lippman, M.D.,
18 and George Sledge, M.D. In addition, Dr. Blayney
19 has been granted a waiver under 505NR of the Food
20 and Drug Administration Modernization Act that
21 permits him to vote on matters concerning
22 Camptosar. Dr. Blayney would like to disclose that
23 he owns stock valued at \$25,001 to \$50,000 in the
24 firm that has a financial interest in a competing
25 firm. A copy of these waiver statements may be

1 obtained by submitting a written request to the
2 agency's Freedom of Information Office, Room 12A30
3 of the Parklawn Building. In addition Stacy
4 Nerenstone, M.D.; James Krook, M.D.; Chris
5 Takimoto, M.D.; and Steven George, Ph.D. have
6 interests which do not constitute financial
7 interest in the particular matter within the
8 meaning of 18 USC Section 208 but which could
9 create the appearance of a conflict. The agency
10 has determined notwithstanding these interests that
11 the interest of the government in their
12 participation outweighs the concern that the
13 integrity of the agency's programs and operations
14 may be questioned. Therefore, Dr. Nerenstone, Dr.
15 Takimoto and Dr. George may participate fully in
16 the discussions and vote concerning Camptosar. Dr.
17 Krook is permitted to participate in the
18 committee's discussion, however, he is excluded
19 from any vote concerning Camptosar. Lastly, David
20 Kelsen, M.D. is excluded from participating in all
21 matters concerning pharmacy as Camptosar. We would
22 like to note for the record that George Ohye is
23 participating in this meeting as an industry
24 representative acting on behalf of regulated
25 industry. As such he has not been screened for any

1 conflicts of interest. In the event that the
2 discussions involve any other products or firms not
3 already on the agenda for which FDA participants
4 have a financial interest, the participants are
5 aware of the need to exclude themselves from such
6 involvement and exclusion will be noted for the
7 record. With respect to all other participants we
8 ask in the interest of fairness that they address
9 any current or previous financial involvement with
10 any firm whose product they may wish to comment
11 upon. Additionally, I would like to note for the
12 record again that our consumer representative, Dr.
13 Jody Pelusi had to cancel her participation in this
14 meeting at the last minute. There was no time to
15 obtain and train a replacement for her. We are,
16 however, fortunate to have Sallie Forman as our
17 patient representative today to provide that
18 particular point of view. Additionally, I've been
19 requested to remind everybody to please speak
20 directly into your microphones so that we can get a
21 good broadcast and a good record for the
22 transcriber. Thank you.

23 DR. NERENSTONE: We turn now to the open
24 public hearing portion of this morning's
25 procedures. Ms. Pamela McAllister, please?

1 **Open Public Hearing**

2 MS. McALLISTER: Good morning. I am
3 Pamela McAllister. I'm a developmental and
4 cellular biologist. And before I begin I would
5 like to thank the Cancer Research Foundation of
6 America whose assistance has allowed me to be here
7 today. The death of my brother to colon cancer at
8 the age of 46 and my own diagnosis inspired me to
9 help others as a result of which I have become
10 actively engaged in assisting others with large
11 bowel cancers. I am currently the chair of the
12 board of the Colorectal Cancer Network, a patient
13 advocate organization made up of those whose lives
14 have been touched in some way by large bowel
15 cancer. I also serve in a variety of other groups
16 as a patient advocate including NCCTG and CALGB. I
17 also was one of the founders of the colon cancer
18 alliance. The irinotecan bolus regimen has a well-
19 documented safety profile and is not clear to me
20 that there has been a demonstrated increase in the
21 risk of early death. With appropriate patient
22 selection and supportive care I believe the regimen
23 can safely treat those with advanced colorectal
24 cancer extending life while maintaining quality of
25 life. If a decision is made to change the

1 recommendations in the use of irinotecan with 5-
2 FU/leucovorin, favoring the use of an infusional
3 regimen this change should be based on sound
4 evidence that such a change is necessary. The
5 affect on community physicians who currently are
6 accustomed to the bolus regimen is of critical
7 importance. Nevertheless, the potential added
8 expense and difficulty of administration of the
9 Douillard infusional regimen is certainly desirable
10 if a clear advantage in either safety or efficacy
11 exists. If no such advantage is demonstrated, it
12 would seem premature to alter that which has been
13 used successfully for some time. Certainly a
14 change to a regimen such as a reduced beginning
15 dose as has been proposed for the Saltz bolus
16 regimen for which efficacy data is not available
17 would seem less desirable than a switch to a
18 regimen which has already been shown to be both
19 safe and effective, that is the Douillard
20 infusional regimen. In the absence of clear
21 evidence of safety problems with the currently used
22 Saltz bolus regimen the best approach from the
23 point of view of patients may be to leave the
24 option as to the best approach as to the regimen to
25 use up to the patients in consultation with their

1 physicians. Having a variety of treatment options
2 is important for patients. Thus, I urge you to
3 maintain this important advance in the treatment of
4 colorectal cancer and to change current practice
5 only if a clear problem with the bolus regimen is
6 demonstrated. Thank you for your time and your
7 consideration.

8 DR. NERENSTONE: Thank you very much. Ms.
9 Barbara Price?

10 We'll go on then. Our next speaker, Mr.
11 Jack Willis.

12 MR. WILLIS: I'm Jack Willis. I'm 83
13 years of age. I'm a colorectal cancer survivor who
14 was treated with Camptosar and I'm pleased to be
15 here today to speak about my battle with this
16 disease. After living a relatively healthy and
17 good life I became ill in 1997 and was diagnosed
18 with colorectal cancer. An immediate surgery
19 removed the cancer but unfortunately it had already
20 metastasized to my liver.

21 My doctor then suggested that I take part
22 in a clinical trial program at UCLA involving
23 Camptosar to which I agreed because I hoped it
24 might be an improvement over the standard
25 medications available at that time. The following

1 weeks of treatment showed it was a wise choice
2 since the large lesion on my liver was
3 substantially reduced and to such an extent that a
4 surgical procedure was possible to remove it.

5 I am now cancer free and have been able to
6 return to a normal life including enjoying
7 traveling, taking my grandchildren to basketball
8 games and my daily jog. It has been almost five
9 years now since I learned I had cancer and began
10 treatment with Camptosar. I am absolutely positive
11 that Camptosar created the opportunity for my
12 operation and eventual survival. As a five-year
13 cancer survivor I can say that I have benefited
14 greatly from Camptosar treatment.

15 I hope you will consider my experience as
16 you evaluate the future of this important treatment
17 option for colorectal cancer patients. I felt
18 compelled to travel across the country to be here
19 today to do my part to ensure that this treatment
20 option is available to those who may need it as
21 they face the reality of a cancer diagnosis.
22 Having treatment options available when facing a
23 diagnosis of cancer is very important. Thank you
24 for your time and attention.

25 DR. NERENSTONE: Thank you very much, Mr.

1 Willis. For the record would you just for our
2 disclosure purposes, would you just comment on any
3 economic support you may have from a Pharmacia and
4 Upjohn?

5 MR. WILLIS: Yes. Pharmacia paid my way
6 over here from California and hotel accommodations.

7 DR. NERENSTONE: Thank you very much. Mr.
8 Kevin Lewis? We have two letters that are
9 available at the front desk.

10 MS. SOMERS: Actually there are four
11 letters now. There have been some coming in. The
12 members of the committee all have the copies of the
13 letter from Peter Goyton and from Cancer Research
14 Foundation of American. We also have received a
15 fax from the Coalition of National Cancer
16 Cooperative Groups that arrived late Monday and one
17 from somebody whose signature is illegible that
18 arrived here at the meeting. And I'll place all of
19 these letters out in the book at the information
20 desk for people who want to see them, but in the
21 interest of time we're not going to read them.
22 Thank you.

23 DR. NERENSTONE: We now turn to the
24 presentation the Camptosar injection by Pharmacia &
25 Upjohn Company, combined with the 5-FU/leucovorin

1 and the Saltz regimen which is approved for the
2 first-line treatment of patients with metastatic
3 colorectal cancer, discussion of post-marketing
4 safety issues. The sponsor Pharmacia & Upjohn will
5 now open our discussion.

6 **Sponsor Presentation [Pharmacia & Upjohn Company]**

7 DR. MILLER: Thank you. Good morning. My
8 name is Langdon Miller and I'm here today
9 representing oncology drug development at
10 Pharmacia. We would like to share with you today
11 important efficacy and safety information regarding
12 combination therapy with Camptosar, also known as
13 irinotecan or CPT-11, given together with 5-
14 Fluorouracil and Leucovorin for the first-line
15 therapy of metastatic colorectal cancer.

16 In April, 2000 the combination received
17 FDA approval because it demonstrated consistent
18 survival benefits over the previous referenced
19 standard 5-FU/leucovorin in two large well-
20 controlled phase III trial. One year later in
21 April, 2001, after widespread adoption of first-
22 line combination therapy for metastatic disease
23 without evident safety problems concerned was
24 raised about an early mortality rate with an
25 approved regimen of CPT-11, 5-FU/leucovorin in the

1 control arm of a cooperative group study. An
2 apparent increase in early deaths was suggested.
3 The word apparent is stressed because as we will
4 show you later the perception of increased
5 mortality was based on what in retrospect was an
6 unfortunate and premature comparison of two
7 dissimilar types of mortality rates.

8 In order to provide you with perspective
9 regarding these events we hope to accomplish
10 several objectives in this morning's presentation.
11 First, we will summarize pertinent background and
12 registration data. Second, we plan to describe the
13 mortality concerns that have been raised regarding
14 bolus use of CPT-11, 5-FU/leucovorin in cooperative
15 group studies. Third, we hope to place these
16 concerns into context for you. Finally, we wish to
17 describe the rationale for Pharmacia's proposals to
18 strength the Camptosar package insert so that we
19 can continue to educate physicians in the safest
20 use of CPT-11, 5-FU/leucovorin therapy in clinical
21 practice.

22 We will review the evidence that use of
23 CPT-11, 5-FU/leucovorin for metastatic disease
24 provides well-established tumor control and
25 survival benefits relative to 5-FU alone. In

1 particular, we plan to document that the use of
2 this combination has no greater mortality risk than
3 use of 5-FU and leucovorin alone and is being used
4 safely in both the clinical trial and community
5 settings. We believe these data will document why
6 both bolus and infusional CPT-11, 5-FU and
7 leucovorin regimens remain first-line survival
8 standards and should be retained in the Camptosar
9 package insert.

10 Before getting to the primary issues that
11 face us here today it is necessary to spend several
12 minutes establishing the background for the
13 development and approval of CPT-11 as therapy of
14 colorectal cancer. To do this let us first go back
15 to before April, 2000. Prior to that time 5-
16 Fluorouracil was standard therapy for metastatic
17 disease.

18 This chemotherapeutic drug, a thymidylate
19 synthase inhibitor had been the mainstay of
20 treatment, in fact the only drug available for over
21 40 years. In the past 15 years it has
22 conventionally been given with the potentiating
23 agent leucovorin. When put into practice different
24 methods of 5-FU and leucovorin therapy have become
25 firmly established in the United States and in

1 Europe. In the U.S. it has become standard to
2 administer bolus 5-FU and leucovorin either via a
3 monthly schedule developed at the Mayo Clinic or
4 using a weekly schedule developed at Roswell Park
5 Cancer Center. Of note the Mayo Clinic regimen of
6 5-FU and leucovorin have been the accepted
7 regulatory standard in the U.S. and was employed as
8 the comparator in registration studies of newer
9 thymidylate synthase inhibitors such as
10 capsidabine.

11 In Europe use of infusional 5-FU and
12 leucovorin was adopted. As in the U.S. regional
13 preferences have been established. For example,
14 French investigators prefer to use the biweekly de
15 Gramont regimen or German investigators adhere to
16 use of the weekly AIO regimen. Unfortunately, no
17 matter how 5-FU was given response rates remain
18 firmly fixed in the range of 20 to 25 percent and
19 median survival could not appreciably be budged
20 above one year. Clearly, a novel agent with a
21 different mechanism of action was needed to further
22 improve survival. CPT-11 offered such a treatment.

23 CPT-11 is a topoisomerase inhibitor that
24 has shown consistent activity in the therapy of
25 metastatic colorectal cancer. CPT-11's distinct

1 mechanism of action was clinically proved in the
2 second-line therapy of metastatic colorectal
3 cancer. As presented by Pharmacia to this
4 committee in 1998 when single agent CPT-11 therapy
5 was compared with best supportive care after
6 failure of first-line 5-FU patients randomized to
7 CPT-11 had significant improvements and survival.
8 Similarly, patients randomized to therapy with
9 second-line CPT-11 versus second-line infusional 5-
10 FU also had significant prolongation of survival.

11 These findings led directly to development
12 of combinations of CPT-11, 5-FU and leucovorin as
13 first-line therapy of metastatic colorectal cancer.
14 The registration trials comprising the basis for
15 approval were two phase III randomized controlled
16 institutional studies with designs that reflected
17 regional practices with regard to use of 5-FU and
18 leucovorin. One of these trials was Pharmacia
19 Study 0038.

20 This trial primarily compared a weekly
21 combination of CPT-11 with bolus 5-FU/leucovorin to
22 a standard bolus regimen of 5-FU and leucovorin.
23 The other study was a Aventis Study V303. This
24 trial assessed CPT-11 in combination with
25 infusional 5-FU and leucovorin regimens that have

1 been developed in Europe. Patients enrolled in
2 Study 0038 were randomized equally to one of three
3 treatment arms. The focus of the trial was on
4 assessment of the comparative efficacy and safety
5 of the weekly CPT-11, 5-FU/leucovorin combination
6 developed by Dr. Leonard Saltz at Memorial Sloan-
7 Kettering Cancer Center with the standard U.S.
8 regimen of Mayo Clinic 5-FU/leucovorin.

9 In Study V303 the primary comparison was
10 between infusional therapy given with CPT-11 and
11 the same infusional 5-FU/leucovorin therapy given
12 without CPT-11. Within each primary treatment
13 group individual study sites were to determine in
14 advance whether they preferred to use the AIO
15 regimen or if they preferred to use the
16 Douillard/de Gramont regimens. As a consequence of
17 the distribution of sites only approximately 25
18 percent of patients enrolled in the study received
19 the AIO combination while 75 percent received the
20 Douillard/de Gramont regimens.

21 As presented to this committee shortly
22 before the April 2000 approval CPT-11, 5-
23 FU/leucovorin demonstrated consistent and
24 significant improvements in survival. In Study
25 0038 median survival improved from 12.6 months with

1 5-FU/leucovorin to 14.8 months with CPT-11, 5-
2 FU/leucovorin. In Study V303 there was also
3 significant prolongation of survival. In this
4 trial the median of 14.1 months improved to 17.4
5 months with the addition of CPT-11, 5-
6 FU/leucovorin.

7 We will present the safety data from these
8 trials side by side, focusing on the relative
9 toxicities between the treatment arms within each
10 study. As might be expected given the known
11 toxicity profiles of CPT-11 and 5-FU treatment with
12 combination therapy was associated with more grade
13 3-4 diarrhea than was treatment with 5-
14 FU/leucovorin alone. In both trials this different
15 was primarily in the incidence of grade 3 diarrhea
16 shown here in yellow. Grade 4 diarrhea largely
17 defined by the need for hospitalization and shown
18 here in blue was comparably and frequent in the
19 treatment and control arms of each of the two
20 trials. However, it is noteworthy that grade 3-4
21 mucositis was quite infrequent with CPT-11
22 containing treatment occurring in less than 4
23 percent of patients.

24 In Study 0038 the two-percent rate
25 associated with the weekly bolus regimen contrasted

1 with a 17-percent rate of severe grade 3-4
2 mucositis associated with the Mayo Clinic schedule
3 of 5-FU/leucovorin. Evaluation of grade 3-4
4 neutropenia in Study 0038 indicated a reduced
5 incidence with CPT-11, 5-FU/leucovorin relative to
6 Mayo Clinic 5-FU/leucovorin. In Study V303 grade
7 3-4 neutropenia was more commonly observed with
8 combination therapy than with 5-FU/leucovorin
9 alone. As might be expected given the lack of
10 increased risk of neutropenia the risk of
11 neutropenic fever or infection with weekly CPT-11,
12 5-FU/leucovorin was no greater than that seen with
13 the Mayo Clinic regimen in Study 0038.

14 In Study V303 there was an increase in
15 neutropenic fever or infection with combination
16 therapy relative to contemporaneously treated
17 control patients receiving 5-FU/leucovorin alone.
18 A review of thromboembolic events provided a mixed
19 picture. In Study 0038 patients receiving CPT-11,
20 5-FU/leucovorin were no more likely to have a
21 vascular event than were patients receiving 5-
22 FU/leucovorin. In contrast to the results in Study
23 0038 patients receiving combination therapy on
24 Study V303 were more likely to experience a
25 thromboembolic event than were control patients.

1 The frequencies of discontinuations due to
2 adverse events were low and similar in the CPT-11,
3 5-FU/leucovorin and 5-FU/leucovorin treatment arms
4 in Study 0038. Discontinuations were increased
5 slightly with combination therapy over control
6 treatment in Study V303. This slide provides
7 information regarding categories of deaths
8 including those documented in the Camptosar package
9 insert.

10 The focus is on the standard regulatory
11 definition which describes the proportion of
12 patients with death during treatment or within 30
13 days of the end of therapy. In Study 0038 this
14 rate with weekly CPT-11, 5-FU/leucovorin was nine
15 percent and with Mayo Clinic 5-FU/leucovorin was
16 seven percent. In Study 0038 differences were
17 primarily due to a higher percentage of patients
18 with progressive disease occurring shortly after
19 cessation of combination therapy than after 5-
20 FU/leucovorin alone.

21 The proportion of patients with the
22 cytotoxic or vascular event at the time of death
23 was actually lower with weekly combination therapy
24 than with 5-FU/leucovorin. In Study V303 the
25 frequency of death within 30 days of end of therapy

1 was four percent with the combination therapy and
2 was three percent with 5-FU and leucovorin alone.
3 The proportion of patients with a myelotoxic or
4 vascular event at the time of death was similar
5 between the two treatment arms, differing by only
6 one patient.

7 These data corroborate those in Study 0038
8 and indicate that there was no discernible increase
9 in fatal events with addition of CPT-11 to 5-
10 FU/leucovorin. The frequency of investigator
11 assessed drug-related deaths were low in both
12 studies at 0.9 percent and 1.4 percent in the two
13 arms of Study 38 and 0.7 and 0 percent in Study
14 V303. Now while it is tempting to compare toxicity
15 profiles between Study 0038 and V303 it is
16 important to note that patients treated on Study
17 0038 had more functional impairment and organ
18 dysfunction than did patients enrolled to Study
19 V303, emphasizing the dangers of cross study
20 comparison for efficacy and safety results. For
21 example, in contrasting the CPT-11, 5-FU/leucovorin
22 arms of the two trials the upper age range was
23 higher in Study 0038.

24 In addition there was a lower proportion
25 of patients with performance status 0 in Study

1 0038. Conversely, there was virtually double the
2 proportion of patients with performance status 2.
3 Adverse prognostic laboratory abnormalities such as
4 LDH or elevated LDH or depressed hemoglobin were
5 also more frequent in Study 0038. What we conclude
6 about these data from Studies 0038 and V303.

7 These well-controlled trials have
8 established CPT-11, 5-FU/leucovorin as the only
9 combination to show significant improvements in
10 survival over 5-FU/leucovorin in 40 years. These
11 studies also offer excellent documentation
12 regarding the safety profiles of each of the
13 combination regimens relative to widely used
14 reference standards. Of particular note these
15 trials indicate that use of CPT-11, 5-FU/leucovorin
16 is not associated with an increased risk of toxic
17 death over concurrently treated control patients
18 receiving 5-FU/leucovorin alone. It is also
19 important to stress that valid conclusions about
20 the relative safety profiles of these regimens
21 cannot be established from cross study comparisons
22 given differences in baseline characteristics as
23 well as frequency of adverse event assessment and
24 supportive care in these two trials.

25 Based on these efficacy and safety data

1 the ODAC members unanimously concluded in March,
2 2000 that CPT-11-based combination therapy
3 represents a new survival standard in the first-
4 line treatment of metastatic disease. The positive
5 clinical benefits established in these studies led
6 to approval in April of 2000 of CPT-11 as a
7 component of first-line therapy in combination with
8 5-Fluorouracil and Leucovorin for patients with
9 metastatic carcinoma of the colon or rectum. Given
10 the relative lack of data supporting use of the AIO
11 regimen it was the consensus of the ODAC, the FDA
12 and Pharmacia that only the Saltz and Douillard
13 regimens be included in the dosage and
14 administration section of the package insert.

15 Approval of these two regimens allowed
16 U.S. patients and clinicians the option of either a
17 more frequently dosing schedule with weekly bolus
18 therapy or less frequently treatment with a
19 biweekly infusional regimen. Coupled with
20 differences in frequency of administration have
21 been trade-offs in terms of complexity of each
22 method of administration. Treatments during each
23 week of Saltz bolus therapy comprised a few hours
24 of time commitment for 90-minute CPT-11 infusion
25 coupled with bolus infusions of Leucovorin and then

1 5-FU.

2 Thus the Saltz regimen is relatively
3 simple, requires relatively modest patient and
4 practitioner time and can be given by peripheral
5 venous administration. While less frequently
6 administered each biweekly treatment with the
7 Douillard regimen comprises three days of
8 involvement with the clinical staff for repeated
9 injections and infusions of Leucovorin and 5-FU.
10 Thus, the Douillard regimen is more complex,
11 mandates a greater time commitment for the patient
12 and the oncology staff and requires a central
13 venous catheter and infusion pump. Collectively,
14 the positive efficacy benefits of CPT-11, 5-FU and
15 leucovorin coupled with these differences in the
16 approved schedules have had substantial
17 implications for the treatment of patients with
18 metastatic colorectal cancer in the United States.

19 Since its registration in the U.S. it has
20 been estimated that approximately 60 percent of
21 patients undergoing first-line therapy for
22 metastatic colorectal cancer received the CPT-11,
23 5-FU/leucovorin combination. An estimated 24,000
24 patients have been treated with CPT-11, 5-
25 FU/leucovorin since its approval. Consistent with

1 long-standing U.S. preference for use of bolus
2 regimens in the treatment of colorectal cancer more
3 than 95 percent of patients given combination
4 treatment have received a weekly bolus regimen.

5 While there are substantial limitations to
6 post-approval surveillance data spontaneous reports
7 of CPT-11, 5-FU/leucovorin-related death have been
8 infrequent. Only seven such observations have been
9 received from U.S. physicians since FDA approval.

10 DR. MILLER: Thus the widespread adoption
11 of bolus combination therapy in clinical practice
12 indicates that practitioners are not experiencing
13 substantial safety concerns. However, in April,
14 2001 information derived from post-approval
15 cooperative group trials ongoing in the U.S.
16 suggested the possibility of an increase in early
17 mortality associated with the use of weekly CPT-11,
18 5-FU/leucovorin bolus therapy.

19 One such study was a multi-arm, first-line
20 trial being conducted by the North Central Cancer
21 Treatment Group, or NCCTG. This study, N9741, have
22 randomized 841 of a planned 1,125 patients who have
23 metastatic disease to any of three regimens, either
24 the weekly bolus CPT-11, 5-FU/leucovorin regimen as
25 the control arm, an investigational arm of

1 oxaliplatin combined with infusional 5-
2 FU/leucovorin, the full Fox 4 regimen, or an
3 investigational combination of CPT-11, oxaliplatin
4 that had been developed in Europe by Dr. Wasserman
5 and colleagues. Dr. Richard Goldberg, the
6 coordinating investigator for this trial is here
7 today to assist in addressing questions.

8 In April of 2001 a recently implemented
9 system for real-time reporting of adverse events
10 suggested a possible increase in early deaths on
11 the N9741 study. With this real-time safety
12 reporting system the NCCTG had employed a new
13 mortality statistic, the 60-day, all-cause
14 mortality. This was defined as all deaths of any
15 cause including both drug and disease-related
16 deaths occurring within 60 days from start of
17 therapy. Applying the new 60-day, all-cause
18 mortality rate it was noted that 4.5 percent of
19 patients treated on the control arm with bolus CPT-
20 11, 5-FU/leucovorin had died within the first 60
21 days of starting treatment while 1.8 percent of
22 patients receiving each of the experimental
23 treatments had died.

24 While the mortality rates between the arms
25 were discrepant the comparison between the arms was

1 not meaningful because the overall therapeutic
2 benefit of the Oxaliplatin containing experimental
3 arms had not been established. In order to
4 determine the mortality rate in the context of past
5 data the NCCTG investigators contrasted the 4.5
6 percent rate of death from any cause within 60 days
7 from start of therapy with the published
8 investigator-designated drug related deaths
9 occurring during treatment or within 30 days from
10 the end of therapy in the U.S. registration Study
11 0038. Unfortunately, this evaluation was quite
12 problematic because as you can see from the
13 definitions here it compared two very different
14 types of statistics.

15 This obviously represented a comparison of
16 apples and oranges. In order to be able to provide
17 a better comparison Pharmacia went back to Study
18 0038 and computed the 60-day, all-cause mortality
19 rates from that study using the new NCCTG method.
20 When this was done these rates were documented to
21 be 6.7 percent for the Saltz bolus CPT-11, 5-
22 FU/leucovorin regimen and 7.3 percent for the Mayo
23 Clinic 5-FU/leucovorin regimen. Thus, the 60-day,
24 all-cause mortality rate that caused the initial
25 concern in study N9741 was actually lower than the

1 rates observed in any of the arms of the Study 0038
2 registration trial.

3 Meanwhile, the Cancer and Leukemia Group
4 B, or CALGB, was conducting a study exploring the
5 investigational use of CPT-11, 5-FU/leucovorin as
6 adjuvant therapy. This trial C89803 had randomized
7 1,263 patients with surgically resected Stage 3
8 colon cancer to either the weekly bolus CPT-11, 5-
9 FU/leucovorin regimen as the experimental arm or
10 the Roswell Park bolus 5-FU/leucovorin regimen as
11 the control arm. The coordinating investigator of
12 this trial, Dr. Leonard Saltz, is also present
13 today to help answer questions you may have.

14 The 60-day, all-cause mortality was also
15 assessed in the investigational setting of adjuvant
16 therapy in Study C89803. This evaluation has
17 indicated that 2.5 percent of patients treated with
18 Saltz CPT-11, 5-FU/leucovorin and 1 percent of
19 patients treated with Roswell Park 5-FU/leucovorin
20 died within 60 days of starting adjuvant therapy.
21 While this difference was concerning these findings
22 and those of the NCCTG lacked context relative to
23 past use of 5-FU/leucovorin.

24 There were three critical questions
25 regarding 60-day, all-cause mortality rates. What

1 have these rates been historically with 5-
2 FU/leucovorin? What are the current rates in CPT-
3 11, 5-FU/leucovorin studies? And what are these
4 rates with CPT-11, 5-FU/leucovorin in community
5 practice? In order to put the results from N9741
6 into a broader perspective Pharmacia has worked
7 with the cooperative groups and other
8 pharmaceutical companies to glean data from
9 numerous trials with regard to 60-day, all-cause
10 mortality rates in the therapy of colorectal
11 cancer.

12 We search for data from clinical trials
13 evaluating therapies for metastatic colorectal
14 cancer. All trials were required to have
15 randomized multi-center faced two or three designs
16 and have 60-day mortality data available. Regimens
17 included the Mayo Clinic, Roswell Park and de
18 Gramont methods of 5-FU/leucovorin administration
19 and Saltz and Douillard methods of CPT-11, 5-
20 FU/leucovorin treatment. The search identified
21 multiple trials from the U.S. cooperative groups,
22 from European cooperative groups and from several
23 pharmaceutical manufacturers. All of the contacted
24 groups and companies graciously agreed to provide
25 the necessary information.

1 The most studied regimen was the Mayo
2 Clinic bolus method of administering 5-
3 FU/leucovorin. Information on this regimen was
4 obtained from seven cooperative group and industry-
5 sponsored trials for which the data had been made
6 available between 1989 and 2001. We have
7 aggregated these results solely for ease of
8 interpretation. The combined 60-day, all-cause
9 mortality from the 1,593 patients in these trials
10 with the Mayo Clinic regimen were 6.1 percent.
11 Similarly, the bolus Roswell Park 5-FU/leucovorin
12 regimen has been employed in six trials, published
13 or ongoing in the period between 1989 and 2001.

14 The collective results from the 1,085
15 patients participating in these studies indicate a
16 60-day, all-cause death rate of 7.6 percent. Only
17 two studies of de Gramont 5-FU/leucovorin were
18 available. When these studies were combined the
19 historical 60-day, all-cause mortality rate in 253
20 patients receiving the regimen was 5.5 percent.
21 Thus, when considering the U.S. registration trial
22 Study 0038 the 60-day mortality rates observed with
23 Mayo Clinic 5-FU/leucovorin and with Saltz CPT-11,
24 5-FU/leucovorin appeared to be quite consistent
25 with the past results observed in trials of bolus

1 or infusional 5-FU/leucovorin therapy.

2 The results from Study V303 with de
3 Gramont infusional 5-FU/leucovorin and with
4 Douillard infusional CPT-11, 5-FU/leucovorin
5 compared quite favorably with those observed in
6 past trials of 5-FU/leucovorin alone. Including
7 the NCCTG N9741 study there are data from five
8 post-approval studies of Saltz bolus CPT-11, 5-
9 FU/leucovorin. Among the 702 patients enrolled to
10 these trials the 60-day, all-cause mortality rate
11 has been only 3.8 percent. The Douillard regimen
12 has been less extensively evaluated in a post-
13 approval setting. Data from four trials are
14 available. In this experience involving 191
15 patients the 60-day post-approval mortality has
16 been 2.6 percent.

17 In summary, this analysis indicates that
18 first-line CPT-11, 5-FU/leucovorin therapy of
19 metastatic disease is associated with 60-day, all-
20 cause mortality rates that are as low as those
21 observed with bolus or infusional 5-FU/leucovorin
22 regimens widely used in the past. While the data
23 just reviewed provide insights into mortality rates
24 in the context of formal studies it is also
25 important to consider the mortality experience with

1 CPT-11, 5-FU/leucovorin in actual community
2 practice in the United States.

3 The objectives of this review were to
4 assess the starting doses of therapy and to
5 determine the 60-day, all-cause mortality rates
6 when CPT-11, 5-FU/leucovorin was given in routine
7 clinical practice. To accomplish this Pharmacia
8 has collected basic information from practice sites
9 throughout the country with the help of the drug-
10 use research organization Tandem. A mix of private
11 practices, community hospitals, VA hospitals and
12 academic centers were selected in order to obtain
13 centers representative of the types of institutions
14 administering chemotherapy in the U.S.

15 This analysis involved a total of 46
16 centers in 20 states. Charts surveyed were for
17 patients who began treatment between January 1st
18 and April 1st, 2001. These dates were after CPT-
19 11, 5-FU/leucovorin was well-established as first-
20 line therapy but before dissemination of safety
21 concerns from the cooperative group trials might
22 have influenced the findings. In order to minimize
23 bias, charts were surveyed sequentially starting
24 with the first patient treated in 2001, resulting
25 in a median of four patients per center. Basic

1 information regarding patient characteristics first
2 cycle CPT-11 and 5-FU administration and 60-day,
3 all-cause mortality was collected.

4 In order to provide a reference with past
5 experience the demographic data from the chart
6 survey are presented along side those from the
7 combination arm of Study 0038. The findings
8 indicate age and gender distributions that are
9 analogous to those observed in patients treated
10 with the Saltz CPT-11, 5-FU/leucovorin regimen in
11 Study 0038. Performance status characteristics
12 were worst than those seen in Study 0038 with a
13 lower proportion of patients with performance
14 status 0 and a greater proportion of patients with
15 performance status of 2 or greater.

16 In clinical practice therapy was given to
17 a higher proportion of patients with evidence of
18 hepatic or renal dysfunction. The majority of
19 patients initiated therapy with full dose CPT-11
20 and 125 milligrams per meter squared and 5-FU at
21 500 milligrams per meter squared. Patients who
22 receive lower starting doses generally were treated
23 at a one-dose level reduction that is 100
24 milligrams per meter squared of CPT-11 and 400
25 milligrams per meter squared of 5-FU. When

1 considering reasons behind the administration of
2 the CPT-11 starting doses patient compromise was
3 the most common reason given for starting dose
4 reduction. There were various reasons. For
5 example, performance status or their age and organ
6 dysfunction for starting therapy at lower doses in
7 some patients. Only five percent of patients had a
8 reduced initial dose level based solely on
9 physician preference to use the lower starting
10 dose.

11 When looking at treatment administration
12 in the critical first cycle in the context of data
13 from Study 0038 it is notable that patients in the
14 practice study were more likely to get full-dose
15 therapy, appear more likely to receive all four
16 planned treatments and median and mean total first-
17 cycle doses that match the treatment administration
18 in Study 0038. Most reassuring that was despite
19 therapy of a greater proportion of patients with
20 poor performance status and compromised organ
21 function the 60-day, all-cause mortality in these
22 240 patients was only 1.3 percent.

23 Please note that this is an updated figure
24 from the 2.5 percent rate in your brochure. Let us
25 place these results into context with the data from

1 the historical registration and post-approval
2 experience. As can be seen the community practice
3 survey results are consistent with the low 60-day,
4 all-cause mortality with CPT-11, 5-FU/leucovorin in
5 the post-approval study. Moreover, the results
6 compare favorably with those observed historically
7 with 5-FU and leucovorin alone.

8 These community practice data document
9 that administration of full dose treatment is given
10 whenever consistent with patient condition. I
11 should stress that arbitrary dose reductions are
12 rare. Practitioners are using clinical judgement
13 regarding patient performance status and other
14 factors as a basis for giving a lower starting
15 dose. It appears based on the existing evidence
16 that first cycle drug delivery is not adversely
17 affected and is consistent with that observed in
18 the registration trial.

19 Of critical importance such use in
20 clinical practice is associated with a very low
21 risk of early mortality. Again, we must conclude
22 that mortality rates in community practice and in
23 the post-approval study settings are as low as with
24 bolus or infusional therapies previously employed.
25 The major implication of all of these findings are

1 that the current package insert appears to offer
2 adequate guidance to encourage safe administration
3 of CPT-11, 5-FU/leucovorin therapy for metastatic
4 disease. However, in the spirit that there is
5 always room for improvement we felt compelled to
6 ask the question of whether the regimen could be
7 made even safer.

8 To address this question the NCI, the
9 NCCTG, the CALGB and Pharmacia agreed that an
10 independent review panel should be convened to
11 review the medical records of all patients on all
12 treatment arms who have died while participating in
13 the two cooperative group trials. This review was
14 performed to understand if any additional
15 supportive care measures might be taken to enhance
16 patient safety. Pharmacia provided an unrestricted
17 grant for the performance of this review.

18 The review was coordinated by NCI contract
19 research organization Theradex. Theradex was
20 solely responsible for selecting panel members,
21 collecting medical records and organizing materials
22 for review. The selected members comprised five
23 colorectal cancer experts who had not participated
24 directly in the cooperative group trials. The
25 committee's findings and recommendations were

1 published in the September JCO. In addition,
2 Pharmacia has posted the committee's report on the
3 company web site and made reprints widely available
4 for dissemination to oncology practitioners.

5 The committee's conclusions and
6 recommendations are summarized on this slide. Most
7 are consistent with known information and with
8 standard oncologic practice. The primary cause of
9 drug-related death was chemotherapy induced
10 gastrointestinal tract and bone marrow cytotoxicity
11 leading to sepsis. A number of patients had fatal
12 vascular events, both arterial and venous although
13 a specific cause and effect relationship between
14 chemotherapy and these events was not evident. The
15 committee recommended that oncologists should be
16 advised of the possibility of such events.

17 Most deaths occurred in the first cycle of
18 therapy, sometimes in conjunction with infrequent
19 patient monitoring leading the panel to recommend
20 that physicians using the bolus regimen see
21 patients weekly during the first cycle.
22 Implementation of the antibiotics sometimes
23 occurred late and antibiotic coverage was not
24 always sufficiently broad. Use of out-patient oral
25 fluoroquinolones for complicated diarrhea was

1 advised. Support with broad spectrum intravenous
2 antibiotics was suggested for patients hospitalized
3 for gastrointestinal toxicity even if there was not
4 evidence of neutropenia or fever.

5 The panel members felt that dosing could
6 be altered. A starting dose change was not advised
7 but it was found that dose modification measures
8 could be improved with minor alterations. It was
9 recommended that there be a 24-hour diarrhea-free
10 period before each chemotherapy treatment. In this
11 regard the panel cited recommendations put forward
12 by Dr. Petrelli and colleagues during the
13 development of the weekly Roswell Park 5-
14 FU/leucovorin regimen and already promulgated in
15 1989. Because the independent review committee had
16 only access to records of patients who had died
17 they could not develop a risk profile.

18 The committee members were unable to
19 answer the question of whether there are important
20 baseline factors that predict for early
21 complications or death. Because Studies 0038 and
22 V303 are completed and fully analyzed there is the
23 opportunity to perform a retrospective review of
24 these trials to discern which baseline factors
25 might best signal clinicians that a patient is

1 likely to have substantial risk of an adverse
2 outcome. Multiple patient clinical and laboratory
3 characteristics were assessed and included those
4 that are recognized as potential markers of patient
5 status or drug disposition that can be readily
6 obtained in clinical practice and that were
7 systematically evaluated in Studies 0038 and V303.
8 Likewise, the most consequential adverse outcomes
9 were included. Statistical significance was
10 assessed by logistic regression with forward
11 selection.

12 The only baseline patient characteristic
13 that was both significantly and consistently
14 predictive for adverse outcomes was poor
15 performance status. As shown on the slide when
16 considering the likelihood of first-cycle events
17 such as neutropenic fever, hospitalization,
18 discontinuations due to adverse events or
19 combinations of these types of events. Patient
20 with performance status 2 represented here in
21 yellow had a higher likelihood of experiencing
22 these type of adverse outcomes. The number of
23 patients with performance status 2 in Study V303
24 was small, only 12 patients. However, similar
25 patterns were observed in this trial as in Study

1 0038. Of note, a similar pattern was also observed
2 among 5-FU/leucovorin treated patients in both
3 trials.

4 In summary, this retrospective analysis of
5 risk factors indicated that patients with
6 performance status of 2 had a higher likelihood of
7 adverse events when receiving any of the therapies.
8 These data corroborate findings in patients
9 receiving other combination therapies for other
10 tumor types. For example, patients with both small
11 cell and non-small cell lung cancer. Other
12 baseline factors including age and gender were not
13 reliable predictors of adverse outcomes.

14 Based on this large body of data from
15 registration trials, from cooperative group
16 studies, from post-approval trials and from
17 clinical practice a number of conclusions should be
18 reemphasized. CPT-11, 5-FU/leucovorin is only
19 approved for use in the treatment of metastatic
20 disease. Until the overall risk and benefits of
21 the use adjuvant therapy are known such use should
22 clearly remain investigational. The approved use
23 of CPT-11, 5-FU/leucovorin for first-line therapy
24 of metastatic disease has shown clear benefits for
25 patients by improving tumor control and prolonging

1 survival. Use of CPT-11, 5-FU/leucovorin together
2 as first-line combination therapy of metastatic
3 disease is the current standard of care and should
4 remain a reference standard.

5 In this regard it is important to remember
6 that reverting to use of 5-FU and leucovorin alone
7 will not protect patients who are risk from early
8 treatment or disease-related mortality and it will
9 deny improved tumor control and survival benefits
10 to many patients. Of course, a critical question
11 for today is whether the new data from the NCCTG
12 demonstrates safety concerns regarding use of this
13 new drug combination for metastatic disease. We
14 have clearly shown you today the 60-day, all-cause
15 mortality rate that caused the initial concern was
16 actually lower than the rates observed in the
17 registration trial. A further critical question is
18 whether the Camptosar package insert should be
19 amended to include new dose modifications.

20 On September 10th of this year Pharmacia
21 made preliminary proposals for package insert
22 changes based on the recommendations from the
23 independent review panel. These draft proposals
24 are reflected in the background information
25 provided by the FDA as part of question number two

1 for discussion today. However, on November 20th
2 Pharmacia informed the FDA that after a thorough
3 review of the new data that I just presented these
4 data did not support these draft proposals for
5 revising the dose modification section of the
6 current package insert.

7 Based on the analysis of the new data from
8 clinical studies and community practice that we
9 have shared with you today Pharmacia would
10 reiterate that the current package insert offers
11 sufficient guidance for safe administration of CPT-
12 11, 5-FU/leucovorin regimens. However, Pharmacia
13 proposes that for both the bolus and infusional
14 regimens the changes in supportive care guidelines
15 consistent with good oncologic practice should be
16 considered.

17 Pharmacia proposes to update the Camptosar
18 package insert to allow the company to foster
19 improved patient selection with a warning regarding
20 the risks of treating performance status to
21 patients, vigilant patient monitoring prior to each
22 chemotherapy administration with both CPT-11, 5-
23 FU/leucovorin regimens. We also propose to include
24 documentation thromboembolic events have occurred
25 in the treatment of colorectal cancer. In

1 addition, we propose to extend the current
2 documentation already in the package insert
3 regarding the use of fluoroquinolones in order to
4 formally recommend such support for combination
5 therapy.

6 Rather than rekindling the debate
7 regarding how 5-FU and leucovorin should be given
8 by bolus or infusion, let us assess the merits of
9 each CPT-11, 5-FU/leucovorin regimen based on the
10 actual data at hand. With this intent it can be
11 stated that the weekly bolus regimen of CPT-11, 5-
12 FU/leucovorin has a well-documented safety profile
13 relative to a former U.S. reference standard. In
14 particular it is important to emphasize that the
15 regimen has demonstrated no increase in the risk of
16 early death relative to control patients receiving
17 5-FU/leucovorin in the registration study, Study
18 0038, relative to historical experience with 5-
19 FU/leucovorin, in post-approval studies including
20 N9741 and in community practice.

21 If anything, mortality in the post-
22 approval clinical trial in community practice
23 setting appears to be moderating. Similarly, it
24 can be documented that CPT-11, 5-FU/leucovorin
25 infusional regimens have a well-documented safety

1 profile relative to the former European practice
2 standard. The Douillard regimen also has
3 demonstrated no increase in risk of early death
4 relative to control patients receiving 5-
5 FU/leucovorin on Study V303, relative to historical
6 experience with 5-FU/leucovorin or in post-approval
7 studies. The safety of the biweekly infusional
8 regimen relative to the weekly bolus regimen
9 remains unknown in U.S. clinical practice.

10 Let me point out that in the absence of
11 data from adequate and well-controlled studies
12 there is no regulatory basis for favoring one
13 schedule over the other. The ultimate implication
14 of all of these findings are that both the Saltz
15 and the Douillard regimens should be retained in
16 the Camptosar package insert. Doing so offers safe
17 and effective treatment regimens, provides a
18 greater range of disease management options for
19 both patients and clinicians employing CPT-11, 5-
20 FU/leucovorin therapy, and allows greater
21 flexibility in developing new drugs such as anti-
22 Cox to anti-VEGF, R and anti-VEGF therapies.

23 As important, doing so allows Pharmacia to
24 continue educational efforts to encourage the
25 safest use of both regimens in clinical practice.

1 This is particularly important for the bolus
2 regimen since it's so commonly employed as first-
3 line treatment of metastatic disease in the United
4 States. These recommendations are supported by
5 statements from multiple patient advocacy
6 organizations urging that the Saltz regimen be
7 maintained in the package insert as a treatment
8 option. In addition it is important to note that
9 Dr. Michael O'Connell, chairman of the NCCTG and
10 the GI intergroup, having reviewed these data now
11 indicates that it would not be appropriate to
12 remove the full dose Saltz regimen from the package
13 insert. In addition, Dr. Robert Comis, the
14 chairman of ECOG and of the Coalition of National
15 Cancer Cooperative Groups has indicated that the
16 Saltz regimen should continue to be made available
17 at the discretion of the treating physician.

18 Thank you very much for your attention.
19 My colleagues and I at Pharmacia, as well as Dr.
20 Saltz and Dr. Goldberg will be pleased to answer
21 any questions that you may have.

22 DR. NERENSTONE: Thank you very much.
23 We'll open it up now to questions from the
24 committee for Pharmacia, questions from the
25 committee. Dr. George?

1 trial are experimental Oxaliplatin-containing
2 regimens.

3 Their therapeutic benefits are unknown and
4 so that's -- it was difficult to know what to make
5 of this mortality rate. That's why the comparison
6 was made with the prior U.S. registration
7 experience with CPT-11, 5-FU/leucovorin. So and
8 that discrepancy, of course, in terms of the types
9 of rates being compared caused the problem in part.

10 MR. GEORGE: And the adjuvant?

11 DR. MILLER: In the adjuvant setting, of
12 course, the comparison is appropriate given that
13 this is within trial comparison. Perhaps Dr.
14 Goldberg and Dr. Saltz might want to comment on
15 some of these issues?

16 DR. GOLDBERG: My name is Richard Goldberg
17 from Mayo Clinic, the chair of N9741, and in many
18 ways I think the person responsible for us being
19 together here this morning. And i think it would
20 be useful for me to explain to you what was going
21 on at NCCTG that led to this. We, as Dr. Miller
22 suggested had implemented a rapid toxicity
23 reporting mechanism. What that did is it notified
24 us by fax within four days of any event that caused
25 hospitalization for a patient, a grade 4 or grade 5

1 toxicity. And nightly that information was
2 incorporated into our data base and generated an e-
3 mail to me as the study chairman and to the study
4 statistician indicating that an adverse event had
5 occurred.

6 In addition, we got a cumulative report on
7 all events on the trial with each of those e-mails.
8 Consequently, every time there was a grade 5
9 toxicity in the morning when I turned on my
10 computer that would come up on my computer screen.
11 And what we had intended with this is to have a
12 gauge by which we could monitor our trial, similar
13 to a gauge on a machine that has a redline on it.
14 The difficult was that such a type of monitoring
15 system had never really been used in a phase III
16 trial like this. And one of the problems was where
17 do you set the redline?

18 What we determined was that if you look
19 back at clinical trials in advanced disease of
20 colon cancer, most reported one percent mortality
21 rate related to treatment at any point in the
22 course of therapy. As Dr. Miller pointed out the
23 regulatory metric that was used was death within 30
24 days of treatment. And what we found as we were
25 reviewing the charts on every patient that died was

1 that investigators would often classify deaths as
2 non-treatment related even though when we went
3 through the chart we thought that they were either
4 caused by treatment or at least treatment
5 exacerbated.

6 Then that led us to choose a metric that
7 was independent of investigator thought in terms of
8 assigning the mortality due to treatment -- or
9 associated within 60 days of the first treatment.
10 So that took out intention. All it did was give us
11 the number of patients that died within 60 days.
12 While that has been a statistic that has been
13 looked at commonly in non-cancer therapy trials,
14 it's not been commonly applied to cancer therapy
15 trials. So it was a metric that we were learning
16 from as we were using it.

17 Now that's a long story about how did we
18 get to where we did. We set ourselves a confidence
19 interval of 95 percent above the one percent
20 mortality factor as the redline. And that meant
21 that if we had more than three percent deaths
22 within 60 days, we would turn off the engine and
23 that's what we did. When we got two additional
24 deaths that brought us up to 13 deaths in the Saltz
25 regimen arm we stopped the trial. And then we had

1 to figure out why this was happening.

2 We also had the comparison that in the
3 other two arms there had been five days within 60
4 days. What has emerged from this in my opinion,
5 and I have spent a lot of time thinking about this,
6 including time when I wish I was sleeping instead
7 of thinking about it, I believe what we saw was
8 really the standard 60-day mortality rate was
9 higher than anybody would have anticipated, this
10 six to seven percent. The mortality rate that we
11 were seeing on the two experimental arms was lower
12 than what we had historical data to support, but of
13 course we don't know the comparable activity
14 between the experimental arms and the two control
15 arms at this point to know whether that lower
16 mortality rate translates into a better survival or
17 activity rate. And so we're in the circumstance of
18 having a very dynamic situation and I have become
19 convinced as I've thought about this more and more
20 that the conclusion that Pharmacia, the cooperative
21 groups and the advocacy groups have come to is the
22 right conclusion.

23 That is that there is not enough data to
24 say that one of the standard ways of giving CPT-11,
25 5-FU and leucovorin should no longer be permitted.

1 The two regimens remain valuable. I've remained
2 convinced of the benefit of CPT-11 in this setting
3 to providing both a survival advantage, a time of
4 progression advantage and a response rate advantage
5 and would not like to see us restrict the use of a
6 drug that I think has moved us forward in colon
7 cancer therapy. I do think that this process has
8 been important in that it has given us the data
9 that it's likely to be more harmful than helpful in
10 patients who have poor performance score and that
11 we need to be attentive to patient side effects
12 during a course of therapy.

13 It's not permissible to just write give
14 four doses and I'll see the patient in six weeks.
15 So I'm hopeful that the events that have transpired
16 will make us able to provide whatever CPT-11, 5-
17 FU/leucovorin regimen a physician and patient
18 chooses to use as safely as possible and avoid
19 deaths that could be prevented.

20 DR. NERENSTONE: Dr. Blayney?

21 DR. BLAYNEY: Thank you. First of all,
22 Dr. Miller, I thought this was a fascinating
23 presentation and I suspect the chair joins me
24 enjoying the statistic you presented that in
25 community practice at least the death rate at 60

1 days is no higher than in academic study centers.
2 So that's something that I wanted to point out. I
3 have recently treated a patient who has developed a
4 vascular event, a thrombosis on 5-FU/leucovorin
5 irinotecan. Can you shed any insight into what we
6 should do in such settings? We, meaning the
7 community, the physicians at large should do,
8 citing you or perhaps your colleagues how to treat
9 that or how to prevent that or what the mechanism
10 might be of that?

11 DR. MILLER: At this juncture I think it's
12 safe to say that we don't know the mechanism. As I
13 pointed out there's somewhat of a mixed picture in
14 one study seeing an increase and the other study
15 not seeing an increase in such events. So it's not
16 clear whether there's a direct attribution that
17 could be made to chemotherapy. Of course, there
18 are issues about risk factors in many patients. I
19 think it's fundamentally important that those risk
20 factors be taken into account, those such as
21 atherosclerotic heart disease and vascular disease.
22 Then, of course, particular vigilance needs to be
23 exercised in patients who, for example, present
24 with chest pain, or dysnia. There were a few
25 patients on the CALGB trial, for example, where

1 things pretty well pointed to a pulmonary embolism
2 as an issue but the work-up just wasn't done and it
3 resulted in catastrophic consequences. Leonard, do
4 you have some other comments perhaps?

5 DR. SALTZ: I'm Leonard Saltz from
6 Memorial Sloan-Kettering Cancer Center. As Langdon
7 alluded to we don't understand the pathophysiology
8 of what's transpiring and it's also not clear
9 whether this is in fact thrombotic events related
10 to the disease that we understand can be a concern
11 or not and whether it's a truly isolated event or
12 to some degree is it related to other ongoing
13 cytotoxic. So issues of maintaining adequate
14 patient hydration and vigilance about being aware
15 when debilitation from therapy may be causing
16 immobility probably need to be considered. Again,
17 whether this is specific to irinotecan-based
18 regimens to fluorouracil-based regimens to
19 combinations, to colon cancer or to cancer in
20 general really remains to be looked at. I think
21 it's raised our awareness in an appropriate way but
22 we have more questions than answers right now.

23 DR. BLAYNEY: So it may be that, you're
24 saying it may be the 5-FU/leucovorin may have a
25 similar vascular event?

1 DR. SALTZ: We certainly see thrombolytic
2 events with 5-FU/leucovorin. In fact, when we look
3 at the cytotoxic deaths on the 0038 study there are
4 more in the 5-FU/leucovorin arm than in any of the
5 other arms and the least in the CPT-11 only arm.
6 So there is not a consistency across studies.
7 There's not a clear pattern and I don't think that
8 we can comfortably draw conclusions at this time.

9 DR. BLAYNEY: Thank you.

10 DR. NERENSTONE: Just a question. What is
11 the status of the two trials that have been closed?
12 Have they been reopened or are they still closed?

13 DR. SALTZ: C89803, the adjuvant study had
14 reached its planned accrual at the time of concern.
15 With dose adjustment modifications that were minor
16 the study was allowed to continue in terms of those
17 several hundred patients that remained on study.
18 At this point the number of patients on study, if
19 there are any is probably 10 or 20. We're just
20 about done. So that's been concluded. In 9741,
21 Rich, do you want to comment specifically on the
22 decision?

23 DR. GOLDBERG: 9741 is open to patient
24 accrual. There had been about 900 patients that
25 were enrolled before the study was closed in May of

1 last year and we are rapidly accruing the data on
2 those patients, have submitted an abstract to ASCO
3 that has in it toxicity data and the promise to
4 report on activity data if we're given the
5 opportunity by the program committee. The study is
6 still open and it is accruing to of the three arms
7 but with one change, and that is that we have
8 chosen to reduce the doses in the Saltz regimen arm
9 to 100 from 125 of irinotecan and 400 from 500 of
10 5-FU, which was dose-level minus one in our
11 protocol, specified by the protocol and that
12 strategy was developed by the NCCTG external data
13 monitoring committee when they reviewed this set of
14 events. And it was done at a time when we had
15 identified the events but had not had an
16 opportunity to learn as much as we have since then
17 about those events.

18 DR. NERENSTONE: Dr. Albain?

19 DR. ALBAIN: I wanted to commend you on
20 this independent report that's been so rapidly
21 published and I think it serves as a model for many
22 future studies in all disease sites. Regarding the
23 description in the JCO paper that you included in
24 our appendix the syndromes, the gastrointestinal
25 and the vascular seem to occur with the

1 constellation of symptoms, in particular the GI
2 symptoms and quite rapidly as they're described, do
3 you have any data yet, either you or perhaps Dr.
4 Saltz that this more vigilant monitoring and
5 supportive care measures you're suggesting for the
6 package insert will in fact prevent the syndrome or
7 might we be dealing with some pharmacokinetics
8 issues in some of these patients with the drugs and
9 in fact, perhaps some deficiencies in metabolizing
10 enzymes and are any of those studies underway?

11 DR. MILLER: Yes, there is the prospect of
12 pharmacogenetics of course plays a role and of
13 course that's well understood that there are
14 potential pharmacogenetic differences with regard
15 to 5-FU metabolism, which is DPD deficiency with
16 CPT-11, which has a rather complicated metabolism,
17 a number of enzymes are known and there is
18 increasing information about the genetics of how
19 the drug is metabolized. We are actively trying to
20 look at those issues. In fact, in the NCCTG N9741
21 study we have been providing support to the
22 cooperative group for the conduct of
23 pharmacogenetic analysis in the patients enrolled
24 to the trial. Those data aren't yet available but
25 that is ongoing. We're also providing similar

1 support to avoid the CALGB adjuvant study as well
2 and plan in future, our own future trials involving
3 CPT-11 with other drugs such as solocoxiv, SU5416,
4 and with other agents to look at the
5 pharmacogenetics of CPT-11 and 5-FU metabolism.

6 DR. SALTZ: To elaborate on two parts of
7 your question, one the issue of vascular versus the
8 gastrointestinal syndrome I think it's worth
9 pointing out that this is sort of early hypothesis
10 generating information and whether these are truly
11 separate syndromes or not is something that we need
12 to delve into further, whether there are
13 gastrointestinal issues involved that may
14 predispose to vascular or whether they're tumor-
15 related and so on. But either way I think the real
16 crux of your question is what can we do to protect
17 people? And I think these are some of the Holy
18 Grails of oncology is try to select rationally the
19 appropriate therapies for the appropriate patients
20 both in terms of increased efficacy and decreased
21 toxicity. And as Langdon alluded to we in the
22 cooperative groups are very dedicated to the
23 concept of looking for predictive markers either
24 through pharmacogenetics or through molecular
25 analysis of the tumors per se. So I think this is

1 a place where all of oncology is moving, not
2 necessarily more in colorectal cancer than anywhere
3 else but the concept that we need to get more
4 sophisticated in the type of science that we can
5 bring into the clinic, into the community clinic in
6 a user-friendly way so that we can minimize the
7 chance of toxicity and maximize efficacy early on
8 in the patient's course.

9 DR. ALBAIN: But until we have those data,
10 is there any evidence that giving the anti-
11 diarrheals and seeing the patient weekly instead of
12 at the end of the four-week prescription is going
13 to matter or does this come on with an onslaught
14 and there is nothing that one can do to reverse it
15 once it starts down its pathway.

16 DR. SALTZ: I think that there are often
17 careful -- a careful history and close monitoring
18 of patients can often pick up things a lot earlier
19 than might otherwise be obtained if a patient is
20 out there with a written order for four or five
21 weeks of therapy. One of the concepts of weekly
22 therapy is that it gives you the opportunity to
23 maximize safety by making the course corrections
24 and making them frequently but in order to do that
25 you have to ascertain the information and

1 physicians and other clinicians need to be clear
2 patients want to please and they want to be
3 optimistic. They're not going to be necessarily
4 inclined to volunteer all of the toxicities,
5 especially if they're getting better by the time
6 you see them and so you may not pick up everything.
7 So I think we as clinicians need to be tuned into
8 the importance of careful communication with our
9 patients so that we can really understand things.
10 And I do believe that that's going to give us an
11 early barometer on these things. In terms of the
12 interventions I think that it's important to note
13 that we did not see any further fatal events with
14 the CPT regimen on the C89803 since the awareness
15 has been raised. Whether we have long-term data
16 we're going to need a time to see just what the
17 toxicities are. We're always looking for ways to
18 identify the toxicity at the earliest possible
19 site. I think we're on the right track but we're
20 going to need time to prove it.

21 DR. ALBAIN: Just one more. You know this
22 regimen better than any, of course, can you in your
23 own practice of taking care of these patients get a
24 hint when this might be occurring, such that what
25 is being proposed for the community practice at

1 large will in fact work if you do --

2 DR. SALTZ: Yes, I really do believe so
3 and I really feel that the experience that I've
4 been privileged to have by treating a large number
5 of patients with this regimen, with other regimens
6 that having a clinician and a clinical staff tuned
7 into what to look for, what to ask for, how to
8 educate the patients early on what to make us aware
9 of, what to be aware of is very effective in
10 maximizing patient safety.

11 DR. NERENSTONE: Dr. Krook?

12 DR. KROOK: I, by circumstance, was
13 involved in the development of the early death rate
14 and Dr. Goldberg has gone to the stand and I think
15 what one has to remember, and I do have a question
16 for Rick, in 9741 this was originally a multi-arm
17 study, seven arms or eight arms when it was first
18 proposed. There were at least three arms which
19 were dropped for toxicity reasons and I guess, and
20 I think I understand this, to Dr. Goldberg, those
21 other arms were dropped for a similar reason, that
22 there was an increase in 60-day mortality and
23 otherwise and then the Saltz became the control
24 arm, the 5-FU/leucovorin arm was also dropped.
25 There was, and I happened to talk to Dr. Goldberg

1 before we got together, there was one death in the
2 first 60 days in the first 60 patients.

3 I've got to say that right in the 5-
4 FU/leucovorin. That arm was dropped early and then
5 continued. So one of the questions to Dr.
6 Goldberg, the other arms were dropped because of
7 the same statistic. Now we don't have numbers on
8 those and what was obvious to us at the data
9 monitoring committee was that the numbers stood out
10 compared to the other two arms. And at the end of
11 the study the issue will be if there is a non-
12 inferiority was there too much toxicity in one arm?
13 So, Rick, were the other arms dropped on the same
14 reason for the 60-day mortality?

15 DR. GOLDBERG: Not exactly. This started
16 out as a six arm study, and there are three arms
17 that are no longer there. One is 5-FU/leucovorin,
18 Mayo Clinic control arm and that was discarded
19 after this committee made the decision that CPT-11,
20 5-FU/leucovorin was the new regulatory standard.
21 And it was felt to be unethical to continue to ask
22 patients to be randomized to a study arm that we
23 knew provided a two-month inferior survival. There
24 were two other arms. One an oxaliplatin with bolus
25 5-FU/leucovorin regimen, the other CPT-11 with

1 bolus 5-FU/leucovorin regimen that were relatively
2 untested in terms of clinical experience. The CPT-
3 11, 5-FU/leucovorin regimen was based around the
4 Mayo approach of five days in a row of 5-
5 FU/leucovorin. We actually had a death rate on
6 that that was in the teens with a small patient
7 experience and it was felt that based on the known
8 activity of the Saltz regimen, the apparent safety
9 advantage of the Saltz regimen, that there was no
10 chance that that sequential CPT-11, 5-FU/leucovorin
11 regimen that we had developed at Mayo Clinic would
12 provide an advantage over the Saltz regimen and
13 that was dropped.

14 We saw a similar increase in toxicity on
15 the oxali 5-FU/leucovorin regimen that was based on
16 multiple consecutive days of 5-FU and again because
17 there was so much experience with the de Gramont
18 regimen and it appeared to be so safe we felt that
19 that did not need to continue. Now there was one
20 other point that I would like to make and that is
21 that we have continued N9741 accruing patients to
22 the modified Saltz regimen to get to Kathy Albain's
23 point. We have had very few grade 4 toxicities, no
24 grade 5 toxicities. There are approximately 60
25 patients who have made it through their first 60

1 days since the new patient protections were
2 implemented. Of course, we don't know if the
3 regimen retains the activity and Dr. Pazdur is
4 smiling over there because he likes to reiterate
5 this point, and I'll reiterate it for him, and
6 that's what the extension of N9741 is looking at is
7 do we retain activity and have a better toxicity
8 profile with the dose reduction but we don't know
9 that now.

10 DR. ALBAIN: Are you increasing your
11 numbers?

12 DR. GOLDBERG: Yes, we are. The study
13 will collapse to two arms and we will compare
14 modified Saltz to de Gramont with about a 350-
15 patient per arm sample.

16 DR. KROOK: Dr. Goldberg, one more. I
17 know what I would do, but I'm going to ask you what
18 you would do if you saw a patient who was going on
19 N9741, would you start at the modified regime or
20 would you go at full dose today with performance
21 status of 1?

22 DR. GOLDBERG: I'll tell you what I do in
23 practice and that is that I have gone to starting
24 at 100 and 400 rather than 125 and 500. And I
25 understand that that is not the approach that

1 Pharmacia is promulgating today. I think that's a
2 conservative approach. There were several reasons
3 that we chose to do that and that our data
4 monitoring committee chose to do that. One is that
5 if you look at the first-course dose reductions in
6 the 0038 trial many patients end up getting a
7 reduced dose by cycle two and I don't know whether
8 that data is available to be shown today.

9 If you look at one of the slides that Dr.
10 Miller put up, the first-course dose intensity was
11 about 450 per meter squared in the 0038 trial, not
12 600 per meter squared as would be prescribed.
13 Again, you may want to review that slide again.
14 But as we thought about this we thought that it
15 would be better to escalate those in patients who
16 were Olympic athletes and who tolerated the 100 and
17 400 with grade 1 or less toxicity rather than to
18 put patients at potential risk by giving the full
19 dose and then dropping dosage back. But we also do
20 believe that within cycle monitoring of patients on
21 a weekly basis has great potential to improve the
22 safety of this regimen.

23 DR. KROOK: Since you would start him on
24 the 100 per meter squared would you escalate on the
25 second cycle of he tolerated it?

1 DR. GOLDBERG: Yes, I would.

2 DR. SALTZ: I'd like to follow up to that
3 just so that you understand that we're not
4 necessarily universally consistent on this. I
5 personally am continuing and have continued
6 throughout to use the full dose starting. I'm
7 comfortable with that but again in my practice I've
8 always been using this close monitoring and
9 supportive mechanism which I believe gives us
10 adequate safety for it.

11 DR. KROOK: Then a question to you, you
12 would not use this regime in an adjuvant setting?

13 DR. SALTZ: I have consistently,
14 throughout the course of C89803 reminded everybody
15 who would ask me that the investigational arm is
16 CPT-11, 5-FU/leucovorin and that the standard of
17 care in stage 3 colon cancer is 5-FU/leucovorin by
18 either the Roswell Park or Mayo Clinic schedule.
19 That's what I do outside of a clinical trial is I
20 personally use the Roswell Park schedule.

21 DR. KROOK: Thank you.

22 DR. NERENSTONE: Dr. Extermann?

23 DR. EXTERMANN: I would like to
24 congratulate the investigators for a very thorough
25 review of these trials. A question I have is one

1 of the things we come to recognize here is the
2 vascular syndrome. And I wanted to know whether
3 you were able to extract data on the comorbidity
4 and note vascular comorbidity that these patients
5 had and if we can have an indication as to
6 recommendations to make and if there is any plans
7 in the ongoing studies to analyze the comorbidity
8 signs and coexisting conditions that may be risk
9 factors for vascular events?

10 DR. MILLER: I should comment in terms of
11 the risk factors that some of these patients did
12 have known risk factors. Of course, those are
13 primarily known for arterial disease, that is as I
14 mentioned proof of vascular disease and
15 atherosclerotic heart disease so that had been
16 established in some of the patients who had
17 thrombolytic events. Now Dr. Gabriella Gruia who
18 has been monitoring the trials at Aventis perhaps
19 could make a comment about some studies that are
20 planned to look at the issue of vascular concerns
21 in these patients.

22 DR. NERENSTONE: Please identify yourself.

23 DR. GRUIA: Dr. Gabriella Gruia for
24 Aventis Pharmaceutical. In Europe we are using the
25 Douillard regimen so we have some concern with

1 thrombolytic event which we consider are also due
2 to the presence of the catheter for the infusional
3 regimen. However, we try to be proactive and to
4 see if there are some studies we can come back in
5 order to find some explanation for thrombotic event
6 and we are planning to do some clinical trials with
7 Dr. Kecker in U.K. to see whether heparin can
8 improve the adverse events, the grade 4 thrombotic
9 adverse events and also to see if Campto changes
10 something in the population cascade. So these
11 trials will start probably beginning 2002.

12 DR. SALTZ: I think it's worth pointing
13 out when you ask a question about predisposing
14 conditions that we already know from clinical
15 experience that coronary artery disease will
16 predispose patients to problems with 5-FU and
17 published rates as high as four percent of coronary
18 arteries spasm in people with known coronary artery
19 disease exist for fluorouracil alone. So we have
20 to bear in mind that there's fluorouracil in these
21 combinations and those risk factors need to be
22 considered.

23 DR. NERENSTONE: Dr. Lippman?

24 DR. LIPPMAN: I have two questions. One
25 regarding the slide that you've had up for quite

1 awhile now. You have the recommendation from the
2 Mayo Clinic cooperative group and ECOG who are
3 leaving these studies, major aspects of these
4 studies. Did you survey the other cooperative
5 group leaders that were involved in this, for
6 instance, Southwest Oncology Group? Do you have
7 any comments that they made?

8 DR. MILLER: I don't have specific
9 comments from SWOG. We have talked to Dr. Richard
10 Schilsky at CALGB who also indicates that he
11 commonly uses the Saltz bolus regimen on trial and
12 off study and that he gives it with full doses to
13 start.

14 DR. LIPPMAN: So this was a letter of some
15 sort to all the cooperative group chairs and SWOG
16 didn't respond; is that what happened? How was the
17 survey done?

18 DR. MILLER: There wasn't a survey, per
19 se. Dr. O'Connell agreed to write a letter in
20 support of the regimen based on his review of the
21 data, these data that you've reviewed were shared
22 with him and in light of these new data and the
23 ability now to place the results of the NCCTG into
24 context he's indicated that he feels that changes
25 are not appropriate.

1 DR. LIPPMAN: Then to clarify, going to
2 the actual objective data on page 41 you show the
3 data that raised all this concern with the 60-day,
4 all-cause mortality, generate a lot of activity and
5 you did the analysis which I again also commend
6 you. It's very comprehensive, even though it did
7 require in many cases cross-study comparisons but I
8 think that's useful in getting the full picture but
9 what you found actually, since again you've brought
10 up the issue, and issue at the table really is just
11 a labeling issue, and how to advise people, is that
12 you went through all this extensive analysis and on
13 the slide that you've shown twice on page 70 and
14 then you came back to it as your key conclusion on
15 page 95 to pick up on what Dr. Blayney says does
16 not show that -- I mean if we're going to stick to
17 the same statistical issues that we live by did not
18 show that the community did -- not worse, in fact,
19 it looks to me like it's going to be highly
20 significantly better than the Mayo and Roswell Park
21 historical controls with 5-FU/leucovorin. So what
22 you found actually is the opposite. It's not just
23 it's not increased, it significantly decreased 60-
24 day mortality. So the question is would you
25 suggest putting in the insert that the addition of

1 CPT-11 reduces 60-day mortality over 5-
2 FU/leucovorin?

3 [Laughter.]

4 DR. MILLER: I think you should take a
5 vote on that right away.

6 [Laughter.]

7 DR. MILLER: I think that we're trying to
8 be careful here to say the rates as low as
9 previously established rates. We haven't done any
10 formal statistical analysis of this. This is
11 purely a descriptive analysis.

12 DR. LIPPMAN: It's not descriptive. You
13 have confidence intervals here and they clearly
14 don't overlap so I think if certainly you've
15 probably done the statistics, maybe not present
16 them but the confidence interval on the 1.3 does
17 not overlap with the two largest studies, the Mayo
18 and Roswell Park.

19 DR. MILLER: I can say quite honestly, we
20 have not looked at that. I just don't think we're
21 advocating that these numbers are necessarily
22 lower, we're just saying that they're not higher
23 certainly.

24 DR. LIPPMAN: But again, if you just draw
25 a line across the table, across the chart, you'll

1 see the confidence levels don't overlap which means
2 that they're significant.

3 DR. GOLDBERG: This is Richard Goldberg
4 and I'd like to make two comments. One is that
5 Robert Comis and Mike O'Connell asked me to speak
6 on behalf of the coalition of cooperative groups if
7 a question arose. The letter that Michael
8 O'Connell sent he sent in his capacity as the
9 designated leader of the NCI GI cancer program in
10 the cooperative groups. It reflects a consensus of
11 all the cooperative group chairs so SLOG, CALGB,
12 ECOG, NCCTG, NCIC all agree with the conclusion
13 that was up there for so long that we would not
14 want to see this restricted.

15 DR. LIPPMAN: I was just wondering why you
16 also included a line from ECOG and not the other
17 individual groups but anyway that's a mute point.
18 I was just trying to clarify where you got --

19 DR. MILLER: In essence, Dr. Comis is the
20 head of the Coalition of Cooperative Groups and his
21 opinion was provided on behalf of ECOG, CALGB,
22 NCCTG and NSAUP. In that regard I'd also note that
23 Dr. Abruzzis from SWOG has reviewed the data and
24 concurs with this opinion.

25 DR. NERENSTONE: Ms. Forman?

1 MS. FORMAN: In looking at the age range
2 of the patients that were in the Saltz studies they
3 range from 25 to 85 years old which certainly is a
4 very wide range and a lot of variables that you
5 would consider in those age differences. Do you
6 have statistics on the average age of those who
7 died on the Saltz regimen or even specific ages?

8 DR. MILLER: Not specific ages, but what I
9 can say is that the 60-day all-cause mortality
10 rate, if we want to arbitrarily divide the
11 population at 65 we're at 6.8 percent for those
12 under 65 and 6.6 percent for those over 65. Of
13 course, the age as a predictor has not been a good
14 predictor. Of course, it's a continuous variable
15 and so how do you establish whether a certain
16 patient is old or young? What is the cut off? And
17 we haven't seen evident cut offs in the data when
18 we've looked at age as a continuous variable. So
19 there hasn't been a clear signal that age would be
20 useful as a predictor of outcome. I can provide
21 some data if you'd like to see those in that regard
22 but we haven't seen that that was useful.

23 MS. FORMAN: So are you saying that that
24 information is available?

25 DR. MILLER: Yes. I'd be happy to show it

1 to you. If we look at efficacy from the group of
2 patients who received the combination therapy on
3 Study 0038 you'll see the times between progression
4 is very similar between those patients younger and
5 older than 65 and the survival is virtually
6 identical. You go to the next slide, you'll see
7 here the TTP curve. And to the next slide the
8 survival curve. And if we go on from there we had
9 done a logistic, a multivariable analysis, Cox
10 regression analysis and survival in this trial.

11 As you can see these are the types of
12 variables present at baseline that predicted
13 significantly for outcome. Treatment was still
14 significant when adjusted for these factors. Age
15 was not among those factors. We have some risk
16 factor slides. The same was true for Study V303
17 with the Douillard and the de Gramont and the AIO
18 regimens that age was not among the prognostic
19 factor for efficacy. Go on. We have the risk
20 factor slides for age? As you pointed out one of
21 the advantages of Study 0038 was that it did
22 provide a broader perspective of what is likely to
23 happen to various patients with different potential
24 risks.

25 In this instance, age, you can see that

1 there is quite a reasonable distribution of ages
2 across the trial. We can go on. So these were
3 well represented in the study. In the overview of
4 patient risk factors that's provided in your ODAC
5 brochure we tried to summarize this in a kind of
6 schematic point here. Let's go to the next one.
7 We have the age one. Unfortunately, that slide
8 isn't there but in any case that row for age would
9 show that there was no significant effect of age in
10 terms of predicting outcome in terms of toxicity.

11 Let's look at age continuously here
12 relative to the likelihood of any grade of
13 diarrhea. You can see that it's just not a good
14 predictor of the likelihood of having severe
15 diarrhea. We go to the next slide. This is in
16 Study V303, you'll see the same pattern and
17 neutropenia as well, you'll see the same pattern,
18 that you really can't use age to predict for
19 outcome. Go to the next slide. The same again for
20 V303.

21 Finally, if we look at the
22 pharmacokinetics perhaps I can have Dr. Larry
23 Schaaf, our clinical pharmacologist comment on the
24 study that actually formally looked at the clinical
25 and pharmacokinetics factors with this drug as

1 related to age.

2 MR. SCHAAF: Larry Schaaf, clinical
3 pharmacology at Pharmacia. This was a study that
4 was specifically conducted to look at the
5 evaluation of patients less than 65 and greater
6 than 65. In this particular slide I'm showing you
7 the pharmacokinetics results. We had 47 patients
8 that were less than 65 and 52 patients that are
9 greater than or equal to 65. On the top half of
10 the slide are the maximum concentrations and area
11 under the curves which represent exposure to CPT-11
12 and on the bottom half of the curve are the C-maxes
13 and their end of the curves for SM38, the active
14 metabolite.

15 I think you can look at these numbers and
16 see that virtually they were right on top of each
17 other and in our trials we have not seen any
18 indication that age relates in any changes in the
19 pharmacokinetics parameters for CPT-11 or SM38.

20 MS. FORMAN: Are those total drug levels
21 or lack --

22 MR. SCHAAF: Those are total drug levels
23 which we have consistently measured in our studies.

24 DR. NERENSTONE: Thank you. Dr. Grem?

25 DR. GREM: Yes, the issue about arbitrary

1 dose reductions in general people think that's a
2 bad thing. It's sort of hard to get a handle on
3 because every patient obviously can only tolerate
4 what they can tolerate and it's an individual
5 thing. A lot of times at the end of the trial
6 there will be retrospective analyses trying to look
7 at does dose intensity correlate with improved
8 outcome and those types of analyses are always
9 fraught with potential biases in that a lot of
10 times the patients with poor performance status
11 tolerate the drugs more poorly so they have a lower
12 dose intensity over the time that they're on study
13 and they have a worse outcome.

14 So even if you tried to do something like
15 look at within patients of performance status 0, by
16 then you're starting to fragment the numbers so you
17 don't really have enough to tell. So I think that
18 Dr. Goldberg's plan right now to sort of
19 prospectively look at the lower dose to see if
20 their outcome -- I mean right now they're not
21 really randomizing to full dose versus the lower
22 doses versus the de Gramont oxaliplatin but at
23 least that's one way to sort of eliminate some of
24 these compounding factors. But I don't know if
25 Pharmacia has done any of those studies, looking at

1 dose intensity and outcome and tried to correct for
2 the potential bias of impact of performance status
3 on any of your trials.

4 DR. MILLER: It's pretty hard to do, as
5 you point out. I think that unfortunately the data
6 in general with chemotherapies tend to show that
7 patients who get less -- it's not that patients who
8 get less dose do worse, it's the patients who do
9 worse get less dose. I think the data tend to show
10 that here. We haven't looked, for example, with
11 patients receiving 125 versus 100 starting in cycle
12 two and the response rates time between progression
13 and survival are virtually identical in that
14 selected population through the data here.

15 You can see that those starting cycle two,
16 125, 500, these are data from Study 0038, the
17 registration trial have similar confirmed response
18 rates time between progression and survival as
19 those starting the second cycle at 100, 400. But
20 once you get below that you start to see a drop off
21 in these numbers and probably -- those patients
22 tend to be the ones with performance status.

23 DR. NERENSTONE: Dr. Takimoto?

24 DR. TAKIMOTO: I wouldn't characterize our
25 discussion here as being unfortunate. I think it's

1 actually a very good thing. I want to just
2 compliment Dr. Goldberg and the NCCTG and also
3 Pharmacia for really jumping on this issue. While
4 it might give Dr. Goldberg insomnia I think there
5 are a lot of people who actually sleep more soundly
6 knowing that these kind of oversight mechanisms for
7 our large trials are in place. I think Dr. Miller
8 as you pointed out a lot of the concerns are raised
9 from a cross study comparison which is really
10 fraught with difficulty.

11 So I think you're correct, we really can't
12 be definitive here but I think we can be prudent.
13 And looking again at some of the recommendations
14 made by the Rothenberg committee, I think the
15 overall message there is to have a healthy respect
16 for some of the toxicities of the combination and
17 probably as you point out too for some of the 5-
18 FU/leucovorin alone regimens that people might
19 overlook a little bit. So one of the questions,
20 I'm a little surprised that the most recent
21 decision by the company is to not make any changes
22 in the dose modifications in the label.

23 The question I have specifically relates
24 to the diarrhea which obviously is a major concern
25 was highlighted by Dr. Rothenberg's report. In the

1 case of somebody getting the Saltz regimen that has
2 grade 2 diarrhea currently the recommendation is to
3 continue to treat those patients with a dose
4 reduction but can you continue to give chemotherapy
5 with the irinotecan, 5-FU? So that means somebody
6 who is having six or even more watery bowel
7 movements a day of their baseline would still
8 continue to get chemotherapy based on the current
9 label recommendations. And as actually you pointed
10 out in your presentation even the Roswell Park
11 regimen where we just give 5-FU and leucovorin
12 actually recommends holding treatment for 24 hours
13 until the diarrhea resolves.

14 So I'd like to know, and actually address
15 this to Dr. Saltz and Dr. Goldberg, if they feel
16 comfortable with the current dose modification
17 recommendations as they exist on the label right
18 now?

19 DR. MILLER: I guess I'd just comment that
20 our recommendation is based on the data we have
21 available and those from the community practice
22 study where we found that practitioners were in
23 fact systematically giving full doses whenever they
24 felt that was appropriate. So it seems as if it
25 was a different circumstance from that perhaps seen

1 with other drugs, doxylcapsidabine, where people
2 have been more reticent about giving full doses
3 arbitrarily and right from the start.

4 In terms of the dose modification
5 provisions you're absolutely correct, we point out
6 that the current provisions are the patients who
7 have grade 3, 4 diarrhea not receive treatment,
8 those who have grade 2 received a reduced level and
9 those who have a grade 1 to continue with the
10 current dose level. I think that that's something
11 that we'd like some help from the committee on in
12 terms of thinking about should we have an
13 interruption in chemotherapy or delay for to ensure
14 a 24-hour diarrhea-free period as Dr. Rothenberg
15 and Dr. Petrelli before him had recommended. I
16 don't know, Len, perhaps you want to comment on
17 where you're heading with this?

18 DR. SALTZ: The issues are complicated
19 primarily because we're trying to balance what is
20 good clinical judgement and what is appropriate and
21 regulatory restriction and so on and what people
22 should be specifically told they can and cannot do.
23 Experience suggests that post-marketing surveys,
24 the studies that presented today suggest that
25 clinicians are making the right judgement in the

1 vast majority of cases. In some degree all
2 chemotherapy safety is going to be dependent on the
3 clinical acumen of the doctors that are
4 administering it.

5 We're going to have to rely on people to
6 exercise judgement regardless of what is written in
7 the package insert. In terms of actually practice
8 I suspect the number of people that are actively
9 having grade 2 diarrhea at the time that they show
10 up and actually get treatment is fairly low and
11 would have virtually no impact on actual use of the
12 regimen regardless of what is written. At CALGB we
13 did make the decision in going forward with the
14 patients on the study to not have patients receive
15 treatment if they had diarrhea the day of or within
16 24 hours of the actual treatment. That seemed like
17 a prudent safety measure at the time and is
18 something that I'm comfortable with, whether it's
19 necessary to legislate or not I think we can leave
20 to the judgement of various people involved.

21 DR. NERENSTONE: I guess I just want to
22 take the chair's prerogative for a moment to
23 continue this line of questions. It seems to me
24 that a package insert should address the best
25 clinical judgement. If you're telling me that the

1 cooperative groups are saying that grade 2 toxicity
2 diarrhea patients do not treatment but the package
3 insert says it's okay to treat them, I think that
4 disconnect is a little bit dangerous. Ironically,
5 maybe the reason that the community oncologists
6 have lower toxicity levels is because nobody
7 believes that that's safe to do. But I think that
8 maybe this needs to be looked at a little bit more
9 carefully.

10 I don't think anyone would say it's
11 mandating that they not get treated but certainly
12 you want your package insert to reflect what is
13 best clinical care and I take exception a little
14 bit to the fact that it's okay to leave that level
15 two toxicity as being okay for treatment at full
16 dose, or at any dose.

17 DR. MILLER: I just want to reiterate that
18 we understand the concern. We have this concern as
19 well. Just that we have the data, the current
20 package insert and the data that I've showed and so
21 we based the judgement at this time on that.
22 There's the prospect that you'd recommend otherwise
23 and we see that as fine, too.

24 DR. NERENSTONE: Dr. Balducci?

25 DR. BALDUCCI: Since the age issue was

1 called into, I feel compelled in to making a couple
2 of issues. First of all I completely agree with
3 you that age is a continuous and it's very
4 difficult to decide who is aged and who is not
5 aged. In fact, more it's very difficult to think
6 that when you talk about people over 65 you are
7 really talking about a homogeneous group of people
8 between 65 and 85 there are 20 years of difference
9 and that probably much more consequential in terms
10 of function than a difference between 20 and 45.

11 On this respect, these are the data from
12 the CALGB mortality data that Dr. Extermann has
13 asked for. As you can see the mean age for people
14 with early death was 70 which was about 10 years
15 higher than the mean age of the people enrolled in
16 the study, so five years higher. But it's the mean
17 age of the people were alive was below 60. And
18 what is interesting is that the early deaths that
19 the mean age for people who died with 5-FU alone
20 was 76 and for people died with CPT-11 was around
21 70. The point I'm trying to make is I think it's
22 difficult to disregard this data, not to think that
23 age makes some difference. Of course, I don't
24 think that age should be used as a single
25 discriminatory factor, the data that you showed

1 about pharmacokinetics are very important. I
2 think, however, that age should be used as a
3 special work. Two issues came out today that have
4 not been discussed in this respect.

5 One is the issue of comorbidity. Older
6 people have much more comorbid condition than
7 younger people. Linda Fried from Johns Hopkins
8 found out that in people in their seventies the
9 average number of conditions was about four. So I
10 think that accounting for that comorbidity in
11 addition to the performance status may be an
12 important issue. The second issue is what came out
13 Dr. Lippman pointed that says the factor in the
14 community, the survival was certainly not worse and
15 possibly better than the academic center and I am
16 wondering if that is due to the fact that in the
17 community admission to the hospital for hydration
18 for completion is much more aggressive of what it
19 is in the academic centers where patients come from
20 afar. In other words, age may not make any
21 difference in the pharmacology of the drugs but if
22 an aged person lives hundred miles away from the
23 treatment center and that person is not admitted
24 for fluid depletion, that person is much more
25 likely to die with the vascular syndrome than a 20-

1 year-old who can come back much easier to the
2 treatment center.

3 So I really think age should -- by all
4 means also on the basis of Sargent's recent meta-
5 analysis and on the basis of the record that show
6 by any means age should not be discriminate about
7 treatment, however, age I think should be a warning
8 signal to look for these problems. I don't know if
9 you comment.

10 DR. MILLER: Of course I'd just again
11 indicate that if we divide the population
12 arbitrarily at 65, you don't see increased
13 mortality in this group. We haven't looked at age
14 as a continuous variable for in conjunction with
15 performance status, for example, for early risk
16 factors. What you tend to find, maybe we can go to
17 a slide here, try to walk you through, but if we
18 look at combined adverse outcomes, for example, in
19 either hospitalization discontinuations or death
20 during the first cycle and look at just the
21 performance status 0, 1 patients by age, this is
22 the curve that shows the frequency of any of these
23 events across the span of years so there's just a -
24 - it's a pretty flat curve overall.

25 If we then put the PS 2 patients on, you

1 see there are far fewer patients and you see more
2 variability in the curve but you don't see that age
3 is clearly a predictor here because of the fewer
4 number of patients. The point I think is that the
5 performance status drives what happens to patients.
6 We go to the next slide, here's the 60-day, all-
7 cause mortality. Again, you see quite a flat curve
8 in general across the age range and if we
9 superimpose the PS 2, in fact, here for some reason
10 it's coming down but in essence the point is that
11 the PS 2 levels are above the age level.

12 So I think your issue about the
13 comorbidity is important, the potential
14 interactions here, the problem is just age isn't a
15 good predictor. I think that that's the issue from
16 the perspective of the package insert. Do we say
17 is there a special precaution at 55, 60, 65, 70?
18 It's just we just don't know we have the data to
19 justify that.

20 DR. BALDUCCI: Absolutely. I agree with
21 this and I subscribe to it completely. My issue is
22 when we come to the package insert should we
23 recommend early hospitalization for people of a
24 certain age if they develop diarrhea and volume
25 depletion? That is the point that I have. Should

1 we make in a climate where hospitalization is
2 avoided as much as possible for economical reasons,
3 should be spend one worth in favor of the older
4 patients to make sure that the treatment to them is
5 safe. That's all I am concerned with.

6 DR. MILLER: I think we're perhaps in an
7 indirect way advocating for that, one of the
8 striking things I think from the independent review
9 findings was that many patients who got to the
10 hospital were not placed on antibiotics
11 sufficiently early and sometimes we're not giving
12 antibiotics with sufficiently broad spectrum. I
13 think that that is an issue that's of particular
14 concern here, that if patients do come in, do get
15 hospitalized, do need hydration in the hospital,
16 have ileus colitis, those sorts of things, even if
17 they don't have a fever, even if they don't have
18 neutropenia, it's probably justified to start
19 antibiotics right away. That's where we're trying
20 to --

21 DR. NERENSTONE: I'd like to ask the
22 committee, to remind you right now that this is
23 really the question time to sort of clarify some of
24 the presentation issues. We're going to have time
25 for discussion after FDA presentation. I think a

1 lot of these issues will come up again for
2 discussion within the committee.

3 DR. SALTZ: Excuse me, may I just clarify
4 on that last question that we answered?

5 DR. NERENSTONE: Briefly, yes.

6 DR. SALTZ: Very briefly. I think it's
7 important to separate what is a very accurate
8 generalization about taking care of elderly cancer
9 patients for what is specific to either irinotecan
10 or either of the irinotecan, fluorouracil-based
11 regimens. When we think about what is particular
12 labeling to a particular product we have to
13 recognize that the same thing may be generalizable,
14 I would suggest would be generalizable to
15 chemotherapy of lung cancer or breast cancer,
16 chemotherapy with or without irinotecan. And we're
17 trying to look at what's specific to these
18 particular ages.

19 DR. NERENSTONE: Dr. Blayney?

20 DR. BLAYNEY: I'll try not to be whimsical
21 this time. One of the recommendations which we're
22 asked to advise on has to do with supportive care.
23 I'm not sure if it's Pharmacia's recommendation or
24 not but one of them for supportive care is GCSF for
25 grade 2 or greater neutropenia. Do you have data

1 to support either dose reduction or use of a growth
2 factor in support of the white count in that
3 setting?

4 DR. MILLER: I think that recommendation
5 in part came out of the independent review
6 committee, that GCSF might be considered in
7 patients who are having trouble with neutropenia.
8 We're not specific -- we haven't so far
9 specifically advocated this given ASCO guidelines
10 and GCSF use the rates of neutropenic fever have in
11 general been low enough that it hasn't necessarily
12 been required. So at this juncture we're not
13 specifically advising it. I think what we're
14 focusing on is more of the issue of the antibiotic
15 support in terms of the infectious risks.

16 DR. NERENSTONE: Dr. Redman?

17 DR. REDMAN: Just a clarification from Dr.
18 Goldberg regarding the decision not to go back to
19 the original dose of 125, 500. Was that decision
20 made because of concerns of patient safety or
21 concern that you wanted to test the hypothesis of
22 the initiating dose having an effect on survival.

23 DR. GOLDBERG: Patient safety, purely.

24 DR. NERENSTONE: Dr. Sledge?

25 DR. SLEDGE: This is somewhere between a

1 query and a comment. I keep hearing people talk
2 about academic versus private practice here in
3 terms of describing these post-marketing versus
4 studies. Dr. Miller, isn't that just totally
5 incorrect? I mean first off the cooperative group
6 studies are conducted two-thirds or three-quarters
7 of the time by clinicians in private practice,
8 putting patients on the study? And secondly, your
9 chart survey included patients from VA hospitals
10 and academic centers so I mean, aren't in essence
11 we're talking about basically very similar groups
12 of practicing physicians in both cases?

13 DR. GOLDBERG: Could I actually make a
14 comment about that? In monitoring N9741, which is
15 a very complex trial being conducted in the U.S.
16 and Canada it's become clear to me because it's
17 protocolized it takes some of the physician's
18 judgement away. I always encourage physicians to
19 make decisions based on patient safety and justify
20 them in the chart regardless of what the protocol
21 says. But when the audit committee comes to audit
22 your charts, if you didn't give a treatment that
23 you were supposed to give a full dose even because
24 your clinical judgement was that that patient
25 wouldn't be best served by doing it, you get

1 dinged. Really the protocolized treatment that
2 we're doing is less flexible so that cases can be
3 compared across the entire study, than is the kind
4 of judgements that you and I make on an every day
5 basis in the room with the patient. So in many
6 ways it doesn't surprise me that as we're learning
7 about this and because it's regimented and
8 prescribed it's less applicable and less safe for
9 patients in some circumstances.

10 DR. MILLER: I'd comment also that you're
11 absolutely right, both in terms of the cooperative
12 groups having non-academic sites and in terms of
13 the private practice or the community practice
14 study that we did since it included primarily
15 private practices. I should mention again that
16 these sites were specifically selected to be
17 representative of the sort of demographics of sites
18 giving chemotherapy throughout this country but it
19 also included cancer centers, a VA hospital
20 generally connected with academic centers and of
21 course a couple of community hospitals.

22 So we were hoping to try to get the
23 representative mix in both circumstances. The
24 other thing I should point out, maybe we could go
25 to the full dose therapy during the first cycle, if

1 we could move onto that. We've seen some of these
2 slides before but this one here, what practitioners
3 are doing, of course, is not reducing the dose
4 across the board. They're reducing the starting
5 dose selectively and the interesting thing is that
6 the median total dose, remember it's 500 milligrams
7 per meter squared is the dose, 125 times four in
8 the first six weeks, they're actually getting
9 pretty close to that here, actually maybe doing a
10 little better with the cross study comparison.
11 Part of what they do is exactly what was prescribed
12 in Study 0038. For example, they give dose, dose,
13 dose, omit in week four and make it up in week
14 five. So they keep the cadence of chemotherapy
15 going and when you look at the number of doses
16 administered in the first cycle you see that it's
17 actually quite good relative to the prior trial
18 setting.

19 This administration, of course, being
20 associated with the survival advantage. So it
21 seems as if they are able to maintain the level of
22 therapy in this critical first cycle similar to the
23 level that was associated with survival benefits.

24 DR. NERENSTONE: Dr. Grem?

25 DR. GREM: I was just wondering, in terms

1 of whenever we're looking at toxicities and trying
2 to see if there are risk factors and we're dealing
3 with a trial with just a couple hundred patients,
4 it's almost always going to be almost serendipity
5 if you see something or not because there's so much
6 inter-patient variability and sensitivity to drugs
7 for all the reasons, comorbidity, pharmacogenetic
8 differences, etcetera, etcetera. I think the meta-
9 analysis Group where they looked at the experience
10 with 5-FU, there they had well over a thousand
11 patients and I think they had pretty significant
12 evidence that elderly patients and female patients
13 were at increased risk for toxicity. Now that
14 doesn't mean that you're going to necessarily
15 mandate a priori dose reductions for them but it is
16 the type of thing that should suggest caution or
17 just more vigilance in monitoring the patients
18 while they're receiving therapy and it might
19 influence what regimen you put them on, something
20 where it's given intermittently you have the chance
21 to interrupt therapy versus giving it all at once
22 and then there's nothing you can do, they've
23 already received all the dosing. But that type of
24 meta-analysis where they had data, let the meta-
25 analysis group have access to the data for all the

1 CPT-11, 5-FU/leucovorin Saltz studies and maybe
2 something will come out of it.

3 DR. NERENSTONE: Dr. Albain?

4 DR. ALBAIN: Actually I wanted to ask you
5 if you performed a multivariate analysis on
6 predictors of grade 4 and deaths within 60 days.
7 You showed multivariate analysis for survival for
8 not predictors for events. Do you have that data?

9 DR. MILLER: Yes, we do. Let me just pull
10 it up for you.

11 DR. ALBAIN: Was age in there as a
12 variable?

13 DR. MILLER: I'll pull those up for you.
14 These are sort of summary descriptions of Tables
15 10, 11, 12, and 13 I think in the ODAC brochure,
16 which I have the actual data. But what we've done
17 here is just try to represent the dependent
18 variables that were looked at -- I'm sorry, the
19 independent variables that were looked at and then
20 the dependent variables here including death within
21 60 days, febrile neutropenia, hospitalizations,
22 etcetera. The chart is divided here into those
23 things that are shown more sort of symptoms and
24 then these that are more consequences so you can
25 see the performance status show up fairly

1 frequently, age and this logistic regression
2 analysis did not.

3 Gender was with women who are a little
4 worse here in grade 3-4 but interestingly not at
5 all in grade 4 sporadic finding with prior adjuvant
6 therapy but that didn't seem to have an influence
7 on any of these other factors. We go to the next
8 slide. Here the same data from V303 and a better
9 risk population. Again you see performance status
10 popping here, febrile neutropenia a little bit more
11 in older patients but that didn't result in more
12 hospitalizations or deaths, etcetera. And then
13 prior radiation therapy seemed to be slightly
14 increased the risk for diarrhea here, on the other
15 hand in a series of phase II studies where this has
16 been looked at the signals have been a little mixed
17 on that.

18 In some instances there's been a
19 suggestion, for example, from some studies done at
20 the NCCTG that prior radiation therapy might
21 increase the risk of neutropenia and then other
22 studies have said no, that's not the case. The
23 same has been true for diarrhea. We go to the next
24 slide and look at the laboratory abnormalities
25 through sporadic types of associations here,

1 generally of fairly marginal significance in such a
2 large analysis. White count interestingly,
3 elevated white count was associated with less
4 neutropenia as we might expect but this is a known
5 prognostic factor for poor outcomes in terms of
6 survival and so showed up here in this analysis.

7 Then the final slide shows the same thing
8 for V303. Then again shows that bone marrow
9 function predicted somewhat for certain types of
10 events. I don't think we can rely upon these too
11 much because there's not a consistent pattern
12 except for performance status.

13 DR. ALBAIN: But actually I think that's
14 pretty powerful support of what Dr. Balducci just
15 pointed out. In fact, in the model age per se was
16 not an independent adverse factor whereas
17 performance status was and perhaps high white
18 count.

19 DR. NERENSTONE: Dr. Lippman?

20 DR. LIPPMAN: Two issues. One, just to
21 clarify for Dr. Sledge that the issue, the
22 community practice which is the term you used
23 really referring to off protocol use was lower but
24 even the cooperative group studies close to
25 approval are consistently lower than in terms of

1 60-day, all-cause mortality than their historical
2 controls with 5-FU/leucovorin alone. But getting
3 to the age issue, and I don't -- maybe you can show
4 that slide in response to Dr. Balducci. Since
5 we're talking about prudent recommendations
6 potentially to put in the label there seems as
7 though there is something going on in the
8 performance status groups we're interested in.

9 In that curve we showed the 30-day
10 mortality, the first slide you showed, 30-day
11 mortality and you divided by performance status.
12 You had two curves, performance status 0-1 and
13 performance status 2 and you plotted the trend by
14 age. The only point I want to make is that that
15 little blip at age 20 or 30 probably represents a
16 very small number of patients and there seems to be
17 something going on. There was a trend in that
18 group.

19 DR. MILLER: If you can go to the prior
20 one with the combined events. These are combined
21 events, so this is the neutropenic fever
22 hospitalization discontinuations or deaths within
23 30 days within the first cycle. So this is any of
24 those potential events.

25 DR. LIPPMAN: One of the issues is

1 eliminating or making a strong recommendation about
2 the poor performance status patients, 2 or 3 and so
3 it's the 0-1 group that we're focusing mostly on.
4 In that group when you eliminate the few patients
5 that are under 40 on this, there is something going
6 on with older age. Again, I don't know if it's to
7 the point where it would make some suggestions on
8 more rigorous supportive care but I think there's
9 some sort of trend there.

10 DR. MILLER: The sense is that perhaps
11 there is --

12 DR. LIPPMAN: No, the performance status
13 0-1.

14 DR. MILLER: No, I understand the
15 performance status 0-1 but perhaps something here,
16 what does this blip mean?

17 DR. LIPPMAN: The point I'm trying to make
18 is that the blip is probably a very small number of
19 patients. They're young patients.

20 DR. MILLER: We're talking about 12
21 patients here.

22 MR. BARKER: The blip on the end is
23 probably a smaller number of patients than the blip
24 on the left. This is just a smooth scatter plot
25 really.