

1 ratios within the population that we studied in
2 collaboration with Genentech, it can be plotted
3 with the number of cases showing each one of these
4 ratios on the Y axis and the ratio on the X axis.
5 In green are those cases that had a ratio of less
6 than 2, and to the right are those cases that had a
7 ratio of 2 or greater.

8 As I think you can appreciate, near the
9 cut-off there is a trough in the overall frequency
10 of distributions of the ratio, and in our
11 experience in this study and in our experience in
12 other cohorts that we have characterized, less than
13 5 percent of the samples tend to be in this
14 critical cut-off range between 1.8 and 2.2 in terms
15 of the ratio.

16 The use of FISH to measure HER2/neu gene
17 copy number also has a number of advantages and
18 disadvantages, which are briefly summarized here.
19 Advantages include especially that DNA is a
20 relatively stable target; is less affected by the
21 tissue fixation and processing. It has a
22 standardized threshold that has been established
23 for positivity, a ratio of greater than 2.

24 There is a built-in internal control.
25 These tumor samples in general are not pure samples

1 of tumor cells; they are a mixed population of
2 normal cells and carcinoma cells so that within the
3 sample there are normal cells that are expected to
4 have 2 copies of HER2/neu and 2 copies of
5 chromosome 17 centromere. So, there is a built-in
6 internal control that allows one to know whether
7 the procedure was successful or whether it failed.
8 When it fails you can cancel out the procedure and
9 say it is a failure.

10 There is relatively low inter-laboratory
11 variability, as was presented by CAP this morning.
12 There is relatively high accuracy in terms of
13 sensitivity and specificity. We can discuss that
14 later if there are questions.

15 In terms of disadvantages, fluorescence
16 microscopy equipped with the appropriate filters is
17 a requirement of this procedure. There are certain
18 fixatives that will interfere with the assay and in
19 those settings the assay will fail and you will get
20 a non-result. There is also limited community
21 experience with tissue-based FISH so there is less
22 familiarity with this procedure in the pathology
23 community.

24 I would like to briefly summarize some of
25 the clinical associations between HER2 alterations

1 and the clinical utility of this particular gene.
2 First of all, it is considered to be a prognostic
3 marker. HER2 gene amplification has been
4 associated with a poor outcome in women who have
5 the disease.

6 This is an example of just one such study
7 that has been conducted. Among those women whose
8 breast cancers lacked gene amplification, they had
9 a more favorable clinical outcome in terms of
10 overall survival than those women whose breast
11 cancers had gene amplification, plotted out to ten
12 years of clinical follow-up, 120 months. The
13 differences were highly statistically significant.
14 So this is a marker. It is a prognostic marker, a
15 marker of poor clinical outcome in women who have
16 the disease.

17 In addition, HER2/neu has been associated
18 as a predictive factor, a predictive marker
19 predicting responsiveness to certain forms of
20 therapy. One of these forms of therapy is the
21 conventional therapy of adriamycin chemotherapy.
22 This just shows an example of how fluorescence in
23 situ hybridization can predict a subpopulation that
24 is responsive.

25 Among those women whose breast cancers do

1 not have gene amplification, it didn't matter
2 whether they were treated with low, medium or high
3 dose adriamycin chemotherapy. Their outcome was
4 essentially similar in terms of their overall
5 survival.

6 Among those women who had gene
7 amplification in their breast cancer, those women
8 who received high dose adriamycin chemotherapy had
9 a more favorable overall survival, and the
10 difference was statistically significantly better
11 than for those women who were treated with low or
12 medium dose adriamycin chemotherapy.

13 We have had some discussion of subgroups.
14 I have tried to address the issue earlier with what
15 I said about molecular characterization of frozen
16 tissue samples. It is difficult to look at cohorts
17 because, as I pointed out, the group in which there
18 is a disagreement, under ideal circumstances,
19 between gene amplification and overexpression is
20 relatively limited. So, one has to have a large
21 cohort to be able to address some of these issues.

22 One of the papers that was recently
23 published from Dennis Slamon and his group
24 addresses this issue in terms of overall survival.
25 In the study from UCLA there were 856 women that

1 were characterized both in terms of gene
2 amplification by FISH and immunohistochemical
3 staining for the protein product. In both of these
4 settings, the women lacking gene amplification had
5 a more favorable overall survival than those women
6 whose breast cancers had gene amplification and
7 were FISH positive, a highly statistical
8 significant difference between the two. Also in
9 this group, those women who were considered to be
10 low expressers, had 0 or 1+ immunostaining, had a
11 more favorable clinical outcome than those women
12 who had positive immunohistochemical staining,
13 either 2+ or 3+ and are considered overexpressers.
14 The difference was also statistical significant.

15 Among the group of cases that they
16 studied, there were patients who had
17 immunohistochemical staining that was either 2+ or
18 3+ and, among those then, when FISH was examined
19 there were 45 women who did not have gene
20 amplification by FISH and a much larger pool, of
21 course, that had gene amplification by FISH. When
22 this was compared, the overall survival was
23 statistically significantly different and the FISH
24 negative group behaved like a group of women that
25 do not have gene amplification and do not have

1 overexpression in spite of the fact that they had
2 2+, 3+ immunohistochemical staining. So, I would
3 contend that this is one of the issues that can be
4 raised with immunohistochemical methods as an
5 analytical technique. It is an artifact of the way
6 this is either scored or processed. It is a false-
7 positive result by immunohisto-chemical staining.

8 In conclusion, I would like to say that
9 there is a direct correlation, in my opinion, that
10 exists between gene amplification as a genetic
11 alteration and overexpression. FISH is a robust
12 method for detecting gene amplification. Finally,
13 amplification as determined by FISH is a clinically
14 meaningful measure that is associated both with
15 poor prognosis and the prediction of therapeutic
16 response.

17 Thank you very much. I would like to turn
18 the podium over to Dr. Robert Mass, the associate
19 director of oncology at Genentech, who will
20 continue our discussion.

21 **Concordance and Clinical Outcome Analyses**

22 DR. MASS: Good afternoon. My name is
23 Robert Mass and I am a medical oncologist, as well
24 as the associate director of oncology at Genentech.

25 You have heard a great deal this morning

1 about HER2 diagnostics, and we fully agree that
2 these discussions are critical as new therapeutics
3 are developed in oncology that target the specific
4 molecular alterations that are associated with
5 cancer. I think it is clear to everyone in the
6 room that we are here to discuss a fairly unique
7 topic for ODAC. We will not be discussing a new
8 indication or an expanded indication for a
9 therapeutic but, rather, we will be discussing a
10 new diagnostic methodology, specifically
11 fluorescence in situ hybridization, to select
12 patients for a targeted therapeutic.

13 Dr. Press has just reviewed with you a
14 number of important observations. He has
15 established the fundamental biologic link between
16 amplification of HER2 and protein overexpression of
17 the target of Herceptin, the HER2 protein. He has
18 also shown you data that PathVysion, by identifying
19 the specific molecular alteration in breast cancer,
20 can provide both prognostic and predictive
21 information in patients with breast cancer.

22 In addition, this morning you heard
23 considerable data presented that
24 immunohistochemistry, which is the only currently
25 approved methodology to select patients for

1 Herceptin therapy, appears to have significant
2 accuracy issues when it is applied to the typical
3 clinical samples of formalin-fixed, paraffin-
4 embedded material. It was really these three
5 fundamental observations that led us to evaluate
6 PathVysion as an alternative method to select
7 patients for Herceptin therapy.

8 This Kaplan-Meier plot demonstrates the
9 significant survival benefit that was achieved when
10 Herceptin was added to chemotherapy in our pivotal
11 labeling trial. I think it also illustrates the
12 critical importance of accurate HER2 assessment.
13 Only patients with HER2 overexpression will derive
14 this survival benefit from Herceptin. Inaccurate
15 HER2 assessment, both false negatives as well as
16 false positive results, will lead to suboptimal
17 clinical results.

18 Our hypothesis in beginning this work was
19 that PathVysion will provide physicians with an
20 alternative non-immunohistochemical assay method to
21 accurately identify patients for Herceptin therapy.

22 My goal over the next twenty minutes will
23 be to provide you with data that support the
24 addition of PathVysion to the Herceptin label in
25 order to identify patients for Herceptin therapy.

1 I will be reviewing two studies that
2 support this labeling supplement. First I will
3 discuss the concordance study which established the
4 concordance or the level of agreement between
5 PathVysion and the clinical trials assay. You have
6 heard that the clinical trials assay was an
7 immunohistochemical method that was used to select
8 patients for the Herceptin pivotal trials. An
9 acceptable level of concordance was the standard
10 that was used for approval of the two
11 immunohistochemical assays that are currently
12 labeled to aid in the selection of patients for
13 Herceptin therapy, that being the HercepTest assay
14 and the Pathway assay.

15 Next, I will discuss with you an
16 exploratory clinical outcomes analysis. This was a
17 retrospective exploratory analysis of FISH status
18 as a predictor of clinical benefit in the pivotal
19 Herceptin trials. As part of this study, I will
20 also be describing an inter-laboratory validation
21 assessment that we conducted. These data,
22 particularly when viewed in the context of the HER2
23 biology that you heard about earlier, support the
24 addition of PathVysion to the Herceptin labeling.

25 At the outset, I would like to comment on

1 the source of the tissue specimens that we used for
2 this work. Both of the studies utilized tissue
3 sections that had been archived from patients who
4 were either screened for enrollment or actually
5 enrolled in the Herceptin pivotal trials. These
6 tissue sections were used specifically because the
7 Herceptin pivotal trials represent the only large
8 database that is currently available to correlate
9 HER2 diagnostics with treatment outcomes.

10 During my talk I will mention issues of
11 non-informative FISH results, and will also review
12 some elements of inter-laboratory variability. We
13 believe that these are a direct result of the age
14 and the condition of the specimens that were
15 utilized for the work I will show you.

16 The primary objective of the concordance
17 study was to establish the concordance or the level
18 of agreement between the clinical trials assay and
19 PathVysion. This was a prospectively defined study
20 which utilized the clinical trial samples that were
21 retrospectively tested with PathVysion.

22 The laboratory was single-blinded to the
23 prior clinical trial assay results. The analysis
24 plan was identical to the HercepTest concordance
25 protocol that was used for FDA approval of that

1 diagnostic assay. Concordance was first
2 established in a population with approximately
3 equal distributions of CTA positive and CTA
4 negative results. As mentioned earlier, a positive
5 result was a CTA score of either 2+ or 3+ and a
6 negative result was a CTA score of either 0 or 1.
7 This equal distribution provides maximal
8 statistical power to assess the level of
9 concordance. For this work, FISH positivity was
10 defined as a HER2 HercepTest ratio of greater than
11 or equal to 2, and FISH negativity was a score of
12 less than 2.

13 The primary endpoint of this study was
14 concordance in this population with an equal
15 distribution of CTA positive and negative scores.

16 The secondary endpoints included
17 discordance extrapolated to a more
18 representative population of breast cancer, that
19 is, the patients who were actually screened for the
20 Herceptin pivotal trials.

21 In addition to concordance, we also
22 assessed the Kappa statistic, which is an
23 alternative statistical measure of the level of
24 agreement between two tests. The assumptions we
25 made were that a concordance level of 75 percent or

1 less was prespecified as an unacceptable level of
2 concordance. We sought 90 percent power to detect
3 a 5 percent improvement over that unacceptable
4 level on a one-sided test on proportion, and those
5 assumptions led to a sample size of approximately
6 600 specimens.

7 During the clinical development program of
8 Herceptin, nearly 6000 patients had clinical tumor
9 samples sent to the Laboratory Corporation of
10 America, a central reference testing laboratory,
11 and the CTA assay was performed on those specimens.
12 From that pool, nearly 90 percent or 5271 patients
13 had at least two unstained tissue sections that
14 remained in the archives of LabCorp.

15 From that sample, 623 patients were
16 randomly selected in an approximate one to one
17 ratio, specifically 317 CTA negative specimens and
18 306 positive specimens were identified and
19 underwent FISH testing.

20 Results were generated in 529 or 85
21 percent of the samples, and this 15 percent non-
22 informative rate is slightly higher than the 8
23 percent non-informative rate that might be expected
24 from PathVysion and is likely, again, due to the
25 age and the condition of the tumor specimens that

1 were used.

2 Here are the results. In this population
3 with an equal distribution of positive to negative
4 scores, the overall concordance was found to be 82
5 percent. The Kappa statistic was 0.64, which
6 indicates a good level of agreement between the two
7 tests. However, in examining the discordant
8 results more carefully, one can see that there is a
9 significant asymmetry in the distribution of
10 discordant results, with the majority being in this
11 category that were originally scored as CTA
12 positive but on FISH testing were noted to be
13 negative.

14 In expanding that 2 X 2 table to a 4 X 2
15 concordance table, one can appreciate that the
16 majority of these 88 discordant samples are found
17 in the patients who were originally scored as 2+ by
18 the clinical trials assay. The overall
19 amplification in this group was noted to be 24
20 percent.

21 The agreement between PathVysion and the
22 clinical trials assay was very high in the other
23 three patient groups, although I want to point out
24 that there were 21 out of these 197 patients who
25 showed no evidence of amplification, with a 3+

1 score, and there were also 9 patients here who were
2 amplified but showed no evidence of protein
3 overexpression using the clinical trials assay. I
4 will come back and discuss these patients a little
5 bit later in the talk.

6 The previous results assessed concordance
7 in this artificial population with an equal
8 distribution of positive and negative scores. But
9 in order to better assess how PathVysion might
10 perform in a typical population of breast cancer,
11 we extrapolated the amplification rates by each CTA
12 score into the population that were actually
13 screened for the pivotal trials. That is, the 6000
14 women with metastatic breast cancer. This is the
15 distribution of scores, 58 percent scored 0; 9
16 percent scored 1; 10 percent scored 2+; and 23
17 percent of the population scored 3+.

18 If one looks at the amplification rates in
19 this distribution, you can see that 2 out of the 58
20 patients scoring as 0 would be amplified; 1 of the
21 9, 1+; 2 of the 10, 2+ and 21 of the 23 3+
22 patients.

23 Taking this data and converting it into a
24 2 X 2 concordance table, one can see that, as
25 expected, in a non-equal distribution population, a

1 more representative population, the overall
2 concordance improved to 88 percent.

3 As you have heard, the only FDA approved
4 HER2 diagnostic assay that has been directly
5 compared to the clinical trials assay is the
6 HercepTest assay. As you can see from this slide,
7 the level of agreement between PathVysion and the
8 clinical trials assay, whether one looks at the one
9 to one population concordance or whether one looks
10 at the extrapolated population concordance, is very
11 similar to the level of agreement between the
12 HercepTest assay and the clinical trials assay.

13 So to summarize the conclusions of the
14 concordance analysis, the concordance between
15 PathVysion and the CTA in a one to one population
16 is 82 percent. This exceeded our prespecified
17 level of acceptability. The level of concordance
18 between PathVysion and the CTA is consistent with
19 that between HercepTest and the CTA. We believe
20 that these conclusions suggest that PathVysion will
21 provide similar performance compared to HercepTest
22 when used as a surrogate for the clinical trials
23 assay to select patients for Herceptin therapy.

24 The concordance data that I have just
25 shown you is sufficient to support the approval of

1 PathVysion as a method to select patients for
2 Herceptin. However, we went on to conduct an
3 additional exploratory assessment of FISH as a
4 predictor of clinical benefit from Herceptin in
5 several different Herceptin trials.

6 The rationale for conducting this work was
7 an important post-approval commitment that we had
8 made to the Food and Drug Administration to explore
9 other HER2 diagnostics in the context of Herceptin
10 clinical trials. But more importantly, this would
11 also provide additional data to support FISH as an
12 appropriate method to select patients for
13 Herceptin.

14 Again, the objective was to explore the
15 relationship between the FISH status, that is, FISH
16 positivity or FISH negativity, and Herceptin
17 clinical benefit as assessed by a retrospective
18 analysis of several different efficacy parameters,
19 including response rate, time to disease
20 progression and survival, in three Herceptin
21 clinical trials. These included the pivotal trial
22 of chemotherapy with or without Herceptin in the
23 first-line treatment of metastatic breast cancer.
24 It also included the pivotal Herceptin monotherapy
25 trial in second- or third-line treatment of

1 metastatic breast cancer. We also evaluated a
2 supportive Phase II trial of Herceptin monotherapy
3 as first-line treatment of metastatic breast
4 cancer.

5 Only the results of the first two trials
6 will be discussed this afternoon, representing 691
7 patients. I want to emphasize again that these
8 trials represent the only large database available
9 to correlate HER2 diagnostics with treatment
10 outcome from Herceptin. This tissue database was
11 not designed for subsequent validation of
12 alternative diagnostic assays.

13 Although tumor blocks or tissue sections
14 were originally requested from sites enrolling
15 patients in these trials, only tissue sections were
16 archived at LabCorp. Obviously, clinical outcomes
17 data is only available for patients who scored 2+
18 or 3+ by the clinical trials assay because that was
19 the eligibility requirement for entry into the
20 clinical trials.

21 There was a total of 799 patients who were
22 enrolled in these three trials, and 784 had
23 archived tissue sections that remained at LabCorp
24 available for FISH testing. We initially utilized
25 unused tissue sections that remained in the archive

1 at LabCorp that we thought were suitable for FISH
2 testing. From those 618 patients results were
3 generated in 540.

4 In order to maximize the number of
5 patients who had FISH results available for our
6 retrospective clinical outcomes analysis, we
7 approached the laboratory of Dr. Michael Press, at
8 the University of Southern California. Dr. Press
9 had developed expertise in performing FISH testing
10 on tissue sections that had been previously
11 immunostained. These 244 samples that represent
12 the difference between 540 and the 784 possible
13 specimens were sent to USC and underwent FISH
14 testing, where 225 results were generated.

15 This total cohort of 765 results, which
16 represented 96 percent of the patients enrolled in
17 these trials, was utilized for the primary analysis
18 data set for retrospective analysis of clinical
19 outcomes.

20 The Herceptin monotherapy trial, leading
21 to approval in this indication, enrolled 222
22 patients. The key eligibility criteria included
23 HER2 overexpression with a CTA at the 2+ or 3+
24 level and disease progression after at least one or
25 two prior chemotherapy regimens. The primary

1 endpoint was response rate as determined by an
2 independent response evaluation committee.

3 Here are the results. There were 163
4 patients of the 222 enrolled that demonstrated gene
5 amplification by FISH. Objective responses were
6 noted in 33 of those patients, for an overall
7 response rate of 20 percent. In this trial there
8 were 46 patients who failed to show amplification
9 by PathVysion, and there was 0 response seen in
10 those 46 percent, for an overall response rate of
11 0. As a point of reference, the response rate in
12 this trial in the total population of 2+ and 3+
13 patients was 15 percent.

14 This is the design of the pivotal first-
15 line trial which randomized 469 patients. Again,
16 HER2 overexpression at the 2+ or 3+ level was
17 required. No prior chemotherapy for metastatic
18 breast cancer was allowed. The primary endpoint of
19 this trial was time to disease progression, again
20 as assessed by an independent response evaluation
21 committee, and response rate and survival were
22 secondary endpoints.

23 Looking first at response rate in this
24 trial, one can see that for the 325 patients
25 showing gene amplification by PathVysion, the

1 response rate improved from 30 to 54 percent.
2 Whereas, the 126 patients who were found not to be
3 amplified by PathVysion had no apparent improvement
4 in their response rate, 38 versus 40 percent, with
5 a p value of 0.74.

6 These Kaplan-Meier plots demonstrate the
7 time to disease progression for the FISH positive
8 and FISH negative subsets. As you can see, there
9 was a highly significant improvement in time to
10 disease progression when Herceptin was added to
11 chemotherapy in the amplified group, with a risk
12 ratio of 0.44. A much smaller benefit was noted in
13 the FISH negative group, with a risk ratio of 0.66.

14 Finally, these Kaplan-Meier plots
15 demonstrate the overall survival for the FISH
16 positive and the FISH negative groups. Survival
17 represents the most clinically important and
18 clinically relevant efficacy endpoint in metastatic
19 breast cancer. As you can see from these curves,
20 there was a highly significant improvement in
21 overall survival in the amplified group, with a
22 risk ratio of 0.69, and there was no apparent
23 benefit with the addition of Herceptin to
24 chemotherapy in the non-amplified group, with a
25 risk ratio of 1.07.

1 To summarize this data, within both
2 pivotal trials FISH positive status appears to
3 consistently identify a population of patients who
4 benefit from Herceptin therapy. In the single-
5 agent trial all of the responses were noted to be
6 in the subgroup. In the combination trial the FISH
7 positive group generated significant clinical
8 benefit looking at all three efficacy variables.

9 The clinical results that I have just
10 shown you were generated from FISH results
11 performed in two different laboratories. Each
12 laboratory was forced to use different types of
13 tissue sections for FISH testing. Previously
14 unused tissue sections were utilized at LabCorp;
15 previously immunostained sections were used at USC.
16 This was necessary in order to maximize the number
17 of patients with FISH results for the clinical
18 outcomes analysis.

19 We conducted an inter-laboratory
20 validation assessment to ensure that the assay
21 methodology differences between the two
22 laboratories would not influence the interpretation
23 of the clinical outcomes results that I have just
24 shown you. In this process, a total of 248
25 patients with known FISH results from LabCorp were

1 sent to USC for repeat FISH testing in two stages.
2 These were, in fact, immunostained tissue sections
3 from samples that had been stained in unused tissue
4 sections originally at LabCorp.

5 During this process all of the patients
6 who had an original FISH negative score at LabCorp
7 were retested at USC, along with a large number of
8 FISH positive specimens. Results were obtained in
9 221 of these 248 samples.

10 Here are the results. The overall level
11 of agreement was 82 percent. For the patients who
12 were found to be FISH positive at LabCorp, that
13 result was almost uniformly confirmed at USC, with
14 an agreement rate of 98 percent. However, for the
15 patients with an original score that was FISH
16 negative at LabCorp, the level of agreement fell to
17 74 percent.

18 When we looked more carefully at these 37
19 discordant specimens between the two laboratories,
20 we discovered that 84 percent of those specimens
21 had tested 3+ by the clinical trials assay. Given
22 the previous concordance results that I shared with
23 you, with an amplification rate of 90 percent in
24 the 3+ group, this was indicative of some degree of
25 underscoring at LabCorp.

1 In your briefing book we extensively
2 review the similarities and the differences in the
3 laboratory techniques between the two centers, that
4 is, LabCorp and USC. After completing this
5 evaluation we determined that fundamental
6 differences in the conditions of the specimens that
7 were used led to the need for differences in the
8 protease digestion step which likely accounted for
9 some degree of underscoring that had occurred at
10 LabCorp.

11 In order to ensure that this observation
12 did not have an effect on the interpretation of the
13 clinical outcomes analysis that I showed you, we
14 conducted an exploratory secondary analysis where
15 preference was given to the result from USC when
16 that result was available.

17 As you can see from this table, there was
18 no impact on the interpretation whether one looks
19 at the primary data set or the secondary data set.
20 The FISH positive patients consistently derived
21 clinical benefit from Herceptin as compared to the
22 FISH negative group.

23 Now, despite the primary and the secondary
24 analysis that I have just shown you, and after the
25 discussions that we heard today, there are a number

1 of unanswered questions that remain with clinical
2 relevance. Dr. Press reviewed with you the current
3 understanding of HER2 biology, that is, the
4 invariable association of protein overexpression
5 when there is amplification of the gene and
6 invariable presence of amplification when there is
7 overexpression of protein.

8 Despite this fundamental biologic fact,
9 because of the assay performance issues that we
10 have talked about today, discordant clinical
11 populations do exist. One might ask do FISH
12 positive patients who have less than 3+ protein
13 overexpression, that is, 0, 1 or 2 by
14 immunohistochemistry benefit to the same extent as
15 patients who are amplified and clearly
16 overexpressed? One might also ask the question do
17 non-amplified patients who show high levels of
18 protein overexpression by immunohistochemistry
19 benefit to the same extent as FISH positive and IHC
20 3+ patients?

21 What can be concluded regarding these
22 subsets from a retrospective analysis of the
23 pivotal trials that I have just shared with you?
24 Well, statisticians will tell you that the patient
25 numbers in these discordant subsets are simply too

1 small to provide a definitive assessment.

2 Are prospective trials feasible? I think
3 this is an important issue and I want to review for
4 you how difficult such trials may be if we take the
5 most clinically important question that remains
6 unanswered, that is, do amplified patients who
7 score less than 3+ on an immunohistochemistry assay
8 derive the same benefit from Herceptin as an
9 amplified and 3+ population?

10 I want to take you back to this
11 extrapolated concordance plot that I showed you
12 earlier. Again, we showed in a typical population
13 of breast cancer that 88 percent of the patients
14 would be fully concordant. They would either be
15 non-amplified and non-overexpressed, or they would
16 be amplified and overexpressed. If we isolate the
17 discordant subset of interest here, you can see
18 that 2 percent of patients with breast cancer will
19 score 0 on an IHC assay and found to be amplified
20 by FISH; 1 percent of the 1+ group and 2 percent of
21 the 2+ group would be amplified as shown here.
22 That said, that represents 5 percent of the total
23 breast cancer population, or roughly 20 percent of
24 the amplified patients.

25 The survival benefit that we have

1 demonstrated for Herceptin would preclude the
2 conduct of an optimal clinical trial, that is, a
3 randomized clinical trial between no Herceptin and
4 Herceptin. An alternative non-randomized trial
5 design we thought was appropriate would be a non-
6 inferiority design, where the objective would be to
7 compare the clinical outcomes of the 3+ and
8 amplified group to the group of interest, those
9 scoring less than 3+ and demonstrating gene
10 amplification.

11 This trial would require a sample size of
12 approximately 3330 patients in order to
13 definitively establish non-inferiority. Because
14 the discordant population represents only 5 percent
15 of women with metastatic breast cancer, this would
16 require screening nearly 30,000 women to populate
17 this trial.

18 If we go back to this slide, one can see
19 that the other discordant subgroup of interest, the
20 3+ but non-amplified group, represents only 2
21 percent of the total breast cancer population and
22 that would require screening nearly 50,000 women to
23 populate such a trial.

24 I think the question of whether this is an
25 appropriate utilization of clinical resources in

1 order to conduct clinical research in breast cancer
2 is an important question for the committee to
3 discuss.

4 In summary, we have shown you two pieces
5 of data to support our supplemental application.
6 The concordance analysis demonstrates that
7 PathVysion will provide similar performance to
8 clinicians compared to the HercepTest when used as
9 a surrogate for the CTA to select patients for
10 Herceptin therapy. The clinical outcomes analysis
11 that I showed you provided additional data to
12 support FISH as an appropriate method to select
13 patients for Herceptin therapy.

14 We believe that those observations support
15 our final conclusion that the Herceptin package
16 insert should be modified to include PathVysion as
17 an appropriate method to aid in the selection of
18 patients for Herceptin therapy. With that I will
19 stop. I thank you for your attention and I will
20 answer questions.

21 **Questions from the Committee**

22 DR. NERENSTONE: Thank you very much. We
23 will now open it up to questions from the
24 committee. Dr. Lippman?

25 DR. LIPPMAN: I think the answer to

1 whether this is an appropriate use of clinical
2 samples and the way you did it is, in my opinion,
3 definitely yes. I think you ought to be commended
4 for this. I mean, clearly the issue with Herceptin
5 might be different than in future drugs like this
6 where we integrate this up front and look at it
7 prospectively. But given where we are with
8 Herceptin, I think it is very compelling and the
9 science is very compelling.

10 I guess my issue has to do with the
11 comparisons with the IHC positive patients. As I
12 understand it, and I may need clarification, Dr.
13 Press, in the subgroup analysis from the Poletti
14 JCL study in 2000, the one with the subgroup of
15 patients in terms of outcome that were IHC positive
16 but FISH negative, do you know what the number of
17 patients was in that that were FISH negative but
18 IHC positive? I don't know what slide it is.

19 DR. PRESS: There were 45 patients in that
20 group. Out of the 856 there were 45.

21 DR. NERENSTONE: Would you please stand
22 and speak at the microscope -- we have been
23 inundated with pathologists so that is a Freudian
24 slip there.

25 DR. PRESS: I understand the slip. I

1 would be more comfortable at the microscope too.

2 [Laughter]

3 Of the 856 patients in that study, there
4 were 45 that fit into that subgroup.

5 DR. LIPPMAN: FISH negative, IHC positive?

6 DR. PRESS: Correct.

7 DR. LIPPMAN: You made a compelling case
8 that done in the right hands, and you clearly have
9 tremendous expertise, if there is a discordance it
10 is probably a technical error of some sort. If
11 there is protein there and that is done correctly,
12 and you do FISH correctly, you are going to find
13 amplification.

14 DR. PRESS: In an ideal world, yes. I can
15 give you one example. In our reference laboratory
16 activity it is not uncommon for us to have cases
17 where we disagree with the outside assessment.
18 Some of those are 3+. When we reevaluate those 3+
19 HercepTest or other immunohistochemical assays in
20 our laboratory, a proportion of them are not
21 amplified. When we do immunohistochemistry in our
22 laboratory they are also not positively
23 immunostained. So, there is an issue with how this
24 is done in different laboratories. Even 3+ can be
25 a false-positive result.

1 DR. LIPPMAN: So, the idea that there is
2 10 percent of overexpressers of the protein that
3 are FISH negative, in your impression, they are all
4 virtually artifacts if done correctly.

5 DR. PRESS: I don't like to say "all" in
6 biology, but the numbers would argue that it is
7 very infrequent; it is a relatively infrequent
8 event.

9 DR. LIPPMAN: Thank you. I guess what
10 bothers me a little bit is we are comparing these
11 2+, 3+ numbers with IHC as if they really are done
12 in the same way by trained laboratories, high
13 volume, what-not and really I am getting the sense
14 that the bigger issue is just the experience of the
15 laboratory and the volume. When you are looking at
16 IHC data, you open it up to all the laboratories
17 that may do very low volumes, and when you look at
18 the FISH, they are very select laboratories that
19 have high volumes and high training. So, I think
20 that is really more of the issue than what to do
21 with a 2+ or 3+ -- you know, like a 3+ positive,
22 FISH negative, that is really not as much the
23 issue. The issue is looking at those labs that are
24 getting 3+ that are not doing the procedure right
25 or need to be trained in some way.

1 DR. PRESS: I agree with that to some
2 degree but I would also emphasize something that
3 Dr. O'Leary discussed earlier this morning. The
4 way in which the tissue is processed will have an
5 effect on the amount of immunostaining that you see
6 in the end product. For example, in some of the
7 most experienced labs, when the tissue has been
8 processed in an alcoholic-based fixative, like an
9 alcohol-based formalin, the amount of
10 immunostaining that you see in that sample will be
11 much higher. So, those basal areas of what is a
12 low expression has to be set not only by the amount
13 of immunostaining but also knowing how the tissue
14 has been processed. So, it is a complicated issue.

15 DR. LIPPMAN: But you have looked at the
16 same tissue that was 3+ and you are getting 0. So,
17 I just think that we may be dealing with a real
18 selection issue. You know, the FISH labs are
19 highly trained, motivated volume labs and they do
20 it better. If those same labs were doing IHC, then
21 the 2+ and 3+ might mean more to us in the protein
22 assessment.

23 DR. NERENSTONE: Dr. George?

24 DR. GEORGE: This may be somewhat of a
25 follow-up from Dr. Lippman. This is a fundamental

1 question. You looked at the concordance of FISH
2 and CTA because CTA was used in a clinical trial
3 setting, and also because the approval of the
4 HercepTest was based on CTA. But then, your
5 conclusion was that the concordance was good and
6 these subgroup analyses led you to conclude that
7 the FISH assay is as good or better than the
8 HercepTest, not the CTA. I guess my question is
9 why didn't you compare it against HercepTest also
10 or instead of.

11 DR. MASS: Compare FISH to the HercepTest?

12 DR. GEORGE: Yes, directly instead of the
13 CTA.

14 DR. MASS: Our primary goal in this work
15 was to be able to link the diagnostic assay to
16 clinical outcomes, and the only way to do that was
17 to link it back to the patients who were selected
18 with the clinical trials assay.

19 DR. GEORGE: But I just wonder why you
20 didn't also do the HercepTest to just confirm that
21 link. In other words, test A is concordant with
22 test B; test B is concordant with test C. Ergo, it
23 follows as the night the day --

24 DR. PRESS: But there would be one
25 difficulty. You have to remember that the sample

1 material that we were working with was not ideal.
2 These were not paraffin blocks that were freshly
3 cut and processed. Those samples that were
4 unstained without cover slips on them had been
5 stored for years and, as is well known with protein
6 antigens with immunohistochemistry with storage,
7 the amount of immunostaining is diminished. So
8 that is a non-ideal sample. Certainly, those that
9 had been previously immunostained and cover slipped
10 would not be appropriate for that kind of study.

11 DR. NERENSTONE: Dr. Kelsen?

12 DR. KELSEN: Understanding the limitations
13 of what you had to deal with, I also think this is
14 very interesting material. I have a question about
15 proposed clinical trials. If I understand this
16 right, it seems that patients who have a score on
17 IHC of 2+ are a more problematical group as you
18 looked at the FISH correlation with them. I might
19 be wrong so I am sort of asking that question. Did
20 you think about a clinical trial where patients are
21 scored by a reputable lab, etc., etc. as 2+ who
22 would get Herceptin, because that would be an
23 appropriate treatment, who would also have a FISH
24 assay? Because it seems to me that if the FISH is
25 negative on this 2+ that you saw very little

1 clinical benefit, and that would be an area where
2 you could sort of make a definitive statement as to
3 the role of FISH in the assessment of patients, and
4 you could sort of think about a two-step paradigm
5 where you do IHC first and if it is 2+, which is a
6 particular area of controversy, they would
7 automatically have FISH and be triaged on that
8 basis. Is that a practical thing to do?

9 DR. MASS: One of the other post-approval
10 commitments that we made back in 1998 was to study
11 the 2+ population in more detail. We have been
12 having collaborative discussions with the National
13 Cancer Institute and the Breast Inter-Group in
14 terms of conducting those kinds of trials. I can
15 tell you, to sort of summarize those discussions,
16 this data, when we first reviewed it a year, year
17 and a half ago, made it much more problematic to
18 conduct that trial. There is a great reluctance to
19 treat non-amplified, non-3+ patients with
20 Herceptin. So, that trial would be difficult to
21 conduct.

22 DR. KELSEN: I look at this material and
23 it seems to me that if you are 2+ on IHC and 0 on
24 FISH there is no benefit from retrospective review.
25 Is that correct?

1 DR. MASS: Say that again.

2 DR. KELSEN: If it is 2+ by the clinical
3 trials assay or, presumably, by the HercepTest and
4 FISH negative, the impression I get from this is
5 that you rarely, if ever, saw any clinical benefit,
6 in retrospect.

7 DR. MASS: Again, we didn't actually show
8 you the subgroups but there were no responses in
9 the non-amplified monotherapy trial. Some of those
10 patients were 2+, some of them were 3+. The
11 combination trial is a bit more problematic to
12 interpret because it is a randomized trial. There
13 are small numbers of patients and there is the
14 confounding issue of chemotherapy in those trials.

15 DR. NERENSTONE: Dr. O'Leary?

16 DR. O'LEARY: I have four questions. The
17 first question goes back to the original efficacy
18 trials. If I recall the panel hearings for both
19 the HercepTest and for Herceptin, I believe that
20 the FDA provided a post-trial analysis suggesting
21 that the clinical trials assay 2+ did not
22 demonstrate any evidence of efficacy. Perhaps I am
23 wrong and perhaps somebody could correct my opinion
24 on that.

25 DR. NERENSTONE: Dr. Jerian?

1 DR. JERIAN: You recall correctly. That
2 is correct.

3 DR. O'LEARY: So maybe this question of
4 2+, FISH and FISH positive, FISH negative may be
5 moot based on at least that data. Do we have other
6 data?

7 DR. MASS: That data is in our label, if I
8 am not mistaking the breakdown of clinical benefit
9 from Herceptin in the pivotal trials. Both the
10 combination trial and the monotherapy trial is in
11 our label. There were either two or three patients
12 who were 2+ who responded, depending on whose
13 analysis one uses. There was some trend benefit in
14 time to disease progression for the 2+ group.
15 Again, 2+ was included in the original labeling,
16 with the understanding that the trial wasn't really
17 designed to evaluate 2+ and 3+ in independently
18 powered strata. Again, I think there was
19 insufficient information from that small subset to
20 make a definitive conclusion about the benefit in
21 the 2+ population.

22 DR. O'LEARY: The second question that I
23 have is, as I recall at the time of the device
24 evaluation panel meeting, I thought I was led to
25 believe that tissues to validate the

1 immunocytochemical assay, the HercepTest, against
2 the clinical trials outcome results was not really
3 available. I am surprised to come up now. I am
4 just curious as to what went on, why we have this
5 tissue available for this purpose. HER2/neu is
6 actually pretty stable according, to some published
7 results, as stored paraffin sections, much more
8 stable than a great many antigens.

9 DR. MASS: Maybe I didn't make it
10 completely clear. These were not tumor blocks.
11 These were 4-6 micron tissue sections that were
12 stored in a drawer. And, I think there is quite a
13 bit of controversy about the loss of epitope in
14 material that is stored under those conditions. We
15 had conducted some preliminary assessments of those
16 tissue sections to do that analysis, and found a
17 considerable discrepancy between the CTA result
18 that we originally recorded and the follow-up one
19 that we attributed to antigen loss. Again, I think
20 Dr. Press may want to comment, but the reason we
21 could do FISH on these samples was because of the
22 robustness of DNA as a target.

23 DR. O'LEARY: I understand the robustness
24 of DNA as a target. Then, just two comments. One
25 is that in my personal opinion two labs isn't

1 really enough to do inter-laboratory concordance.
2 You can get some idea of big problems if they show
3 up there, but if they don't show up you have
4 learned only a very limited amount, and I have
5 questions as to whether the studies that I have
6 heard are really sufficient. This really echoes, I
7 think, something we have heard before.

8 Then, looking at the crossover studies,
9 those that were FISH positive in one lab and FISH
10 negative in another and trying to resolve the
11 difference between those two and attribute it to
12 something reminds me of a concept referred to as
13 discrepant analysis. It is statistically suspect
14 at best, and I wonder whether it is really adequate
15 to address that issue of the discordant results.
16 Thank you.

17 DR. NERENSTONE: Dr. Carpenter?

18 DR. CARPENTER: There were about 8 to 15
19 percent of people for whom a FISH analysis didn't
20 get a result. Since these were obtained from the
21 group treated, I presume that they stained
22 positively, either 2+ or 3+. Were there any
23 clinical outcome data on those people?

24 DR. MASS: It is fairly complicated. The
25 15 percent non-informative rate was the rate in the

1 623 specimens as part of the concordance analysis.
2 So, half of those patients were 0 or 1+ and half of
3 them were 2+ and 3+. Because we drew that
4 population from the entire 6000 patients who were
5 screened, there was only a small number, actually
6 about a third of the positive patients from the
7 concordance analysis who were actually enrolled in
8 one of the clinical trials. So, I don't know if
9 that addresses that issue or not. We lacked FISH
10 results in only 4 percent of the patients in the
11 trial and we have looked at the outcome in the
12 patients who were missing results, and there were
13 so few patients that it was really not a useful
14 undertaking.

15 DR. CARPENTER: There were any responses?

16 DR. MASS: In the 4 percent of the
17 patients?

18 DR. CARPENTER: Because the negative
19 predicted value of the FISH assay is fairly
20 convincing. You had 0 of 49 I think. So, it would
21 just be interesting to know, even though it is a
22 handful of patients, if there were any responses in
23 that other group to let you know that they might be
24 heterogeneous.

25 DR. NERENSTONE: Dr. George, did you want

1 to make a statistical comment?

2 DR. GEORGE: Yes, just a comment about
3 that. You said that the numbers were split between
4 the negative and positive on the CTA, but the
5 missing was not split the same way. I just
6 wondered, since you have explanations for other
7 things that cropped up that were discrepant, maybe
8 you have one for this -- it looked like 10 percent
9 were missing in the CTA positive patients and 20
10 percent were missing in the CTA negative patients,
11 missing being non-informative. In that concordance
12 analysis you did, you said it looked like there
13 were 94 that were non-informative and 62 of them
14 were in the negative group and 32 in the positive.
15 Why is that?

16 DR. MASS: Again, one of the problems here
17 is that we don't have frozen tissue to know what
18 truth really is. So, it is hard to be conclusive
19 about our findings. But if we look at the non-
20 informative results, as you point out, it was about
21 twice as frequent in the CTA negative group as the
22 CTA positive group. The overwhelming cause of no
23 result was inability to accurately score the
24 sample, meaning that the signals were weak. We
25 believe that that may be due to preanalytical

1 processing. Some of the issues that affect
2 immunohistochemistry may affect FISH, and the
3 ability to generate signals by FISH may be
4 influenced by fixatives which render FISH non-
5 scorable. It also may lead to a higher ability to
6 generate a true positive CTA result. So, I don't
7 have an answer for you because, again, I have no
8 ability to know what truth was in these specimens.

9 DR. NERENSTONE: Dr. Barker?

10 DR. BARKER: To put sort of a point on the
11 comments of Dr. Lippman -- this is for Dr. Press,
12 are you aware, in your own experience or in the
13 literature, of any amplification positive but
14 normal expressing tumor that has been rigorously
15 documented as such, or the converse of that? That
16 is, a high expresser with normal copy number of
17 HER2?

18 DR. PRESS: In frozen tissue samples, not
19 in paraffin-embedded samples.

20 DR. BARKER: In anything. Is there any
21 example that has been rigorously documented?

22 DR. PRESS: Not to my knowledge. We
23 relatively commonly see them come into our
24 reference laboratory from outside institutions in
25 paraffin-embedded samples.

1 DR. NERENSTONE: Dr. Watson?

2 DR. WATSON: It is mostly a curiosity as
3 to the added benefit of the chromosome 17 marker in
4 the system. Did you ever look at the patients for
5 those who have, independent of that marker, four or
6 more HER2 signals, ErbB2 signals versus those that
7 are normalized against trisomy 17 and polysomy 17?

8 DR. PRESS: At this point we haven't
9 looked at it rigorously. That is one of the things
10 that we may do with this cohort if there is a large
11 enough group. We have talked about doing it with
12 the BCIRG, which will screen in total between the
13 U.S. and Europe 15,000 patients. So, in that sense
14 the numbers are much larger. So, in the future it
15 is something I think that is a potential question.

16 DR. NERENSTONE: Dr. Albain?

17 DR. ALBAIN: I have two questions. First
18 of all, on this issue of non-informative FISH to
19 Dr. Press, in your reference lab practice how often
20 would you say -- not this data set but where you
21 are getting tissue perhaps processed better, how
22 often would you say that you still need IHC? Or,
23 do you feel that the field is going to the point
24 where optimally FISH will be the only assay?

25 DR. PRESS: Let me answer the first part

1 of that. I anticipated that might come up. I
2 asked my laboratory administrator to go through the
3 BCIRG cases that we have received to date, and
4 those are coming in from all different laboratories
5 to be evaluated for FISH. There are 680 that we
6 have received so far. We have failed to generate a
7 FISH result in four of those samples. So, the
8 failure rate in material that is freshly cut up
9 paraffin blocks and processed is much lower in our
10 laboratory than it is on this material that we
11 received in the collaboration with Genentech.

12 DR. ALBAIN: Are we moving to the issue on
13 the labeling eventually where FISH would be the
14 only one? Do you see that coming soon?

15 DR. PRESS: Do I see it coming soon? I am
16 not going to be the person to make this decision, I
17 don't think.

18 [Laughter]

19 I can tell you what my personal view is of
20 this. If this is a member of my family or patient
21 that is referred to me from a physician that I am
22 dealing with, I definitely want to have a FISH
23 assay in order to make a decision. We routinely,
24 in our practice for our own institution, do both
25 immunohistochemistry and FISH. For referral

1 material from the outside, the referring physician
2 can specify which assay they want and so they can
3 limit us, but we do recommend to them that we
4 continue to do both. What is done in the future
5 remains to be seen.

6 DR. ALBAIN: That is what I am trying to
7 get at. How are you using both, given what you
8 have just said about BCIRG?

9 DR. PRESS: The BCIRG is a little bit
10 different. FISH is being used in a central
11 laboratory to screen for entry to the clinical
12 trial, FISH alone in that particular setting. So,
13 the immunohistochemistry is not relevant, although
14 we will be doing it in those samples but it doesn't
15 have the same turnaround time that the FISH does.
16 FISH we have to turn around immediately and that is
17 used for entry to the trial. So, in the future we
18 will have that data but we don't have it now.

19 DR. ALBAIN: Then a corollary question on
20 the 2+ to Dr. Mass. Do you think we need to
21 clarify the labeling further, in addition to the
22 FISH issue, on the 2+ cases with some other wording
23 that FISH confirmation is needed?

24 DR. MASS: Well, I think that is a
25 question that I think should be discussed by the

1 panel. The data that we showed suggests that the
2 doc who is taking care of patients gets to pick
3 between HercepTest or they get to pick between
4 PathVysion. The don't get to pick the clinical
5 trials assay. So, when you look at those two
6 assays together, we showed that they would give a
7 clinician the same information in terms of acting
8 as a surrogate for the clinical trials assay.

9 In the clinical outcomes analysis, when
10 you look at the subgroup analysis there are small
11 numbers of patients, and it is provocative -- I
12 think that is the appropriate term to use for the
13 data -- and suggests that FISH may discriminate
14 between the 2+, 3+ population. There are patients
15 where, again, immunohistochemistry doesn't detect
16 that are clearly amplified through concordance.
17 So, how an individual physician chooses to use
18 these two different techniques I think will depend
19 a little bit on their volume, some of the
20 individual issues that we heard about this morning.
21 But, again, that is an issue that I think the panel
22 may want to spend more time discussing.

23 DR. NERENSTONE: Dr. Lippman?

24 DR. LIPPMAN: Again, in terms of your
25 conclusion, I believe that you have shown that this

1 is useful and correlates FISH with clinical
2 outcome. But since Kathy brought up the issue of
3 the label, I am not ready to say that FISH is
4 better, based on the data that you have shown, than
5 IHC. I am ready to accept the fact that there is
6 very little quality control for who is doing IHC
7 and so the 2+, 3+ may not really be so if done
8 correctly. Again, this is based on small numbers,
9 retrospective, the things that you pointed out.

10 So, I think it is an acceptable
11 alternative and may be better. I think it is
12 provocative, but in terms of labeling and how we do
13 this, I think the approach ought to be sort of what
14 we talked about this morning in the sense that this
15 is useful; you have shown it nicely; and the
16 decision of whether it is FISH or IHC may depend on
17 the experience of the lab. This is where you talk
18 to pathologists. I mean, if you have a very strong
19 pathologist with excellent experience in IHC who
20 has concordance data, and so on, I think IHC may be
21 totally appropriate, especially since we have heard
22 from Dr. Press that there is really very little, if
23 any, difference if done correctly. They are
24 monitoring the same thing. So, if it is really IHC
25 positive, it is really FISH positive and vice

1 versa, which is obviously unique to a lot of
2 situations we will face later with other genes
3 where there really is established discordance
4 between expression and amplification that have
5 biologic implications. This seems to be pretty
6 unique to me, this very tight relationship between
7 the amplification and expression.

8 DR. NERENSTONE: We are going to have time
9 to get into discussion in a little bit. I would
10 like to keep now to questions to the sponsor, if we
11 can, because the FDA has to do their presentation
12 and then we will have more time for discussion.
13 Dr. Blayney?

14 DR. BLAYNEY: Two questions to Dr. Mass.
15 I understand there are two available FISH assays.
16 Why did you pick PathVysion?

17 DR. MASS: There were two reasons that we
18 used it. One was the direct labeling that was
19 talked about both this morning and this afternoon,
20 and that gives higher assay reliability. In our
21 experience there is less assay failure with a
22 directly labeled probe systems as opposed to the
23 two-step procedure that was discussed with the
24 indirect FISH. The other reason is the fact that
25 there is a centromere control probe in the

1 PathVysion assay system that is lacking in the
2 Inform system.

3 DR. BLAYNEY: I think I will defer the
4 next question. It is more of a labeling question.

5 DR. NERENSTONE: Ms. Mayer?

6 MS. MAYER: In view of the fact that, as
7 presented this morning, what we are hearing is that
8 these tests are often, particularly the IHC
9 testing, not done under ideal or standardized
10 conditions, yet, we are looking at clinical trials
11 testing that is done in this way. What
12 implications do you think there are for patients to
13 begin to think about what kinds of testing to
14 demand from physicians to ascertain, in a reliable
15 way based on your results, just what their status
16 is and whether or not they are, in fact, candidates
17 for Herceptin?

18 DR. PRESS: I think your question probably
19 gets to how HER2 is being tested in the community
20 of laboratories that are doing that assay. I think
21 the results that Dr. Hammond presented this
22 morning, from the College of American Pathologists,
23 is one of the appropriate venues for that kind of
24 assessment in terms of their survey program. I
25 think those kinds of survey programs are very

1 important. Again, it tends to be I think the
2 laboratories that are larger volume labs that
3 participate on immunohistochemistry and the FISH
4 sides but I think her data was provocative.

5 DR. NERENSTONE: Dr. O'Leary?

6 DR. O'LEARY: It is sort of interesting to
7 hear this being brought forth for a labeling
8 change. I am still concerned about the inter-
9 observer variability and I presume that Vysis is
10 bringing PathVysion back for indications for use
11 change as well and that they would perhaps have
12 more inter-laboratory variability data. If so, are
13 you aware of what that data might be?

14 DR. NERENSTONE: Dr. Gutman?

15 DR. GUTMAN: Yes, I would like to point
16 out that there is a parallel submission. Actually,
17 it is not the first submission we have seen for
18 this particular FISH device, and there is
19 considerable additional data in that submission
20 which we could share but are not prepared to share
21 with the panel at this point in time. But the
22 analytic performance of the assay has been studied,
23 and it has been studied at multiple sites.

24 DR. NERENSTONE: I would like to ask a
25 question. I know it is not appropriate for the FDA

1 but I think, as a clinician out in the community,
2 it is appropriate for me. My understanding is that
3 the FISH assay is extraordinarily intensive in
4 terms of personnel to do versus the immuno-
5 histochemistry. So, can you tell me what the cost
6 is in terms of units? If the immunohistochemical
7 evaluation is one, how much more is the FISH assay?
8 Because we are talking potentially about hundreds
9 of thousands of specimens across the United States
10 every year.

11 DR. PRESS: I can tell you what my
12 personal view of this is, if you will. If
13 immunohistochemistry is one, FISH is approximately
14 two. It costs approximately, I would say, from
15 twice as much to two and a half times as much to do
16 a FISH assay. The range for that, I would say, in
17 most of the clinical labs goes from somewhere \$300
18 to \$450 as a clinical test, depending upon the
19 laboratory across the country where it is being
20 performed. From my point of view, the difference
21 between and immunohistochemical assay and a FISH
22 assay in terms of the price of the test that is
23 being charged is negligible because the therapeutic
24 needs to be applied appropriately.

25 As wonderful as Herceptin is as an

1 engineered therapeutic, it "ain't" cheap. It costs
2 money. The first vial that gets cracked of the
3 therapeutic is more expensive than the diagnostic
4 test. So, I think it is worthwhile to have these
5 assay results as accurate as possible so that the
6 right people get into treatment. That isn't even
7 considering sort of the human cost of being
8 assigned to the wrong group for the wrong therapy.
9 That is my personal view, that it is very cost
10 effective to pick the most accurate assay approach,
11 even if you were to do both assays.

12 DR. NERENSTONE: Other questions?

13 [No response]

14 I would like to then break, if we can be
15 back at four o'clock for the FDA presentation.

16 Thank you.

17 [Recess]

18 DR. NERENSTONE: Dr. Jerian?

19 **FDA Presentation**

20 DR. JERIAN: Good afternoon. I am Susan
21 Jerian, and I will be presenting the FDA clinical
22 review for the trastuzumab labeling supplement to
23 include FISH testing as a method to select patients
24 for treatment with trastuzumab.

25 The objective of the submission is to add

1 information on the use of fluorescence in situ
2 hybridization for HER2 amplification to the
3 trastuzumab package insert.

4 As a note of background, the original
5 application was approved in September of 1998, and
6 trastuzumab is indicated as a single agent for use
7 second- or third-line in metastatic breast cancer,
8 and in combination with paclitaxel first-line in
9 metastatic breast cancer.

10 In addition, the indications statement
11 also says that Herceptin should only be used in
12 patients whose tumors have HER2 protein
13 overexpression. The reason for this statement was
14 that the mechanism for the antibody binding effect
15 was felt to be directly directed to protein on the
16 cell surface, and the second issue was that FISH
17 had not been performed at that time.

18 In reviewing the original data, Dr.
19 O'Leary was correct in recalling that we analyzed
20 2+ and 3+ patients separately as an exploratory
21 analysis, and found actually quite profound
22 differences in the degree of benefit in those two
23 groups.

24 A section in the label, entitled HER2
25 protein overexpression, was included which states

1 that data from both efficacy trials suggests that
2 the beneficial treatment effects were largely
3 limited to patients with the highest level of HER2
4 protein overexpression, namely 3+. Although this
5 statement isn't to imply that it is a quantitative
6 assay.

7 An additional section, entitled
8 immunohisto-chemical detection of HER2 protein,
9 appears in the label. As you have already heard
10 extensively, the clinical trial assay was what was
11 used to select patients for the clinical trials
12 upon which Herceptin was approved, but the
13 HercepTest is the approved assay. So, the label
14 states that the HercepTest has not been directly
15 studied for its ability to predict Herceptin
16 treatment effect, but has been compared to the CTA
17 on over 500 breast cancer histology specimens.

18 The label goes further to state that of
19 those specimens testing 2+ on HercepTest, only 34
20 percent would be expected to test at least 2+ on
21 the CTA, including 14 percent which would be
22 expected to test 3+.

23 In addition, of specimens testing 3+ on
24 HercepTest, 94 percent would be expected to test at
25 least 2+ on CTA, including 82 percent which would

1 be expected to test 3+.

2 At the time of approval, there clearly was
3 some uncertainty regarding the optimal method for
4 selection of patients who would benefit from
5 therapy. Should it only be 3+ patients or 2+ and
6 3+ patients who receive the drug? Looking at the
7 two immunohistochemistry assays that were explored,
8 there clearly was variability in the results.

9 This was the impetus for a postmarketing
10 commitment that Genentech made to assess the
11 clinical outcome of patients selected for treatment
12 on the basis of the DAKO test, or the HercepTest,
13 and other HER2 diagnostics in the context of
14 Herceptin clinical trials.

15 Following the approval, Genentech came to
16 us in March of 2000 and informed FDA about results
17 of exploratory retrospective FISH analysis of the
18 clinical trial specimens. The original proposal
19 was rejected by FDA due to a large amount of
20 missing data. The data appeared to be missing in a
21 non-random fashion. When we examined the clinical
22 outcome of the patients for whom there was no FISH
23 result, for whom there was missing data, we found
24 that in the control arm patients there was a very
25 long survival, disproportionate to what would be

1 expected or what was reflected in the clinical
2 trial overall, and that would make the results for
3 the patients who did have a FISH result seem
4 artificially more largely different between the
5 treatment and the control arms.

6 Subsequent to that, Genentech came back in
7 August of 2000 and discussed a proposal to minimize
8 the amount of missing data by running FISH on
9 previously stained specimens, and that is where Dr.
10 Michael Press' lab came into the picture. The
11 supplement was filed in April of 2001 and,
12 simultaneous with this, Vysis filed a supplemental
13 PMA with the Center for Devices.

14 The BLA under consideration today does not
15 fulfill the postmarketing commitment. There are
16 other trials currently being conducted in the
17 adjuvant setting, the pathology data of which you
18 heard about earlier this morning, that will address
19 these commitments but those trials will not be
20 completed for another four to five years.

21 In addition, in the background to this is
22 our perception of the field of HER2 testing. Our
23 perception is that HER2 assessment is not
24 straightforward; that there is marked variability
25 in results between different laboratories, as we

1 have all been made aware of exquisitely today; that
2 there is extensive off-label use of other
3 antibodies for immunohistochemistry, the home brew
4 assays; and there is extensive off-label use of
5 FISH.

6 In addition, we feel that there are
7 misunderstandings on the part of the treating
8 physicians regarding the advantages and limitations
9 of the various assay methodologies. In light of
10 all these factors, we felt that there was great
11 importance in reviewing the FISH data obtained from
12 the clinical trial specimens as it is unlikely that
13 another randomized trial of this particular sort
14 will be conducted.

15 What is the nature of the data? We feel
16 it is useful to make this point to begin with.
17 What they are not is data that derive from
18 prospective randomized, double-blinded, controlled
19 multicenter trials providing data regarding
20 definitive predictive capability of FISH and data
21 regarding the comparability of FISH versus
22 immunohisto-chemistry. Therefore, any conclusions
23 drawn from these data should take those limitations
24 into account.

25 What they are, they are exploratory

1 retrospective data from two laboratory sites with
2 very provocative results, which may warrant
3 inclusion into the package insert in some capacity.

4 Three basic studies were done, and you
5 have heard about these today; I won't go into a
6 great detail again. The concordance study which
7 looked at screened specimens and the IHC scores
8 ranged from 0, to 1+, 2+ or 3+; the clinical
9 outcome study which looked at specimens which were
10 only 2+ and 3+, in other words, those patients
11 enrolled on the trial; and a validation study which
12 was undertaken when the second laboratory was
13 brought into the picture.

14 All laboratories used the PathVysion FISH
15 assay by Vysis. The two laboratory sites were
16 Laboratory Corporation and the lab of Dr. Michael
17 Press. Specimens were obtained from the three
18 clinical trials that you have already heard
19 described.

20 We looked at the success and failure rate
21 of obtaining a FISH result from these samples. In
22 the concordance study, conducted at LabCorp, 623
23 samples were tested from which either a negative or
24 positive result was obtained in 529, for a 15
25 percent testing failure rate.

1 In the clinical outcome study both
2 laboratories were assessed. A total of 784 patient
3 samples were tested altogether with results in 765.
4 The individual laboratory testing failure rates
5 were 14 percent at LabCorp and 8 percent at the
6 Press lab.

7 In the validation study 250 samples from
8 which a result had been obtained at LabCorp were
9 tested in the Press lab, with an 11 percent failure
10 rate.

11 Both laboratories employed slightly
12 different techniques even from those in the package
13 insert for PathVysion. In part, this was
14 necessitated by the type of tissue samples that
15 they were dealing with, and the briefing documents
16 go through these differences in detail. I will not
17 reiterate them here.

18 In reviewing the case report forms for the
19 FISH scoring that occurred at both laboratories, we
20 noted that there were lower FISH scores on samples
21 at the LabCorp site compared to those at the Press
22 lab. When we looked at discordant results, we saw
23 that 32 percent of samples testing positive at the
24 Press site tested negative at LabCorp, where only 2
25 percent of samples testing positive at LabCorp

1 tested negative at the Press site.

2 We conducted additional exploratory
3 analyses on the data provided, and estimate that
4 between 10-30 percent of the LabCorp values in the
5 range of 1.0 to 2.0 -- this is the FISH ratio score
6 which would have been a FISH negative result --
7 might be patients who would benefit from
8 trastuzumab, namely, would have been 3+ by the CTA.

9 Moving on to the concordance study, in
10 general the FDA primary analyses agreed with those
11 of the sponsor. There was moderate concordance
12 with the Kappa statistic of 0.64, when CTA positive
13 defined as 2+ and 3+. We also did the same
14 analysis but defining CTA positive as 3+ only, and
15 there we found better concordance, with a Kappa
16 statistic of 0.8.

17 FISH testing missed 11 percent of the 3+
18 samples. On the other hand, it selected 4 percent
19 of the 0 to 1+ samples, and FISH testing was
20 positive in 24 percent of the 2+ samples.

21 We also looked at the concordance in the
22 clinical trial outcome data to see if the effect
23 was consistent, and in fact it did appear to be,
24 with 13 percent of 3+ samples being FISH negative
25 and 34 percent of 2+ samples being FISH positive.

1 For the clinical outcome study, again our
2 primary analyses agreed with those of the sponsor,
3 but I do want to make a special note that there are
4 no clinical outcome data for patients who were
5 immunohistochemistry 0 or 1+ and either FISH
6 positive or FISH negative. The two studies
7 included in this analysis were the randomized
8 trials 648g and the single-arm Phase II study 649.
9 Endpoints assessed were time to progression, which
10 was the primary endpoint; overall survival and
11 overall response rate.

12 In looking at the randomized study
13 comparing trastuzumab with chemotherapy versus
14 chemotherapy alone, we looked at relative risk
15 where relative risk refers to the risk for
16 progression in the trastuzumab plus chemotherapy
17 group versus that in the chemotherapy group. Thus,
18 a lower value in relative risk would denote greater
19 clinical benefit in the trastuzumab arm. We have
20 included here the 95 percent confidence intervals,
21 and the far column includes the number of patients
22 in each group. Roughly, you can divide this number
23 by two to get the number of patients per arm.

24 Going back to the original trial where we
25 analyzed 3+ and 2+, the relative risk for 3+

1 patients was 0.42. There was a clear clinical
2 benefit for those patients in time to progression.
3 For 2+ patients it was 0.82. The confidence
4 interval crosses 1. There was no apparent benefit
5 in time to progression.

6 With the new data using FISH, we see very
7 similar results for FISH positive and FISH
8 negative, except the FISH negative group does
9 appear to have some benefit. If you look at the p
10 value, it is around 0.04. So, we were interested
11 in breaking out these groups to see what was going
12 on in the smaller subgroups, recognizing this is
13 very exploratory and the numbers do become very
14 small.

15 In the FISH positive 3+ group we see the
16 beneficial effect preserved. In the FISH positive
17 2+ group there was no clinical benefit for time to
18 progression. Again, the numbers are very small.
19 Interestingly, for the FISH negative 3+ group there
20 did seem to be a benefit in time to progression,
21 and for FISH negative 2+ patients there was no
22 clinical benefit.

23 Let me go through the Kaplan-Meier curves.
24 Again, going back to the original study, these are
25 3+ patients only. They may be FISH positive or

1 FISH negative. The top arm is the trastuzumab plus
2 chemotherapy arm. The bottom curve is the chemo
3 alone arm. The curves separate early and stay
4 separate for the duration of the follow-up, and
5 there is clear clinical benefit.

6 These are the 2+ patients from the
7 original analysis. There is no clear benefit here.
8 There is no difference between the curves.

9 Looking at FISH positive patients, this is
10 very reminiscent of the 3+ group, the curves
11 separate early and have a very clear difference
12 throughout.

13 For the FISH negative group the curves
14 also separate and remain separate throughout. The
15 relative risk was 0.66 and the p value was 0.04.
16 We were concerned about what was going on here.
17 The FISH positive 3+ group seemed to benefit the
18 most. For the FISH positive 2+ there were no
19 differences in the curves statistically.

20 When we looked at FISH negative 3+ --
21 again, anecdotal information with only 20 patients
22 per arm, but this was intriguing. For the FISH
23 negative 2+ patients the curves are superimposable.

24 So to recap, if we look at 3+ patients,
25 whether they were 3+ overall, FISH positive 3+ or

1 FISH negative 3+, there appeared to be a clinical
2 benefit. When we looked at 2+ patients there was
3 no clinical benefit in the overall 2+ group or the
4 subgroups.

5 We ran the same analyses for overall
6 survival, and there is a similar effect. The
7 relative risk for 3+ patients was 0.7; 2+, there
8 was no clinical benefit. We see almost the same
9 numbers and same confidence intervals for FISH
10 positive and FISH negative.

11 When we get to the subgroups, the FISH
12 positive 3+ subgroup had a relative risk of 0.57.
13 But when we go back down to the FISH negative 3+
14 group, which in time to progression appeared to
15 show a benefit, that does not pan out for overall
16 survival. There was no apparent benefit there.

17 I will go through the curves quickly.
18 These are the original analysis 3+ patients
19 overall, clinical benefit; 2+ patients, overall
20 survival, no difference.

21 FISH positive patients, regardless of
22 immuno-histochemistry status, clinical benefit.
23 FISH negative patients, again superimposable curves
24 for overall survival.

25 FISH positive 3+, the group that appeared

1 to benefit the most; FISH positive 2+, we saw no
2 difference between the curves. Again, small
3 numbers.

4 FISH negative 3+, no difference. FISH
5 negative 2+, no difference.

6 To recap on overall survival, for the 3+
7 group there appeared to be a benefit in 3+ overall
8 and FISH positive 3+ but not in FISH negative 3+.
9 For the 2+ group, regardless of FISH status, there
10 was no clinical benefit in overall survival.

11 Finally, we looked at overall response
12 rate. Here would had the grouping of the
13 immunohistochemistry scores together and here we
14 have separated out the 3+ patients from the 2+
15 patients. We looked at those that were FISH
16 positive, those that were FISH negative and then
17 overall, all patients.

18 For the groups overall, the addition of
19 trastuzumab provided clinical benefit. For FISH
20 positive the addition provided clinical benefit.
21 But for those that were FISH negative there was no
22 evidence of a response rate.

23 When we go to the 3+ group, again we see a
24 benefit for FISH positive patients. No benefit for
25 FISH negative patients but a benefit overall.

1 Here, I will remind you, the numbers are very
2 small. It is difficult to explain this high number
3 on the control arm but I would venture to say there
4 is no difference between these two arms.

5 Then going to the 2+ patients, no matter
6 how we looked at the data, there was no evidence of
7 clinical benefit from the addition of trastuzumab
8 to chemotherapy.

9 Finally, there was the single agent
10 trastuzumab trial looking at overall response rate.
11 You have already seen this data. We also further
12 broke it out by CTA 3+ and CTA 2+. I think the
13 effect overall was similar in terms of response
14 rate.

15 Taking the data together, the concordance
16 data, the clinical outcome data and the validation
17 studies, we come to the following conclusions:
18 First, that inter-laboratory variability in test
19 results can be seen with the FISH testing as
20 evidence by differences observed between the two
21 selectee laboratories and that there is an expected
22 failure rate for obtaining a FISH result by the
23 HER2 FISH assay.

24 That concordance between FISH and CTA
25 testing is moderate, but we will see between 11

1 percent and 13 percent of patients who might
2 benefit from trastuzumab therapy, namely the
3 immunohistochemistry 3+ patients who would not be
4 selected by FISH. On the other hand, we would see
5 nearly 4 percent of patients who would not have
6 been eligible for the clinical trials, in other
7 words, those who were immuno-histochemistry 0 or 1+
8 test positive by FISH.

9 For that reason, we feel it is not
10 possible to determine the utility of treating
11 patients whose tumors test FISH positive and
12 immunohistochemistry 0 and 1+ because they were not
13 enrolled onto these trials.

14 There are insufficient data to
15 definitively describe the predictive capability of
16 FISH as the first and only test to identify
17 patients who would benefit from trastuzumab
18 therapy.

19 Direct comparative claims or statements of
20 equivalence or superiority between FISH and
21 immunohisto-chemistry cannot be made.

22 What we can say is that the clinical
23 outcome study in a preselected population indicates
24 that FISH appears to be a useful method for
25 selection of patients who are known to be

1 immunohistochemistry 2+ or 3+.

2 But we are left with some questions.

3 First, do patients whose tumors test as FISH
4 positive and either immunohistochemistry 0, 1+ or
5 2+ benefit from trastuzumab therapy? We simply
6 don't have the data for the 0 and 1+ patients and
7 the data for the 2+ patients is, at best, anecdotal
8 and doesn't look too promising.

9 Secondly, how much inter-laboratory
10 variability exists in the community for FISH and
11 immunohistochemistry testing of HER2 once these
12 tests are out there and are used more extensively?

13 Finally, what types of educational
14 programs targeting oncology professionals need to
15 be in place to optimize testing and interpretation
16 of results?

17 DR. NERENSTONE: Thank you. Now I would
18 like to open the floor for questions for FDA. Dr.
19 Blayney?

20 **Questions from the Committee**

21 DR. BLAYNEY: Thank you. I guess, like
22 many around the table, I am intrigued by your
23 analysis on the FISH negative, 3+ positive
24 patients, 20-some patients in each arm showing a
25 0.04 significant level benefit in this group which

1 is FISH negative. Reflecting on this morning's and
2 the rest of the day's conversations, first of all,
3 do you have an explanation for that? Second, was
4 this p value adjusted for multiple comparisons?

5 DR. JERIAN: The p value was in the FISH
6 negative curve overall.

7 DR. BLAYNEY: FISH negative 3+? It is on
8 page 13 of your handout. I don't know the slide
9 number.

10 DR. JERIAN: I hesitate to even use p
11 values for exactly that reason. I don't purport to
12 make a whole lot out of the p value in these
13 analyses.

14 DR. BLAYNEY: So, I guess the fundamental
15 biologic question, as fundamental as we can be, is
16 do you have an explanation for why your exploratory
17 analysis may have shown this result?

18 DR. JERIAN: From the data, I can only
19 describe what the data show. It is intriguing; it
20 is hypothesis generating. Perhaps the 3+ patients
21 who are FISH negative do benefit. Perhaps they
22 were not truly FISH negative. Perhaps -- I mean,
23 you could go on and hypothesize a number of things.
24 I don't purport to say I know the reason why.

25 DR. BLAYNEY: I take it from this that I

1 agree with your conclusion that both assays may
2 provide benefit, the availability of both assays to
3 physicians and pathologists. That would be a
4 useful thing.

5 DR. JERIAN: This is the analysis that had
6 the p value that I referred to, FISH overall.

7 DR. NERENSTONE: Dr. Lippman?

8 DR. LIPPMAN: Following up on that same
9 subgroup, the FISH negative, 3+ group, on page 18
10 where you put response data, you discarded that
11 completely although some of the other subgroups you
12 thought made more sense. But this is very
13 consistent with the patterns you see with survival.
14 It is page 18; it is where you look at response
15 rates on a table of FISH negative and positive.
16 What that shows is that in the FISH negative, 3+
17 group, the most striking aspect of this table is
18 that they had by far the highest response rates and
19 it was a little higher in the Herceptin group.

20 But, you know, it is 62 and 55 percent
21 with chemotherapy with or without Herceptin versus
22 29 percent in the 2+. Dr. George can help us, but
23 either this is why we shouldn't do subgroup
24 analyses or there is something really going on here
25 because that is pretty striking.

1 The other thing is if you assert that FISH
2 is the gold standard and the data are very clean,
3 so I guess I don't understand why in the FISH
4 positive, 2+ group there wasn't a benefit. Because
5 2+ may not mean anything but FISH positive should.

6 DR. JERIAN: Well, we were very struck by
7 that too. We were expecting that the FISH might be
8 able to help you discriminate those 2+ patients
9 that has always been the problematic group for us
10 to know how to deal with.

11 DR. LIPPMAN: But to follow-up then, I
12 guess I don't understand your conclusion, one of
13 your conclusion slides where you say -- the last
14 conclusion slide -- where you say the clinical
15 outcome suggests that FISH appears to be a useful
16 method for selection of patients who are known to
17 be IHC 2+ or 3+. Where do you have the data to
18 make the comment about 2+?

19 DR. JERIAN: I am simply describing the
20 population of patients that was assessed. The
21 population assessed in this trial were only 2+ and
22 3+ patients.

23 DR. LIPPMAN: But the 2+, even in the
24 subgroups, FISH positivity didn't help at all.
25 Right? In the subgroup that was 2+, FISH

1 positivity didn't declare a group that benefited.

2 DR. JERIAN: Applying this assay to this
3 group of patients seems to select out or cull out a
4 group of patients who have clinical benefit. I am
5 not concluded that per se in that particular
6 subgroup there is a benefit. I don't think, from
7 this data, you can make that conclusion.

8 DR. NERENSTONE: Dr. George, did you want
9 to comment?

10 DR. GEORGE: Just a quick comment. Susan,
11 you have set a dangerous precedent here for
12 sponsors to come in here with too many subgroup
13 analyses. But I think this is okay but we ought to
14 use the same kind of interpretation that we do in
15 other settings. You used the right adjective, this
16 is provocative, intriguing, certainly not
17 definitive in any way, not even approaching that.
18 So, I think sometimes we get carried away with too
19 much discussion of this and don't make a proper
20 account of the fact that it is small groups,
21 subgroups, and so forth. I think it was presented
22 in that spirit so we shouldn't try to over-
23 interpret it now.

24 DR. LIPPMAN: But one of the most
25 consistent findings in the subgroups, both in

1 survival and response, was the 3+ FISH negative,
2 much higher responses and so on. All I am saying
3 is if we do subgroups we ought to be careful. Some
4 of them we think are more important and others we
5 dismiss.

6 DR. NERENSTONE: Dr. Kelsen?

7 DR. KELSEN: If I look at the survival
8 curves for 648g, on page 15 and 16 for either --
9 since we are talking about adding a test, for
10 either 3+ or for FISH positive, putting aside all
11 the other subgroups and understanding all the
12 questions about subgroups, those curves look
13 strikingly similar. Without drawing firm
14 conclusions because of the retrospective nature of
15 all of this, one could imagine a scenario where you
16 could talk about either 3+ positive on
17 immunohistochemistry or FISH positive, which seems
18 to give clinical benefit with some degree of
19 comfort. So, I am struck by the use of FISH in
20 that setting. Because the problematical group to
21 me is still the 2+ patients. What I am struck the
22 most by is if it is 2+ immunohistochemical,
23 understanding all the problems with that, and FISH
24 negative, those patients don't seem to benefit by
25 any of the analyses that you did. Is that correct?

1 They didn't seem to benefit by response if it is
2 monotherapy. Their survival curves really look
3 overlapping. Time to progression is overlapping.
4 So, FISH is useful in this analysis in looking at
5 that subgroup of patients as a negative predictor.
6 If it is positive it doesn't help you a lot more
7 than 3+. Is that a fair interpretation?

8 DR. JERIAN: I would agree with your
9 interpretation.

10 DR. NERENSTONE: Dr. Albain?

11 DR. ALBAIN: I just wanted to add that
12 this 3+ IHC, FISH negative has only 43 patients
13 total, and the 2+, FISH positive only 32. These
14 differences can even be explained by various
15 prognostic factor differences among the women in
16 these two groups. So, have any multivariate
17 analyses been performed where you can adjust the
18 hazard for treatment effect by the other predictive
19 factors in the multivariate model, such as number
20 of sites of metastatic disease etc? To me, I can't
21 really make much out of this without knowing where
22 this sits. This is just a univariate analysis in a
23 very small subset.

24 DR. JERIAN: We did some multivariate
25 analyses and nothing weighed out in particular. I

1 don't have that data here to discuss in detail and
2 it actually isn't in your briefing document. But
3 we looked at a variety of factors from the original
4 trial. We really didn't feel that those analyses
5 would necessarily be as appropriate in this
6 setting.

7 DR. KEEGAN: Could I clarify for the
8 committee some of the reasons why we went through a
9 lot of these analyses? In part, we wanted to
10 explore them as much as I think you all wanted to
11 hear them, and expressed that, because of all the
12 public statements that we frequently hear being
13 made about FISH. Having the data set here, we
14 said, okay, let's look. It is being promoted as
15 something that can discriminate 2+ positive
16 patients, who benefits and who doesn't.

17 So, these analyses are not done to do
18 anything but provide information about what we do
19 know, and how little data we have, and how
20 insufficient those data are both because of the
21 nature of the data to make comparative claims, as
22 well as just the size and the amount of data. So,
23 we thought that it would be useful to make those
24 data publicly available so that people can see what
25 data supports some of the statements that we, at

1 the FDA, have been hearing.

2 DR. NERENSTONE: Dr. Lippman?

3 DR. LIPPMAN: I would like to follow-up on
4 what Dave Kelsen mentioned and what was just said
5 about the 2+. Dave, you said that in the 2+ group
6 that are FISH negative, FISH could be useful to
7 separate out the group that don't benefit, those
8 that are 2+ and FISH negative. But I guess I am
9 having trouble when I look at the relative risk
10 data and the confidence intervals. Maybe I am just
11 missing the data when you look at survival and so
12 on that FISH helps distinguish 2+ if it is
13 positive. I mean, the FISH positive, 2+ -- you can
14 make the same statement, Dave, about the 2+, FISH
15 negative as you can about the 2+, FISH positive.
16 Right?

17 DR. KELSEN: I was thinking about not
18 wanting to give a therapy that you are reasonably
19 confident won't work. It struck me, looking at
20 these curves, that although they are exploratory
21 etc., they sure look like if it is FISH negative at
22 2+ --

23 DR. LIPPMAN: But where is the data if it
24 is 2+ on survival? I may have missed it because
25 there was a lot of data presented, but where is the

1 data that if you are 2+ and FISH positive you
2 benefit?

3 One of the issues that was raised because
4 of all the claims that FISH has, what was just put
5 into perspective by CBER is that this may help
6 clarify this 2+ mid-range, and you pointed out if
7 it is 2+, FISH negative it is useful. I guess I am
8 missing where if it is 2+ how FISH helps you any
9 way? Because if it is 2+ and FISH positive, at
10 least from what you presented, it doesn't help you
11 either. The confidence intervals overlap one
12 another.

13 DR. KELSEN: I will defer this to the FDA,
14 but if I look at the single agent data, on page 19,
15 for response rate, if it was FISH negative and 2+
16 positive, if I remember correctly, you saw no
17 responses in those patients.

18 DR. LIPPMAN: But I am looking at the
19 survival where you have the relative risks and the
20 confidence intervals, all those tables on survival.
21 Where can we look there to show how in a 2+ case a
22 FISH positive --

23 DR. KELSEN: I am looking at the last
24 survival graph on page 17, FISH negative, 2+
25 positive. They look like they overlap, overall

1 survival, H0648g.

2 DR. LIPPMAN: But then look at the top of
3 that page, here you have a 2+ which is FISH
4 positive and you see the same curves. They still
5 overlap. So my point is if you have 2+ FISH
6 doesn't help you one way or the other. Again, with
7 the caveats of subgroups, we don't get any leads
8 that FISH helps us dissect the 2+ whether it is
9 FISH positive or FISH negative.

10 DR. KELSEN: Can I ask a different
11 question, going back to the group studies this
12 morning? The eligibility requirements for the
13 current trials involving use of Herceptin, could
14 you just refresh my memory, was it at 3+ on
15 immunohistochemistry or FISH?

16 DR. JERIAN: That is correct.

17 DR. KELSEN: That sort of implies that
18 some cooperative groups have accepted either of
19 those two as appropriate entrance criteria for a
20 study. I mean, it doesn't imply it; it says it.

21 DR. KEEGAN: In fact, at least one of
22 those studies -- Susan can correct me -- form part
23 of the postmarketing commitments to answer that
24 question specifically, what is the role of FISH
25 when tested prospectively as an eligibility

1 criteria? You saw that they are going to be
2 assessed after the fact central laboratory-wise,
3 etc.

4 DR. KELSEN: But that means we have
5 accepted that. There is enough data to say that if
6 you are positive on one of the two tests that is
7 all you need to get into the trial, understanding
8 that one of the aims is to see if that is true but
9 that hypothesis was thought to be ethical and you
10 could treat patients on the basis of that analysis.

11 DR. KEEGAN: Yes, and recall also that
12 that is the adjuvant population.

13 DR. KELSEN: Yes, I do understand that,
14 which is an even more pressing issue to me
15 personally.

16 DR. NERENSTONE: Dr. O'Leary?

17 DR. O'LEARY: I am trying to make sure I
18 understand the implications, so if you could tell
19 me if I am getting the gist of this correctly, I
20 would interpret that what you are saying is that
21 there is no evidence that FISH adds significant
22 information to the clinical trials assay in terms
23 of the clinical outcomes studies. Is that correct?
24 I mean, because of that issue of overlapping
25 confidence intervals? I have three specific

1 questions.

2 DR. JERIAN: So, the first question is did
3 FISH testing add anything in the selected
4 population --

5 DR. O'LEARY: To the clinical trials
6 assay? Do we have evidence that it does? My
7 interpretation was no based on the data.

8 DR. JERIAN: I don't think we can
9 necessarily extrapolate because we don't have the 0
10 and 1+ patients.

11 DR. O'LEARY: Right, we don't have any
12 data on FISH for selection because we don't have
13 the 0 and 1+ patients. What we do have is a
14 correlation with the clinical trials assay, and
15 that correlation study gives results that are
16 similar to that of the HercepTest. Is that
17 correctly summarizing?

18 DR. JERIAN: Yes.

19 DR. O'LEARY: Thank you.

20 DR. NERENSTONE: Other questions for FDA?

21 [No response]

22 Thank you very much. I think I am left
23 with the feeling that this is even more of a mess
24 than I thought before.

25 [Laughter]

1 So, I am going to need help here, folks.
2 I do want to reiterate what someone said. I think
3 that this is even more of a compelling question
4 because this drug is being introduced into the
5 adjuvant setting, where people are going to have to
6 live with the side effects and potentially the
7 long-term side effects of a lot of medication. I
8 think we really are going to need to look at this
9 to figure out if there is a benefit, who benefits.

10 Turning to our questions, given the
11 current practice of oncology, FDA feels that the
12 concordance data in this sBLA comparing the
13 fluorescence in situ hybridization testing using
14 PathVysion and the immuno-histochemistry assay,
15 referred to as the clinical trials assay, provides
16 information useful to physicians who need to
17 determine whether a patient should receive
18 treatment with trastuzumab. However, the clinical
19 outcome data for FISH are problematic in that they
20 do not definitively address issues of
21 predictiveness of FISH in regard to clinical
22 outcome and comparability of FISH to IHC.

23 The first question, does the committee
24 concur that the concordance data re useful? I will
25 open it up for discussion. Dr. Ohye?

1 MR. OHYE: As the non-voting industry rep,
2 I just have a general comment. When I think of
3 labeling and what does industry think of labeling,
4 we think about the requirement to provide adequate
5 directions for us so that both the physician and
6 patient can jointly make intelligent decisions.
7 When I think of that, I think in terms of trying to
8 bring into the label the latest information, and
9 also think about what is happening in the medical
10 field at the moment.

11 Given the fact that there are already home
12 brew assay methodologies being applied here, and
13 some off-label FISH assays being applied here, I
14 think this weighs very heavily on inserting
15 information about the applicability and the use of
16 FISH, with whatever caveats the committee deems
17 appropriate. You know, we live in an imperfect
18 world here but we need information and we have to
19 accept that challenge and try to insert as much
20 information as we deem appropriate so intelligent
21 decisions can be made given what else is going on
22 in the field. Thank you.

23 DR. NERENSTONE: Dr. George?

24 **ODAC Discussant**

25 DR. GEORGE: Thanks. I was supposed to

1 give some discussant comments. What I would like
2 to do is not repeat everything that has been said
3 but to talk about a few things that I don't think
4 have been mentioned, at least not clearly. That
5 has to do with some fundamental issues with respect
6 to concordance, lack of concordance and gold
7 standards, and what it implies with respect to what
8 we need to be looking at with respect to clinical
9 outcome.

10 So, to start off, we don't have a gold
11 standard here. In fact, it could be argued that a
12 gold standard with respect to these two types of
13 tests we are doing doesn't, by definition, doesn't
14 exist because they are really testing two different
15 things. Maybe one is a surrogate for the other but
16 it is still different, one looking for gene
17 amplification, the other looking for protein
18 overexpression. Maybe they are the same thing but
19 they are not exactly the same thing.

20 Another issue with respect to just
21 concordance is that the scoring system in the two
22 assays is not the same. That is why we are running
23 into this whole issue of how does a 2+ or 3+ relate
24 to a positive result, which is really actually a
25 ratio as we heard today. So there are two

1 different scale systems there and we are having to
2 play around with looking to see where we draw the
3 line. This is known in the statistical literature
4 doing things like receiver operator characteristic
5 curves, kind of where you draw these lines makes a
6 difference in how concordant things are. So, we
7 don't even get the same for what concordance is,
8 depending on how we draw those lines.

9 Another thing about the gold standard or
10 lack of a gold standard is that the issues that I
11 heard mentioned a number of times today with
12 respect to sensitivity and specificity is sort of,
13 to me, misleading. I mean, the accuracy of these
14 things when we don't even know what the truth is,
15 is hard to judge. So, it is not known what
16 sensitivity and specificity is.

17 With respect to concordance, there were
18 great pains taken to show that the CTA test and the
19 FISH assay were, in fact, highly concordant, which
20 I think was nicely done and it seems to be true,
21 concordant no matter how you look at it. But there
22 is an issue here. If you had two assays that were
23 100 percent concordant with respect to information,
24 you have redundant systems. Let's just suppose
25 that happens, suppose we were presented with

1 results that the FISH assay gave you exactly the
2 same results as the IHC results, we would have
3 nothing to go on with respect to additional
4 information we get with respect to clinical
5 outcome. So, then the choice between the two would
6 be based on ease of use, cost, whatever is
7 important.

8 But the reason that has an important
9 implication is that is precisely the discordant
10 cases that provide the information. So, in a way,
11 we should have been looking for tests that are less
12 concordant; not more concordant. It is almost a
13 paradox because it is only in those discordant
14 cases that we can get the key information.

15 Now, when you start looking at those, in
16 this particular case what you see, of course, is
17 that it is only a certain type of discordance that
18 really is of major concern because in the results
19 that were IHC negative very few were FISH positive,
20 very few in the extrapolated population which is
21 really, I think, the one that should have been the
22 main focus. So, it is in that group we have been
23 talking about, these ones that seem to be 2+ or 3+,
24 however you call it, and the FISH negative -- how
25 do they do? How do we go about evaluating that?

1 Well, first of all, it has been pointed
2 out that this is a rare group. It is a small
3 percentage. It depends on which result you look at
4 exactly, but somewhere less than 10 percent of the
5 total cases would fall in that category, it looks
6 like. So, what do we do about that? Do you plan
7 to do some kind of prospective clinical trial? As
8 a clinical trialist myself, I am always in favor of
9 clinical trials, however, I think we are in a
10 situation here that is different. That is, in an
11 era of this rapidly evolving technology and
12 changing assays, refinements of existing assays,
13 this is probably a silly thing to set up. I mean,
14 to even think of doing this is almost impossible
15 because of the large the numbers that would be
16 required, and because of the impracticality of
17 doing it, and be by the time you got the results
18 the field would have moved way beyond what makes it
19 even interesting.

20 So, I think these kinds of retrospective
21 analyses are about the only way we can proceed. We
22 have to do them, though, very carefully. In other
23 words, you can't just distinguish between
24 retrospective and prospective studies. There are
25 good retrospective studies and bad retrospective

1 studies, and retrospective studies that have been
2 planned carefully with clear-cut objectives, and
3 endpoints and control data of various kinds, even
4 though they are retrospective it makes them a lot
5 more useful than just some fishing expedition where
6 none of those things were controlled.

7 So, I am just throwing all this out
8 because they relate to these questions, and I have
9 already given some of my answers I think to some of
10 them. That is all I have now.

11 DR. NERENSTONE: Other discussion? Ms.
12 Mayer?

13 MS. MAYER: I guess I just want to make
14 the probably all too obvious point that when making
15 treatment decisions, patients are very often faced
16 with no information at all, particularly advanced
17 breast cancer patients, about which treatment is
18 likely to benefit them and for how long. I just
19 want to caution the FDA. In a situation where we
20 have two kinds of testing, both of which are
21 clearly imperfect, both of which do yield some
22 information, I think it is perhaps tempting to
23 criticize them because of their imperfections but
24 important to embrace them because they do provide
25 the kinds of information that patients have really

1 never had before in making treatment decisions.

2 So, if there is some way of accepting this
3 test with its imperfections, with the caveat that
4 there be further research to further refine the
5 tests, that is what I think would be most
6 beneficial for patients.

7 DR. NERENSTONE: Dr. Lippman?

8 DR. LIPPMAN: Since Dr. George raised the
9 issue of good retrospective studies and not so good
10 retrospective studies, I believe this was a very
11 good retrospective study given where we are, given
12 that it was in the context of clinical trials,
13 getting all the blocks. So, I think the survival
14 correlations are as compelling as we are going to
15 get. We can't do another study, I don't think, and
16 I think they did a very good job.

17 I think it is when you get into these
18 subgroups and you get 14 in one group -- although
19 it is useful information, it would have been great
20 if there were a striking ability of FISH to dissect
21 the 2+ group, and if that were very compelling it
22 might have influenced us. But short of that, I
23 think that is just a limitation of subgroup
24 analyses, even more so than retrospective studies.

25 My answer to the question is that this

1 concordance data are useful. You represented the
2 statistical aspects of those but, because of the
3 biologic basis of this -- we have heard very nice
4 presentations on the biology behind why there
5 should be concordance, and taking the statistical
6 concordance figures, the Kappa statistics or
7 whatever, in the context of the biology I think is
8 very useful.

9 DR. NERENSTONE: Dr. O'Leary?

10 DR. O'LEARY: The concordance studies, as
11 I said, are very reminiscent of what we had to work
12 with, with the HercepTest. So, I think it is
13 probably incumbent in making a device decision to
14 decide whether those studies are adequate or not
15 adequate to recommend approval at this point. I
16 probably would have disagreed with the panel as a
17 whole at the time we went forward the last time.

18 But I think that maybe as one thinks about
19 what information one provides to the clinician, we
20 actually need to think about backing away or doing
21 something a little bit different, perhaps giving
22 information about the general types of assays that
23 are available, that there are widely different
24 performance characteristics, that for home brew
25 assays of whatever sort the performance

1 characteristics may not have been well defined, and
2 in some way convey the information that the
3 clinician needs to know that their laboratory is
4 using a test for which the performance
5 characteristics have been well defined. We should
6 allude to the fact that there are approved to the
7 tests, but maybe it should either list all of the
8 tests approved for this indication or none of them,
9 and maybe that would change with time. If it is
10 two or three tests, maybe it is appropriate to list
11 them all. If it gets to be 15 or 20 you may get
12 into the situation where you are wasting a lot of
13 space in the package insert.

14 I suspect though that with time one may
15 want to back away from specifics of the individual
16 tests that are available, back to pointing out and
17 making sure that the oncologist gets together with
18 the laboratory to understand the test that is being
19 used, with it is a test that has been validated and
20 then how to interpret it in the context of their
21 patients.

22 DR. NERENSTONE: I guess my question is if
23 we look at these two tests as potentially being
24 complementary, if somebody has a 3+
25 immunohistochemistry from a good lab and we feel

1 that that is reproducible for however you want to
2 define that in an imperfect world, what will FISH
3 add? Because according to some of our data, 3+, no
4 matter what, is a predictor of a relatively high
5 response rate. So, I think in that situation you
6 don't have to do another test. You have your
7 answer.

8 I am even willing to go out on a limb a
9 little bit and say if you have a 0 to 1+, the
10 likelihood of the FISH being positive is very low,
11 almost in the realm of noise, less than 5 percent.
12 Likewise, it is unlikely to sway your decision-
13 making. But it really is in the 2+, although I
14 have to admit I am not sure exactly which subset
15 analysis you want to follow, but I think there,
16 because we don't want to miss a potentially
17 beneficial treatment, especially in somebody who
18 has metastatic disease who may convey a survival
19 advantage, then in a 2+ who was FISH positive we
20 might go ahead and treat and a 2+ who was FISH
21 negative we may or may not want to treat them, at
22 least initially, with the antibody.

23 But I think that I would look at this as
24 complementary. I agree, there is no gold standard
25 and I think that by looking at the FDA analysis,

1 where I think before the feeling was the new gold
2 standard was going to be FISH, I look at this data
3 and feel that the immunohisto-chemistry of 3+ is
4 actually the most predictive of clinical benefit if
5 you look at the parameters that were evaluate.

6 So, I don't think we can say FISH is the
7 new gold standard, and I agree that they are
8 different and we have to accept imperfections. Dr.
9 O'Leary?

10 DR. O'LEARY: We are saying 3+ on the
11 clinical trials assay, and the clinical trials
12 assay isn't what is out there. What is out there
13 is HercepTest which was a correlation with the
14 clinical trials assay. Really, the basis of the
15 decision was how predictive do we think that the
16 HercepTest is going to be of what was used to
17 select for clinical trials. I think that is a
18 univariate decision point, one that says you may
19 want to use a FISH instead because that is the same
20 kind of a correlation analysis, and there may be a
21 case to be made for that. I haven't heard enough
22 to really know whether that case can be made
23 forcefully but it seems to me that the data may be
24 more compelling for that than it is for
25 discriminating between 2+ and 3+ by IHC.

1 DR. NERENSTONE: Say that again.

2 DR. O'LEARY: The data for making a
3 primary decision may be more compelling, or the
4 analysis of that may possibly be more compelling
5 than is the data to use FISH for making a decision
6 on a 2+ immunohistochemistry. That was pretty
7 marginal. Actually, there was just no data to say
8 that that worked. It might. There wasn't any data
9 to say for sure it didn't. We were guessing.

10 DR. BRAWLEY: Can I follow-up?

11 DR. NERENSTONE: Yes, Dr. Brawley?

12 DR. BRAWLEY: I am sort of jumping ahead
13 here in front of a couple of people, but this is in
14 follow-up of what you said Dr. Nerenstone and Dr.
15 O'Leary. If I go to page 14 of Dr. Jerian's
16 presentation, looking at the 3+ subgroup -- and I
17 have made a career out of criticizing people for
18 doing subset analysis but I am going to go ahead
19 and look at subset analysis data right now. If we
20 relied fully on FISH, this implies that of the 685
21 people who had immunohistochemistry, 3+ tumors FISH
22 would have told us not to give Herceptin to 43 of
23 the 685.

24 So, if I am a patient, that means that
25 there is a substantial chance that if I get FISH,

1 FISH is going to give me the wrong answer. Am I
2 reading that correctly?

3 DR. JERIAN: The denominator is different.
4 The population enrolled on this trial is 469
5 patients, and in the 3+ arm it was 300-something
6 patients.

7 DR. BRAWLEY: Oh, okay. You are actually
8 increasing it. I thought it was 43 out of 685 and
9 you are now telling me it is about 43 out of 300.

10 DR. JERIAN: Of the overall group it would
11 be around 10 percent.

12 DR. NERENSTONE: Dr. Lippman?

13 DR. LIPPMAN: Stacy, I would just like to
14 clarify because I must really be missing this, but
15 you again said that, well, you know, in the 2+,
16 FISH positive I might lean towards giving it and in
17 the 2+, FISH negative I wouldn't. I just don't see
18 the data that supports that from the FDA
19 presentation.

20 DR. NERENSTONE: There is no data because
21 the subset analysis is so small. But if you look
22 at the overall curves for FISH negative patients,
23 there doesn't seem to be very much clinical benefit
24 when you look at the large group of FISH negative.
25 So, if you look at 3+ positive IHC, there is

1 benefit. If you look at the overall group of FISH
2 positive patients, there is benefit. But you are
3 absolutely right, there is no data.

4 DR. LIPPMAN: Okay. Then, the issue that
5 I guess was raised by Dr. O'Leary, I mean, every
6 test that comes out is going to go through this
7 committee and get formally put in the label and so
8 on, I think what we learned here is that FISH done
9 well by this particular assay is a good predictor
10 of outcome. It correlates reasonably well with
11 protein. We are not looking at two measures, two
12 IHC measures or two FISH assays. We are saying
13 gene amplification a useful predictor of outcome in
14 response to chemotherapy and it happens to
15 correlate with protein.

16 We know there are other genes that are
17 going to come through here where that correlation
18 is terrible, in which case Dr. George would be
19 happy because it would give different information,
20 really discordant. But going back to the imperfect
21 world that we are in, I just think that we don't
22 know, we can't really say and I think that in terms
23 of how we would label this is that FISH done in the
24 right way is useful; immunohistochemistry done in
25 the right way, if 3+, is useful, and I don't think

1 we have the data to say which is better. They may
2 be complementary. And, I think we want to give our
3 institutions and our clinicians and patients and
4 pathologists the ability to choose from those based
5 on their expertise and experience. We know there
6 is data to support both.

7 DR. NERENSTONE: Dr. Kelsen?

8 DR. KELSEN: I agree with Scott. I am not
9 sure I see these at this point as complementary so
10 much as that either is acceptable because if you
11 look at the survival curves that Susan showed us,
12 if either test is positive, by that I mean a
13 strongly positive IHC which we call a 3+ or a
14 positive FISH by this PathVysion technique, those
15 patients have the same likelihood of clinical
16 benefit at that level, and requiring use of both
17 tests -- I am not exactly sure where I see that
18 information, but I do see the point that if you
19 test A or you do test B and either one is positive,
20 then it is appropriate to offer the patient
21 Herceptin.

22 In fact, to get back to the clinical
23 trials issue, I do understand that it is a test of
24 a hypothesis but it is felt to be a reasonable test
25 and you don't require both of those assays in order

1 to enter those national studies.

2 DR. NERENSTONE: Dr. O'Leary?

3 DR. O'LEARY: I think it is important not
4 to use the term immunohistochemistry generically
5 here because we tend to confuse the clinical trials
6 assay and the HercepTest when we do that. If we
7 have a gold standard here of any sort, it is the
8 clinical trials assay that was used to select
9 patients. What we have here are two different sets
10 of correlation studies, and it is really hard to
11 take this terribly hard. When we talk about
12 acceptability of the test in terms of the in situ
13 hybridization, I am not sure that we have the full
14 answer. It appears that the concordance is very
15 similar between the two different systems and that
16 would seem to favor that either may be an
17 alternative but there are also all sorts of issues
18 of assay performance, lot stability, all sorts of
19 things like that that haven't been presented here
20 that would be very important, I suspect, to
21 clinical laboratory devices before they would say
22 that this is ready for prime time. So, I think we
23 should be careful about over-interpreting things
24 from the laboratory side. We have only heard a
25 portion of what is needed on that side of FDA to

1 decide that a laboratory test is ready for prime
2 time.

3 DR. NERENSTONE: Dr. Albain?

4 DR. ALBAIN: I think it is just important
5 that the label reflect -- and it is not yet in the
6 label about survival benefit. Hopefully, that is
7 coming soon, that the survival data will make it
8 into the label, that you can see a survival
9 advantage if you apply yourself to chemotherapy
10 whether it be 3+ or whether it be FISH positive.
11 That is the important thing to get out there.

12 The other important thing is that to date
13 in a 2+ setting we haven't been overwhelmed with
14 Herceptin benefit. The labeling does state it
15 somewhat but I think we now have updated survival
16 data that should show that as well, as was
17 published in The New England Journal. So, in that
18 clinical scenario which is not uncommon -- 30-some
19 percent here, 34 percent of 2+ samples were FISH
20 positive and we see this every week when we have a
21 large referral population. I think many of these
22 women deserve FISH testing in that scenario.

23 DR. NERENSTONE: Dr. Keegan, can I take
24 the chair's privilege and ask to condense the
25 question --

1 DR. KEEGAN: Sure.

2 DR. NERENSTONE: -- which really is do we
3 think FISH should be added to the package insert as
4 another test for patients who would be eligible for
5 Herceptin therapy? Is that your question?

6 DR. KEEGAN: Yes, that is the basic
7 question, although if you would like to add any
8 comments on specific information from these studies
9 that you think is important to include in the
10 labeling, if we should make any specific statements
11 about, for instance, there is a rate of FISH
12 negative and IHC 3+ positive patients, or the lack
13 of information on any discriminating ability of
14 FISH status in IHC 2+ patients, that sort of stuff,
15 if you have any specific requests for certain types
16 of information to be in the label, assuming that
17 you are going to recommend that it be in the label
18 in some form at all, would you please specify what
19 you think might be important?

20 DR. NERENSTONE: Why don't we start with a
21 vote because I think that is the basis? Because if
22 it is voted down, then you have your answer. Are
23 there other comments right now because we will
24 discuss this? Dr. Redman?

25 DR. REDMAN: Are we voting on including

1 FISH or are voting on including a brand name?

2 DR. KEEGAN: The proposal would not change
3 the indication statement, but if we were to
4 describe the information about FISH we would have
5 to describe it in the setting of the data obtained
6 with a specific FISH assay and test, yes. So, it
7 would likely be in some portion of the labeling but
8 not in the indication statement.

9 DR. NERENSTONE: So, I take that to mean
10 that we will accept the methodology, FISH
11 methodology, and specifics will be described in the
12 body of the text.

13 DR. KEEGAN: I think it will be handled
14 similarly to what we have now for the
15 immunohistochemistry test. If we provide data that
16 would relate to that test, if people have questions
17 about other assays, other FISH assays they probably
18 should discuss it with their pathologist, as they
19 would need to do with other types of
20 immunohistochemistry tests. We wouldn't restrict
21 that use, the labeling would not restrict it but it
22 would not have a generic endorsement of FISH
23 unspecified. It is not necessarily going to
24 endorse any test but it will provide the data as it
25 relates to a single test.

1 DR. NERENSTONE: Dr. Lippman?

2 DR. LIPPMAN: So, on that issue, I would
3 like to ask Dr. O'Leary to clarify something he
4 said earlier, that we are eventually going to get
5 to a point where we are not going to approve a test
6 but a brand, but just FISH, IHC or what-have-you.
7 I thought that is what you said in one of your
8 comments. I gather that we are not there yet with
9 this and we need to specifically talk about a
10 brand.

11 DR. O'LEARY: I think that there are
12 probably legal reasons. You have to talk about
13 exactly what was done if you put it in the package
14 insert. It may be that eventually that you will
15 have 15 or 20 different things and it becomes just
16 prohibitive to put everything in the package insert
17 and you have to think about things in other ways.
18 If you have two or three, then it is not an issue.

19 My only presumption would be that as we
20 are talking about putting things in the package
21 insert we are not going to be advocating any sort
22 of off-label use. So, we are making the assumption
23 that everything that will be described in a package
24 insert would be on-label for what that product was
25 approved for.