

1 inferior, and in order to be approved, you have to be
2 better than tamoxifen. I'm not 100 percent sure where that
3 would lead us in designing a comparator arm.

4 DR. NERENSTONE: Dr. Lippman?

5 DR. LIPPMAN: That was sort of exactly my
6 point. I think Dr. Carpenter summarized it very nicely,
7 and I agree with Dr. Kelsen as well. I think a lot of us
8 could probably agree with that trial design -- practicality
9 aside of whether you could do a tamoxifen trial in this
10 country. But, assuming you could, I certainly could easily
11 live with, given the amount of wiggle room you've
12 described, the non-inferiority versus superiority trial, as
13 long as we stick with the superiority endpoint.

14 In the tamoxifen trial, I would certainly feel
15 comfortable approving a drug that was shown to be superior
16 to tamoxifen or equivalent to the AIs.

17 DR. NERENSTONE: We do have to note that two of
18 the aromatase inhibitor's that have been approved would not
19 meet that new bar at this point. They have not been proven
20 to be superior to tamoxifen. They were only shown to be
21 not inferior.

22 Dr. George?

23 DR. GEORGE: Although I said earlier I would
24 vote no for both of these, actually I would like to see
25 letrozole used as the comparator, but not required. The

1 reason is, for me anyway, that would give a lot of good
2 information about letrozole, again, from another trial,
3 which isn't a replication of the earlier trial, but it
4 would provide information.

5 I have a suspicion that if you do the trial
6 with letrozole versus another agent X, that you're going to
7 see letrozole do worse than it did before. That's my
8 prediction. That's why I would like to see it as the
9 comparator. That's a little different than the flavor of
10 what's going on here.

11 DR. NERENSTONE: Any other comments?

12 (No response.)

13 DR. NERENSTONE: You want an official vote on
14 this, and I'm going to need a show of hands. And we need
15 for the transcript to know who voted which way, I'm told.

16 So, number 1a: Do the data presented allow the
17 FDA to designate one hormonal drug as the comparator in
18 future randomized clinical trials of new hormonal drugs for
19 this use?

20 Dr. Kelsen, you're at the beginning of the
21 voting. And you can comment as well.

22 DR. KELSEN: I would vote no for the reasons I
23 said before, that I don't think that the data is compelling
24 enough yet to say that only one drug, letrozole, in our
25 discussion, should be the comparator as opposed to one 1b,

1 | which may be a different issue.

2 | DR. NERENSTONE: Dr. Albain?

3 | DR. ALBAIN: No.

4 | DR. NERENSTONE: Ms. Mayer?

5 | MS. MAYER: I would vote yes.

6 | DR. NERENSTONE: Dr. Lippman?

7 | DR. LIPPMAN: We can make some comments?

8 | DR. NERENSTONE: Yes.

9 | DR. LIPPMAN: I would vote yes if we were
10 | designing a non-inferiority trial, and I would indicate
11 | that letrozole should be the control. If the design of the
12 | trial is not at issue, then I would vote no, and the other
13 | acceptable trial would be a superiority trial with
14 | tamoxifen.

15 | DR. NERENSTONE: Why don't we just stick to
16 | this? Can you do that specifically?

17 | DR. LIPPMAN: Given that the design is there,
18 | then I guess it would be no.

19 | DR. TEMPLE: But, Stacy, it is helpful, because
20 | the question is, now that we look at it, a little defective
21 | in not taking those two possibilities into account.

22 | DR. NERENSTONE: Ambiguous, yes.

23 | DR. LIPPMAN: So, how should we interpret this
24 | in terms of design, as a non-inferiority comparator?

25 | DR. PAZDUR: Non-inferiority.

1 DR. LIPPMAN: Then my answer would be yes.

2 DR. NERENSTONE: Dr. Carpenter?

3 DR. CARPENTER: Seeing as how I would prefer to
4 see an either/or, I would vote no to this.

5 DR. REDMAN: Before you do that, it sounds to
6 me like you were agreeing with Dr. Lippman; you just want
7 to be sure that you could do a superiority trial, right?
8 Is that what you mean? The superiority could be to
9 tamoxifen.

10 DR. CARPENTER: If it was superiority to
11 tamoxifen, I would be comfortable with it.

12 DR. TEMPLE: Suppose you're talking only about
13 a non-inferiority trial; that was sort of the ground rule
14 that I think you just imposed for this question, right?

15 DR. NERENSTONE: That's what the question was,
16 yes.

17 DR. CARPENTER: I think no.

18 DR. PRZEPIORKA: I think there's enough data
19 out there for physicians to make decisions in clinical
20 practice, but I don't know that there's enough data for the
21 FDA to make rules, so I would answer no.

22 DR. NERENSTONE: And I would say yes, because I
23 think there's one very large trial that needs to raise the
24 bar for future studies.

25 DR. SLEDGE: I would vote no, again, for the

1 specific reason that I don't think we have enough data to
2 suggest that any particular aromatase inhibitor is superior
3 to any other. And indeed, the North American anastrozole
4 trial, to me, looks to have results that are essentially
5 equivalent to the letrozole trial. So that if you are
6 looking at a well-defined steroid receptor positive
7 population, you get pretty equivalent results.

8 DR. NERENSTONE: Dr. Pelusi?

9 DR. PELUSI: I would vote no.

10 DR. GEORGE: I vote no for allowing the FDA to
11 designate one, but I would prefer letrozole used.

12 DR. REDMAN: I vote no.

13 DR. TAYLOR: I vote no.

14 DR. BLAYNEY: I vote no.

15 DR. NERENSTONE: And the tally is 3 yes, 10 no.

16 For 1b: If the answer to 1a is no -- which it
17 is -- do the data presented allow the FDA to designate one
18 class of hormonal drugs as the comparator in future
19 randomized clinical trials of new hormonal drugs for this
20 use?

21 DR. BLAYNEY: Did they want to amend the
22 question as to the type of trial design?

23 DR. NERENSTONE: Non-inferiority.

24 Dr. Blayney, would you like to start? We'll
25 change direction.

1 DR. BLAYNEY: I need to think about this
2 amended question, so I wish to defer my vote.

3 DR. NERENSTONE: Dr. Taylor?

4 DR. TAYLOR: I vote no.

5 DR. REDMAN: As asked, I'm assuming the only
6 thing that is changing is a hormonal drug versus a class of
7 drug, and I vote no.

8 DR. GEORGE: I vote no.

9 DR. PELUSI: I vote no.

10 DR. SLEDGE: I vote yes.

11 DR. NERENSTONE: And I vote no, because I don't
12 think as a class we have seen that this class of drugs is
13 better. I think we have data on one drug. And so we have
14 a lot of theoretical explanations as to why they're the
15 same, but I don't think we have the scientific proof or the
16 statistical data to support that. So, I would vote no.

17 DR. PRZEPIORKA: I would agree that we don't
18 have the scientific data regarding efficacy, but if in fact
19 the safety profile of the aromatase inhibitors is better
20 than that of tamoxifen, then ethically that should be the
21 comparator, so I would vote yes.

22 DR. CARPENTER: I vote no.

23 DR. LIPPMAN: I wondered if we answered yes to
24 the first one, do we still have to vote on this?

25 (Laughter.)

1 DR. LIPPMAN: If I get a second vote, I would
2 vote no for the exact reasons that you raised. I think, in
3 addition to the scientific issues -- and I have to go on
4 record, I do believe that anastrozole is going to be
5 similar; I agree with George on this. But my point is we
6 don't have the data, and there have been a number of
7 instances where the biology, everything pointed in the
8 right direction, and we were surprised. And I think that
9 is why we have to do clinical trials. We have to prove
10 things using the method that's established.

11 And of course, we don't have as much data to
12 really have a solid control arm in terms of the endpoints
13 we are looking at, if we look at all AIs as being
14 equivalent. So, I guess my answer is no.

15 MS. MAYER: I would vote no as well for the
16 reasons articulated by Dr. Lippman.

17 DR. ALBAIN: I strongly vote yes, because I
18 believe that the North American trial for anastrozole and
19 the letrozole trial are giving you nearly identical
20 results. You have, I said it earlier, a time to
21 progression that's identical for the tamoxifen arms and an
22 almost identical time to progression for the two AI arms.
23 So, I vote yes.

24 DR. KELSEN: And I would also vote yes, because
25 they are at least equivalent to, and may be superior to,

1 | tamoxifen and less toxic.

2 | DR. NERENSTONE: Dr. Blayney?

3 | DR. BLAYNEY: And I vote no.

4 | DR. NERENSTONE: 4 yes, 9 no.

5 | Dr. Temple?

6 | DR. TEMPLE: Well, I have a practical question.

7 | What I hear from the people who thought any one of the
8 | members might be reasonable, or at least more than one
9 | might be reasonable -- does anybody want to just briefly
10 | comment?

11 | My presumption is that if time to progression
12 | is going to be the endpoint -- that's a big question, of
13 | course -- then we'd have to do some sort of pooled analysis
14 | or meta-analysis and estimate a class effect based on the
15 | letrozole study and the favorable anastrozole study,
16 | presuming that must be the one that's true and the other
17 | one must be wrong, and devise a sort of combined rating.
18 | Because you have to have a margin to do a non-inferiority
19 | study. You have to. You can't do one without it. So, we
20 | have to develop one somewhere.

21 | I just wondered if people had thoughts on what
22 | that would be and how to do it. But maybe you are
23 | presuming response rate should still be the response. So,
24 | I don't know that.

25 | DR. NERENSTONE: Dr. Albain?

1 DR. ALBAIN: You would have to, though, if you
2 are going to do a -- I hesitate to use the term
3 "meta-analysis," because it's really not a proper use of
4 the term when you have two trials. If you are going to do
5 some sort of pooled analysis, though, you'd have to focus
6 on the receptor-positive ER or PR in both of those trials,
7 not just take it by trial. And it was based on that I
8 voted yes, from those analyses of those trials.

9 DR. TEMPLE: Okay, but the thought would be
10 that somehow we could -- and it's not clear whether we
11 could but we would try -- to develop an effect size for
12 time to progression that would then be the basis for a
13 non-inferiority trial using at least more than one of the
14 aromatase inhibitors.

15 DR. PAZDUR: But if we move ahead in future
16 discussions with companies in limiting the inclusion of
17 patients to only ER-positive patients, we are really going
18 to have to look very carefully at what is the effect size,
19 and go back in many of these trials to take a look at that
20 population. I think that needs to be real clear here.

21 DR. NERENSTONE: Dr. Lippman?

22 DR. LIPPMAN: I would strongly urge against
23 using pooled analyses to get these endpoints. Although I'm
24 a big believe in molecular targeted therapy, no question
25 about it, the more we know about different agents that work

1 on the same target, the more we find out that they are not
2 all the same. Not all cox-2 inhibitors are the same, not
3 all things are the same. And I just think if we abandon
4 the normal way that we develop drugs because we get kind of
5 sucked into this, oh, they all work on the same target, we
6 are going to get burned.

7 DR. NERENSTONE: Dr. George, do you have any
8 comments about the statistical questions that were raised?

9 DR. GEORGE: Yes, I think the one that Rick
10 raised is especially important with respect to the features
11 or the eligibility requirements on the subsequent trials --
12 are they going to be different than past ones? -- that has
13 to be definitely taken into account in how you do things.
14 Receptor status is an obvious one, but there may be other
15 ones, too. And so that means what you are doing is going
16 back and not only pooling but doing various types of
17 subgroup analyses.

18 It would be pretty tricky to support what the
19 effect size is, which you do have to do to do a
20 non-inferiority trial. It is going to be subject to even
21 more uncertainty than what we have right now, I think. So,
22 that's the tricky business.

23 DR. NERENSTONE: Dr. Sridhara?

24 DR. SRIDHARA: Just so that it's clear, in the
25 letrozole study, 65 percent of them were ER positive; and

1 | in the ODAC presentation, they did show separately in the
2 | ER-positive patients what was the time to progression and
3 | what was the time to progression in the unknown category.
4 | It was almost identical. So, the differences were very
5 | similar in the two groups.

6 | DR. NERENSTONE: Dr. Carpenter, you had a
7 | question?

8 | DR. CARPENTER: Would it be helpful if we voted
9 | on an either/or, either superior to tamoxifen or
10 | non-inferior to an aromatase inhibitor?

11 | DR. NERENSTONE: That's the next question.
12 | Dr. Albain?

13 | DR. ALBAIN: I may be totally out of order, but
14 | might we hear from our esteemed colleagues to the left, how
15 | they might have voted had they been voting members on these
16 | questions? Or is that out of order?

17 | DR. NERENSTONE: In other words, you want to
18 | hear what persuasive arguments they would have?

19 | DR. ALBAIN: Yes, I would like to hear how they
20 | came out on this, too.

21 | DR. NERENSTONE: That's fine, sure.

22 | DR. DAVIDSON: I've already changed to page 2.
23 | But going back to page 1, I would have voted no for both.
24 | I actually came in thinking I would vote yes to the notion
25 | of using the aromatase inhibitors as a class as a

1 | comparator, but I was persuaded by Dr. Lippman that we
2 | don't know as much as I think we might know.

3 | DR. HENDERSON: I would have voted no for both
4 | of them. And probably the single most important factor is
5 | the point that I made, that is, that I distinguished
6 | regulatory from non-regulatory functions. And I think that
7 | the FDA serves a great purpose by forcing us to generate
8 | the kind of information that helps physicians and patients
9 | make decisions. So, anything that allows them to do that
10 | and makes them more powerful in that regard I'm for.

11 | Things that restrict our ability to utilize
12 | drugs or to take that information, or that possibly might
13 | bury a future drug that would have promise -- because I
14 | think it's even after the initial approval that we really
15 | find out about most cancer drugs. It's 5 years, 10 years
16 | and even 30 years afterwards, when the patents have run out
17 | and so on that we still continue to learn. So, I would
18 | like to make sure there are as many drugs out there as
19 | possible, but that there is also a lot of data to support
20 | them.

21 | DR. NERENSTONE: Okay, let's go to question
22 | number 2: If the committee believes that any first-line
23 | hormonal agent is an acceptable comparator, should new
24 | agents be required to demonstrate superior efficacy to
25 | tamoxifen, either by direct comparison to tamoxifen or by

1 non-inferiority analysis compared to letrozole? What are
2 acceptable comparators for non-inferiority designs?

3 DR. ALBAIN: I have a question about the
4 question.

5 DR. NERENSTONE: Yes, Dr. Albain?

6 DR. ALBAIN: So, not anastrozole, only
7 letrozole. Do you mean to say letrozole only there?

8 DR. HONIG: The problem again is that to use
9 anastrozole for a non-inferiority comparison, it's going to
10 be even more difficult to set the margin and find the
11 effect size than it is for letrozole, where at least
12 there's one large significant study. But then we asked,
13 what are acceptable comparators for non-inferiority design?
14 So, the first part would be voting and the second half of
15 that would be some discussion of what's appropriate.

16 DR. NERENSTONE: And you want us to vote?

17 DR. HONIG: At least on the first part.

18 DR. NERENSTONE: On the first part. And maybe
19 if you want to comment then on the second question at the
20 same time, we can go around. Dr. Kelsen, would you like to
21 start?

22 DR. KELSEN: Since we said no-no the first time
23 around, then I think any hormonal agent would be
24 acceptable. That would be tamoxifen or any of the
25 aromatase inhibitors.

1 The implication I get from the second part of
2 that, though, would be that you would no longer approve a
3 drug like Arimidex because it would be not superior to
4 tamoxifen. So, a new Arimidex would not be approved unless
5 it showed superiority to tamoxifen. And you would only
6 approve a new agent of this class if it was at least as
7 good as letrozole. And I think that that's the way that is
8 written. Am I right?

9 DR. HONIG: The first part is asking what do
10 you think. Must everything be superior to tamoxifen, or
11 would you still accept non-inferiority to tamoxifen?

12 DR. KELSEN: I think, from our answer to 1b,
13 the answer could be not inferior to tamoxifen, as good as
14 tamoxifen. That's the only way you can interpret the
15 implication of that. Otherwise you are saying that it has
16 to be superior to tamoxifen, but it only has to be as good
17 as letrozole. The logic of that seems to me to be that if
18 you're as good as letrozole, you get approved; if you are
19 inferior to letrozole and only as good as tamoxifen, you
20 don't get approved. That Arimidex would never pass this
21 bar. Maybe I'm misinterpreting.

22 DR. NERENSTONE: Dr. Temple?

23 DR. TEMPLE: Again, although we didn't ask --
24 in retrospect, perhaps we should have switched the order of
25 these. But there isn't any way to have a non-inferiority

1 study to tamoxifen on time to progression. That's not
2 meaningful. We don't know what the effect is.

3 DR. KELSEN: Because you don't have the data.

4 DR. TEMPLE: So, the only interpretable result
5 there would in fact be superiority. Response rate you
6 still could if that were the right endpoint.

7 DR. KELSEN: Wouldn't that mean that we would,
8 for the purposes of discussion, be saying that because the
9 only data for time to progression is from letrozole, that
10 will be the new standard for time to progression; am I
11 misinterpreting that, just for the statistical reasons?

12 DR. TEMPLE: No, you could still show superior
13 time to progression -- maybe anastrozole could be used too;
14 that's been something we've been discussing. But you could
15 also be superior to tamoxifen. That would be informative
16 about time to progression. That's an interpretable study.
17 That doesn't mean necessarily you're as good as letrozole,
18 but it probably actually does. But that would be an
19 interpretable finding.

20 What's not interpretable is a time to
21 progression endpoint using tamoxifen, because you have no
22 good estimate of the effect of tamoxifen on that endpoint.

23 DR. KELSEN: How are you going to design the
24 trial? You're going to have to make some estimate to have
25 the superiority assessment.

1 DR. TEMPLE: Oh, you just make it up, the way
2 people do for power calculations. You say a 20 percent
3 improvement, then you run the trial.

4 DR. KELSEN: To what you actually see?

5 DR. TEMPLE: Well, the results give you the
6 answer. The power estimates are how you choose your sample
7 size, and we all know people just make those up.

8 DR. KELSEN: Don't we have really good time to
9 progression data from the aromatase inhibitor trials for
10 tamoxifen in that control arm? You showed us 6.4 months or
11 something like that in two trials.

12 DR. ALBAIN: Yes.

13 DR. TEMPLE: Yes, you know that, but you don't
14 know whether that's better than nothing, because there is
15 no placebo in these trials.

16 DR. NERENSTONE: Just a clarification. You
17 haven't asked the question: Should tamoxifen
18 non-inferiority still be acceptable? Isn't that the first
19 question you need to get answered?

20 DR. TEMPLE: Well, in retrospect, yes.

21 DR. KELSEN: That's what I'm trying to figure
22 out.

23 DR. NERENSTONE: Well, maybe we should give you
24 a new question 2a.

25 DR. TEMPLE: It's really on what endpoint is

1 acceptable now. That's really what determines that. If
2 response rate is acceptable, then you could do a
3 non-inferiority study to tamoxifen. It would be
4 interpretable easily, just like all the past ones have
5 been. If time to progression is needed, then really you
6 can't do a non-inferiority study except to something where
7 you know the effect size, which includes letrozole and,
8 conceivably, anastrozole.

9 DR. NERENSTONE: Do you want to hear the answer
10 to the first question in terms of a poll? Do you want to
11 simplify the question?

12 DR. HONIG: Would you rather answer question 3
13 first, which asks the endpoint question?

14 DR. NERENSTONE: No. I think the first
15 question is: Is tamoxifen still an appropriate standard?
16 Before talking about what the endpoint is, maybe we should
17 just talk about the drug, the specifics.

18 DR. KELSEN: Yes. My answer to that was yes,
19 based on our saying no-no to the first one.

20 DR. NERENSTONE: Well, wait a minute. Let's
21 ask the question. The question then is: Is tamoxifen
22 non-inferiority still acceptable as an endpoint for new
23 drugs?

24 DR. PAZDUR: Yes, that would be fine. And
25 we're talking about response rates here, because obviously

1 | you can't look at time to progression.

2 | DR. NERENSTONE: So, non-inferiority of
3 | tamoxifen?

4 | DR. KELSEN: Yes.

5 | DR. NERENSTONE: In first-line metastatic
6 | breast cancer, is the use of tamoxifen as a comparator in a
7 | non-inferiority study with response rate acceptable for new
8 | drug comparison?

9 | DR. KELSEN: I'll try to explain what I'm going
10 | to say. Because our answer to 1a and 1b was no, then I
11 | think the answer to this has to be yes.

12 | DR. NERENSTONE: It doesn't have to be yes,
13 | because you could say it has to be better. This is saying
14 | non-inferior to tamoxifen. It's not saying that it's
15 | tamoxifen or nothing; it's saying non-inferiority.

16 | DR. KELSEN: Right. So, we're changing the way
17 | 2 is written. I voted yes for 1b, and I would vote again
18 | here that it has to be better than tamoxifen. We already
19 | have two drugs that are at least as good or better than
20 | tamoxifen.

21 | DR. NERENSTONE: So, you're saying?

22 | DR. KELSEN: It should be superior to
23 | tamoxifen.

24 | DR. NERENSTONE: Superior. So, you would not
25 | accept non-inferior to tamoxifen?

1 DR. KELSEN: I would not accept not inferior to
2 tamoxifen. Does that make sense?

3 DR. NERENSTONE: So, just to make sure that
4 everybody is clear: Is tamoxifen as the comparator in a
5 non-inferiority trial acceptable as the comparator?

6 We're not talking about the endpoint. Right
7 now let's just talk about the drug. And the first vote is
8 no, it's not.

9 Dr. Albain?

10 DR. ALBAIN: No.

11 DR. NERENSTONE: Ms. Mayer?

12 MS. MAYER: No.

13 DR. LIPPMAN: No.

14 DR. CARPENTER: No.

15 DR. PRZEPIORKA: No.

16 DR. NERENSTONE: No.

17 DR. SLEDGE: No.

18 DR. PELUSI: No.

19 DR. GEORGE: No. But my answer is tied up with
20 the endpoint.

21 DR. REDMAN: No. And I have difficulty with
22 the endpoint.

23 DR. TAYLOR: No.

24 DR. BLAYNEY: Yes.

25 DR. NERENSTONE: Do you want to explain that,

1 | Dr. Blayney?

2 | DR. BLAYNEY: As I said, tamoxifen is a drug
3 | that we have used for 20 years, that is well accepted in
4 | clinical practice. We know what its side effects are.
5 | Those side effects often emerged 10 years into its use.
6 | And I would be reluctant to abandon it as a comparator even
7 | for a non-inferiority trial, given the amount of time it
8 | takes for long-term toxicities to emerge.

9 | DR. NERENSTONE: So, the vote is 1 yes, 12 no.
10 | Could we go to perhaps number 3 now? Does that
11 | make more sense? We've accepted in general that tamoxifen
12 | is still an appropriate comparator, and now this really
13 | addresses the endpoint that we are going to be looking at.

14 | Just to read it: Tamoxifen has not been
15 | demonstrated to affect time to progression or survival in
16 | randomized control trials. Because approval of subsequent
17 | hormonal therapies was based on non-inferiority or
18 | similarity to tamoxifen, time to progression data are not
19 | available for these agents. Anastrozole demonstrated
20 | superior time to progression to tamoxifen, but in a single
21 | small study; no difference was observed in a second larger
22 | study. Letrozole demonstrated superior time to progression
23 | compared to tamoxifen; however, data from only a single
24 | trial are available to estimate the effect size. A change
25 | in primary endpoint in the regulatory setting from response

1 rate to time to progression would require trial designs
2 that demonstrate superiority to tamoxifen or
3 non-inferiority to letrozole.

4 As we talked about, that's the only one that
5 has data that people think is reliable.

6 For the first-line treatment of metastatic
7 breast cancer with hormonal agents, should the traditional
8 endpoint of response rate be replaced by time to
9 progression?

10 Dr. Kelsen?

11 DR. KELSEN: So, my answer would be I would
12 replace it with time to progression. And I do think that
13 since we voted against tamoxifen non-inferiority, and said
14 it has to be superior to tamoxifen -- and it sounds to me
15 like you have good data for time to progression from the
16 two previous studies -- you do have baseline numbers to
17 draw your statistics from, since it must now be superior to
18 trials in which tamoxifen was the control arm and you have
19 at least two fairly large trials with time to progression
20 in the 6- to 7-month range. And that will be your "got to
21 be better than that."

22 DR. NERENSTONE: We can go around. That's a
23 yes?

24 DR. KELSEN: That's a yes.

25 DR. NERENSTONE: Dr. Albain?

1 DR. ALBAIN: I would replace it also, a yes.
2 Because I think that with this class of drugs, you can do
3 so much with prolonged stable disease, into several years
4 sometimes, with truly hormone-dependent cancers. And
5 response rates do not capture that value for this class of
6 drugs. And I think if you can design trials with placebos,
7 that will add rigor to the time to progression endpoint.

8 MS. MAYER: I would vote yes.

9 DR. ALBAIN: I'm sorry. Strike "placebo."
10 Double-blind is what I meant to say.

11 MS. MAYER: I would vote yes. I think it's
12 crucially important that these trials look at response
13 rates in women who have bone-only metastases. This is a
14 very large group of women who, as Dr. Albain says, often
15 respond for significant periods of time and cannot be
16 measured in response rate studies.

17 DR. LIPPMAN: I'm assuming that when we talk
18 about endpoints here, we are talking about the primary
19 endpoint of the study.

20 I have mixed feelings. I'm leaning towards
21 voting no because by making time to progression as the
22 primary endpoint, I think we've heard that the sample sizes
23 become very large. And I think that clearly time to
24 progression should be a prespecified major secondary
25 endpoint.

1 I would be comfortable approving drugs as
2 non-inferiority to letrozole based on a design of response
3 rate. And as we always do, we look at these other
4 endpoints to make sure that they're consistent with that,
5 although maybe not reaching statistical significance. So,
6 in that context, I would vote no.

7 DR. NERENSTONE: Scott, except I'm going to
8 remind you that we lost. So, the comparator is not going
9 to be letrozole; it's going to be tamoxifen. And under
10 those circumstances --

11 DR. TEMPLE: It could be.

12 DR. NERENSTONE: It could be. And if it is
13 tamoxifen, is response rate still appropriate?

14 DR. LIPPMAN: If it is tamoxifen, I may take
15 the approach Dr. Blayney took earlier on this and think
16 about it a little longer. I'm going to defer my vote.

17 DR. CARPENTER: I would vote yes, because I
18 think while there are problems with sample size and there
19 are problems in the precise way that you define
20 non-inferiority, that time to progression comes closer to
21 the benefit that we're trying to measure than response rate
22 does.

23 DR. PRZEPIORKA: I think there are two
24 questions here posed into one, and I can answer one of them
25 but I can't answer the other. One of them is: Is time to

1 progression a more clinically meaningful endpoint than
2 response rate? To which I would answer yes. And so my
3 answer to 3 would be yes.

4 And the other question which I am inferring is:
5 Are there statistics available to do that sort of a study?
6 And I don't know that all statistics have been provided to
7 the FDA or that all data has been published. And so I
8 don't know that the committee is in a position to actually
9 address that particular question.

10 So, my answer is yes to the question of
11 clinically relevant endpoint.

12 DR. NERENSTONE: My answer is yes. And I think
13 it's a strength that these trials need to be larger.
14 Because then we're going to have more acceptance of the
15 results. I think it may change our requirement of two
16 trials. But if you have one 1,600-patient trial, then I
17 think you can believe the answer and feel that it is going
18 to be applicable to a wide variety of patients. So, I'd
19 say yes.

20 DR. SLEDGE: I vote no, because I think this is
21 a false dichotomy. I mean, do we have to have either/or?
22 As I mentioned earlier, clinical trialists in breast cancer
23 over the past decade -- if you look at many of the trials
24 published in the past decade -- look at CR plus PR plus
25 prolonged stable disease as an endpoint. That strikes me

1 as being an endpoint that is fairly similar to time to
2 progression in many ways, in terms of what you are actually
3 looking at. I would personally be comfortable with either
4 of those endpoints, or both.

5 DR. PELUSI: I would vote yes.

6 DR. GEORGE: I would vote yes, but a couple of
7 comments. The reason I'm voting yes is I don't
8 particularly like response rate all that much as an
9 endpoint.

10 But to take up what Dr. Sledge just mentioned,
11 if I were looking at this, I would personally like to see
12 non-inferiority -- if that's what it was -- in at least
13 both of these endpoints, and maybe others. I still worry
14 about survival, for example, that seems to get sloughed off
15 as something that's not easily looked at or treated as a
16 safety issue. I would like to see non-inferiority in all
17 of these things. The effect of that on the sample size, I
18 would hate to imagine.

19 The other thing did have to do with the sample
20 size, as Dr. Sridhara mentioned earlier. I think that the
21 things that were presented -- and she can correct me if I'm
22 wrong -- are the result of some internal research that's
23 going on, and there could be some refinement in some of
24 those things. That's the only way I could put it now, but
25 maybe the sample sizes are not quite as big as some of

1 | those presented.

2 | DR. REDMAN: I believe time to progression is a
3 | valid clinical endpoint. The idea of superior to tamoxifen
4 | versus non-inferior I think is a difficult one, and we're
5 | probably not going to be able to answer that. But overall
6 | to the question, I will answer yes.

7 | DR. TAYLOR: I would vote yes, but I don't
8 | think we should ignore the response rate. It should not be
9 | excluded.

10 | DR. BLAYNEY: As the question is phrased, I
11 | vote no. If the question was phrased, "could TTP replace
12 | in a predefined study design," my answer would be yes. I
13 | think TTP is a valuable endpoint. So, it would be up to
14 | the sponsor to specify that. And if they specified TTP as
15 | their primary endpoint and it could meet the study number
16 | hurdle, as my colleague across the way pointed out, it
17 | would expand to bone-only disease and increase the number
18 | of women who might be available for such trials.

19 | DR. NERENSTONE: Is that a yes or a no?

20 | DR. BLAYNEY: As the question is phrased, it's
21 | a no.

22 | DR. NERENSTONE: And, Dr. Lippman, do you want
23 | to weigh in?

24 | DR. LIPPMAN: Again, I am leaning towards the
25 | response that Dr. Sledge gave, and for the exact reasons,

1 and the point that you raised about the issue of one versus
2 two trials. I am concerned, if we say that the trials have
3 to be designed on a time to progression endpoint, we are
4 requiring two pivotal trials. It could be up to 3,000 to
5 5,000 women.

6 So, I think either endpoint, although I believe
7 that time to progression is very valid and I would be very
8 concerned if we saw a barely significant response
9 difference and time to progression was going the wrong way.
10 And that's what we do when we review these. So, I think
11 having time to progression prominently as a prespecified
12 secondary endpoint, but with designs being on response
13 rates would be acceptable.

14 So, I guess my answer is no.

15 DR. NERENSTONE: Dr. Temple?

16 DR. TEMPLE: Just one point. We would always
17 look at and do always look at overall survival, but because
18 of crossovers and others reasons, we don't expect an
19 effect. And since we don't know that any of these
20 therapies have an affect on survival, we can't design a
21 non-inferiority study literally. All you can do is take a
22 qualitative look at it and conclude, oh, well, that doesn't
23 look bad. And that is what we do. If it was going the
24 wrong way, we would surely be very nervous.

25 DR. NERENSTONE: Do you need us to take a vote

1 on question 2 as it's written?

2 DR. ALBAIN: What was the outcome of the last
3 vote?

4 DR. NERENSTONE: Oh, sorry, the outcome of the
5 last vote. 10 yes, 3 no.

6 DR. PAZDUR: I have a question. The way we
7 wrote the change -- or in our paragraph -- I wonder if
8 there is a de facto discrepancy kind of between question
9 number 1 in our vote and question number 3. And I want to
10 bring that up. Because when we took a look at the designs
11 of non-inferiority for TTP, it appeared to us -- and I
12 don't know if Raje wants to comment on this -- that it
13 would be very difficult to do this with Arimidex based on
14 one trial, in a relatively small trial.

15 If we are demanding basically TTP be the
16 endpoint, we are virtually saying that the new comparator
17 here is being letrozole if it's for a non-inferiority
18 analysis, and could people comment on that?

19 DR. NERENSTONE: I'm entirely consistent, but I
20 understand your point. That's right.

21 DR. PAZDUR: I just want to know if people know
22 that. There is a discrepancy here. And accepting one, the
23 TTP endpoint via clinical methodology problems -- and
24 perhaps Raje wants to comment on this, the problems with
25 Arimidex in a non-inferiority analysis.

1 DR. SRIDHARA: Yes. I think although some of
2 the TTP sure has to do with looking at superiority to
3 tamoxifen, I think the words have also come to look at
4 superiority with respect to tamoxifen and TTP. So, in that
5 sense, the trials are really not large when you are looking
6 at superiority versus tamoxifen.

7 With respect to non-inferiority, yes, we have
8 data from one trial with letrozole on TTP. That's the best
9 data that we have.

10 DR. TEMPLE: So, as a practical matter and not
11 because there is a theoretical belief that letrozole is
12 better than anything else, if you were following the
13 non-inferiority route to approval as opposed to beating
14 tamoxifen, there really wouldn't be much choice in any way
15 that we can figure out yet. Someone could make the case
16 that Arimidex really has enough data or something, and then
17 it could. But without that, it would be very difficult to
18 write a design that had a credible non-inferiority margin.

19 DR. PAZDUR: That's the point I was trying to
20 make. So, I want people to have that analytical -- we're
21 making a de facto type of suggestion here as far as the
22 comparator, which is somewhat in contrast to the previous
23 vote, but this is just on the practicality of the
24 information available to us.

25 DR. NERENSTONE: I think the committee's

1 feeling is that it should not be required just because of
2 lack of data. But if it is a de facto requirement because
3 there is nothing else, then they obviously voted that that
4 was okay. But in a purely scientific way, they felt
5 uncomfortable saying that this guy was the winner.

6 Am I adequately reflecting the consensus of the
7 committee? Dr. Henderson?

8 DR. HENDERSON: If I've heard things correctly,
9 what you're saying is that -- let's just say that there is
10 a company out there that has anti-progestational agent.
11 And I don't know that there is such a company, but let's
12 just say that somebody has an anti-progestational agent.
13 And they're now down to their last 50 patients of accrual.
14 And they come in 14-15 months from now and they've shown
15 that in fact this new anti-progestational agent is only --
16 the lower limits are maybe 1 or 2 percent lower than
17 tamoxifen.

18 What you're saying is that that wouldn't be
19 approvable now. Is that really what the committee is
20 trying to -- I mean, as I read the votes, that is what
21 you've just said, is that a company brings in this new
22 anti-progestational agent, they have completed the study.
23 These studies often take five to 10 years by the time you
24 go through the development process and so on, and what we
25 are talking about is fairly new. If you follow what you

1 just said, you wouldn't approve that drug?

2 It's a hormone therapy. It would fall into
3 this overall class, new treatments. It's kind of an
4 interesting new area, anti-progestin. We don't have much
5 of that, but we do know that that's a possibility. So,
6 this is something that could in fact happen.

7 DR. PAZDUR: I think that's question 5, for
8 ongoing trials. We will address this. It's coming up. We
9 would like to hear your opinion.

10 DR. NERENSTONE: Do you need us to go back to
11 number 2, or has that been discussed at length enough for
12 you?

13 DR. PAZDUR: I think we can move on. There are
14 several other issues that we need to cover.

15 DR. NERENSTONE: So, question number 4,
16 questions about the definition of efficacy: In
17 non-inferiority studies, it is important to know the size
18 of the treatment effect of the comparator agent, and to
19 decide on the amount of comparator effect that should be
20 preserved when testing a new treatment. The estimate of
21 the effect size, the amount of efficacy to be preserved,
22 and the choice of endpoint influence the sample size of
23 non-inferiority studies. Sample sizes may range from
24 several hundred to many thousands of patients, depending on
25 the combination of these factors.

1 Based on the committee's clinical expertise,
2 what amount of the comparator effect should be preserved in
3 a non-inferiority trial of a new hormonal agent in the
4 first-line treatment of metastatic disease?

5 And this is open for discussion. And certainly
6 our additional colleagues, please weigh in.

7 Dr. Henderson?

8 DR. HENDERSON: The problem with a question
9 like this is that, with almost any drug, there are huge
10 tradeoffs. So, let's just say, for example, that you had
11 in either class, either the anti-estrogen class or the
12 aromatase inhibitor class, a drug which, for some reason or
13 another, had exactly the same outcome, or even smaller.
14 Let's say you've lost 50 percent. But you have no hot
15 flashes, for some reason.

16 That's a big tradeoff. I could tell you, lots
17 of women out there would be willing to trade off 50 percent
18 of the benefit to get rid of some of the negative effects,
19 which we tend to discount when we are talking about tables
20 but, I can tell you, when you're at the bedside, are not
21 minor. So, if the patients didn't have these side effects,
22 sure, they would prefer to have the drug that gives them
23 the whole benefit guaranteed. But if they did have some of
24 these benefits, they're quite willing to make a trade of
25 that magnitude.

1 DR. NERENSTONE: Dr. Lippman?

2 DR. LIPPMAN: For that reason that was just
3 raised, I believe that we should cast the net sort of
4 broadly. It's hard to pick an exact number -- 52 percent,
5 whatever -- but I think 50 percent seems to be reasonable,
6 again, for the reasons mentioned. Because part of what we
7 do is evaluate all the other effects, side effects and
8 other things that come up. And you would hate to have a
9 drug not make it because it lost 52 percent of its effects
10 but was much more favorable in terms of toxicity profile.

11 So, I wouldn't do 25; I don't know if I would
12 do 75; I think 50 percent seems to be reasonable.

13 DR. NERENSTONE: Dr. Carpenter?

14 DR. CARPENTER: I would support that. That
15 keeps your sample size from being prohibitively large. And
16 if we make the bar too high, then a small company with a
17 new drug that is very interesting may simply not be able to
18 mount a study of that magnitude, even though they have an
19 agent that really might be quite interesting. The 50
20 percent range gives us reasonably large sample sizes and
21 does allow for the play of other clinical effects of the
22 drug which, as Dr. Henderson pointed out, may be very
23 important.

24 DR. NERENSTONE: Dr. Blayney.

25 DR. BLAYNEY: I think 50 percent is a good

1 number, but I'd want some lower limit also. At 50 percent
2 of a 20 percent effect, which is what you're talking about
3 in tamoxifen, you're down in the noise. A 10 percent
4 effect is probably equivalent to a placebo effect. So, I
5 think you would need some lower limits on what that 50
6 percent cut was.

7 DR. NERENSTONE: Other comments?

8 DR. PAZDUR: Is the committee basing their
9 decision on a clinical decision of a 50 percent retention
10 or simply looking at the number of patients that would be
11 entered on the trial? Let me just throw that question out.

12 DR. LIPPMAN: I think both.

13 DR. NERENSTONE: Dr. George.

14 DR. GEORGE: Well, I can't answer the clinical
15 thing.

16 What I was going to get at in my comment was
17 that these non-inferiority trials are so sensitive to
18 things like the effect size and this effect retained, that
19 it's very difficult to separate your clinical judgment from
20 what effect that would have on the subsequent trials and
21 ability to get anything approved. So, it's a really tricky
22 business in that sense.

23 50 percent does have an advantage, but then it
24 doesn't matter whether you're talking about the effect
25 retained or the effect lost. It has a nice symmetry in

1 | that sense.

2 | DR. NERENSTONE: Dr. Sledge.

3 | DR. SLEDGE: Actually I very definitely was
4 | doing it on a practical matter. To use one of the examples
5 | that Raje gave, a 3,500-patient metastatic trial would just
6 | simply not be doable in the United States in any sort of
7 | timely fashion. I can't image any drug company that would
8 | want to do it in the metastatic setting.

9 | DR. NERENSTONE: Dr. Temple.

10 | DR. TEMPLE: The tradition of how to set the
11 | non-inferiority margin is not lengthy and is still being
12 | worked on, and different answers have been concluded for
13 | thrombolytics and for other things. In oncology, we've
14 | actually felt that we could be a little less conservative
15 | because you do get to measure response rate, which is
16 | another independent measure of activity, and you might also
17 | feel similarly inclined, if drugs are within the same
18 | class, that you think you know something. You could call
19 | those Bayesian priors if you were inclined that way. So,
20 | we have, for example, not insisted on the lower bound of
21 | the 95 percent confidence interval which leads to
22 | stratospheric sample sizes and have instead, based on some
23 | internal analyses, done this gamma confidence interval,
24 | which leads to more reasonable sample sizes. They're still
25 | pretty large sometimes, but they're more reasonable.

1 The other observation I would make is that if
2 you're talking about time to progression, remember we're
3 only looking at the difference between the drug and
4 tamoxifen. That's the figure we're looking at. So,
5 preserving any portion of that doesn't get you down into
6 the noise level really, whereas with response rates, if you
7 had a half or 25 percent of 20 percent, you might not feel
8 very reassured. This means that you are positive on what
9 you're pretty sure is the time to progression effect of the
10 other drug. So, there's less worry about meaningless
11 things.

12 DR. NERENSTONE: Dr. Pazdur.

13 DR. PAZDUR: One of the other questions that I
14 have that I'd like to see some discussion and potential
15 vote on is two trials versus one trial. One of the aspects
16 that we talked about in the presentations was that
17 sloppiness obviously obscures a non-inferiority analysis
18 here, and many times we have internally discussed the
19 requisite of requiring two trials for confirmation of the
20 results. We're talking about large numbers of patients
21 here with the time to progression and a 50 percent
22 retention, perhaps 1,500 patients in each trial.

23 Many sponsors have come up and wanted to split
24 the patient numbers and combine these trials together.
25 Obviously, there are problems in pooling results, which

1 will be discussed on applications you'll see coming toward
2 you this session of ODAC.

3 But when we're talking about confirmation of
4 results and requiring and saying we're not going to approve
5 a drug, because we are looking for two trials, with this
6 magnitude of the number of patients, is this realistic?
7 And I'd like some discussion on this.

8 DR. NERENSTONE: Dr. Lippman.

9 DR. LIPPMAN: Well, I agree with Dr. Henderson
10 on this. I'd like to have my cake and eat it, too. I'd
11 like a one well-designed, large, multi-center trial that's
12 very compelling, and it would be nice to have a
13 confirmatory smaller trial. We'd feel better. But I don't
14 think we should mandate that.

15 Assuming that the application comes with other
16 supportive data from biologic plausibility, particularly
17 with these molecular targeting agents, phase II studies,
18 some of this other data, I think in that setting, if they
19 come in with one very well-designed and well-conducted
20 large trial, I think that should be enough. I'd like it
21 better if there were two, but I'd rather see that than what
22 we're going to see later in this meeting of combining
23 smaller trials and interpreting sort of apples and oranges.
24 Then I think we really invoke the sloppiness point that Dr.
25 Temple raised.

1 DR. NERENSTONE: My question is, how large is
2 large? In this disease, 1,500 patients is not
3 unreasonable. I think it probably is unreasonable to
4 demand two of those kind of trials, but I think if you have
5 an aggregate number, whether it's going to be that you have
6 two trials that equal 1,500 or if you have one large trial,
7 that's less important. The problem is some of the trials
8 that we see are marginal to begin with and then they have
9 marginal responses, and you never know, when you get
10 marginal on top of marginal, what you have at the end.

11 DR. PAZDUR: When we do accept one trial,
12 generally we do ask and discuss with the companies that
13 there is going to be internal consistency and precision in
14 doing the trial, both from a methodological and clinical
15 trials' execution endpoint. So, that would be demanded
16 basically.

17 DR. NERENSTONE: Dr. Temple.

18 DR. TEMPLE: We have a long document about when
19 we are prepared to rely on single trials.

20 But one of the things that's often helpful is
21 two really completely independent endpoints within the
22 trial, so that, for example, if you're non-inferiority on
23 time to progression and you also are looking good on
24 response rate, that's two separate things. Those don't
25 necessarily have anything that much to do with each other.

1 They're sort of independent.

2 The other thing that's worth remembering is if
3 you set the bar as requiring that you demonstrate retention
4 of 50 percent of the effect, you may be statistically not
5 so powerful for that finding, but you're very powerful for
6 the presence of some effect.

7 So, those are all things we think about in an
8 attempt to be reasonable.

9 DR. NERENSTONE: Dr. Henderson.

10 DR. HENDERSON: One thing I think is kind of a
11 fact of life that the FDA has to deal with, but not
12 necessarily a pleasant one, is that you're oftentimes not
13 allowed as much flexibility as desirable. That is, what
14 you do with one company you sort have to do with all the
15 others.

16 But the best of all possible worlds is if you
17 could sit down -- for example, the letrozole trial.
18 Sometimes I encourage people to actually write a paper
19 based on what they think the outcome of a trial is going to
20 be and then see if they want to redesign the trial once
21 they've done that.

22 For example, the letrozole trial. If you had
23 anticipated these results, at least that was one of the
24 options, and you realized that this would be a sea change,
25 certainly regardless of the issue of the companies, in

1 terms of how society would be best served, society would
2 have been better served if we had two letrozole trials of
3 that size because we're taking about such a momentous
4 effect.

5 So, I think again it depends a little bit on
6 the setting. It's just like on the last question, nobody
7 emphasized it but, in fact, on question 3 it does say for
8 first-line treatment of metastatic breast cancer. It seems
9 to me it's reasonable to say that the barrier should be
10 higher there and that larger numbers are more reasonable
11 and they are also obtainable. Let's say you have an
12 initial approval. You already have now positive data for
13 that drug. Then going on for your next indication as a
14 first-line indication, I think it is reasonable to get two
15 fairly large trials in that setting or you wouldn't require
16 that for your initial approval, let's say, in second- or
17 third- or fourth-line therapy.

18 DR. NERENSTONE: Dr. Przepiorka.

19 DR. PRZEPIORKA: A question. Now that we have
20 multiple drugs that could potentially be comparators, would
21 you accept, instead of two large studies that looked at
22 exactly the same study design, two different comparators,
23 one in each trial?

24 DR. PAZDUR: Yes.

25 DR. TEMPLE: But still you have to be able to

1 do it. So, one non-inferiority against letrozole and one
2 beat tamoxifen? We'd be delighted.

3 DR. NERENSTONE: Dr. Lippman.

4 DR. LIPPMAN: I think the issue with the one
5 large trial and the issue of how large does it need to be,
6 that's what I meant when I said by how compelling the data
7 are and the issue of two independent endpoints. I think
8 one large, well-done trial and large well-powered -- and
9 these are kind of the discussions we have -- where the
10 primary endpoint is significant, the important prespecified
11 secondary endpoints are going in the right direction, this
12 is part of the subjective reason we have this meeting. If
13 it was boiler plate, we wouldn't need a meeting if they met
14 these criteria, at least the ones that get brought to us.
15 So, I think that if we determine that all of these are in
16 the right direction and it's extremely compelling from all
17 these directions, I don't think that we should require or
18 mandate a second trial.

19 DR. NERENSTONE: Dr. George.

20 DR. GEORGE: I think it's clear. I think
21 everyone understands that there's no definitive answer to
22 the question of whether you should do one or two trials,
23 but there are certain characteristics. That is, size does
24 matter. It is good to have bigger trials.

25 But also, even if you do one trial, there are

1 various kinds of internal consistency things that you would
2 look for, you could look for, particularly in these multi-
3 institutional trials, statistical techniques where you look
4 at sampling again from the trial to see if you get the same
5 kind of results and by institutions. And all these kinds
6 of things that are normally done add weight to a single
7 trial. If you saw something strange, for example, in it,
8 that there was a vast difference by site, it may cause you
9 to worry a little bit, more than if there was more
10 consistency across sites and across other things.

11 So, there is no definitive answer, and I for
12 one never have liked the idea that there has to be two
13 trials. It certainly makes you feel more comfortable when
14 you see two large, well-done trials, but that's an obvious
15 point.

16 DR. NERENSTONE: Dr. Lippman.

17 DR. LIPPMAN: And I agree. I think when there
18 is one large trial like this, we should really torture it.
19 We should look at it by site. We should do all of these
20 internal controls to convince us that the quality is very
21 high and there aren't factors that may be biasing it.

22 My concern with the two-trial issue, quite
23 frankly, at least the kinds that come to the committee
24 often with two trials, is they're two sort of borderline
25 trials. The power is not great. There are a lot of issues

1 and bias. So, it isn't usually the case where we get two
2 definitive, large-scale trials. Certainly given that kind
3 of scenario, I prefer a very large, well-done -- what we've
4 talked about -- trial where we look at all the issues and
5 internal consistency and so on.

6 DR. PAZDUR: One of the problems that we face
7 is you don't know a priori what the results for the trial
8 area. Obviously, everybody goes in wishing their drug has
9 an unequivocal p value that everybody has confidence in,
10 that there's internal consistency. Then once you have kind
11 of an iffy trial, you're five years down the line here, and
12 nobody wants to be overburdensome in requiring two trials.

13 But the flip side of the issue is that if you
14 do have that iffy trial where things aren't looking right
15 -- maybe the randomization code wasn't quite on par; there
16 are questions within the trial -- then you're stuck, and it
17 puts everybody in a quandary of is the drug really
18 effective, should we approve this drug, should it not be
19 approved. And it's kind of late to start going back after
20 five years. It puts the development plan tremendously
21 behind schedule, et cetera.

22 I just want to get the flip side of the issue.
23 Nobody wants to be overburdensome in requiring trials, but
24 the flip side of that is it could definitely hinder a drug
25 getting approved, as well as denying the American public,

1 obviously, of potential effective therapies.

2 DR. NERENSTONE: Dr. Sridhara.

3 DR. SRIDHARA: I just want to make sure that
4 you understand that if there's superiority in one trial,
5 probably we have less concern about it when we see some
6 effect. But when it's a non-inferiority trial, we are
7 basing on many assumptions, percent effect that we want to
8 retain, and what's the effect size, and so on and so forth.
9 So, it all depends on how you have estimated and what
10 you're doing.

11 So, in the setting of a non-inferiority trial,
12 we have more concern when we have just one trial. But if
13 it is a superiority trial, as I said, if it's a large study
14 proving something definitive, then it's not that much of an
15 issue.

16 DR. NERENSTONE: Dr. Sledge.

17 DR. SLEDGE: I must say, having sat on the
18 committee now for a while, whenever I've seen more than one
19 trial brought before the committee, it has virtually always
20 been that there's one powerhouse trial and then one
21 mediocre, second-rate, smaller trial. While I agree with
22 the sentiment that two trials are generally better than
23 one, I'm not always sure that that's the case, particularly
24 if the second one has broad enough confidence intervals
25 that I'm not quite sure how to interpret it. It's the old

1 question of if you're looking at home run hitting, do you
2 learn more from Babe Ruth or from all of the 1927 Yankees?
3 I suspect you learn more from Babe Ruth.

4 DR. NERENSTONE: Dr. Lippman.

5 DR. LIPPMAN: Exactly. That sort of indicated
6 my point better than I did. In some cases that you may
7 see, you get two small trials, but in many cases, you get
8 one great one and one sort of gratuitous trial that's
9 thrown in, huge confidence intervals, and you say it's
10 consistent with almost anything you find in the big trial.
11 So, I don't know if any applications have come in with two
12 real pivotal trials designed in the same way.

13 But then the question about the statistics.
14 you said that you would feel more comfortable with two
15 trials with non-inferiority. Would you feel more
16 comfortable with two small -- I won't say mediocre, but
17 borderline -- trials, maybe the same size as the big one
18 all together that demonstrate non-inferiority or one very
19 large, multi-center trial that we've been talking about?
20 It seems to me that the endpoint of whether it's superior
21 or non-inferior really doesn't relate to the two versus one
22 trial issue.

23 DR. PAZDUR: It does.

24 DR. SRIDHARA: It does very much. If you can
25 flip over the slides actually, you'll see that for

1 superiority, you don't require as many patients or as many
2 events, but with non-inferiority, you do require larger
3 events. Again, by their nature, the non-inferiority trials
4 are always bigger than superiority trials. In whichever
5 setting you are talking about, the non-inferiority trials
6 are going to be larger.

7 But as I said, the fact is that we are basing
8 it on some kind of estimates of what percent retention that
9 we want to do, what's the effect size, none of which we
10 have a good handle on. So, that's a kind of uneasiness
11 that we would rather have two studies rather than one
12 study.

13 DR. LIPPMAN: But just to clarify my point. It
14 depends on how you design a study. If you have two smaller
15 trials, based on non-inferiority on response rate, so
16 they're larger than superiority trials, but not that much,
17 not that large, would you prefer that situation? Again,
18 two smaller trials with non-inferiority with broad
19 confidence intervals and so on versus one very well-done
20 large trial that shows non-inferiority.

21 DR. PAZDUR: It's impossible to answer that
22 question. Basically, to summarize this, we look at the
23 totality of the evidence that comes in, internal
24 consistency within a trial, between the trials, et cetera.
25 So, your question is very difficult to answer.

1 But getting back to I think a central point
2 here, when we do have a non-inferiority analysis, it
3 presents some difficulties to us. To put this in kind of
4 crude terms, to show garbage equals garbage is not a
5 difficult task. To show a superiority trial is a difficult
6 task and it's an onerous one on the part of a drug to show
7 that you're better. So, it gives us much more confidence.

8 But a poorly done trial, a poorly done control
9 arm in a non-inferiority trial where the therapeutic effect
10 may be relatively marginal, non-inferiority may not be that
11 difficult to show because of the inconsistencies in the
12 trial, the poor conduct of the trial, et cetera.

13 But one trials versus two trials. It's not so
14 much the number here. At the end of the day, it's what is
15 the convincing body of evidence that we have, and I think
16 that is the focus that I wanted to end the discussion on.

17 DR. NERENSTONE: Dr. Henderson, did you have
18 one other point?

19 DR. HENDERSON: It's just a quick one.
20 George's analogy to baseball went by so fast I almost
21 missed it. But I certainly wouldn't judge the future of
22 Yankee batters on the basis of Babe Ruth.

23 (Laughter.)

24 DR. NERENSTONE: We have one more question I
25 think, and we're running out of time.

1 There are many ongoing studies of hormonal
2 agents for the first-line treatment of metastatic breast
3 cancer. Some of these studies are designed to demonstrate
4 non-inferiority to tamoxifen and some are designed to
5 demonstrate non-inferiority to other approved first-line
6 agents from various classes of hormonal therapies using
7 response rate as the primary endpoint.

8 Are there any potential trial designs that
9 would need to be changed based on the answers to the above
10 questions? And the answer was yes, at least starting from
11 now, depending on how retroactive you think it's
12 appropriate to go back.

13 But let's open it up. Dr. Ohye.

14 MR. OHYE: It's Mr. Ohye.

15 DR. NERENSTONE: Okay.

16 MR. OHYE: Perhaps before I begin, I could say
17 words of how I arrived on this committee because perhaps
18 I'm a bit of a surprise or a mystery to some.

19 I was asked to serve on this committee by the
20 Pharmaceutical Research and Manufacturing Association.
21 They asked a group of retired pharmaceutical people if they
22 would like to serve. And I specifically asked for this
23 committee because I believe this committee and the Oncology
24 Division have done more to relieve suffering of Americans
25 than any other therapeutic group regulated by the FDA. I

1 think you have done so by keeping the care of patients in
2 mind primarily and not getting bogged down with the macro-
3 elements of study data.

4 I also have a personal reason for being here:
5 My mother succumbed to cancer at an early age, and I too am
6 a cancer survivor.

7 That being said, I have only two points that
8 the industry has asked me to bring forward. The companies
9 are concerned about the consequences of changing either
10 controls or endpoints to ongoing studies and how that might
11 complicate evaluation, particularly since these studies
12 take a long time to accrue patients. If changes are made
13 midway in a study, particularly when some study centers are
14 closed, et cetera, it would be very difficult to come up
15 with really the profound data that we all would like to
16 see.

17 They say if this is demanded of them, they
18 would suggest that for these ongoing studies, that approval
19 could still be obtained under the accelerated approval
20 route where confirmatory phase IV studies would still be
21 required.

22 Thank you.

23 DR. NERENSTONE: Dr. Lippman.

24 DR. LIPPMAN: I was going to make this point
25 when Dr. Henderson brought up the issue of the progestins

1 and 50 patients to go. I really think we have to approach
2 trials that are ongoing differently than new trials. I
3 thought what we were talking about here is what to tell
4 industry now are the designs that are acceptable based on
5 2001 September data. I think that if a drug came in that
6 was done differently, we'd evaluate it differently.

7 I think the accelerated approval is an
8 interesting concept in terms of how to handle that. I
9 actually like that idea. I hadn't thought about that. But
10 I think that that should come up as part of the discussion
11 and that we shouldn't mandate changes in design in the
12 middle of trial. That would be the kiss of death for a lot
13 of the analyses we're talking about.

14 DR. NERENSTONE: And I would agree with that
15 approach, which is if you're in trial, you stay in trial,
16 especially large studies. You can't do that. You can't
17 hold somebody responsible to a new level if it was already
18 designed and started 5 or 10 years ago.

19 I think, though, for a practical matter, that
20 the publicity is going to take care of itself, which is a
21 drug that does not come up to the new standard is not going
22 to be widely accepted in the oncologic community as a drug
23 that has beaten the new standard. So, I think we don't
24 want inactive drugs to be put out there, but I don't think
25 that we have a fear that that will happen.

1 DR. PAZDUR: To summarize this, I think we
2 would only demand changes if there was a very strong sense
3 that we would see a safety issue that would emerge. From
4 the discussions that we've had, I don't get that feeling
5 especially from the first answer where there is not a
6 consensus of changing to one single new comparator arm, et
7 cetera. So, we appreciate your comments on this last
8 question.

9 DR. BLAYNEY: Yes, I agree. I think it's
10 unfair to change in the middle of the stream in the absence
11 of a safety issue. I was going to raise that before you
12 did. I don't see the safety issue. I think let's go.

13 DR. PAZDUR: Heaven forbid. We wouldn't want
14 anyone to accuse the FDA of being inconsistent.

15 (Laughter.)

16 DR. NERENSTONE: Dr. Temple.

17 DR. TEMPLE: We try to keep those quiet.

18 (Laughter.)

19 DR. TEMPLE: We fairly recently approved
20 capecitabine as an alternative to fluorouracil/leucovorin
21 even though the studies didn't have any CPT-11 around. And
22 the label says we don't know how this regimen interacts
23 with CPT-11, but we didn't think it shouldn't be approved
24 because of that. I guess there is a post-marketing
25 obligation to do a trial in the presence of CPT-11.

1 DR. NERENSTONE: Further comments? Dr. Albain.

2 DR. ALBAIN: I'll go back to something Dr.
3 Sledge said earlier, about the tendency in many trials now
4 to use, for response rate endpoints, CR, PR, plus a 6-month
5 stable disease or some other interval. Is there a
6 precedent for accepting that as a primary endpoint in any
7 pivotal trial that you're aware of? Because it seems to
8 have crept in, and I'm not quite sure that we know that
9 stable disease for 6 months --

10 DR. PAZDUR: No. We have not traditionally
11 accepted stable disease as being incorporated into the
12 response rate because we look at that in a different
13 fashion. Response rate is a unique endpoint in that all of
14 the effect of a response rate is attributable to the
15 therapy that is being introduced, and we look at that as
16 kind of a different type of endpoint because of that.

17 Obviously, the problem with stable disease is
18 what is the contribution to the natural history of the
19 disease. Again, you could probably set a parameter there,
20 whether it be 6 months, 8 months, 3 months. Here again, I
21 think it would probably confound what we're actually after
22 when we look at response rate. And that could be easily
23 measured by an analysis of time to progression.

24 DR. NERENSTONE: Any other comments?

25 (No response.)

1 DR. NERENSTONE: Well, I'd like to thank
2 everybody for a relatively free-wheeling discussion.

3 DR. ALBAIN: Stacy, there's one more question.

4 DR. NERENSTONE: Oh, sorry. Over-eager to go
5 to lunch I guess. Okay.

6 Number 6. Please discuss whether these
7 recommendations would change if patients treated with a
8 hormonal therapy are found to have improved survival
9 compared to patients treated with tamoxifen with respect to
10 the comparator drug and endpoints.

11 Open for discussion. Are those data accruing
12 so that we will have some legitimate survival endpoints?

13 DR. PAZDUR: Yes.

14 DR. NERENSTONE: Dr. Henderson.

15 DR. HENDERSON: It comes back to what we were
16 discussing before. I think if you know definitely that
17 there's a survival difference associated with a class of
18 drugs, I think it should change things. If you've got one
19 trial with one drug and the rest of the class doesn't show
20 that and no scientific explanation for that, I think you
21 should be skeptical. I think you should always be
22 skeptical of all clinical data to begin with, and then you
23 break down that process of being skeptical as you get more
24 and more evidence.

25 DR. PAZDUR: I think, since the time is late,

1 | what we would be looking at, obviously, is the consistency
2 | of the data. If it's one trial, how would that change
3 | versus having it confirmed in other trials, et cetera.

4 | DR. HONIG: Right. And it probably, I assume,
5 | would depend on the magnitude of the survival benefit.

6 | DR. NERENSTONE: I think it would be very
7 | important to know that, and I think it would then take the
8 | hormone drug discussion out of, "oh, well, it's not very
9 | toxic and it doesn't matter" to we have to look at survival
10 | as an endpoint much more seriously and make it much more
11 | like a cytotoxic where survival is a primary endpoint.

12 | DR. PAZDUR: But here again, it's not only the
13 | magnitude, but how reliable we feel that endpoint is. Was
14 | the survival advantage really attributable to the study
15 | drug? What are the crossovers that, especially with this
16 | long natural history of many of these patients, would have
17 | contributed to a difference? So, I think the analysis
18 | could be quite complicated of a survival claim.

19 | DR. NERENSTONE: Dr. Lippman.

20 | DR. LIPPMAN: On the face of it, not knowing
21 | about the issues specific to hormonal therapy, survival in
22 | my view trumps all the other endpoints. So, it would be a
23 | no-brainer. But because of the reasons raised by Dr.
24 | Carpenter and we all know there's a lot of sequential
25 | therapy that goes on, it seems to me that it would be very

1 | difficult to prove it. But if you did and felt comfortable
2 | with it, I think it would be an easy answer.

3 | DR. NERENSTONE: Dr. Blayney.

4 | DR. BLAYNEY: And there are supportive
5 | therapies as well that have an impact on survival that may
6 | or may not be applied to any given patient population in
7 | one country or one center or another, which also confounds
8 | and introduces noise into this system.

9 | DR. NERENSTONE: Okay. The committee needs to
10 | be back at 1:30. Thank you very much for your attention.

11 | (Whereupon, at 12:20 p.m., the committee was
12 | recessed, to reconvene at 1:30 p.m., this same day.)

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