

FOOD AND DRUG ADMINISTRATION
SIXTY-EIGHTH MEETING
OF THE
ONCOLOGIC DRUGS ADVISORY COMMITTEE
- - -
MORNING SESSION

8:33 a.m.

Monday, September 10, 2001

Versailles Ballroom
Holiday Inn - Bethesda
8120 Wisconsin Avenue
Bethesda, Maryland

ATTENDEES

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ATTENDEES (Continued)

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ATTENDEES (Continued)

FOOD AND DRUG ADMINISTRATION STAFF:

PATRICIA CORTAZAR, M.D.

SUSAN HONIG, M.D.

RICHARD PAZDUR, M.D.

RAJESHWARI SRIDHARA, PH.D.

ROBERT TEMPLE, M.D.

ALSO PRESENT:

AMAN U. BUZDAR, M.D.
Professor of Medicine
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C O N T E N T S

MORNING SESSION

Clinical Trial Design for First-line Hormonal
Treatment of Metastatic Breast Cancer

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P R O C E E D I N G S

(8:33 a.m.)

1
2
3 DR. NERENSTONE: I would like to thank everyone
4 for joining us this morning. As you can see from your
5 agenda, we're going to be starting with the discussion
6 about the clinical trial designs for first-line hormonal
7 treatment of metastatic breast cancer.

8 If we could, could we please go around the
9 table and introduce ourselves. Dr. Henderson, if you would
10 like to start.

11 DR. HENDERSON: Craig Henderson, University of
12 California, San Francisco.

13 DR. DAVIDSON: Nancy Davidson, Johns Hopkins.

14 DR. OHYE: George Ohye, nominee for industry
15 representative.

16 DR. KELSON: Dave Kelson, Sloan Kettering.

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

19 MS. MAYER: Musa Mayer, patient representative.

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

22 DR. CARPENTER: John Carpenter, University of
23 Alabama at Birmingham.

24 DR. PRZEPIORKA: Donna Przepiorka, from Baylor
25 Houston.

1 DR. NERENSTONE: Stacy Nerenstone, community
2 oncologist, Hartford, Connecticut.

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

5 DR. SLEDGE: George Sledge, Indiana University.

6 DR. PELUSI: Jody Pelusi, Phoenix Indian
7 Medical Center and community representative.

8 DR. GEORGE: Stephen George, Duke University.

9 DR. REDMAN: Bruce Redman, University of
10 Michigan.

11 DR. TAYLOR: Sarah Taylor, University of
12 Kansas.

13 DR. BLAYNEY: Douglas Blayney, Wilshire
14 Oncology Medical Group, Pasadena, California.

15 DR. SRIDHARA: Raje Sridhara, statistician,
16 FDA.

17 DR. CORTAZAR: Patricia Cortazar, FDA.

18 DR. HONIG: Susan Honig, FDA.

19 DR. PAZDUR: Richard Pazdur, FDA.

20 DR. TEMPLE: Bob Temple, FDA.

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

1 Based on the submitted agenda and information
2 provided by the participants, the agency has determined
3 that all reported interests in firms regulated by the
4 Center for Drug Evaluation and Research present no
5 potential for a conflict of interest at this meeting with
6 the following exceptions.

7 In accordance with 18 U.S.C., section 208(b),
8 full waivers have been granted to Dr. Douglas Blayney,
9 Dr. John Carpenter, Dr. Scott Lippman, and Dr. George
10 Sledge. Further, in accordance with 21 U.S.C. 355(n)(4),
11 Doug Blayney, M.D., Bruce Redman, D.O., and Sarah Taylor,
12 M.D., have been granted waivers that permit them to vote on
13 matters related to this morning's discussions.

14 A copy of these waiver statements may be
15 obtained by submitting a written request to the agency's
16 Freedom of Information Office, room 12A-30 of the Parklawn
17 Building.

18 In addition, Dr. Kathy Albain and her employer,
19 the Loyola University Medical Center, have interests which
20 do not constitute financial interests in a particular
21 matter within the meaning of 18 U.S.C., section 208, but
22 which could create the appearance of a conflict. The
23 agency has determined, notwithstanding these interests,
24 that the interests of the government in Dr. Albain's
25 participation outweighs the concern that the integrity of

1 | tha agency's programs and operations may be questioned.
2 | Therefore, Dr. Albain may participate fully in this
3 | morning's discussions and vote.

4 | With respect to FDA's invited guests, Dr. Craig
5 | Henderson and Dr. Nancy Davidson have reported interests
6 | that we believe should be made public to allow the
7 | participants to objectively evaluate their comments. In
8 | 2000, Dr. Henderson received a consulting fee from
9 | AstraZeneca and he has received speaker fees from Bristol-
10 | Myers Squibb for lectures on paclitaxel. Dr. Davidson
11 | received unrestricted research support from AstraZeneca
12 | more than three years ago. She has also received
13 | consulting fees and speaker fees from AstraZeneca.

14 | Lastly, we would like to note for the record
15 | that George Ohye is participating in this meeting as an
16 | industry representative, acting on behalf of the regulated
17 | industry. As such, he has not been screened for any
18 | conflicts of interest.

19 | In the event that the discussions involve any
20 | other products or firms not already on the agenda for which
21 | FDA participants have a financial interest, the
22 | participants are aware of the need to exclude themselves
23 | from such involvement and their exclusion will be noted for
24 | the record.

25 | With respect to all other participants, we ask

1 | in the interest of fairness that they address any current
2 | or previous financial involvement with any firm whose
3 | product they may wish to comment upon.

4 | Thank you.

5 | DR. NERENSTONE: We are going to do the open
6 | public hearing now. And, Dr. Buzdar, we need you to have a
7 | financial disclosure in terms of who is paying for your
8 | talking here.

9 | DR. BUZDAR: Actually, I would like to make it
10 | public that I have research grants from AstraZeneca, from
11 | Bristol, from Lilly Pharmaceutical, and also from Roche.
12 | But I have no agreements or any other financial conflicts
13 | with any other pharmaceutical company except I have
14 | participated in talks with different pharmaceutical
15 | companies, but I have no agreements or any stocks or shares
16 | in any other pharmaceutical company.

17 | I would like to take this moment to thank the
18 | committee for the opportunity to express my thoughts on
19 | this issue. It is an important issue, at least in my
20 | judgment, whose time has come to address at this point.

21 | Since the availability of front-line data, at
22 | M.D. Anderson we have changed our thinking. And following
23 | the availability of data, the treatment scheme that we have
24 | adopted at our institution is shown over here. The sole
25 | place held by anti-estrogen as the initial therapy of

1 postmenopausal women with hormonal receptor positive
2 disease was revised, and AIs have been moved from the
3 second-line therapy to the first-line therapy.

4 This slide shows the structure of three AIs
5 which are available for clinical use in this country.
6 Anastrozole and letrozole are nonsteroidal aromatase
7 inhibitors, and exemestane is a steroidal aromatase
8 inhibitor.

9 This slide summarizes the clinical pharmacology
10 of these agents. The recommended doses of the three agents
11 are different. Two are competitive inhibitors and
12 exemestane is a suicidal or irreversible inhibitor. All
13 agents are very effective in suppressing the estrogen.
14 There is limited data that letrozole was superior in
15 inhibition of estrone sulfate and anastrozole, but clinical
16 significance of this remains to be defined. Estradiol
17 suppressions were similar in this one small study.

18 The summary of the second-line randomized trial
19 is shown over here, which illustrates that median survivals
20 were longer with AIs than progestin in these trials. In
21 two out of the four studies these differences were
22 significant. Median time to progression was similar in all
23 studies. The letrozole initial study findings demonstrated
24 a dose-dependent antitumor activity and a higher response
25 rate with 2.5 milligrams, which was not reproduced in the

1 second independent study with a similar design. These
2 data, in spite of these differences, I think have more
3 similarities and similar patterns in time to progression,
4 survival and response rates.

5 Let me say a few words now on the first-line
6 therapy. The study design of two anastrozole trials is
7 shown over here. All the front-line therapies essentially
8 have a very similar design. In the North American study,
9 which had almost 90 percent of the patients who were
10 hormone receptor positive, anastrozole showed superior
11 antitumor activity. A higher fraction of patients got also
12 clinical benefit, and the duration of the control of the
13 disease, or time to progression, as shown graphically, was
14 also in favor of anastrozole.

15 In the second European study, both drugs had
16 similar antitumor activity but only 45 percent of the
17 patients in this trial were known to be receptor positive.
18 Time to progression for both therapies was similar in the
19 European trial, as graphically shown over here.

20 If one looks at the hormone receptor positive
21 patients in both trials, the data looks similar to the
22 North American trial. In known receptor positive patients,
23 anastrozole treated patients had longer time to progression
24 compared to the tamoxifen.

25 The letrozole study had a similar design as the

1 anastrozole study, but there is one major difference in
2 this, that there is a planned crossover to prospectively
3 evaluate the efficacy of anti-estrogen following letrozole
4 therapy. The letrozole study had also shown, from an
5 efficacy point, that all the efficacy endpoints were
6 superior, and the antitumor activity of this drug was
7 superior compared to the tamoxifen in this study, as shown
8 on this table. The time to progression was also superior
9 in the letrozole arm compared to the tamoxifen.

10 One subgroup of patients, i.e., the patients
11 who had prior tamoxifen exposure, the tamoxifen arm of the
12 study had only 8 percent antitumor activity in the
13 letrozole study. This subgroup represents a sizable
14 fraction of the patient population in this study. A poor
15 response rate was observed in spite of a long interval from
16 discontinuation of the earlier tamoxifen therapy in this
17 subgroup.

18 In the anastrozole trials, if we look at it,
19 prior tamoxifen therapy had no adverse effect, contrary to
20 the letrozole study in which you saw much a lower response
21 rate in the tamoxifen arm.

22 Stratified analyses of time to progression for
23 anastrozole and letrozole studies are shown over here.
24 Another subgroup of patients in which the tamoxifen arm and
25 the letrozole trial also had a very short median time to

1 progression -- which was the rest of the world -- this
2 represents another large segment of the trial population in
3 which efficacy of tamoxifen was very low. Efficacy of AIs
4 in this study was similar, which stands out that the only
5 difference is that tamoxifen did somewhat poorer in the
6 letrozole study compared to the other two drugs.

7 A side-by-side look at the data of anastrozole
8 and letrozole with intent-to-treat analysis. These
9 findings show more similarities in time to progression,
10 fraction of patients who achieve clinical benefit from
11 these therapies.

12 A similar side-by-side look at the data of both
13 drugs in ER-positive patients shows similar findings to
14 suggest the superiority of AIs over tamoxifen therapy.

15 Exemestane is a steroidal aromatase inhibitor.
16 Phase II data which is available show similar findings in a
17 small study. Phase III studies with this agent are ongoing
18 in front-line therapy.

19 From this clinical efficacy point of view, I
20 think aromatase inhibitors are better agents than
21 anti-estrogen therapy and could be considered as an initial
22 therapy new standard. To determine if one agent is better
23 than the other, I think blinded prospective studies are
24 needed to evaluate their efficacy and safety in this type
25 of setting.

1 In the year 2000, also we should only do these
2 type of studies in ER known positive patients so that we
3 don't have the problem which we have seen in the earlier
4 studies, where we have half or more than half of the
5 patients who are not receptor positive or unknown.

6 Just to illustrate this point, if we look at
7 all the data which is available, studies with a higher
8 fraction of patients with known receptor positive disease
9 show higher clinical benefit in favor of the AI arm of the
10 studies across the board, all the studies which are
11 available in the literature.

12 Similarly, if you look at the review of earlier
13 studies and look at the time to progression in favor of
14 AIs, it is again related to the hormonal receptor status of
15 the study population.

16 Future studies also need to take into account
17 the fraction of patients who had prior tamoxifen or prior
18 endocrine adjuvant therapy, as I tried to make the point,
19 that it can modify the impact of one arm or the other.

20 I think it is high time to look at different
21 clinical endpoints besides survival, as survival is a
22 composite sum of all therapies offered to the patient
23 population in the course of the disease or their illness.

24 Also, we need to keep in mind when we look at
25 these endpoints that there are drug-drug interactions, like

1 | AIs that could affect the other pathways which could
2 | adversely affect the levels of these drugs which may be
3 | utilized in subsequent therapies.

4 | Finally, the last two words I wanted to say
5 | about the safety profile of these agents, and there are
6 | subtle differences between the safety profile of these
7 | agents. And if we look at it just over here, AIs
8 | definitely have fewer thromboembolic complications. I just
9 | use one of the studies, but if we look at it across the
10 | AIs, that is a similar pattern which emerges.

11 | Last but not the least, there are also
12 | differences in the selectivity of these agents. Some of
13 | the AIs I've shown over here can cause subtle changes in
14 | the other steroid synthesis pathways, which we must be
15 | aware of, as these effects may become important if patients
16 | are under acute stress or therapies are offered for a
17 | longer duration like adjuvant therapy.

18 | I appreciate this opportunity to express my
19 | thoughts, and I believe we are all on the same page to find
20 | better therapies and safer therapies for our patients.
21 | Thank you very much.

22 | DR. NERENSTONE: Thank you very much,
23 | Dr. Buzdar.

24 | Is there anyone else who wanted to speak during
25 | the open public hearing?

1 (No response.)

2 DR. NERENSTONE: There being no one else,
3 Dr. Honig is going to start the FDA presentation.

4 DR. HONIG: Good morning. This morning's
5 session is entitled "Clinical Trial Designs for the
6 First-Line Hormonal Treatment of Metastatic Breast Cancer."
7 Dr. Cortazar, Dr. Sridhara and I are going to provide a
8 regulatory history of approvals for this indication and
9 then present some issues for discussion by the committee.

10 The three of us would first like to acknowledge
11 everyone listed on this slide, all of whom made major
12 contributions to this presentation this morning.

13 The purpose of this meeting is to discuss the
14 rationale and the basis for the past approvals of hormonal
15 therapy for metastatic breast cancer, and then to solicit
16 input from the committee in order to improve and
17 standardize their approach to approval of similar drugs in
18 the future.

19 Traditionally, the division has distinguished
20 the approval of hormonal drugs for this indication from
21 cytotoxic drugs, predominantly on the basis of the
22 different toxicity profile between the hormonal agents and
23 traditional chemotherapy. The basis for approval of
24 hormonal agents in the more modern era has been based on
25 the original approvals for Megace and tamoxifen. And so I

1 would like to take a minute just to review these particular
2 applications.

3 Megace was first approved in 1976 for the
4 palliative treatment of advanced carcinoma of the breast.
5 Approval was based on response rate reported in several
6 phase II studies, and a total of 116 patients were treated.
7 No information was available about Megace's effect on time
8 to progression or survival, and the response rate was
9 interpreted in the context of that for historical controls.

10 Tamoxifen was first approved in 1977, and of
11 course has been the basis of many supplements since that
12 time. However, the original approval was based on response
13 rate from 14 phase II clinical trials, as well as the
14 response rate that was reported in the literature for 9
15 additional studies. A little over 1,100 patients were
16 treated in these studies. And again, a point that you will
17 hear echoed several times this morning, no information was
18 available about tamoxifen's effect on time to progression
19 or survival, and the response rate was interpreted in the
20 context, again, of historical controls.

21 Well, clearly, in the modern era we have
22 required randomized clinical trials for approval, but we
23 have continued to use response rate as the primary endpoint
24 for approval in this particular setting. It is a surrogate
25 endpoint, but was considered to be acceptable for

1 treatments with modest toxicities, like the hormonal-type
2 treatments. Response can be attributed to drug effect, as
3 cancer rarely shrinks without some form of treatment. And
4 again, just to underscore this point again, in the
5 first-line hormonal setting, it has been used as FDA's
6 primary endpoint for traditional, or full, approval, not
7 for accelerated approval under subpart H.

8 We have not required submission of survival
9 data as a primary endpoint. We have looked at it. But as
10 we've talked about, there is a lack of a demonstrated
11 survival advantage for the control compared to no therapy.
12 And so survival has been used as a safety rather than an
13 efficacy endpoint. And similarly, time to progression data
14 have been submitted and reviewed, but they have not been
15 used as the sole basis of approval.

16 Using response rate as the primary endpoint, as
17 you will hear in a minute, most of the drugs have been
18 approved on the basis of non-inferiority. And the
19 definition of non-inferiority that has been most frequently
20 used is listed here, that the lower limit of the two-sided
21 95 percent confidence interval for the difference in
22 response between the two drugs should be less than or equal
23 to 10 percent. So that, in other words, a new drug should
24 have a response rate that's not lower than 10 percent than
25 that of the comparator.

1 We have required submission of time to
2 progression and survival data and have asked for similarity
3 and have also asked generally for a total database of
4 approximately 1,000 patients.

5 Again, as you will hear in a minute, the
6 comparator in the first-line settings to date has been
7 tamoxifen. And overall, the response rate for tamoxifen in
8 these studies has been 20 percent.

9 The difference in response rate that has been
10 used as the definition for non-inferiority can be
11 interpreted in several ways. The first is that we are
12 ruling out inferiority of a new drug by an absolute
13 difference of 10 percent. A simple subtraction of 20
14 percent minus 10 percent equals 10. But another way to
15 interpret this difference is that we are ruling out a loss
16 of half of tamoxifen's effect. In this particular case, we
17 get the same answer either way. But, as you will see, if
18 you use different comparators, the different interpretation
19 could lead to different response rates that are desired and
20 has an impact on trial design and sample size.

21 What I would like to do now is to stop and
22 Dr. Cortazar is going to summarize the recent approvals.

23 DR. CORTAZAR: Thank you, Dr. Honig.

24 Good morning, Dr. Nerenstone, members of the
25 advisory committee, colleagues, ladies and gentlemen. I am

1 going to present a summary of the FDA approval of hormonal
2 drugs for metastatic breast cancer. I am briefly going to
3 comment on the hormonal drugs approved in second-line
4 metastatic breast cancer, and then I will spend most of my
5 talk on the first-line setting, which is our topic of
6 interest for today.

7 This slide shows the hormonal drugs that the
8 FDA has approved for second-line metastatic breast cancer.
9 Megestrol acetate was approved in 1971. Dr. Honig already
10 described the basis of approval for this drug. It was
11 almost 25 years before additional hormonal drugs were
12 approved for this use. But in the last six years, the FDA
13 has approved three additional drugs: anastrozole,
14 letrozole, and exemestane.

15 The study design of these hormones have been
16 very similar. We have generally required randomized trials
17 in order to compare response rates. In these studies, the
18 aromatase inhibitors were non-inferior or better than the
19 comparator, megestrol acetate. Anastrozole and letrozole
20 trials were designed for superiority. However, neither
21 hormone achieved their protocol specified primary endpoint
22 of demonstration of superiority, and each was approved for
23 similarity.

24 This slide shows the hormonal drugs that the
25 FDA has approved for the initial treatment of metastatic

1 breast cancer. Tamoxifen was approved in 1977. As
2 Dr. Honig already mentioned, the basis of approval was a
3 favorable effect on tumor response in nonrandomized phase
4 II studies. Tamoxifen has never been shown to have a
5 favorable effect on time to progression or survival in this
6 setting.

7 There is a gap of 18 years between the approval
8 of tamoxifen and the approval of additional hormonal drugs
9 for this use. However, in the last five years the FDA has
10 approved three additional drugs -- toremifene, anastrozole
11 and letrozole -- for first-line treatment of metastatic
12 breast cancer.

13 The FDA requirements for approval of new
14 hormonal drugs for first-line treatment of metastatic
15 breast cancer is non-inferiority or superiority to
16 tamoxifen for tumor response rate in randomized control
17 trials. This is conditional that the new hormone is not
18 worse than tamoxifen for time to progression and survival.
19 Usually, by the time the applications are submitted, the
20 survival data is not mature. Therefore, FDA requires a
21 phase IV commitment to submit follow-up survival.

22 Toremifene was approved for first-line
23 metastatic breast cancer in October 1995. Registration
24 trials were three randomized phase III studies, comparing
25 toremifene with tamoxifen in postmenopausal women with

1 metastatic breast cancer who were tamoxifen-naive. Over
2 1,500 patients were enrolled in the three trials. The U.S.
3 trial was the largest, with 648 patients, while the Nordic
4 and Eastern European trials had a similar number of
5 patients, around 400 each.

6 In the Nordic and Eastern European trials,
7 inoperable primaries were allowed. This was not specific
8 to stage, and there might have been some bias in terms of
9 who does the investigator consider inoperable.

10 Most patients were estrogen receptor positive
11 in the U.S. trial, 60 to 66 percent, and the Nordic trial,
12 over 50 percent, while most of the patients in the Eastern
13 European trial were estrogen receptor unknown, 66 percent.

14 The primary endpoints of the three trials were
15 response rate and time to progression. The trials were
16 designed to show non-inferiority in response rate.

17 Non-inferiority was defined in the protocol in
18 terms of the lower bounds of the confidence intervals for
19 response rate and time to progression. For response rate,
20 non-inferiority was to be met if the lower limit of the
21 two-sided 95 percent confidence interval for the difference
22 in response rates, toremifene minus tamoxifen, was not more
23 than 10 percent worse than tamoxifen. For example, if
24 tamoxifen has a response rate of 50 percent, a comparator
25 might have a response as low as, but no lower than, 40

1 | percent. If tamoxifen had a response rate of 20 percent, a
2 | comparator might have a response rate as low as, but no
3 | lower than 10 percent.

4 | For time to progression, non-inferiority was
5 | assessed in terms of the two-sided 95 percent confidence
6 | intervals for the hazard ratio of tamoxifen to toremifene.
7 | If the lower limit was fixed at 0.8, then it could be
8 | concluded that toremifene was at least non-inferior to
9 | tamoxifen.

10 | I would like to clarify that 0.8 is a number
11 | that was chosen arbitrarily. This is not appropriate by
12 | today's standards. Now we base the margin on the control
13 | effect. Dr. Sridhara will discuss this issue later.

14 | In addition, non-inferiority of a new hormonal
15 | agent to tamoxifen for time to progression is not adequate
16 | for approval because tamoxifen has never been shown to have
17 | a favorable effect on time to progression in this patient
18 | population.

19 | This slide shows efficacy results for
20 | toremifene in first-line metastatic breast cancer. The
21 | response rates in the U.S. and Eastern European trials were
22 | non-inferior. Both have a lower limit of the confidence
23 | interval of less than 10 percent. The Nordic trial did not
24 | meet the protocol definition of non-inferiority. The lower
25 | confidence interval is greater than 10 percent. The

1 reasons for the difference in the results are not clear,
2 since there were no imbalances for prognostic factors
3 compared to the other trials.

4 Time to progression was non-inferior by
5 protocol definition in the U.S. and Eastern European
6 trials. The two trials meet the lower limit of 0.8 in the
7 confidence interval of the hazard ratio. However, we
8 consider this result uninterpretable since the comparator
9 has not been shown to have a favorable effect on time to
10 progression.

11 The Nordic trial results did not meet the
12 protocol-specified definition for non-inferiority to
13 tamoxifen. In fact, there was a significantly worse time
14 to progression in patients who received toremifene. The
15 upper bound is less than 1.

16 In summary, the Nordic trial did not meet the
17 protocol definition of non-inferiority. This trial has
18 significantly worse time to progression with toremifene.
19 There was a concern with the lack of explanation for the
20 deviance of the results in the Nordic trial. Therefore,
21 toremifene was approved because of non-inferiority in
22 response rate in two of the three trials.

23 Anastrozole was approved for first-line
24 metastatic breast cancer on September 2000. The
25 registration trials were two double-blind, well-controlled

1 | clinical studies of similar design: 0030, a North American
2 | study, and 0027, a predominantly European study. The
3 | studies compare anastrozole 1 milligram to tamoxifen 20
4 | milligrams once daily, in over 1,000 patients: 353 in the
5 | U.S. trial and almost double the number of patients in the
6 | European study. Most of the patients in the U.S. trial, 88
7 | percent, had positive receptors, compared to less than half
8 | of the patients, 45 percent, in the European trial.

9 | The primary endpoints of the trials were
10 | objective tumor response and time to progression. The
11 | trials were designed to show non-inferiority.
12 | Non-inferiority was defined in terms of the lower bounds of
13 | the 95 percent confidence interval. The margin for the
14 | response rate was defined in the protocol as 10 percent.
15 | The lower 95 percent confidence interval of the difference,
16 | anastrozole minus tamoxifen, should not be more than 10
17 | percent worse than tamoxifen.

18 | FDA does not have a general policy on how much
19 | of the tamoxifen response rate may be lost by the new
20 | hormonal drug and still consider it non-inferior to
21 | tamoxifen. This margin has been determined on a
22 | case-by-case basis.

23 | The margin for time to progression was defined
24 | in the protocol as 20 percent. The lower 95 percent
25 | confidence interval of the hazard ratio, tamoxifen to

1 anastrozole, should be greater than the fixed margin of
2 0.8. Again, this definition is not adequate since the
3 margin is not based in the control effect. In addition,
4 non-inferiority and time to progression is problematic
5 because the comparator has not shown a favorable effect in
6 time to progression.

7 This slide summarizes the efficacy results of
8 anastrozole in first-line metastatic breast cancer.
9 Arimidex and tamoxifen tumor response rates are
10 statistically non-inferior in both studies. The lower
11 limits of the confidence intervals are less than 10
12 percent.

13 Arimidex time to progression is statistically
14 superior to tamoxifen in the U.S. study, with a p value of
15 0.006, and similar in the other study. The lack of
16 difference in time to progression could be attributed to
17 the increased number of patients with unknown receptor
18 status -- 55 percent in the European study.

19 This slide summarizes the basis for approval of
20 anastrozole in first-line metastatic breast cancer. In
21 summary, anastrozole was approved because of
22 non-inferiority in response rate in both trials, and
23 superiority in time to progression in the U.S. trial.

24 Letrozole was approved for first-line
25 metastatic breast cancer in December 2000. The

1 registration trial consisted of one randomized, controlled
2 double-blind multinational clinical study, comparing
3 letrozole at 2.5 milligrams with tamoxifen 20 milligrams
4 orally once daily in 916 women.

5 The design of the trial changed over time.
6 Initially, there was a third combination
7 letrozole-tamoxifen arm, but this arm was dropped after the
8 results of a pharmacokinetic interaction study. There was
9 also a crossover feature to the study at the time of
10 progression in 43 percent of the patients, but the data was
11 too premature.

12 Two-thirds of the patients were estrogen
13 receptor positive, and one third had unknown receptor
14 status. The primary endpoint of the trial was time to
15 progression. The trials were designed to show superiority
16 by demonstrating a 20 percent reduction in the risk of
17 progression with an 80 percent power.

18 This slide summarizes the efficacy of letrozole
19 in first-line metastatic breast cancer. The median time to
20 progression for letrozole was 9.4 months, versus 6 months
21 for tamoxifen. This result is statistically significant,
22 reducing the risk of progression by 30 percent; a hazard
23 ratio of 0.70.

24 Response rate was significantly higher with
25 letrozole treatment, 30 percent, compared to 20 percent for

1 tamoxifen, with 71 percent higher odds of responding to
2 letrozole than tamoxifen; a p value of 0.0006.

3 So, in summary, letrozole was approved because
4 of statistically significant superiority in time to
5 progression and response rate. This is the first hormonal
6 drug that has shown superiority to tamoxifen.

7 Issues to consider with primary endpoints in
8 future trial designs will be discussed by Dr. Honig.

9 Thank you.

10 DR. HONIG: So, as we have just heard,
11 anastrozole was approved on the basis of non-inferiority to
12 tamoxifen, and letrozole was the first to demonstrate
13 statistical significance in terms of superiority to
14 tamoxifen.

15 However, there has never been a direct
16 comparison of these two agents. And these data raise the
17 question as to whether or not letrozole is uniquely
18 superior to tamoxifen or whether in fact there is a class
19 effect raised by the superior time to progression seen in
20 one small study for anastrozole, in which a high percentage
21 of the patients were known to be estrogen receptor
22 positive, with a higher likelihood of responding.

23 These data raise some issues that we hope you
24 will help discuss with us this morning. The first one
25 concerns the choice of the endpoint. Should we, instead of

1 using response rate, now use time to progression as the
2 primary endpoint for future studies of the first-line
3 hormonal treatment of metastatic breast cancer?

4 Before we discuss the pros and cons of this
5 approach, I would like to just briefly review the
6 information that would be needed to design such a trial.
7 First, of course, there would need to be an estimate of the
8 treatment effect of the comparator from historical data.
9 Here are some ways in which this could be performed. You
10 could choose the point estimate of the response rate. You
11 could look at a 95 percent confidence interval boundary.
12 You could choose a more conservative or more liberal
13 boundary, which would of course affect sample size, as you
14 will hear from Dr. Sridhara. And also influencing these
15 outcomes would be a determination of what fraction of the
16 effect should be retained.

17 Well, in favor of switching to time to
18 progression would be some discussion from the committee
19 that would suggest that time to progression is
20 intrinsically more meaningful than response rate. Against
21 using time to progression is the fact that neither of the
22 aromatase inhibitors may be acceptable to design a
23 non-inferiority comparative trial, since neither has
24 reproducibly demonstrated a time to progression advantage.
25 For anastrozole, it was seen in one study; for letrozole,

1 | although it was a large, well-controlled study with a
2 | convincing statistical outcome, it is a sole study. And as
3 | we have heard several times this morning, we don't have
4 | data available for time to progression for other
5 | comparators. And as Dr. Sridhara will review for you
6 | shortly, the sample size needed for a non-inferiority study
7 | using a time to progression endpoint may be large.

8 | Should we instead continue to use response rate
9 | as we have? This would assume that response rate still
10 | sufficiently identifies efficacy in this setting.

11 | If we continue to use response rate, then
12 | another issue for discussion is how we should design the
13 | trials. Is non-inferiority to tamoxifen or another
14 | approved first-line agent still an acceptable basis for
15 | approval?

16 | In favor of this approach, again, is the fact
17 | that in most cases FDA does not have a comparative efficacy
18 | standard. Against it is the finding in this one study that
19 | letrozole's response rate was statistically significantly
20 | superior to tamoxifen. And some discussion from the
21 | committee about this finding would be helpful, as well.

22 | Alternatively, should new drugs now be required
23 | to show superiority to tamoxifen? And this could be done
24 | in one of two ways, either by a direct comparison to
25 | tamoxifen in a superiority study or by a non-inferiority

1 comparison to letrozole.

2 The issues to consider if we decided that we
3 should use response rate as the primary endpoint and that
4 we would need to demonstrate superiority to tamoxifen,
5 either directly or indirectly, are listed here. We would
6 still need to estimate the treatment effect size. For this
7 example, I've just used the point estimate of the response
8 rate for letrozole of 30 percent. What fraction of the
9 effect should be retained?

10 You have heard this morning that our frequent
11 definition has been to rule out an absolute 10 percent
12 difference. This would mean that a new drug should not be
13 10 percent worse in its response rate; so we would be
14 ruling out a response rate of less than 20 percent in this
15 setting.

16 However, we mentioned before that that 10
17 percent absolute difference could be interpreted as
18 retaining at least half of the effect of tamoxifen's
19 effect. If we took that approach here, we would want to
20 retain half of letrozole's response rate; and that would
21 mean that a new drug should not have a response rate less
22 than 15 percent.

23 However, the third approach is that we would
24 want to retain some fraction of letrozole's advantage over
25 tamoxifen. So that 30 percent minus the 20 percent

1 response rate of tamoxifen in most of these trials is 10
2 percent and that we would want to retain some fraction of
3 that -- say half, for example -- and that we would be then
4 asking that a new drug have a response rate that is not
5 less than 25 percent. So, again, you can see that you can
6 get three different lower bounds for your response rate,
7 and again, you would need to power and design your study
8 accordingly. And Dr. Sridhara will give you some more
9 concrete examples of what that effect is on sample size.

10 Now, in addition to these specific concerns
11 about endpoints and comparators we just wanted to mention
12 some of the concerns that we always have about these
13 studies. If we continue to use response rate, we exclude
14 patients with bone-only disease. And clearly these are the
15 patients that tend to get this drug in clinical practice
16 and are likely to benefit from it.

17 If we instead use time to progression, I would
18 refer to the ODAC discussion session in June of 1999. At
19 that time, the topic under discussion was the use of time
20 to progression for cytotoxic drug therapies. But there was
21 a lot of discussion by the committee of the limitations of
22 measuring time to progression, and those limitations or
23 difficulties would still be applicable in the hormonal
24 setting. Certainly it would be strengthened by the use of
25 blinded trials in assessing time to progression.

1 An additional concern is about non-inferiority
2 trial designs, and I think you have many times heard
3 Dr. Temple say that sloppiness obscures differences. But
4 the practical implications of that are that, again,
5 independent substantiation of results are particularly
6 important in the non-inferiority setting, and that we need
7 to pay special attention to the study conduct. Dr. Buzdar
8 mentioned some of these points in his presentation earlier.

9 Inclusion of patients with estrogen receptor
10 unknown status can contribute to the lack of an observed
11 difference between studies. If we include patients with
12 bone-predominant disease, it may make response assessment
13 somewhat more difficult. And again, we need to be willing
14 to adapt inclusion criteria, as science moves forward, to
15 be sure that we are selecting a patient population most
16 likely to benefit from these treatments.

17 Some broader concerns that we have mentioned in
18 the questions for your discussion later this morning also
19 are: Would any of the discussion this morning impact
20 ongoing trials of new hormonal agents under development?
21 And, finally, what about the possibility that overall
22 survival with another hormonal agent might be superior to
23 that observed with tamoxifen? Would that influence or
24 change our thinking on these topics?

25 Dr. Sridhara will now present some of the

1 | statistical considerations that go along with these
2 | questions.

3 | DR. SRIDHARA: Thank you, Drs. Honig and
4 | Cortazar.

5 | I am here today to lay out some of the
6 | statistical considerations that need to be examined in
7 | designing future clinical trials for first-line hormonal
8 | treatment of metastatic breast cancer.

9 | The outline of my presentation is as follows.
10 | First, I will go through the active control comparators
11 | that are under consideration, then present clarification
12 | regarding the terminology used, move on to lay out the
13 | assumptions that are made in designing non-inferiority
14 | trials, then discuss the different designs under
15 | consideration, then present estimates of sample sizes that
16 | are required under each design. All designs considered
17 | here are planned with 80 percent power and a one-sided
18 | alpha of .025. I will then highlight points to be kept in
19 | perspective in conducting non-inferiority trials in this
20 | setting. With this background, I will then put forward the
21 | issues that need to be discussed for designing future
22 | trials.

23 | The future drug product X could potentially be
24 | compared to the old standard tamoxifen; the debate here
25 | today is: Should we use letrozole as the active control

1 | comparator instead of tamoxifen, as it has shown convincing
2 | superiority over tamoxifen in one randomized trial?

3 | Regarding the terminology that we commonly use,
4 | there is little confusion regarding superiority, where we
5 | mean that drug X is superior; that is, statistically
6 | significantly better in efficacy with respect to active
7 | control.

8 | However, non-inferiority is a more recent
9 | misleading terminology. There are basically three types of
10 | non-superiority trials. They are that X works and that X
11 | is not much less effective than the active control, and
12 | that X and active control are equivalent. In the studies
13 | that we are considering here, by non-inferiority we mean
14 | that X is not much less effective than the active control.

15 | In earlier approvals we have used terms like
16 | "was not different," or that "the two drugs were similar."
17 | These are incorrect terminology. However, it should be
18 | kept in mind that the earlier studies were not really
19 | designed as non-inferiority studies, and hence the
20 | terminology was not as rigorous.

21 | For the purpose of design considerations of
22 | non-inferiority trials and illustration only, we will
23 | consider letrozole as the active control comparator in the
24 | remainder of this presentation.

25 | The basic assumptions in designing

1 non-inferiority trials are that: One, the active
2 control -- in this case letrozole -- is effective compared
3 to placebo. Secondly, we can reliably estimate this effect
4 size.

5 If response rate is the endpoint under
6 consideration, then all the effect can be attributed to the
7 treatment. However, for the time to progression endpoint,
8 we have a comparison of letrozole to tamoxifen and not to
9 placebo. And we also do not have an estimate of the
10 tamoxifen effect size with respect to time to progression.

11 Another important assumption, which is
12 generally termed as constancy assumption, is that the
13 active control effect in the historical studies is carried
14 over to the future study.

15 Before designing any trial, including a
16 non-inferiority trial, we need to be certain about the
17 final outcome of interest. The two endpoints under
18 consideration here are response rate and time to
19 progression. Both of these are surrogate endpoints, and we
20 have no proven data which is a better surrogate of the gold
21 standard, final outcome survival, in the first-line
22 metastatic breast cancer setting. Future studies of other
23 agents and updated data on letrozole study may shed some
24 light on this aspect.

25 The next issue to be considered is the estimate

1 of active control effect size, as we never know the true
2 effect size. In the letrozole study, the point estimate of
3 response rate was 30 percent, with a 95 percent confidence
4 interval between 26 and 35 percent. The point estimate of
5 hazard ratio of tamoxifen versus letrozole was 1.4. And
6 the two-sided 95 percent confidence interval for the hazard
7 ratio was 1.24 to 1.56. We have to make a decision on
8 which of these estimates is to be used as the control
9 effect size for computing sample sizes for the future
10 studies.

11 We also need to know how much of the effect we
12 are willing to give up or, putting it another way, what
13 proportion of the active control effect should be preferred
14 that is deemed clinically meaningful.

15 As a first step, we need to estimate the sample
16 size of the active control effect. From a given study or
17 studies, we generally describe the effect by a point
18 estimate and a two-sided 95-percent confidence interval.
19 That is, we can say with 95 percent confidence that the
20 true effect is anywhere between these two limits.

21 Potentially, we can consider four methods to
22 estimate the true control effect. If we choose the point
23 estimate as the estimated active control effect, then this
24 will inflate the type 1 error. On the other hand, if we
25 choose the other extreme, the lower 95 percent confidence

1 limit as the estimated control effect, then the type 1
2 error will be very small.

3 A compromise is to use a lower gamma percent
4 limit as the estimated control effect, which will ensure
5 type 1 error to be .025. Choosing a fixed margin approach,
6 such as less than or equal to 10 percent, or any other
7 fixed margin, is quite arbitrary. Whatever we choose as
8 our estimate of the control effect, we have to then decide
9 on which of that effect we are willing to give up or, in
10 other words, how much of that effect we feel compelled
11 should be retained by the new drug.

12 In the next few slides, I will present
13 estimated sample sizes under different design criteria,
14 with response rate as the endpoint. In this slide, I'm
15 using point estimate as the estimate of true letrozole
16 effect. As I mentioned earlier, I'm using letrozole for
17 illustration purposes only as the comparator here. That
18 is, the point estimate of control effect size of letrozole
19 is 30 percent. The first column gives the sample sizes
20 required, retaining delta percent of the 30 percent.

21 For example, if 50 percent of the effect, or 15
22 percent response rate, should be retained, then a sample
23 size of 300 is necessary. When simulations of studies
24 designed where the point estimates are conducted, it can be
25 shown that in fact the type 1 error alpha is always greater

1 | than .025. This can also be proved mathematically, and
2 | therefore this is a less than optimum design and not
3 | recommended to be used. The purpose of presenting this
4 | approach here is only to illustrate the concept and not to
5 | use in the future designing of the trials.

6 | Suppose we want to retain some fraction of
7 | letrozole advantage over tamoxifen. That is, we define
8 | active control effect as the difference in effect between
9 | letrozole and tamoxifen. And assume letrozole has a
10 | response rate of 30 percent and tamoxifen 20 percent.
11 | Then, for example, to retain 50 percent of the effect --
12 | that is, the response rate of at least 25 percent with a
13 | new drug product X -- the total sample size required is
14 | 1,319.

15 | If we consider the lower 95 percent confidence
16 | limit as the estimate of active control, then the
17 | letrozole-tamoxifen study, the lower two-sided 95 percent
18 | confidence limit of response rate was 26 percent. In order
19 | to retain 50 percent of this effect, a total sample size of
20 | 360 patients is required.

21 | However, using a fixed margin that we have used
22 | historically with tamoxifen as the active control -- that
23 | is, the lower limit of the 95 percent confidence interval
24 | for the difference in response between drug X and letrozole
25 | to be less than or equal to 10 percent -- the sample size

1 required is a total of 660 patients.

2 In the next few slides time to progression is
3 considered as the endpoint of interest. In this slide, the
4 effect size used is the point estimate of hazard ratio of
5 tamoxifen to letrozole. Note that this is not the placebo
6 versus letrozole effect size. The point estimate of the
7 hazard ratio of tamoxifen to letrozole in the
8 tamoxifen-letrozole study was 1.4. If, for example, we
9 retain 50 percent of the letrozole effect over tamoxifen,
10 then the total number of events, and not patients, required
11 is 944.

12 Incidentally, the point estimate of the hazard
13 ratio of tamoxifen to anastrozole was also 1.4 when a
14 meta-analysis of the two registration studies was conducted
15 using point estimate, again, as a suboptimal approach and
16 not recommended, as it inflates type 1 error.

17 On the other hand, if we consider the lower 95
18 percent confidence limit of the hazard ratio of tamoxifen
19 to letrozole as the estimate of the active control effect,
20 with time to progression as the endpoint, then in order to
21 retain, for example, 50 percent of letrozole effect over
22 tamoxifen, a total of 3,542 events -- and again, not number
23 of patients -- are required, as presented in the table
24 under the title "Letrozole" here.

25 This is a conservative approach. Simulations

1 of such designs show that the type 1 error is much less
2 than .025. For example, the type 1 error can be as low as
3 0.007.

4 For purposes of illustration only, a
5 meta-analysis of two registrations studies of anastrozole
6 was conducted. We do not recommend meta-analysis of these
7 two studies. Just to recap Dr. Cortazar and Dr. Honig's
8 remark, there were two randomized trials -- one conducted
9 in the U.S. and the other in Europe -- of anastrozole
10 compared to tamoxifen. Both studies demonstrated
11 non-inferiority with respect to response rate. And the
12 smaller of the two studies, the U.S. study, demonstrated
13 superiority in time to progression.

14 The patient population characteristics were
15 different in the two studies, particularly with respect to
16 number of ER-positive patients. Thus, we do not recommend
17 conducting a meta-analysis of these two studies. And, once
18 again, it is presented here for purposes of illustration
19 only.

20 Using the results of this "meta-analysis," and
21 using the lower 95 percent confidence limit of hazard ratio
22 of tamoxifen to anastrozole as the estimate of the active
23 control effect, sample size estimates are presented in the
24 second table under the title "Anastrozole." The sample
25 size estimates using anastrozole as the active control are

1 much larger than the estimates using letrozole as the
2 active control.

3 A less conservative approach but one that
4 preserves type 1 error of .025 is currently under
5 development and testing by the CDER Oncology Statistical
6 Reviewers Team. In this approach, for example, in order to
7 retain 50 percent of the letrozole effect over tamoxifen
8 with respect to time to progression and preserve type 1
9 error of .025, the total number of events -- again, not
10 number of patients -- required is 1,427. This translates
11 to using a 55 percent lower confidence limit as an estimate
12 of the control effect instead of the conservative lower 95
13 percent confidence limit. Because of the fact that in this
14 approach type 1 error is fixed depending on the percent of
15 effect retained, the percent confidence limit varies, as
16 listed in this table.

17 Similarly, using the meta-analysis results of
18 the two anastrozole studies for the purposes of
19 illustration only, the sample size estimates are presented
20 in the table under the title "Anastrozole." Again, we do
21 not recommend this meta-analysis, and the sample size
22 estimates using anastrozole as the active control are
23 larger than the estimates using letrozole as the active
24 control, as presented here.

25 In summary, with response rate as the endpoint,

1 and say, for example, we decide that 50 percent of the
2 active control effect should be retained, then the sample
3 sizes, using the different estimates of control effect, are
4 presented in this summary slide. The sample sizes range
5 from about 300 to about 1,300. It should be kept in mind
6 that, generally, using point estimates are not recommended,
7 as they tend to inflate type 1 error.

8 This slide summarizes the sample sizes using
9 different estimates of control effect, with time to
10 progression as the endpoint, and assuming 50 percent of the
11 active control effect should be retained. The sample sizes
12 vary, approximately from about 1,000 to 3,500 events -- and
13 not patients.

14 Again, the point estimate approach tends to
15 increase type 1 error. The lower 95 percent confidence
16 limit approach is a conservative approach. And also,
17 retaining 50 percent of control effect is not set in stone,
18 and it depends on specific disease setting and the control
19 effect that we are willing to give up.

20 We should also seriously consider conducting
21 superiority studies with tamoxifen or letrozole as the
22 active control comparator. Here are sample sizes estimates
23 when tamoxifen is used as the comparator, and assuming new
24 drug product X will have an effect similar to letrozole.
25 If response rate is used as the endpoint, then to

1 demonstrate superiority, a total sample size of 586
2 patients are required. Whereas, if time to progression is
3 used as the endpoint, then a total of 200 events are
4 necessary to detect a significant difference. In both
5 cases, a power of 80 percent and a one-sided alpha of .025
6 is assumed.

7 The important points to be kept in perspective
8 in designing future first-line metastatic breast cancer
9 trials are that the active control letrozole effect is
10 estimated from a single, large, well-conducted randomized
11 study, which has shown convincing evidence of superiority.
12 However, we do not have information on between-study
13 variability, and it is possible that the effect size is
14 overestimated.

15 Secondly, the effect size with respect to time
16 to progression is letrozole versus tamoxifen, and not the
17 way we generally define active control effect, which is
18 comparing control to placebo. In general, when the active
19 control effect size is estimated from a single study, if a
20 non-inferiority study is being considered, then it is
21 advisable to use a conservative approach.

22 Furthermore, we do not have data to estimate
23 tamoxifen effect versus placebo with respect to time to
24 progression.

25 Also, when we are considering especially

1 non-inferiority trials, replication of well-controlled
2 randomized studies are mandatory. To prove non-inferiority
3 compared to an active control, a large number of patients
4 are necessary. And if time to progression is used as the
5 endpoint, then even more patients will be necessary.

6 In conclusion, the issues that need to be
7 discussed for designing future trials in first-line
8 treatment of metastatic breast cancer are: Should we
9 conduct studies where the new drug product X is superior to
10 letrozole or drug X is superior to tamoxifen? Or should we
11 conduct future studies as non-inferiority trials, comparing
12 to letrozole, since letrozole has shown superiority over
13 tamoxifen?

14 If in fact we are considering non-inferiority
15 trials, should we preserve 75 percent of the active control
16 effect or 50 percent of the active control effect? That
17 is, how much of the active control effect are we willing to
18 give up?

19 The other important issue is regarding
20 selection of endpoint, given that both response rate and
21 time to progression are surrogate endpoints. We are
22 waiting for updated data on survival from the
23 letrozole-tamoxifen study. If in fact letrozole
24 demonstrates superiority over tamoxifen with respect to
25 survival, then should we consider survival as the endpoint?

1 Finally, I have presented to you the
2 approximate estimated sample sizes using different
3 approaches and endpoints. Given this data, are
4 non-inferiority studies feasible?

5 Thank you.

6 DR. HONIG: So, in summary, some of the things
7 that we want you to think about and discuss with us this
8 morning are the fact that, as you've seen, tamoxifen has
9 been the comparator most frequently used in the first-line
10 setting. Is letrozole superior? Are all aromatase
11 inhibitors superior? Should we consider some change in the
12 comparator standard? What about the endpoints? We've
13 traditionally used response rate; should we continue to use
14 it? Should we change to time to progression?

15 If we do, because of the data set that you've
16 heard described several times this morning, it would
17 require non-inferiority to letrozole or superiority to
18 tamoxifen, because of available data, and probably a larger
19 sample size.

20 Finally, what about the trial design? Can we
21 continue to ask for non-inferiority to any first-line
22 hormonal drug, or does superiority to tamoxifen need to be
23 demonstrated, either directly or indirectly?

24 So, with that perspective, we would like to
25 then turn the session back over to Dr. Nerenstone for some

1 discussion and questions to the committee. Thank you.

2 DR. NERENSTONE: Why don't we start with actual
3 questions from the committee to FDA about the presentation.

4 Dr. Blayney?

5 DR. BLAYNEY: I would like to make a statement.
6 I congratulate the speakers on their archaeologic
7 investigation.

8 But I think I was a little disappointed that
9 the discussion was not framed more broadly because we're
10 really talking, as I see it, as focusing on anti-estrogen
11 therapies. But this discussion could have, as a prototype
12 for drugs and agents, which are given with the intent of
13 targeting a defined receptor which has a high affinity
14 ligand, like the estrogen receptor in this particular
15 instance, but I think much more broadly, these agents are
16 orally available and given chronically. So, this says
17 something about how the endpoints are determined. Often
18 these agents are naturally occurring or analogs of
19 naturally occurring agents. They have minimal acute
20 toxicities and can have substantial long-term or cumulative
21 toxicities and difficult-to-measure endpoints.

22 And as I see this committee's work over the
23 next two or three years, there are a lot of agents we're
24 going to be asked to render advice on that could sort of
25 fit that construct, and it goes much more broadly than just

1 the anti-estrogens or the compounds that target the
2 estrogen receptor. I'm wondering if you're using this as a
3 prototype for those kinds of regulatory discussions or not?

4 DR. NERENSTONE: Dr. Temple?

5 DR. PAZDUR: No, we're not using it as a
6 prototype for future agents. We really have a concrete
7 example or a concrete discussion here on hormonal therapy
8 of breast cancer, particularly first-line therapy.

9 Obviously, we don't develop drugs in a vacuum
10 and interpret the results. So, could the results of this
11 discussion potentially have effects on future clinical
12 trials of agents that may be more in the cytostatic area?
13 Possibly they could. But our real attention now is to
14 focus on the hormonal therapies, and that's why we brought
15 this to the committee.

16 DR. BLAYNEY: You could substitute herceptin
17 for everything that we heard about this morning. And you
18 chose to view that as a chemotherapy agent. Is that right?

19 DR. TEMPLE: Here, again, that's handled by
20 CBER. So, you will have plenty of time to question them
21 tomorrow on their approvals on the drugs that they
22 regulate. However, we really want to focus on the hormonal
23 areas here.

24 Again, I can't say that this will never impact
25 what we do in other areas, but there are specific issues

1 with which comparators we use, how do we look at sample
2 sizes in hormonal therapies. And breast cancer and other
3 diseases probably have to be taken in some type of
4 perspective. The larger number of patients that have this
5 disease would perhaps reflect on the sample size that one
6 would be willing to commit to.

7 So, I think to just make broad statements
8 regarding classes of drugs without any definition of
9 disease has some limitations. And for this purpose we
10 really would like to focus on the breast cancer issue and
11 that's why we made this quite specific.

12 DR. NERENSTONE: Dr. Temple?

13 DR. TEMPLE: This is also something of a
14 historical oddity. With the continuing advice and counsel
15 of this committee for a wide variety of agents, whether
16 cytotoxic or cytostatic, we've been told over and over
17 again that meaningful clinical endpoints -- such as
18 survival or symptomatic improvement -- are what is needed.
19 There has been even skepticism about time to progression.
20 When we have put that forth as a possible endpoint, we've
21 mostly had our head handed to us, I would say.

22 But here is a longstanding practice of
23 approving based entirely on response rates. Well, for the
24 first time, one drug seems to have been shown to improve
25 something that some people would say is more clinically

1 | meaningful. I'm sure you could have a debate about that,
2 | too. And so we are asking about what to do now that the
3 | ground may be shifting a little bit. How does the
4 | committee feel about what we used to do? And we are also
5 | trying to point out what the alternatives involve in terms
6 | of sample size assumptions and difficulties. Because, as
7 | you can see, the studies get up to pretty large numbers
8 | pretty quickly once you leave response rate.

9 | DR. NERENSTONE: Dr. George?

10 | DR. GEORGE: I have a question about the
11 | survival. There was a statement made somewhere that
12 | survival was being considered as a safety issue, not an
13 | efficacy issue. And I didn't understand that comment, so I
14 | need a little explanation of that. And just to be clear,
15 | what would happen if the letrozole results come in with
16 | inferior survival at this point?

17 | DR. NERENSTONE: Dr. Honig?

18 | DR. HONIG: Let me take the first part of your
19 | question first. When we said it's a safety endpoint, it's
20 | more that because we've considered response rate to be a
21 | sufficient endpoint in and of itself, we have not required
22 | the very large studies that would be needed to show that
23 | survival was not inferior in a strict statistical sense.
24 | When we said they have been submitted as a safety concern,
25 | it has been to make sure that they are approximately

1 similar and, as you mentioned, that one drug is not clearly
2 worse than the other.

3 If letrozole were inferior, I think we would be
4 analyzing the data carefully and probably coming back to
5 the committee. That is not impossible, I suppose, but
6 would be a little bit different from what we have observed
7 in most studies, where you're ahead on response rate and
8 time to progression and it would be unusual to see a
9 survival decrement.

10 DR. NERENSTONE: Dr. Przepiorka?

11 DR. PRZEPIORKA: Dr. Honig, just for the
12 record, could you please let us know how the FDA deals with
13 deaths when determining time to progression?

14 DR. HONIG: I'm not sure that we have a blanket
15 standing on that. Survival is analyzed separately. And
16 generally, what I think most of us have done for time to
17 progression is we have tried to use -- and other people can
18 chime in if they wish -- tried to use the date that
19 patients were last evaluated. It's a little bit difficult
20 if someone is lost to follow-up and then you get a death
21 data that's significantly longer and then use that as a
22 progression date. You don't know what's happened to them
23 in the meantime. If there has been careful follow-up, it
24 doesn't appreciably affect your analysis of that outcome.
25 But that's, I think, what we have generally tried to do.

1 They're censored at the date of last evaluation.

2 DR. NERENSTONE: Dr. Temple?

3 DR. TEMPLE: They're censored at time of the
4 last visit. They are not considered to have progressed.
5 People could argue about that. They could say, well, at
6 least consider them to have had the event when they are
7 dead. But, as Susan said, if you don't have good
8 follow-up, that may be giving them a little extra credit
9 for time to event. So, there is a controversy about that,
10 I would say. It's much better to follow everybody well.

11 DR. PRZEPIORKA: So, potentially, if someone
12 could be dying of an effect of their cancer, despite the
13 fact that they don't have an objective increase in tumor
14 size, that would be censored, that would not be considered
15 progression.

16 DR. TEMPLE: Yes, that's right. That's why
17 there is an argument about it. That doesn't seem entirely
18 satisfactory either.

19 DR. PRZEPIORKA: And historically, have you not
20 considered failure-free survival rather than time to
21 progression? And what are your objections to using
22 failure-free survival, i.e., progression or death?

23 DR. HONIG: We have always considered them to
24 be really two separate things. I mean, we're looking at
25 survival/death versus time to progression. Time to

1 treatment failure, which is a little bit different, we have
2 tended not to look at so much because we think that it
3 combines a number of different aspects that can be
4 difficult to sort out. Did someone fail treatment because
5 of an adverse event? Did they progress? Did they just not
6 want to be in a clinical trial anymore? We have tended to
7 limit it to time to progression and survival.

8 And again, time to treatment failure actually
9 came up at our cytotoxic time to progression meeting where,
10 again, it was discussed and felt to not be a particularly
11 valid endpoint. I think Dr. Swain specifically mentioned
12 that in her talk.

13 DR. TEMPLE: But progression-free survival, if
14 you thought you had reasonable access to people and would
15 know if they progressed, would be a very attractive
16 endpoint. I don't think there is any doubt about that.

17 DR. NERENSTONE: Other questions? Dr. Sledge?

18 DR. SLEDGE: Typically, response has been
19 defined as CR plus PR. But in the breast cancer literature
20 for most of the last decade, the literature refers to CR
21 plus PR plus stable disease for, say, 6 months or longer as
22 sort of a clinical benefit endpoint. Does FDA, in
23 analyzing these studies, consider stable disease greater
24 than 6 months as a meaningful endpoint?

25 DR. HONIG: We haven't to date.

1 DR. TEMPLE: Of course, time to progression
2 endpoints capture some of that.

3 DR. NERENSTONE: I have a question. Just on
4 the basis of the letrozole studies, which a lot of the
5 committee has seen in some detail, the number of patients
6 involved was quite large. In fact, almost as large as two
7 independent studies with some of the other aromatase
8 inhibitors. How strongly do you feel that what I thought
9 was quite a significant and powerful improvement over the
10 tamoxifen, in terms of time to progression and response
11 rate, has to be repeated before the new drug can be used as
12 the new comparator?

13 DR. PAZDUR: I think this is why we are
14 bringing this to the committee, to get your opinion
15 regarding the data that we presented or was presented
16 previously. So, this is open for discussion.

17 DR. NERENSTONE: So, you don't have a
18 preconceived notion? Because some of the presenters did
19 say something about a single randomized trial is not
20 enough, or the implication in terms of regulatory
21 requirement.

22 DR. TEMPLE: This is an ongoing debate we have
23 all the time. There is a lot of situations in which people
24 no longer want to use placebos or no longer want to use
25 therapies that are considered inferior. So, the question

1 is, how can you use the available data to set a
2 non-inferiority margin? Well, when you only have one
3 study, that's a formidable task. You have to make a lot of
4 assumptions about constancy and all kinds of things.

5 As you saw, though, there are more and less
6 conservative ways to use the data you have. If you use the
7 point estimate, with its variance, that does not take into
8 account any change really. So that sometimes you resort to
9 a relatively conservative measure like the 95-percent lower
10 bound, which in this case isn't very far from the point
11 estimate because the study was very large. And the
12 response rate lower bound is 26 percent and not 30; that's
13 not so far. That is a more conservative way to use a
14 single study to set your non-inferiority margin. But there
15 is very little experience with this in either the oncology
16 or non-oncology world and it's an important current
17 problem.

18 DR. NERENSTONE: Dr. Sridhara?

19 DR. SRIDHARA: I was just going to complement
20 what Dr. Temple was saying just now, that whenever we are
21 designing non-inferiority trials and we have just one
22 study, then we don't have between-study variation that we
23 can get from several studies. So, the effect probably is
24 there, but is it really as big as it is seen in this one
25 study? That we can never tell. And so we will have to

1 take the conservative approach, which will really blow the
2 sample sizes quite high. But certainly I think there is
3 effect, and the p values were pretty strong in that study.

4 DR. NERENSTONE: Yes. Dr. Henderson.

5 DR. HENDERSON: I have two questions. The
6 first one, which maybe you should ask you before I ask the
7 second one, is what you are proposing here is a real sea
8 change based on one trial. And I think you have
9 acknowledged that. But is there any other time that you
10 can think of in regulating any of the cancer drugs where
11 such a huge change has taken place on the basis of a single
12 study? Have we done that before?

13 DR. TEMPLE: Well, you could say that some of
14 the tamoxifen adjuvant therapy places a new burden on
15 everybody to do something. Of course, there were multiple
16 trials, even though we relied on one or two ourselves. But
17 that sort of changed everything. You really had to be at
18 least as good as tamoxifen from that point on. But, to be
19 fair, that's more than one trial.

20 DR. HENDERSON: That's an interesting answer,
21 because you have switched. In that particular answer,
22 there are two things that are quite different, of course.
23 One is that you are talking about survival in a population
24 where many patients are going to have potentially very,
25 very long survival, and that is really the only endpoint in

1 that particular setting.

2 DR. TEMPLE: Well, oddly enough, not initially.
3 Our initial approval was based on time to progression. It
4 was only the meta-analyses that allowed one to conclude
5 that you actually had a survival effect. So, I don't know
6 how important you think that distinction is.

7 DR. HENDERSON: Good point. I think that is
8 relevant.

9 The second thing, of course, is that in the
10 metastatic disease setting, where you are dealing with
11 patients, 98 to 100 percent of whom are going to die, the
12 major issues become much more complex in terms of the way
13 physicians go about making decisions. Which kind of leads
14 into the second question that I wanted to ask. And that is
15 the implication of what you're saying is that you are
16 saying that drugs could be approved in one of two ways,
17 either by equivalence to letrozole or superiority to
18 tamoxifen. So, you're saying that if we have a new hormone
19 therapy that is equal to tamoxifen, at this point it
20 wouldn't be approved.

21 Now, if it were equivalent, and let's say you
22 had very tight confidence intervals. Let's say you are
23 losing only 3 or 4 percent of your control or 10 percent of
24 your control, but really tight confidence intervals and a
25 robust data set. You are saying, if that were equivalent

1 | to tamoxifen, even though tamoxifen is on the market, and
2 | even though anastrozole is on the market, that drug
3 | wouldn't be approved because it is equivalent to tamoxifen.

4 | But under those circumstances, wouldn't the
5 | drug fulfill the fundamental requirement that I always come
6 | back to, that it is effective, it's as effective as
7 | tamoxifen, and it is safe? As a class, all of these
8 | hormone drugs -- as a cancer doctor -- are remarkably safe,
9 | compared to everything else we use. Would we want to be in
10 | a position to say that that drug could not be used by
11 | patients?

12 | DR. NERENSTONE: Dr. Honig?

13 | DR. HONIG: That is really what we are asking
14 | today: Is it still enough? Do you think that this finding
15 | in the letrozole study is so clinically convincing that you
16 | don't think it is appropriate to compare it to tamoxifen,
17 | that you really do need to be better? It also gets into
18 | some, I guess, ethical questions, really, but that is what
19 | we are asking you.

20 | DR. HENDERSON: That's what you are proposing,
21 | either/or one of those two approaches; so there are many
22 | more options that we could get to?

23 | DR. HONIG: That's right.

24 | DR. NERENSTONE: Dr. Temple?

25 | DR. TEMPLE: Can I just add something. If the

1 | only thing you had was the difference in response rate, we
2 | might become quite uncomfortable saying, oh, well, you have
3 | to achieve the somewhat better response rate, because you
4 | wouldn't really know how much that mattered. It is the
5 | improvement in time to progression that raises this issue
6 | most strikingly, because, in some ways, that's the point
7 | and seems more important. If you had an increased
8 | survival, it would be almost obvious that you would use the
9 | better drug, unless it had unacceptable toxicity. So,
10 | there is some graded response.

11 | I mean, as an agency, we don't generally try to
12 | impose relative effectiveness requirements, but we make an
13 | exception when relative effectiveness has something to do
14 | with things like survival and other important endpoints.
15 | Whether time to progression is in that category is part of
16 | what is being talked about.

17 | DR. NERENSTONE: Dr. Carpenter?

18 | DR. CARPENTER: Would you be open to using or
19 | trying to get survival data on some of these things to use
20 | in a little different way? I think it is quite possible
21 | that no matter what the response rates or the duration of
22 | disease control or time to progression, whatever you want
23 | to use, they may vary from one class to another or one drug
24 | to another, but it is quite possible that in the long run
25 | we will do better as we have more classes of hormonal

1 | drugs. We may provide longer benefit, but we may not
2 | impact survival very much at all.

3 | So, the question will be in the clinic, which
4 | do you start with first? Because is probably gives you the
5 | highest chance of improvement now, even though you are
6 | logically going to progress to use the other drug classes,
7 | and sometimes perhaps different drugs in a class, to get
8 | the sequential benefit to get as much as you can for that
9 | patient of hormonal therapy. If you had a non-inferiority
10 | of survival, these other endpoints get to be points of
11 | discussion, but perhaps not as serious a point as long as
12 | the provide some level of effectiveness.

13 | The other issue is that what we are all trying
14 | to get at I think is clinical benefit. As Dr. Sledge
15 | noted, some degree of stability in the clinic at least
16 | seems to be rather a useful concept. Although it has been
17 | defined in different ways, the current one is the one most
18 | widely used, which he gives. When I tell people to
19 | evaluate these studies, I frequently tell them that, if you
20 | want to get a fair -- because of the bone-only problem,
21 | which is the biggest single group of people, response rate
22 | just doesn't capture clinical benefit very much. And even
23 | when it does, it only captures it for a subset of the
24 | patient population.

25 | Some way of looking at the degree of

1 progression on study probably gives you the best idea about
2 how to compare the different agents. And if we can push
3 our endpoint in that direction, I think, if survival is not
4 inferior, then would you consider that to be a relatively
5 fair way to do this?

6 DR. NERENSTONE: Dr. Pazdur?

7 DR. PAZDUR: Basically, what you're trying to
8 propose is more of a sequential approach to the hormonal
9 therapies, because obviously everybody realizes that these
10 hormones, in general practice or in an oncology practice,
11 are used sequentially as long as there is no inferiority in
12 terms of survival. I think this is also a point that we
13 would like discussion on. It reflects what is going on in
14 real practice obviously.

15 On all of these approvals, we do look at
16 survival, even though we approve the drugs on response rate
17 or time to progression. Obviously formal non-inferiority
18 analysis of these survivals have not been done to date, for
19 the most part, but we have taken a look and we do take a
20 look at the survival of the patients even after approval of
21 the drug.

22 DR. NERENSTONE: Dr. Blayney, then Dr. Temple.

23 DR. BLAYNEY: I would like to come back to two
24 things Dr. Henderson mentioned. One, this business of a
25 sea change in the regulation, I think the addition of

1 CPT-11, or when CPT-11 was approved and that set a new
2 adjuvant standard for a comparator arm, I think that may be
3 an example of the sea change you were talking about. And
4 two years later, I think we are rethinking that issue.

5 Which sort of goes to my second point, also,
6 that 98 percent of women with this illness will die of the
7 illness. I think with the serial responses that we are
8 seeing to one after another, as was pointed out earlier,
9 member of these women don't die of breast cancer and go on
10 to long productive lives and have comorbidity. I think
11 that I take from this that we ought to set the bar rather
12 low for approval of these things so that women who are
13 candidates for the fourth- and fifth-line hormone
14 anti-estrogen treatment will have those drugs available to
15 them.

16 DR. TEMPLE: One thing about survival, as has
17 been said, nobody has been insisting on an advantage in
18 survival here partly because of what you said -- maybe you
19 just can't achieve that -- but also partly because
20 everybody crosses over. And unless being on one drug stops
21 the effect of the other, the crossover will obliterate any
22 conceivable survival advantage. That has come up in
23 discussions before, and I think it is a problem all over.

24 One of the things we have been pestering people
25 about is time to symptomatic progression, which would be an

1 unequivocal beneficial effect that we could all say, oh,
2 yes, that is not a surrogate, but we haven't seen much
3 attempt to do that so far.

4 DR. NERENSTONE: I would like to go back -- and
5 right now the committee is supposed to be asking questions
6 about the presentation to FDA before getting into
7 discussion -- because otherwise then we will break for a
8 few minutes. Does anyone have any other questions
9 specifically about the FDA presentation or clarification of
10 regulatory issues?

11 Dr. Davidson?

12 DR. DAVIDSON: In the question you asked you
13 avoided anything related to receptor status, is that in
14 fact your intent?

15 DR. NERENSTONE: Dr. Pazdur?

16 DR. PAZDUR: We discussed this at our last
17 meeting. And it was the feeling really of the committee,
18 basically, that we would like to encourage the population
19 to have estrogen receptor positivity rather than this
20 admixture of estrogen unknown, estrogen positive. And I
21 think, to reflect a more U.S. standard, where the test is
22 relatively universally available in the United States, that
23 as we approach newer trials, we're going to probably be
24 demanding estrogen receptor status known rather than this
25 garbage bag of estrogen receptor unknown. And that's per

1 previous discussion we had with letrozole.

2 DR. NERENSTONE: Dr. George?

3 DR. GEORGE: I have a question about the issue
4 of superiority and non-inferiority. Suppose you did a
5 superiority trial with tamoxifen as the comparator. It
6 didn't quite make it as a superior agent, but it was
7 clearly non-inferior by the usual standards. Is there any
8 history or background in approving such a thing after the
9 fact?

10 DR. SRIDHARA: I think Dr. Cortazar presented
11 this. Most of these studies were actually designed as
12 superiority studies and they ended up being non-inferior
13 studies. So, we have done that before.

14 But the question is, with a superior drug now,
15 can we do that anymore? Is it ethical to consider then,
16 having designed a superiority trial, to give a
17 non-inferiority approval?

18 DR. NERENSTONE: Dr. Pazdur?

19 DR. PAZDUR: I think we have to be realistic of
20 how we develop and eventually use these drugs in the United
21 States. If we want to say we'll be doing superiority
22 studies against tamoxifen in the first-line setting, one
23 would have to say that clinicians and physicians would be
24 willing to go on tamoxifen as a first-line comparator to a
25 new agent. And that's a question that we are asking you

1 | also: Does that make sense, given data of time to
2 | progression improvement and improvement in response rate
3 | for the aromatase inhibitors?

4 | Secondly, we have to be cognizant of the fact
5 | that many patients are receiving tamoxifen in the adjuvant
6 | setting. Does that have an impact on whether we could even
7 | use tamoxifen, and what would be the accrual of first-line
8 | hormonal studies in that setting also? So, we have to take
9 | a look not only at the statistical issues but what makes
10 | sense from a perspective of developing these drugs.

11 | DR. NERENSTONE: Ms. Mayer?

12 | MS. MAYER: Getting back to Dr. Carpenter's
13 | comments about sequencing hormonal therapies, I am
14 | wondering if there is any consideration being given to
15 | looking at requiring comparators within classes of hormonal
16 | drugs or whether that is possible to do so that a single
17 | standard -- say letrozole -- is not then going to replace
18 | tamoxifen, since, as he and others pointed out, that's not
19 | really the reality of clinical practice.

20 | DR. PAZDUR: I think it would be difficult to
21 | answer that question. We have been traditionally doing
22 | studies against tamoxifen, since that had been kind of the
23 | gold standard. We do not have obviously a comparison of
24 | the aromatase inhibitors head to head, as was pointed out.
25 | And therefore it makes comparisons much more difficult to

1 claim one as the victor and one as the second drug here.
2 And we are by no means doing that.

3 I think as was pointed out by Pat Cortazar's
4 presentation and also Dr. Buzdar's presentation, there are
5 multiple problems when one tries to make cross-study
6 comparisons. The number of estrogen unknown status
7 patients that could dramatically influence the results of
8 time to comparison response rates really makes cross-study
9 comparisons very difficult. There has been no head-to-head
10 comparisons of the aromatase inhibitors. And here again,
11 if somebody is developing a new aromatase inhibitor, this
12 is one of the reasons we are bringing it to the committee.
13 Should we demand them to look at an aromatase inhibitor?

14 DR. NERENSTONE: Dr. Temple?

15 DR. TEMPLE: I just wanted to go back to
16 Dr. George's question, which is actually extremely complex
17 and interacts with all the various questions we are asking.
18 If the committee still believes that response rate alone is
19 informative and that being about as good as tamoxifen is
20 still good enough, then the answer is if you tried to be
21 better than tamoxifen but didn't quite make it, you would
22 easily be able to conclude that you met a fairly high
23 non-inferiority standard for response rate.

24 On the other hand, for time to progression, if
25 you tried to be superior and didn't make it, since we have

1 | no idea what the effect of tamoxifen on time to progression
2 | is, in a technical sense, we wouldn't know what you could
3 | do with time to progression.

4 | Now, in other settings, including some that
5 | came to this committee, in lung cancer, there was some
6 | sense that, well, we may not know exactly what tamoxifen
7 | does, but it must have at least a little effect. So, if
8 | you almost made it, there would probably be some sentiment
9 | to say, well, time to progression is probably okay, too,
10 | but that would be very hard to do rigorously without being
11 | able to set a non-inferiority delta.

12 | So, all of the questions that are being asked
13 | really go to interpreting that study: Is response rate
14 | good enough? Do you have to have some information about
15 | time to progression? And so on. So, you can't answer it
16 | abstractly.

17 | DR. NERENSTONE: Dr. Przepiorka?

18 | DR. PRZEPIORKA: A theoretical question. If
19 | drug X is shown to be effective and 20 years later drugs A,
20 | B, and C come out and are shown to be more effective than
21 | drug X for a first-line therapy, what do you do with your
22 | approval for drug X?

23 | DR. TEMPLE: It's unusual. Again, superior
24 | here would have to be something so important that you'd
25 | consider the last satisfactory drugs just not acceptable

1 | anymore. There are cases where I am sure we would consider
2 | saying it's not reasonable to use this anymore. I can't
3 | come up with one, however, off the top of my head, because
4 | you don't often have the precise data you want. You
5 | usually, for example, don't know that the new drug is
6 | better than the old one; you just know that something new
7 | and good has been shown about the new one and you didn't
8 | know that about the old one.

9 | For example, leaving oncology, we know that the
10 | statins improve survival when you give them to people who
11 | have had a heart attack and in a variety of other settings.
12 | Well, we don't know about that about clofibrate. And in
13 | fact some attempts to show that clofibrate does that have
14 | failed.

15 | I don't think anybody is too eager to get rid
16 | of clofibrate despite that, because everybody knows that
17 | one group of drugs does it and you still need the
18 | alternatives around for people who don't respond or can't
19 | tolerate it or something like that. But there would be
20 | circumstances in which a drug would truly become outmoded.
21 | And I think if that were absolutely very clear, we might
22 | try to make it so. But I can't think of very many
23 | examples.

24 | DR. PAZDUR: But then that is usually handled
25 | by medical practice in general.

1 The issue when we would take something off is
2 mainly a safety issue. And is there such a lack of
3 efficacy in that drug, in the proposed indication, that it
4 would constitute a safety issue? That may be a
5 consideration where we might consider formal action against
6 a drug.

7 DR. NERENSTONE: Dr. Lippman?

8 DR. LIPPMAN: You say you can't think of an
9 example, but isn't that sort of the issue with tamoxifen
10 here? We heard Dr. Buzdar saying that it's no longer used
11 first-line. They believe the aromatase inhibitors are
12 better. And so in the case, this is exactly the point that
13 Dr. Przepiorka made.

14 Now, again, the debate is whether one large
15 trial will do that. But if you believe this one large
16 trial and it's definitive, then, in a sense, you are going
17 back to what to say about tamoxifen in this setting. So,
18 it seems that this discussion is very relevant to that
19 point.

20 DR. NERENSTONE: Okay. Why don't we take a
21 break at this point. If everyone could be back by 10:20,
22 and we'll resume discussion within the committee.

23 (Recess.)

24 DR. NERENSTONE: What I would like to do now is
25 open this up for general discussion before we get to the

1 specific questions. Any general comments people want to
2 make?

3 (No response.)

4 DR. NERENSTONE: Okay. Then why don't we look
5 at the questions to the committee. The first one:

6 Toremifene, anastrozole and letrozole were all
7 approved by the FDA based on randomized clinical trials
8 using tamoxifen as the comparator.

9 Letrozole was approved by the FDA based on
10 superiority to tamoxifen for response rate and time to
11 progression, while the toremifene and anastrozole were
12 approved by the FDA based on non-inferiority to tamoxifen
13 for response rate and/or time to progression. Anastrozole
14 demonstrated superiority in time to progression in one of
15 their small trials.

16 There has been no direct comparison in the same
17 randomized clinical trial of the three drugs.

18 The first question: Do the data presented
19 allow the FDA to designate one hormonal drug as the
20 comparator in future randomized clinical trials of new
21 hormonal drugs for this use?

22 Actually, I would be happy to open the
23 discussion. I have to have a little bit of a disclaimer,
24 because I was really not on ODAC at the time of the other
25 approvals. I was only here for the letrozole. And I was

1 | impressed by the quality of their data, the clinical trial
2 | design, and the numbers. That's the one trial that did
3 | show a superiority for time to progression and response
4 | rate. And I have to say that, on the basis of that one
5 | trial, it has changed my clinical practice, as well as the
6 | clinical practice of many of the oncologists in practice.

7 | So, from my perspective, I do think that the
8 | bar has been raised by this trial and that looking at that
9 | as a new gold standard could certainly be considered, and I
10 | think appropriate, for the design of future clinical trials
11 | in first-line metastatic breast cancer in the ER/PR
12 | postmenopausal women.

13 | Any other discussion? Dr. Kelsen?

14 | DR. KELSEN: I think the way this question is
15 | written, it does address that point. Is this agent of this
16 | class -- as I read this question -- this drug, Femara, from
17 | this class -- so clearly superior to other agents of that
18 | class -- looking sort of at 1b as well -- that it should be
19 | the comparator arm for all future studies, and that
20 | designing trials for other aromatase inhibitors would be
21 | inappropriate?

22 | I would be a little nervous about making that
23 | leap, because I don't know of data in which one aromatase
24 | inhibitor was clearly superior to another aromatase
25 | inhibitor. And although I certainly agree with your

1 | comments about the well-done design that led to the
2 | indication for therapy for Femara, is it such a powerful
3 | finding that it should override the ability of
4 | investigators to use another drug of that class?

5 | I might be anticipating a little bit 1b. I
6 | guess my question would be: What would be the data to say
7 | that that agent is much better than all other agents in
8 | that class?

9 | DR. NERENSTONE: Dr. Davidson?

10 | DR. DAVIDSON: I think I would support
11 | Dr. Kelsen. It seems to me that we've learned our lesson
12 | with supporting a single randomized trial. Sometimes it's
13 | right and sometimes follow-up studies suggest it's not.
14 | So, I'm nervous about using that as our sole source of
15 | information here.

16 | I think it is hard to do indirect comparisons
17 | between these trials, and I don't think we have any reason
18 | to know or not know that anastrozole or exemestane are as
19 | good as, worse or better. So, I would be uncomfortable
20 | about excluding them.

21 | DR. NERENSTONE: Dr. Albain?

22 | DR. ALBAIN: I think, too, if you look at the
23 | time to progression for the tamoxifen alone arm -- if you
24 | take the anastrozole ER-positive group and you take the
25 | letrozole trial -- the TTP's for tamoxifen are very

1 similar. So that gives some credence, I think, to the
2 concept that this may be more a class effect than a single
3 drug -- with all the other comments I agree with. I think
4 anastrozole and letrozole provide a similar degree of
5 benefit, if you look at the ER-positive group, then you
6 have some confidence that the control arms are giving a
7 very similar time to progression for tamoxifen in each of
8 those two trials.

9 I think toremifene is another. It's included
10 here in this question, but I think that would require a
11 different discussion than anastrozole or letrozole.

12 DR. NERENSTONE: Dr. Henderson?

13 DR. HENDERSON: First, with regard to your
14 beginning remarks, I was here when some of the earlier
15 trials took place. And in that era, we thought they were
16 pretty good, too, partly because this class of drug has
17 been characterized frequently by high-quality trials with a
18 lot more statistical power, and of course a lot less
19 toxicity than most of the stuff that this panel deals with.

20 But more important to the point here is that I
21 think if there were a compelling scientific reason why
22 letrozole should be superior, that would weigh in here, as
23 well. And although you can generate hypotheses about what
24 we know about the differences in the aromatase inhibitor,
25 those hypotheses have not really been borne out yet by

1 rigorous scientific testing of the hypotheses. That is,
2 for example, the degree to which they may inhibit the
3 aromatase. We dealt with this with levamisole and 5-FU.

4 It was very difficult to approve those two
5 drugs as adjuvant for colon in part because the scientific
6 reason why levamisole should be additive there was not
7 clear and it caused the panel a great deal of agony,
8 saying, we are skeptical, inherently skeptical. And I
9 think that that kind of skepticism should apply here, as
10 well, because we don't know why letrozole should be
11 superior. It may in fact be correct, but there is a lot of
12 work yet to be done at both the basic and even at the
13 clinical level before we can reach that conclusion.

14 DR. NERENSTONE: Dr. Lippman?

15 DR. LIPPMAN: Some of this relates to
16 philosophical differences. I actually would prefer a very
17 large, well-done, multi-center trial -- in this case -- of
18 about 1,000 women to two trials of 300 patients, and say
19 that they were confirmatory, but there are different
20 opinions regarding that. But in general what I think we do
21 here is when we evaluate a drug and we are comparing to a
22 standard of care and we determine with letrozole that the
23 drug is superior, that in many cases we have that question:
24 Have we redefined the standard of care to which other drugs
25 should be compared?

1 And to me, maybe this is more of a purist
2 approach, but I think, with that drug and that class, we
3 did define that. And letrozole may be the same as other
4 aromatase inhibitors, but we don't know that. So, this is
5 an incremental advance, and this becomes now the standard
6 of care, in my view, to compare other drugs.

7 DR. NERENSTONE: Dr. Sledge?

8 DR. SLEDGE: I would approach this slightly
9 differently, which is, looking at these two questions, 1a
10 and 1b, I probably would have done 1b before 1a.

11 I think the answer to 1b is yes. I think my
12 personal bias is that the aromatase inhibitors as a class
13 should represent the new comparator for future trials. I
14 say that partly for practical reasons. That is to say
15 that, in the United States at least, the vast majority of
16 estrogen receptor positive women get adjuvant tamoxifen.
17 So that when they fail, many clinicians are uncomfortable
18 going back to tamoxifen in that group.

19 But also partly because my suspicion is that,
20 based not only on the letrozole trial but also based on the
21 North American anastrozole trial, which I think is the
22 relevant comparator for that drug, we do see fairly
23 significant evidence of benefit as a class compared to
24 tamoxifen. The European anastrozole trial is, I think,
25 further evidence that the FDA should not accept trials that

1 fail to have estrogen and progesterone receptor
2 measurements as part of the analysis. I think that trial
3 is likely to have shown equivalence to tamoxifen in large
4 part because half of the patients we don't know the steroid
5 receptor status on.

6 So, again, the answer to question 1b, my bias
7 is, yes, we ought to be using the aromatase inhibitors as
8 our future comparator arm. I agree with several of my
9 colleagues around the table that I don't think we have a
10 clue which aromatase inhibitor is better. And I agree in
11 particular with Craig, we don't have any compelling
12 scientific reason to believe that any of the aromatase
13 inhibitors is superior to any of the others.

14 DR. NERENSTONE: Dr. Temple?

15 DR. TEMPLE: Just as a reminder, and I hope you
16 will discuss this as you go along, if one wanted, for
17 example, to do a non-inferiority study using time to
18 progression, you have to be able to describe what the
19 effect of the active control is. And even if all of the
20 aromatase inhibitors are really the same, you only have
21 data on that point for perhaps two of them, and much
22 stronger data for one of them. So, as a practical matter
23 in doing a trial, you have to be able to do that. You
24 can't do the trial until you can say what the effect size
25 is.

1 I guess you could say, oh, well, the effect
2 size is the same for all of them, even the ones that
3 haven't been studied, but that's quite a leap. So, there
4 is a practical component of this question, and if you were
5 to conclude that time to progression is the right endpoint
6 for study, because you only really have data on one or
7 maybe two.

8 DR. NERENSTONE: Dr. Blayney?

9 DR. BLAYNEY: I would take a somewhat contrary
10 position. I think that no is the answer to both questions.
11 I think breast cancer in postmenopausal women is one of our
12 wins in oncology, and the use of these hormonal agents, the
13 serial hormonal agents and serial responses, is predicated
14 upon the ability to have multiple agents available. And in
15 2001, as we sit here, we don't know what some of the
16 predictors of response are going to be two and three and
17 five years down the road. So, I would set the bar low.

18 And again, the letrozole study, while well
19 done, was primarily an offshore or non-U.S. study
20 population, many of the non-hard endpoints, such as death
21 and time to progression, are not strictly comparable to the
22 patients here in this country. So, while it was a good and
23 well-powered and it appeared to be a well-conducted study,
24 it is one study. And the example of CPT-11 changing the
25 treatment of adjuvant colon cancer for a year or two based

1 on one or two studies, I think we are backing away from
2 that now.

3 I would be very reluctant to jeopardize the
4 progress, both clinically and in a drug development arena,
5 that I see in metastatic breast cancer in estrogen receptor
6 positive women by setting the bar for new drug approval too
7 high.

8 DR. NERENSTONE: Dr. Redman?

9 DR. REDMAN: Yes, I agree with Dr. Blayney --
10 an example being if industry wants to use tamoxifen as a
11 comparator, I don't think you can say they can't use it and
12 they have to use anastrozole or letrozole. An example
13 being if they do choose it and they are able to get it
14 done, considering the standard of care hasn't shifted too
15 dramatically and a drug is shown to be superior to
16 tamoxifen, are you going to go back to them and say, well,
17 you have to compare it against letrozole? And I don't
18 think we're at that point at this time.

19 DR. NERENSTONE: Dr. Henderson?

20 DR. HENDERSON: I would like to respond to a
21 couple of points. First of all, the point that George
22 made. George, I would urge you to think about the
23 difference between what information is needed for you to
24 make a clinical decision as opposed to the information that
25 is required for approval. Because, in a sense, I think

1 that you have to always be careful that you're not making a
2 clinical decision based on your interpretation of the data
3 that you would now force every other doctor and patient in
4 the country to subscribe to. So, people may have different
5 views about a single trial, about statistical significance
6 and so on.

7 DR. SLEDGE: I'm not that presumptuous.

8 DR. HENDERSON: But once the FDA takes a
9 position that restricts choices, because they said this is
10 now the standard of care based on one trial, it can have an
11 impact that goes way beyond just a simple regulatory
12 process.

13 I think the issue of single versus multiple
14 trials -- I guess I would like to have my cake and eat it,
15 too. I would like to have both large trials but, in
16 addition to that, I think, fundamental to science, the
17 scientific method, the heart of science is that something
18 is reproducible. And therefore I'm always comfortable,
19 even if the second trial is smaller than the first, with
20 the idea of having a reproducible trial.

21 Why would that make a difference in this
22 particular setting? Well, we have already seen in the data
23 presented this morning that there can be a big difference
24 whether you have a mix of patients that is ER unknown or
25 even ER-negative with ER-positive patients, that the noise

1 can overwhelm the benefit. But one of the things that we
2 haven't dealt with very much in the regulatory arena, and
3 even outside the regulatory arena, is that there is
4 probably good correlation with the effect and the actual
5 level of receptor, and it's actually a continuum. This is
6 not something where it's either on or off. And we know
7 that very well.

8 So, if you have a trial of, let's say, 300
9 patients, by chance alone you could have an imbalance in
10 what is clearly a very important measurement that we don't
11 routinely do. So, it is another reason why you want to
12 wait until you have a couple of trials -- ideally, a couple
13 of large trials -- before making a decision.

14 And, finally, I think we have to be very
15 careful with one trial. We have to recognize that --
16 and the FDA did, in all fairness, make this point. I'm
17 just underscoring a point that was made very well, and that
18 is that we can be quite comfortable that within the
19 patients treated in the letrozole trial, that letrozole was
20 better and was significantly better, but there is probably
21 much, much less certainty about the size of the effect.
22 So, when we begin to make something the standard comparator
23 and we build into it an expectation of a size difference
24 which may in fact be quite a bit less -- and this is,
25 again, where multiple trials come in -- I think it causes

1 | problems down the line.

2 | So, for those three reasons, I would be very
3 | careful about defining either a drug or a class at this
4 | point in time. I just don't think we are there yet.

5 | DR. NERENSTONE: Dr. Lippman?

6 | DR. LIPPMAN: Just following up on the class
7 | issue that I think Dr. Blayney and others raised, I think
8 | that biologically we know how these drugs work, and there
9 | are a lot of agents coming down that have similar molecular
10 | targets. And so we feel more comfortable about talking
11 | about classes that may be similar. But I think there are a
12 | lot of examples where -- well, certainly all the
13 | anti-estrogens aren't the same, all interferon alphas
14 | aren't the same. And interferon alpha is a good example
15 | because two different brands produce different results, and
16 | one is FDA approved and one isn't in the same indication.
17 | We didn't make the leap that because it's a class, it was
18 | now a standard.

19 | And although I think probably the aromatase
20 | inhibitors as a group, at least listening to Dr. Buzdar's
21 | discussion, are superior, or appear to be better, than
22 | tamoxifen, I don't think we can lump them together. And I
23 | think the standards for comparison, if we pick one, are
24 | ones that actually have shown that it's superior and, of
25 | course, as Dr. Temple mentioned, in which we have data on

1 | the endpoints that we want to use in our control group.

2 | DR. NERENSTONE: I wanted to reiterate what
3 | Dr. Lippman said. I think that we are not saying that the
4 | other aromatase inhibitors are potentially inferior, it's
5 | just that we don't know where they are. But I don't think
6 | it is up to the FDA to make up the data. I think it is up
7 | to the other companies then to, if we pick a standard or we
8 | suggest a standard, it is up to the other companies then to
9 | do their non-inferiority trial if they want to be included
10 | as that new standard for other trials.

11 | It does not mean they are going to be pulled
12 | off the market. It does not mean that doctors are not
13 | going to have access to them. But my feeling is that the
14 | FDA should be looking forward, and saying what is the best
15 | data that we have. I think the question of whether this is
16 | the right time to do that or not is a legitimate one. But
17 | rather than say this whole class should be the new
18 | standard, I disagree with that. I think the other drugs
19 | have not proven that they have raised the bar. I think we
20 | only have one study where that, I feel, is relatively well
21 | described.

22 | Dr. George?

23 | DR. GEORGE: I will just vote here: no for
24 | both of these.

25 | Part of my reason has to do, I think, with what

1 Craig was getting at -- the strength of evidence from this
2 one study -- that a single study can have a very high
3 powered, a very high precision in the estimate,
4 particularly in this case, of response rate, but we are
5 uncomfortable that that study would be replicated exactly.
6 That is, there are a lot of other things that studies may
7 differ on, some of which we can't measure. And so it does
8 make us feel a lot more comfortable to have more than one.

9 And I in particular, if I were doing something
10 like trying to determine what the margin should be with
11 letrozole, I would have to pick a pretty low one; that is,
12 probably toward 25 percent rather than that 30 percent that
13 was observed. So, that would cause big troubles in the
14 design of studies, as we heard earlier.

15 DR. NERENSTONE: Dr. Sledge?

16 DR. SLEDGE: Getting back to something Craig
17 said earlier, I think, Craig, in all honesty, there is a
18 difference between being a purist and being relevant. And
19 my real concern here is that if we continue to use
20 tamoxifen as a standard comparator arm, we are going to
21 have a series of trials that will be essentially clinically
22 irrelevant.

23 The standard of care certainly does appear to
24 have moved in the direction of aromatase inhibitors as
25 first-line therapy for metastatic breast cancer. There is

1 a decreasing number of patients who will be available to go
2 on those trials. And the end result is that we are going
3 to have an increasing number of trials that are done
4 ex-U.S. rather than inside the U.S. And they will be done
5 in patient populations that are less relevant to what
6 practitioners see in the United States. I think that's a
7 real and legitimate concern. I think we need to have some
8 sense that the patient populations being studied are
9 similar to the patients we are treating in the United
10 States.

11 DR. NERENSTONE: Dr. Lippman?

12 DR. LIPPMAN: And we are now, retrospectively,
13 trying to remember what we saw at the letrozole meeting,
14 and it's difficult. But I remember at the time, as did Dr.
15 Nerenstone, that this was very compelling. The pivotal
16 trial was extremely compelling. And there were other data,
17 biologic data, clinical data, that were supportive of that.
18 And I think the committee at the time were overwhelmed and
19 it was extremely compelling. Now we're saying, oh, it's
20 only one trial; if we had another study of 50 patients that
21 was randomized to confirm it, we would feel better.

22 The point I'm trying to make is that it seems
23 to me every time we have a situation like that -- and I
24 don't remember this specifically -- but the FDA has a
25 question: Is this now the standard of care? Or at least

1 | we have these discussions. And it seems to me that, if it
2 | wasn't, it should be one of the questions at the end if
3 | it's approved. And at that time, when we are seeing the
4 | data and we're into it, then we make those sorts of
5 | decisions.

6 | And in some cases, I feel one trial may be
7 | definitive enough. The risk reduction trial of 13,000 I
8 | felt was definitive enough. I think in some cases it may
9 | not be. But it's hard now to do this without going through
10 | all the data and seeing that. I think that, again, on
11 | other sorts of issues like this, that is the time to make
12 | these kind of decisions and to go on record and say we feel
13 | that this should be the new standard of care, or maybe not,
14 | but that's the time.

15 | DR. NERENSTONE: Dr. Henderson?

16 | DR. HENDERSON: George, I take your point on
17 | relevance completely. But, again, I think this is not
18 | necessarily a regulatory issue.

19 | First of all, if you are trying to conduct a
20 | trial in which the results are not going to be relevant to
21 | practice, it is going to be very difficult to complete that
22 | trial. That is my first reaction. But you did address
23 | that very well by saying, well, the companies will go
24 | outside the U.S.

25 | But the second thing is that if a company wants

1 to market a drug in the United States, it is still going to
2 have to be relevant to physicians and patients in the
3 United States. So, I'm saying that I think the issue of
4 relevance is very important, again, for a physician and a
5 patient making a decision.

6 But is it critical for the regulatory process?
7 The regulatory process says, fundamentally, is the drug
8 safe and is it effective? The issue isn't whether it's
9 more effective than something else.

10 I think that was what Bob was getting at when
11 he was talking about response rates versus time to
12 treatment progression. And Nancy and I were kind of having
13 a side discussion. And our first reaction was, well, we
14 know what the time to treatment progression is. But the
15 problem is that if you stop and think it through, you know
16 that the probability of tumors shrinking without any
17 intervention is certainly substantially less than 20
18 percent, taking your cut point. But we can't do the same
19 thing with time to treatment failure. So, we were kind of
20 arguing that, and I didn't bring it up earlier.

21 But I always come back to the issue that the
22 role of the regulatory process is not to determine how
23 medicine is practiced, but ultimately to determine, does
24 this drug really work? The American public I think says,
25 we want to make sure it works. So, it has to do with

1 certainty. And then the second thing is it has to do with
2 is safety. We want to know if this is going to kill us or
3 if this is going to cause some side effect. Once that is
4 done, then how it is used is the job of doctors. That is
5 why we still train them and so on. We don't just sort of
6 give out a formula and say, here, everybody do what they
7 want.

8 So, I think relevance, again, is not a
9 regulatory issue; it is a practice issue.

10 DR. SLEDGE: But you know, Craig, if I were a
11 drug developer with a new hormonal therapy, only a fool,
12 given the choice of comparing it to an aromatase inhibitor
13 or tamoxifen, would choose the aromatase inhibitor.

14 DR. HENDERSON: That's why then the regulatory
15 process doesn't have to be worried about it.

16 DR. SLEDGE: I disagree.

17 DR. NERENSTONE: Ms. Mayer?

18 MS. MAYER: I will speak to that. I think that
19 patients with metastatic disease have a ticking clock.
20 They have a limited amount of time in which their disease
21 can be controlled by hormonal agents. And they really need
22 to know which are the most effective.

23 Right now there is confusion for patients among
24 the various aromatase inhibitors. If we continue to
25 compare new drugs to tamoxifen, when will the clarity come

1 for patients, knowing that they have a limited time and an
2 increasing number of drugs to choose from?

3 DR. NERENSTONE: Dr. Lippman?

4 DR. LIPPMAN: Again, when we talk about the
5 role of the regulatory agency -- and I would like to hear
6 from the FDA on this -- but I think that if we approve a
7 drug based on a tamoxifen control arm and then say, well,
8 physicians are trained and they all look at the data and
9 they will read all the articles and they will have journal
10 clubs and they will do all these things and make their
11 decisions, I'm not sure that that's appropriate.

12 Certainly at places like M.D. Anderson, where
13 doctors only see breast cancer and know every paper that's
14 published and they are up on this, that's fine. But I
15 think in many other settings, the FDA's recommendations are
16 interpreted as active drugs and equivalent. And I think
17 that if you approve a drug based on a tamoxifen control
18 arm, there may be many patients that get this drug that are
19 maybe unaware of the fact that it is inferior. I don't
20 know if you want to address that issue.

21 DR. NERENSTONE: Dr. Temple?

22 DR. TEMPLE: I'm only partly going to address
23 that, because we, more than anything, are worried about the
24 practicalities of these things. As a practical matter, for
25 a comparator of time to progression, a comparison in which

1 | you are better than tamoxifen is actually quite informative
2 | and would probably be as informative about the effect of
3 | the superior drug as a comparison to one of the aromatase
4 | inhibitors would be.

5 | I gather that there is a fair amount of doubt
6 | that anybody can do that study in this country anymore
7 | because nobody wants to be on the inferior drug. I mean,
8 | being part of a superiority study means that one of the
9 | drugs is inferior, so people probably wouldn't like that.
10 | But it would be informative.

11 | If time to progression turns out, as part of
12 | your discussion, to be the right endpoint, you really do
13 | have two choices that are not as far from each other as one
14 | might think. Being superior to tamoxifen and being
15 | non-inferior by some well-defined amount to one of the
16 | aromatase inhibitors are very close to the same thing.
17 | There is not that much room to be better than tamoxifen and
18 | clearly worse than one of the aromatase inhibitors.

19 | So, a lot depends on what endpoint is the right
20 | endpoint. Because what I just said doesn't apply if you
21 | continue to look at response rate. You can do a
22 | non-inferiority study to tamoxifen with respect to response
23 | rate if that is still considered a reasonable endpoint.
24 | And various people have said different things about whether
25 | they think that's still a reasonable thing to do.

1 As far as trying to set policy for the entire
2 country, we know that, to some extent, what the labeling
3 says could have the effect of doing that. Of course, we
4 are widely assured that oncologists ignore the labeling.
5 So, I don't know where to come out on that.

6 (Laughter.)

7 DR. PAZDUR: One of the other aspects is, can
8 you even do a tamoxifen trial for first-line, given the
9 data that is out there? Do you feel you are offering to
10 your patients in the United States the best therapy here?
11 So, I think this is also a practical question that needs to
12 be considered in discussing this question.

13 Don't forget, much of the data that came from
14 the letrozole study came from China and the former Soviet
15 Union. I'm not saying that that was the reason, but would
16 we force a situation where drug trials are done in
17 potentially disadvantaged countries just because they don't
18 have access to some of the newer agents? And how
19 meaningful and relevant would that data be then to the
20 United States?

21 DR. NERENSTONE: Other discussion? Dr.
22 Blayney?

23 DR. BLAYNEY: Let me ask you this. If you had
24 a drug that you wanted to test second-line against
25 tamoxifen, perhaps in letrozole failures or in anastrozole

1 failures or whatever, that is a place where tamoxifen might
2 be an appropriate comparator arm. I think this committee
3 should not handcuff you or the sponsors. I think we should
4 give you as broad a latitude as possible. And if a company
5 thinks that they can carry off a tamoxifen trial arm, then
6 they should be free to do that, as long as there are
7 certain constraints, most of which we have heard today.

8 DR. NERENSTONE: I think, though, you really
9 want first-line metastatic; the second-line and whatever
10 would be wide open.

11 DR. BLAYNEY: And may I just amend my remark,
12 too. I think the letrozole is one study, and I am very
13 reluctant to make big changes based on one study, however
14 well it was carried off. I think there are several drugs
15 that we have reviewed at this committee and earlier that
16 have been approved but have had very little impact on the
17 practice of oncology today -- some of the growth factors
18 and some of the others that we have mentioned.

19 DR. NERENSTONE: Dr. Lippman?

20 DR. LIPPMAN: Getting at the issue that
21 Dr. George raised about designing a superiority trial and
22 coming out with non-inferiority, and Dr. Sledge also raised
23 this, I think that if one were to use a tamoxifen control
24 arm in a study and were able to get it done, I think we
25 would have to sort of really hold the hard line that it has

1 | to be superior. I can easily envision the discussion where
2 | it is designed as a superiority trial, comes out to be
3 | equivalent, and then we have a discussion here saying,
4 | well, it is active and we want to get another drug out
5 | there and let's not throw the baby out with the bath water.

6 | So, I think that's the problem with using the
7 | tamoxifen control arm. If we stick with what Dr. Temple
8 | said -- and it has to be superior to tamoxifen -- in which
9 | case you have very little difference between an equivalence
10 | trial with an aromatase inhibitor and tamoxifen. The
11 | question is whether we can mandate that or at least make it
12 | clear that it has to be superior if it's a tamoxifen
13 | control arm.

14 | DR. NERENSTONE: Dr. Przepiorka?

15 | DR. PRZEPIORKA: One comment to follow up on
16 | some earlier logistic comments from Dr. Lippman is that
17 | perhaps if a company does come by with a single trial for
18 | approval, one might consider making it a phase IV
19 | commitment to do a confirmatory trial in a smaller number
20 | of patients so that in the future we don't have this
21 | problem about whether or not it's truly a new standard of
22 | care that will be there for us.

23 | But I would also like to agree with Dr. Lippman
24 | about, what are we going to do with tamoxifen. If we
25 | should decide that the answer to questions 1a and 1b are

1 both no, then essentially all the drugs are the same and we
2 either have to say that the studies have to be superiority
3 against all of them or equivalence to all of them. And I
4 would agree, I don't think anybody would be happy to
5 approve a drug that is equivalent to tamoxifen at this time
6 point.

7 DR. NERENSTONE: Dr. Albain?

8 DR. ALBAIN: The other piece to put into the
9 mix here -- and we don't know the answer yet -- but the
10 adjuvant trial of the aromatase inhibitors against
11 tamoxifen, and the combination, should be available soon --
12 from scuttlebutt at least. And of course, if it would then
13 emerge that the aromatase inhibitor is superior in that
14 setting, that's really going to affect this some more.
15 Because, as I recall, the pivotal trials for both the AIs
16 did allow prior adjuvant tamoxifen. I can't remember.

17 DR. NERENSTONE: Yes.

18 DR. ALBAIN: And do you remember what
19 percentage in those trials, approximately?

20 DR. HONIG: Marty, who is the letrozole
21 reviewer, says it was 20 percent of patients in the
22 letrozole study that had had prior tamoxifen.

23 DR. ALBAIN: So, if you were -- and this is not
24 necessarily how I'm going to vote -- but if you were going
25 to allow tamoxifen as the comparator for front-line trials,

1 I think you would have to be very rigorous not just in
2 receptor status but also prior adjuvant tamoxifen.

3 The other point I wanted to make was in terms
4 of safety profiles and risk/benefit profiles, and perhaps
5 the AIs have an edge there as well over tamoxifen, at least
6 in clinical practice, in that many women who cannot receive
7 tamoxifen for various reasons can still receive AIs. And
8 that's another reason why it has gone into widespread use
9 in the clinical setting.

10 DR. NERENSTONE: Dr. Temple?

11 DR. TEMPLE: Just a reminder that when one drug
12 does something that everybody considers extremely important
13 in a very convincing trial, it is not easy to mount the
14 second trial post-marketing. People don't want to be in
15 it. Survival is easy; you just can't. So, you never see
16 that. But even in this case it might be very difficult to
17 get anybody to do that trial.

18 DR. NERENSTONE: Dr. Pazdur?

19 DR. PAZDUR: I think this goes to Donna's
20 question. I think the data that we have is basically the
21 data that we're going to get. The likelihood of anybody
22 doing another trial of letrozole versus tamoxifen is
23 probably nonexistent. The cooperative groups obviously do
24 not have an interest in doing this. They are looking, and
25 they will be viewed at how innovative their scientific

1 | accomplishments are when it comes time for their grant
2 | reviews. Once the company has the approval, there is very
3 | little emphasis on redoing a trial.

4 | So, I think the point that Donna made is one
5 | that we will look closely at and discuss internally about
6 | the one-trial issue and asking, as far as phase IV
7 | commitments, greater replication of results.

8 | Getting back to something that Scott mentioned,
9 | when we present a drug at the original ODAC, should we then
10 | be making comments regarding whether this drug should be a
11 | new comparator, it gets into a real kind of dicey
12 | situation. We did spend a lot of time in developing these
13 | presentations, going through and showing you comparative
14 | data. When we are bringing a drug here, basically, with a
15 | sponsor, the question is: Is this drug safe and effective?
16 | And that's the bottom-line question that we are asking.

17 | To try to establish in that context of that
18 | ODAC meeting, what is a new comparator, could be quite
19 | difficult. Because obviously you then need to start
20 | bringing in a whole consideration of comparative data and a
21 | rather lengthy discussion that may not have consensus, as
22 | evidenced by this meeting here.

23 | DR. NERENSTONE: Dr. Lippman?

24 | DR. LIPPMAN: That's a very good point. I
25 | don't remember if it was a specific question that you gave

1 | us, but I certainly remember the discussion with CPT-11,
2 | of, does this now become a new standard of care, i.e., a
3 | new control arm, to compare other treatments? So, you are
4 | right, maybe it is hard to resolve it completely, but it
5 | seems to always come up when you have a real change in
6 | standard of care. And the question is, although there are
7 | other issues, to spend more time on that issue.

8 | Obviously it's of less interest to the industry
9 | and to our goal at the time to approve a drug. But if we
10 | are in a situation where we are really changing the
11 | standard of care -- and it doesn't happen too often --
12 | maybe a little more time spent on that issue will save us
13 | time now, when we are trying to remember how many patients
14 | had adjuvant tamoxifen and what were this and that. It's
15 | hard to go back and remember the three-hour hearing that we
16 | had on these agents.

17 | DR. NERENSTONE: Dr. Carpenter?

18 | DR. CARPENTER: It seems one of the things
19 | we're being asked about is, how high should the bar be set
20 | for a new drug to be approvable? How active does it have
21 | to be for everyone to be comfortable that it's good enough
22 | to put another agent on the market?

23 | Is the agency comfortable with a dual design
24 | that says superior to tamoxifen and not inferior to a --
25 | perhaps not even that generic -- superior to an

1 anti-estrogen, so-called, and not inferior to an aromatase
2 inhibitor? Is that a handle-able, manageable thing?

3 Because I think most people would accept either
4 as evidence of some baseline level of activity, and if the
5 study were done in a receptor-known population, you would
6 have some credibility.

7 DR. TEMPLE: Are you referring specifically to
8 a three-arm trial, or would some of these be deduced?

9 DR. CARPENTER: Not necessarily, but an
10 either/or.

11 DR. TEMPLE: As I was saying before, one of the
12 things we have been talking about is how persuasive being
13 superior to tamoxifen would be as evidence that you are not
14 much worse than one of the aromatase inhibitors. My own
15 view is that would be pretty persuasive. There is not that
16 much room to be better than one and not --

17 DR. CARPENTER: You are going to get a range
18 either way. I think the question about the letrozole study
19 is not that it's positive but, rather, it's so positive, is
20 it representative? And if the difference in response rate
21 is a little bit less, and a little bit less is actually
22 representative, then to be superior to tamoxifen you're
23 just necessarily going to be in the same range. But is an
24 either/or manageable from a regulatory point of view?

25 DR. TEMPLE: I think the questions later

1 indicate that. But I think one could argue that if you can
2 show that you are superior, as letrozole did, to tamoxifen,
3 it's not really possible in a study size that we can
4 contemplate for you to not meet the non-inferiority design
5 if you had studied it against letrozole. I think that's
6 true; I mean, we'd have to look at that. But those two
7 might be considered almost the same conclusion, although
8 obviously developed in quite different ways.

9 DR. PAZDUR: I think Raje presented some of
10 those examples. It depends on how much of the effect are
11 you willing to lose. And if that loss of effect, still for
12 a non-inferiority analysis, is higher than one would expect
13 for tamoxifen, then you could have a combination of both,
14 and those designs were presented even.

15 DR. NERENSTONE: Dr. Kelsen?

16 DR. KELSEN: Putting the statistics aside for a
17 second, the implication of that kind of statement would be
18 you would almost be explicitly stating that the aromatase
19 inhibitors are superior because you can't be worse than
20 them, you've got to be a little better than tamoxifen.

21 I understand your point about the differences
22 in practicalities are relatively small. But the
23 implication to a patient and a physician would be the
24 aromatase inhibitors are superior; in order to be approved,
25 you must be at least as good as them; tamoxifen is