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by Lynne Peterson

SUMMARY

Genentech failed to convince members of the FDA's Oncologic Drugs Advisory Committee that Avastin should be approved to treat first-line metastatic breast cancer. Yes, Avastin prolongs progression-free survival, the panel agreed, but the meaningfulness of that was unclear since it didn't significantly improve either quality of life or survival – and Avastin added some significant side effects and even a few deaths. The FDA is likely to make its final decision on approval by February 23, 2008.

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Stephen Snyder, Publisher
2731 N.E. Pinecrest Lakes Blvd.
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com
TrendsInMedicine@aol.com

FDA Advisory Committee Split on Avastin for Breast Cancer

Gaithersburg, MD
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The FDA's Oncologic Drugs Advisory Committee (ODAC) voted 5 to 4 that the data were not sufficient to establish a favorable risk:benefit analysis for the addition of Genentech's Avastin (bevacizumab) to paclitaxel for first-line treatment of women with metastatic breast cancer. While the panel acknowledged that there was a 5.5-month improvement in progression-free survival (PFS) with Avastin, they were unsure of the clinical meaningfulness of this, and the panel was concerned with a lack of any statistically significant survival benefit as well as Avastin toxicity.

Why did Avastin go before ODAC in the first place? Dr. Richard Pazdur, director of Oncology Drug Products in the FDA's Center for Drug Evaluation and Research (CDER), said the Agency also was divided internally, "We had the same discussions as the panel, and that's why we took it to panel."

The FDA briefing documents and presentation suggested Genentech was rather arrogant with the FDA throughout the Avastin/breast development process, repeatedly ignoring FDA instructions and guidance. Dr. Pazdur opened the panel meeting with some fairly negative remarks, warning that this approval would be precedent-setting and would change oncology drug approval guidelines, something he did not appear to favor. Dr. Pazdur was followed by an FDA medical officer who reviewed the approval history of seven other oncology drugs – none of which was approved on the basis Genentech is seeking.

The FDA is likely to make its final decision by February 23, 2008, the Avastin PDUFA (action) date. Dr. Pazdur spoke with reporters after the vote, calling this a "neutral" panel and suggesting that an Avastin approval is not out of the ballgame yet. He said, "The take-home message on PFS is that we used it in other diseases. This was a relatively split (panel) vote, and we will have to go back and discuss it (internally at FDA). We will look at the totality of the data and the panel discussion…It is a difficult decision…We are not bound by the vote. We are more interested in the (panel) discussion."

The one thing that appears certain is that the FDA is unlikely to ask for additional data before making a decision. Dr. Pazdur said, "This is not a data question."

Genentech officials did not speak with reporters after the panel, but the company issued a press release saying: "We are disappointed by the split vote of the advisory committee, as the addition of Avastin to chemotherapy showed the longest reported progression-free survival in any first-line clinical trial of patients with

advanced breast cancer, and we believe progression-free survival is a meaningful endpoint for patients and physicians. We believe that Avastin can help meet a significant unmet medical need for women with metastatic breast cancer, and we remain committed to working with the FDA to make Avastin a viable treatment option for these patients."

According to Dr. Pazdur, the message from this panel for other oncology drugs was that studies in first-line metastatic breast cancer should be powered for overall survival, with PFS as a secondary endpoint, though if there is a ***big*** benefit in PFS, a trend might be sufficient in overall survival.

BACKGROUND

Genentech is seeking approval for Avastin to be used in combination with paclitaxel for the first-line treatment of locally recurrent or metastatic breast cancer (MBC). Avastin already was approved for use in (a) first- and second-line metastatic colorectal cancer (CRC) in combination with intravenous (IV) 5-fluorouracil (5-FU)-based chemotherapy, and (b) first-line treatment, in combination with carboplatin and paclitaxel, in patients with unresectable or metastatic non-squamous, non-small cell lung cancer. Avastin is also widely used off-label for age-related macular degeneration. Approval for both colorectal and lung cancer indications were based on randomized clinical trials demonstrating a statistical improvement in overall survival.

The application in MBC was based on three trials: One was a randomized trial (E2100) that showed a benefit in progression-free survival but no statistically significant improvement in survival. That trial was supported by another trial in refractory second/third-line MBC which showed a better response rate with Avastin but a shorter duration of response. The third trial was a proof-of-concept study.

1. **E2100.** This pivotal, randomized, open-label, Phase III trial in 722 patients with locally recurrent or MBC was sponsored by the National Cancer Institute (NCI) and conducted by ECOG (Eastern Cooperative Oncology Group). All patients in the trial were chemotherapy-naïve, and all patients received paclitaxel 90 mg/m^2 IV over 1 hour every week for 3 weeks followed by 1 week of rest. In one arm patients also got Avastin 10 mg/kg following the paclitaxel on Weeks 1 and 3 of every cycle. The trial was originally designed to detect a 33% improvement in median PFS from 6 to 8 months. Instead it found almost a doubling of PFS, from 5.8 months to 11.3 months.

2. **AVF-2119g.** This randomized, multicenter, open-label, Phase III trial was in second/third-line treatment of MBC, comparing Avastin plus capecitabine (Roche's Xeloda) to capecitabine alone in 462 patients with disease progression after both anthracycline- and taxane-based regimens.

3. **AVF-0776g.** This was a Phase II, single-arm, 2-site, 75-patient, dose-ranging and pharmacokinetic monotherapy study in relapsed MBC. Patients received one of three doses: 3 mg/kg, 10 mg/kg, or 20 mg/kg every two weeks. Enrollment at the higher dose was suspended because of toxicity (mostly headache, nausea, and vomiting). There were also two reports of Grade 3 congestive heart failure. Objective responses were observed in 6.7% of patients, with a median duration of 5.5 months.

Avastin is a recombinant humanized monoclonal IgG1 antibody that selectively binds to and neutralizes the biologic activity of human vascular endothelial growth factor (VEGF). The major safety issues with Avastin are: hypertension, thromboembolic events, left ventricular dysfunction, myocardial infarction, gastrointestinal perforation, and proteinuria. The most common reasons for discontinuation in the paclitaxel arm of the E2100 trial were for neuropathy (60%) and allergic reactions (5.7%). In the Avastin arm, the reasons were neuropathy (25%), thrombosis (12.5%), proteinuria (9.7%), hypertension (6.0%), arterial thromboembolic event (5.6%), left ventricular dysfunction (5.6%), fatigue (5.6%), and multiple medical events.

Efficacy Results of Avastin First-Line in E2100 Trial

Measurement	Placebo + paclitaxel n=354	Avastin + paclitaxel n=368	Difference	p-value	Hazard ratio
Duration of treatment	5 months	9 months	Longer with Avastin	---	---
Number of cycles per patient	6	10	More with Avastin	---	---
Total cumulative dose of paclitaxel	1440 mg/m^2	1926 mg/m^2	Higher with Avastin	---	---
Results					
Primary endpoint: PFS	5.8 months	11.3 months	Avastin increased 5.5 months	<.0001	0.483
Secondary endpoint #1: Overall survival	24.8 months	26.5 months	Avastin longer by 1.7 months	Nss, 0.1374	0.869
Secondary endpoint #2: Objective response rate	22.2%	48.9%	Avastin better by 26.7%	<.0001	---
Secondary endpoint #3: Duration of objective response	9.7 months	9.4 months	Avastin worse by 0.3 months	Nss	---
Secondary endpoint #4: Deterioration in quality of life	- 12.7	- 6.6	Avastin better	0.0069	N/A

FDA View of Adverse Events in Avastin E2100 Trial

Adverse event	Placebo + paclitaxel n=354	Avastin + paclitaxel n=368	Difference
Grade 3-5 adverse events			
Any Grade 3-5 adverse event	50.6%	70.8% *	Avastin increased Grade 3 toxicity by 20.2%
Neurologic adverse events	21.3%	30.0%	Avastin worse
Sensory neuropathy	17.5%	24.2%	Similar
Pain	9.5%	16.3%	---
GI	6%	15.7%	Avastin worse
Hemorrhage	0.3%	1.7%	Slightly worse with Avastin
Infection/fever/neutropenia (Grade 4-5)	5.7%	13.8%	Avastin worse
Death	2.0%	3.0% **	Avastin worse
Other adverse events			
Hypertension	1.4%	15.7%	Avastin worse
Arterial thromboembolic events	0	2.8%	Avastin worse
Cerebrovascular ischemia	0	1.9%	Avastin worse
Cardiac ischemia	0	0.8%	Avastin worse
Venous thromboembolic events	4.3%	2.5%	Paclitaxel worse
Congestive heart failure	0.3%	1.4%	Avastin worse
Dose changes/discontinuations			
Dose modification/omissions	64.9%	88.4%	More with Avastin
Dose delay ≥1 week	29.2%	41.3%	More with Avastin
Dose omission	23.7%	40.8% pcl 46.4% Avastin	More with Avastin
Dose reduction	32.8%	49.2% pcl 3.1% Avastin	More with Avastin
Discontinuations due to toxicity	20%	19.8%	Similar

*** 71.1% if NCI database reports are included** **** 4.1% if NCI database reports are included**

FDA Perspective

Dr. Pazdur told the panel that a recommendation for approval of Avastin in first-line MBC would mean a change in approval guidelines – something he did not appear to favor. He noted that in June 1999 ODAC discussed the use of time-to-progression (TTP) in first-line MBC and decided it was ***not*** an appropriate primary endpoint for approval, that overall survival should remain the primary efficacy endpoint for registration trials, "At today's ODAC we will be revisiting that… TTP and the closely related PFS…have been used where survival benefit may be difficult. Past ODAC felt that PFS was better than TTP …Important considerations in the use of PFS should include: the magnitude of effect on PFS, the treatment toxicity profile, and the clinical benefits and toxicities of available therapies."

He cited both advantages and disadvantages of PFS vs. overall survival as a registration endpoint: It reflects tumor growth, can be assessed prior to demonstration of a survival benefit, is not subject to confounding impact of subsequent therapies, and the effect occurs earlier than overall survival. The key disadvantage is that bias can easily be introduced in the assessment of PFS, so its use requires careful planning in the protocol and statistical analysis.

Safety Results of Avastin 2nd or 3rd Line in AVF-2119g Trial

Measurement	Placebo + capecitabine n=230	Avastin + capecitabine n=232
Death	166 patients	178 patients
Any adverse event		
Any adverse event	98.1%	100%
Stomatitis	19.1%	25.8%
Thrombolic events	6.0%	7.9%
Cardiovascular/hypertension	2.8%	25.3%
Dyspnea	19.1%	28.8%
Urogenital/albuminuria	8.4%	22.7%
Bleeding events	12.2%	29.7%
Hypertension	2.8%	25.3%
Venous thrombosis	4.2%	7.4%
Grade 3-4 adverse events		
Any Grade 3-4 adverse event	57.7%	72.1%
Stomatitis	0.5%	1.7%
Cardiovascular/hypertension	0.5%	20.1%
Dyspnea	5.1%	8.3%
Urogenital/albuminuria	0	0.9%
Hypertension	0.5%	20.1%
Venous thrombosis	1.9%	4.8%

Advantages and Disadvantage of PFS Endpoint

Advantages	Disadvantages
Reflects tumor growth	Requires careful planning
Can be assessed prior to demonstration of survival benefit	Bias can easily be introduced in assessment of PFS
Not subject to confounding impact of subsequent therapies	Incomplete or missing assessments at baseline or at periodic evaluation
Effect occurs earlier than overall survival	

Efficacy Results of Avastin 2nd or 3rd Line in AVF-2119g Trial

Measurement	Placebo + capecitabine n=230	Avastin + capecitabine n=232	p-value
Primary endpoint: PFS	4.17 months	4.86 months	Nss, 0.85 HR 0.98
Secondary endpoint #1: Overall survival	14.5 months	15.0 months	Nss, 0.62
Secondary endpoint #2: Objective response rate	9.1%	19.8%	Nss

Dr. Pazdur did not appear impressed with the efficacy results in the pivotal E2100 Avastin trial when the toxicity of Avastin is considered. He said, "The sponsor claims a 5.5-month improvement in PFS…which is confirmed by an independent review facility (IRF)…and this was accompanied by an improved response rate but no improvement in overall survival. The addition of Avastin to paclitaxel resulted in a greater than 20% increase in Grade 3-5 toxicity and an increase in treatment-related death…A second trial was submitted (in second- and third-line MBC)…This trial showed neither improvement in PFS nor overall survival with the addition of Avastin to capecitabine."

He said Avastin has not met the usual standards for approval, "For approval the sponsor must show a direct benefit…Clinical benefit has generally been improvement in survival or disease-related symptoms…In this, there is improvement in PFS without improvement in overall survival. Hence, PFS in this application cannot be considered a surrogate for clinical benefit. We will ask ODAC (1) to determine if PFS alone should be considered a direct benefit…and (2) whether the risk vs. benefit relationship associated with improvement in PFS and the increased toxicities and toxic death associated with Avastin in this indication are sufficient."

Dr. Pazdur also stressed that the panel should "consider the totality of the information – the lack of effect on PFS or overall survival in 2nd and 3rd line MBC."

FDA briefing documents

It was clear from the briefing documents the FDA sent to the panel in advance of the meeting that the FDA has had problems with the Avastin MBC application at least since late 2004. The FDA advised Genentech all through the development process that it would eventually want survival data. Last year, the application was rejected, but Genentech resubmitted it in August 2007 with additional data and analysis requested by the FDA. Among the Agency's concerns have been:

- The open-label trial design.
- Lack of pre-specified, detailed, and objective radiological and clinical parameters for determination of disease progression.
- Initial lack of an independent radiology review for confirmation of progression events. An IRF eventually did the radiology analysis, but it was retrospective.
- Failure by Genentech to reach agreement on a plan for data analysis prior to public release of the E2100 interim results.
- Use by the ECOG data monitoring committee (DMC) of multiple cutoff dates in its analysis of PFS. The FDA estimated that 17% of patients had their ECOG-determined PFS censored >3 months before the data cutoff date.
- Supplemental BLA submitted in May 2006 was rejected as inadequate and incomplete with respect to documentation of patient eligibility, baseline tumor description, study violations, drug exposure, and treatment delays/ discontinuation due to toxicity.

The FDA had additional concerns with the final submission including:

- A discordance in E2100 between the ECOG analysis of PFS and the IRF analysis in 51% of patients.
- The failure of the E2100 trial to show a statistically significant survival benefit. While the Kaplan-Meier curves for PFS separated early and remained separated, the curves for overall survival were almost superimposable.
- The FDA questioned the clinical significance of the improvement in E2100 quality of life, even though it was statistically significant.
- In E2100 Avastin patients required more frequent dose modifications/omissions, delays, and reductions due to more adverse events.
- The AVF-2119g trial also failed to show any benefit on survival, while adverse events were higher in the Avastin arm. In fact, the Kaplan-Meier curves were virtually identical throughout the trial.

A key issue for the FDA is whether the statistically significant 5.5-month improvement in PFS with Avastin, in the absence of an improvement in overall survival, is a measure of direct clinical benefit that supports regular approval of Avastin plus paclitaxel for first-line treatment, especially given the increase in adverse events with Avastin. The FDA staff also argued that a lack of an Avastin survival benefit in the second- and third-line settings for breast cancer in the AVF-2119g study should be considered.

The FDA explained that, until recently – on the advice of ODAC – the FDA's efficacy requirements for regular marketing approval for oncology drugs required demonstration of clinical benefit, specifically, prolongation of life or better quality of life. Established surrogate endpoints such as durable complete remission (CR) in acute leukemias and disease-free survival (DFS) in adjuvant therapy for breast cancer have been accepted to support regular drug approval in these settings. However, in May 2004, gemcitabine (Lilly's Gemzar) in combination with paclitaxel received regular approval for first-line treatment of patients with MBC based on an interim analysis showing a strong trend toward overall survival (HR 0.823, p=0.0489). This trend toward an overall survival effect, supported by the superiority of the Gemzar/ paclitaxel arm in time to documented tumor progression and objective tumor response rate – along with good objective tumor response rates in the single-arm Phase 2 studies – was sufficient for regular approval.

In contrast, the FDA pointed out that the final overall survival results for Avastin in E2100 were not statistically significant, and Avastin also failed to show an improvement in either PFS or overall survival in the AVF-2119g trial. FDA reviewers noted, "In the E2100 study, PFS is clearly not a surrogate endpoint for survival in first-line breast cancer. The question is whether PFS is an established surrogate for clinical benefit other than survival in this setting."

The FDA urged the panel to take two issues into consideration in its deliberations:

1. **The failure to show a survival benefit.** And the FDA warned against concluding this was due to crossovers.
2. **The increase in Grade 3-5 toxicity and death with Avastin.** The FDA noted that it is not known whether the lack of survival advantage in the E2100 and AVF-2119g trials is due to increased toxicity of Avastin.

ODAC presentation

At the advisory committee meeting, Dr. Lee Pai-Scherf, an FDA reviewer, told panel members that PFS had not been used in other Avastin approvals: For colorectal cancer (CRC), the Avastin approval endpoint was overall survival, and for non-small cell lung cancer (NSCLC), the approval endpoint was overall survival. She provided a history timeline and reviewed the E2100 trial. Interestingly, the FDA appeared to be putting unusually strong emphasis on what Genentech ***didn't*** do and historical problems with the submission.

Dr. Pai-Scherf questioned the validity of the PFS primary endpoint, saying, "In considering Genentech's claim on PFS as the primary efficacy endpoint, the FDA needs to verify:

1. **Robustness** (i.e., is there an effect?) **Yes.** "The FDA believes the effect is robust."
2. **Magnitude** (i.e., is the 5.5-month improvement in PFS reliable?) **No.**

She commented: "E2100 may not be sufficient to support licensure."

On safety, Dr. Pai-Scherf noted several problems with data collection that made a comprehensive review of the safety of Avastin in this setting difficult:

- Adverse events were collected only once every three cycles (every 12 weeks).
- The date of onset and resolution of adverse events were not collected.
- Only Grade 3-5 non-hematologic adverse events and Grade 4-5 hematologic adverse events were collected.
- NCI/AdEERS collected serious events only from the Avastin arm.
- Laboratory data were not collected.
- There was a 20.2% increase in Grade 3-5 toxicity.
- There was 1.7% treatment-related death in the Avastin arm.

Treatment-emergent Grade 3-4 adverse events were higher with Avastin, notably sensory neuropathy, vomiting, diarrhea, dehydration, fatigue, and pain.

Genentech claimed there were no deaths due to protocol treatment in the Avastin arm of the E2100 trial, and that raised a red flag at the FDA. Dr. Pai-Scherf said, "We were very puzzled with the lack of a survival benefit despite the reported improvement in PFS, and, knowing the toxicity profile of bevacizumab, we were concerned with possible toxicity." She said the FDA attributed 2 deaths definitely to Avastin treatment and three were thought to be possibly related to Avastin use, plus one more that occurred later that the FDA attributed to Avastin.

Dr. Pai-Scherf reviewed six Avastin deaths in E2100 that were ascribed by Genentech either to breast cancer or other causes but which the FDA felt were related to the use of Avastin. She highlighted these adverse events in those patients:

Patient #1: Severe diarrhea, fatigue.

Patient #2: GI perforation, neutropenia, sepsis.

Patient #3: Acute abdomen with GI perforation.

Patient #4: Ischemia/infarction and LV dysfunction.

Patient #5: Severe diarrhea, black tarry stool, abdominal pain, hypotension, and bradycardia.

Patient #6: Grade 4 proteinuria (nephrotic syndrome) and a fatal MI.

Hong Lu, PhD, another FDA reviewer, said the FDA has problems with confidence in the PFS finding in the E2100 trial because:

- It was unblinded.
- Data were incomplete. "In a retrospective collection, Genentech was unable to obtain scans in 73 (10%) of patients."
- Loss to follow-up was too high. "247 (34%) of patients were not followed until IRF-PFS event or end of study."
- There was a lack of consistent scan readings. "There was 34% discordance between IRF radiologists in PFS status or date and 51% discordance between IRF and ECOG in PFS status or date." She admitted the FDA doesn't know the significance of this discordance but concluded it raises serious concerns.
- There was no effect on overall survival.

In the AVF-2119g trial, the reviewers concluded Avastin:

- Did not increase PFS.
- Showed no survival advantage.
- Increased objective response, but for a short duration.
- Increased Grade 3-4 toxicity by 14.4%.

Use of TTP/PFS endpoint in other approval decisions

Dr. Patricia Cortazar, a medical officer in the FDA's Division of Oncology Drug Products, CDER, reviewed FDA approval decisions of other breast cancer drugs. She commented, "We have required an improvement in survival both as a safety and as an efficacy parameter…Survival is also considered a safety endpoint…Another reason for requiring survival is that effective drugs prolong survival…The FDA wants assurance that survival gains are not lost when a new drug is introduced."

Dr. Cortazar also reminded the panel that ODAC in 1999 determined that (1) crossover therapy did not confound any survival effect, and (2) TTP was not acceptable for traditional approval in first-line cytotoxic therapy for metastatic breast cancer. She added, "A drug used after tumor progression should have the same effect in both arms and should not obscure the effect of the drug tested." She cited the examples of:

- Pfizer's Camptosar (irinotecan) + 5-FU/leucovorin was better than 5-FU/leucovorin despite a 40% crossover rate.
- Genentech's Herceptin (trastuzumab) + chemotherapy which was better than chemotherapy despite a 65% crossover rate.

Dr. Cortazar also said PFS has not been used as the basis for approval in first-line MBC, but it has been used as the basis of approval for second/third-line therapy. The problems with PFS include:

- Needs blinded trial.
- Needs blinded assessment by an IRF.
- Issues with patients without measurable disease.
- Missed assessments or incomplete assessments at baseline.
- Infrequent assessments.
- Uneven assessment in each arm.
- Risk of not seeing survival data in future trials.

Basis of FDA Approval of MBC Therapies

Drug	Treatment	Basis of approval
Herceptin + paclitaxel	First-line MBC	Survival
Lilly's Gemzar (gemcitabine) + paclitaxel	First-line MBC	Survival
Sanofi-Aventis's Taxotere (docetaxel) monotherapy	Second-line MBC	Survival
Taxotere + capecitabine (Roche's Xeloda) after failure of prior chemotherapy	Second-line MBC	Survival
Paclitaxel	Second- and third-line MBC	TTP
GSK's Tykerb (lapatinib)	Second- and third-line MBC	TTP/PFS

FDA Approval of Other Metastatic Breast Cancer Therapies

Drug	Type of approval	Benefit in TTP/PFS vs. control	Survival benefit	Objective response rate
Second- and third-line agents				
Bristol-Myers Squibb's Taxol (paclitaxel)	Full	Yes, 1.2 months p=0.27	Nss p=0.321	Nss p=0.135
Taxotere	Accelerated approval (1996)	---	---	41%
	Full approval	Yes, 1.8 months p=0.01	Yes, 3 months p=0.01	---
Herceptin monotherapy	Full approval	---	Yes, 5 months	14%
Xeloda monotherapy	Accelerated approval	Yes, 38 days	Yes, 3 months	25.6%
	Full approval	Yes, 58 days p=0.01	Yes, 90 days p=0.0126	---
Tykerb, by independent radiology review	Full approval	Yes, 8.5 weeks p=0.00013	---	23.7%
Bristol-Myers Squibb's Ixempra (ixabepilone), combination therapy	Full approval	Yes, 1.6 months p<.0001	---	---
Ixempra monotherapy	---	---	---	12.4%

GENENTECH PERSPECTIVE

Not surprisingly, Genentech looked at the same data from these two trials (E2100 and AVF-2119g) and came to very different conclusions.

Genentech briefing documents

In the panel briefing documents, Genentech called the E2100 trial "a strongly positive" study, "conducted by a pre-eminent oncology cooperative group," adding, "The results of Study E2100 provide strong and clinically meaningful evidence of the clinical effectiveness and benefit" of Avastin in MBC. Genentech insisted the trial provided a "rigorous assessment" of PFS by a blinded, central IRF that demonstrated "statistically persuasive" improvement in PFS, with the increase in PFS "clinically important for patients."

Much of the Genentech briefing documents appeared to be defensive, with the company defending the trial design, the choice of endpoint, and the findings. Genentech insisted, "This trial was declared positive by the independent Data Monitoring Committee at the first interim analysis based on clearly meeting its primary endpoint...The addition of bevacizumab to first-line paclitaxel resulted in a statistically significant and clinically meaningful improvement in the primary endpoint, progression-free survival based on an independent review of radiographs… with a 5.5-month increase in median PFS…The PFS benefit was consistent across patient subgroups. The robustness of the PFS result was demonstrated by multiple sensitivity

analyses, with benefit maintained even in two worst-case analyses…The risk:benefit profile was highly favorable in the MBC setting."

On the use of PFS as the primary endpoint, Genentech commented, "Regulatory precedence for PFS as an endpoint for approval in breast cancer has been established, as PFS has served as the primary endpoint for the approval of most of the chemotherapy agents and hormonal agents currently and recently approved for use in MBC."

Other points the company made about the E2100 and AVF-2119g trials in the panel's briefing documents included:

- **Protocol changes.** "When ECOG released the study results in April 2005, Study E2100 was fully enrolled; there was no change to the protocol to provide bevacizumab to patients in the paclitaxel-alone arm."
- **Independent analysis.** "An independent review facility was established, and radiographs and pertinent medical information for all patients were reviewed retrospectively to verify the primary endpoint of PFS for this open-label study…The primary endpoint of the study was changed to PFS based on the IRF's assessment of progression, given the inherent biases that may be present in unblinded PFS studies…The rigorous IRF assessment of the primary endpoint by a blinded, central IRF indicates that any bias entering into the trial as the result of the open-label design did not impact the conduct of the study or the assessment of the primary endpoint of PFS. The IRF assessment of progression not only demonstrated statistically persuasive findings of improved PFS…but also served to validate the rigorous conduct of the study since the IRF assessment was consistent with PFS based on the investigator-reported, ECOG-reviewed tumor data…Even though the IRF review was conducted retrospectively, scan collection efforts were robust, and there was no evidence that missing data affected the outcome of the study. The robustness of the PFS result was demonstrated by a variety of sensitivity analyses; benefit was maintained even in two worst-case analyses."
- **Value of PFS findings.** The median PFS of 11.3 months for Avastin patients "represents the longest PFS yet reported in any first-line clinical trial in MBC and the greatest absolute improvement" in median PFS in randomized clinical trials of chemotherapy for MBC.
- **Data.** Data cleaning of the E2100 database was completed, and a survival sweep was conducted. Data cutoff dates for efficacy and safety were applied to the database.
- **Subgroups.** "A consistent PFS benefit was observed in patient subgroups irrespective of age, prior therapy (anthracyclines or taxanes), disease-free interval, sites of disease or tumor burden (as measured by the baseline sum of longest diameters of all target lesions), and hormone receptor status, including triple-negative patients whose tumors did not express estrogen or progesterone receptors and did not overexpress the human epidermal growth factor receptor 2 (HER2). The consistency of the PFS benefit across all subgroups supports the generalizability of the overall results."
- **Consistency of findings.** When Genentech applied the same primary endpoint analysis to the investigator-reported, ECOG-reviewed progression data (rather than to the IRF data), patients who received Avastin achieved a 5.6-month absolute increase in median PFS…compared with those who received paclitaxel alone. "The consistency observed in the Genentech analysis between the PFS results based on IRF data and those based on investigator-reported, ECOG-reviewed data served to validate the rigor of investigator assessments and the ECOG review process in this multicenter study."
- **Safety.** No ***new*** safety findings were identified in E2100. The addition of Avastin did increase Grade 3-5 adverse events, but "nearly all of this increase was in the incidence of Grade 3 hypertension and sensory neuropathy. Grade 3 hypertension rarely resulted in drug discontinuation and...means that medical management, such as starting or changing an anti-hypertensive agent, is required. The higher incidence of sensory neuropathy reflects, in large part, the greater time on therapy." Clinically, the most serious Avastin toxicity was arteriothromboembolic events (ATEs), but they were within the range expected with the drug in other cancers.
- **Explanation for AVF-2119g failure.** Possible explanations for why this trial failed to show a survival benefit include: 23% of patients overexpressed HER2, but the regimen did not include a HER2-targeted therapy; patients were highly pretreated (85% had prior chemotherapy); and the benefits of Avastin may be most apparent in combination with weekly paclitaxel.
- **Comparator.** Paclitaxel performed as expected.
- **FDA guidance.** "The PFS results from Study E2100 met (the) criteria defined in the FDA Guidance."
- **Elderly patients.**

Data Cutoff Dates in E2100 Trial

Cutoff date	Database applied	Analyses affected	Rationale for cutoff date
February 9, 2005	ECOG and IRF	All efficacy analyses except overall survival	The cutoff date of the ECOG interim analyses that lead to stopping the trial
October 21, 2006	ECOG	Overall survival	The date overall survival matured (481 deaths)
No cutoff	ECOG	Cause of death	For the purpose of safety, no cutoff was applied
August 9, 2005	ECOG	Safety analyses	6-month follow-up post-interim cutoff to provide more safety information
October 30, 2006	NCI/AdEERS	Safety analyses	20-month follow-up post-interim cutoff to provide more safety information

Exploratory Subset Analysis of E2100 in Patients ≥Age 65

Measurement in patients ≥age 65	Paclitaxel	Avastin	Notes
PFS	6.1 months	10.4 months	HR 0.67 in favor of Avastin
Objective response rate	19.0%	37.3%	---
Overall survival	---	---	Negative effect with Avastin HR 1.55
Arteriothrombo-embolic events	7.4%		---
Bleeding	4.9%		---
Grade 5 events	4: renal failure, left ventricular dysfunction, other	1 GI perforation 2 fatal MIs 1 bradycardia 6 MBC deaths	Similar

Genentech insisted that FDA criteria for approval were met: "Examination of the data from Study E2100 indicates that the criteria delineated by the FDA regarding approval based on PFS have been met and that the PFS endpoint in Study E2100 may serve as the basis for full approval."

The company also noted, "In addition, maintaining disease control can delay symptomatic decline of patients at or following disease progression, again supporting the relevancy of PFS as a measure of benefit." The company concluded that the risk:benefit profile is positive for Avastin overall and in nearly all the subgroups evaluated, but patients ≥age 65 merit "additional discussion."

The company insisted Study E2100 provides "evidence of the highly meaningful clinical effectiveness of Avastin."

√ **PFS.** The magnitude of the effect of adding Avastin on PFS is "statistically very persuasive," the median PFS "represents a high mark" vs. the paclitaxel-alone arm, and the improvement in PFS was consistent across all patient subgroups irrespective of age or other baseline factors.

√ **Response rate.** "The more than doubling of the objective response rate…indicates that the addition of bevacizumab to paclitaxel did more than just delay progression."

√ **Overall survival.** The HR for overall survival with Avastin "corresponds to a 15% improvement in overall survival, (though this) improvement did not reach statistical significance, but…the Kaplan-Meier curves separated early and remained separated for well over 2 years…Post hoc landmark survival analyses demonstrated improvements in 1-year survival (74.0% vs. 81.4%; p=0.017) and 2-year survival (50.1% vs. 55%; p=0.191)."

√ **Quality of life.** "There is no evidence of additional quality of life burden" for Avastin vs. paclitaxel-only.

Genentech ODAC presentation

In the formal presentation to the panel, Dr. David Schenkein, senior vice president of Clinical Hematology/Oncology at Genentech, emphasized that the company reached several key agreements with the FDA to support re-submission of Avastin for first-line MBC:

- An IRF assessment of all 722 patients.
- Primary endpoint of PFS by IRF review.
- Data cutoff in line with ECOG interim analysis applied to final clean database.
- Mature survival data.

He called the Avastin treatment effect in E2100 "compelling" and described Avastin as "an important advance for women with breast cancer," noting that:

- PFS was appropriately measured and consistent across subsets.
- Objective response rate improved.
- Overall survival improved.
- The risk:benefit ratio was favorable, with no new safety signals observed.

Dr. Kathy Miller, an oncologist from Indiana University speaking on behalf of Genentech, reviewed the findings in the E2100 trial. She called PFS "an important endpoint in the first-line (MBC) setting" and insisted there is a clinical benefit to prolonging PFS: maintaining disease control, preventing symptoms of disease progression, and preventing toxicities, psychological burden, and uncertainty of disease progression. She also noted that the PFS endpoint is not obscured by subsequent therapy.

In E2100, Dr. Miller said the PFS results were consistent across all subgroups – number of metastatic sites, measurable disease at baseline, age, prior adjuvant chemotherapy, and ER status. The results also were consistent in both the investigator and IRF analyses as well as in sensitivity analyses.

On quality of life, Dr. Miller said the primary analysis favors Avastin at both Week 17 (-6.6 with Avastin vs. -12.7 with capecitabine alone) and Week 33 (-15.9 vs. -24.6).

She concluded that Avastin in combination with paclitaxel for first-line MBC is beneficial:

- There was a clinically meaningful improvement in PFS.
- The magnitude of PFS benefit was consistent for all patient subgroups.
- Similar PFS results were found based on IRF or investigator assessments, validating the ECOG review process.
- The robust PFS result was verified by sensitivity analyses.
- There was a doubling of the objective response rate, with improvement in 1-year survival and no additional quality of life burden.

Dr. Barbara Klencke, associate group medical director at Genentech, reviewed the safety of Avastin in the E2100 trial.

Safety of Avastin in E2100 Trial

Measurement	Paclitaxel-only	Avastin + paclitaxel
Discontinued for disease progression	55%	45%
Discontinued for toxicity/complications	19%	20%
Deaths	73.6%	70.2%
Death due to protocol therapy (investigator analysis)	0.3%	0
Death due to protocol therapy (by Genentech review)	Not assessable	1.7%

Dr. Klencke insisted that in E2100:

- Avastin + paclitaxel was relatively well tolerated despite longer treatment.
- Discontinuation for treatment toxicity was equally balanced in the two arms of the trial.
- The safety profile was consistent with known Avastin toxicity profile.

When the AVF-2119g and E2100 trials are considered together, Dr. Klencke concluded:

- The side effects were consistent with current Avastin labeling.
- The overall safety profile and quality of life outcomes from E2100 support acceptability of the safety profile for Avastin + paclitaxel.

Dr. Eric Winer, director of the breast oncology center at Dana-Farber Cancer Institute, commented that the FDA approval criteria "seem somewhat arbitrary to me and my colleagues." He told the panel that the goals in treating women with MBC are to maximize survival and improve quality of life – which he defined as maintaining disease control, minimizing symptoms from disease, and minimizing toxicity from treatment.

Is PFS a meaningful endpoint? Dr. Winer said, "Symptoms become more and more common as breast cancer progresses. Moreover, improving PFS avoids the psychological consequences associated with disease progression and changing therapy and eliminates, at least for some time, the uncertainty as to whether a new treatment will be effective…Patients become used to changing therapy…I refer to it as surfing the wave of breast cancer therapy…So, yes, prolonging progression-free survival can be highly meaningful!"

However, Dr. Winer also agreed that for PFS to be meaningful, it needs to be of substantial magnitude, established with confidence, and, ideally, supported by other measures, such as overall survival or objective response rate. He argued that Avastin has met that criteria in MBC, "In terms of the magnitude of benefit, the improvement in outcomes in PFS is substantial. I think there is little doubt that, with the improvement in PFS, this has been established with confidence. There is a high and striking degree between investigator-assessment in TTP and that of the independent review. And there have been a number of sensitivity analyses, and in each of these, the benefit in PFS was shown…There was no statistically significant difference in overall survival, but the hazard ratio was 0.87, with an absolute difference of 1.7 months, there was a doubling of the response rate, and quality of life favors Avastin."

On safety, Dr. Winer said the 20% increase in Grade 3-5 adverse events were mostly asymptomatic Grade 3 hypertension and proteinuria, which he described as "easy to manage." He added that neuropathy was more common with Avastin but noted that "this is thought to be due to the greater total dose of paclitaxel" given with Avastin. He admitted there was a small increase in severe toxicity but said those events "thankfully...were extremely rare."

The bottom line, according to Dr. Winer, is that "the added day-to-day toxicity…is quite limited…I believe that PFS is a meaningful endpoint in this first-line setting since it has been accepted in the setting of endocrine therapy…***It doesn't seem to be a high bar to convince all of you that it should be a meaningful endpoint here as well***…Avastin + paclitaxel results in substantial improvement in PFS with modest additional toxicity for the majority of patients…(It) is a valuable treatment option for women with breast cancer. It is by no means the only treatment, but it is a treatment that should be on the menu. It is a treatment that has been on the menu for the past two years, and it should remain on the menu."

Dr. Chris Bowden, senior group medical director at Genentech, offered the closing remarks in the company presentation. On benefit, he said, "Avastin plus paclitaxel shows a clinically meaningful effect on PFS. PFS was supported by all secondary endpoints." On risk, he said: "The safety profile of Avastin is familiar to prescribing oncologists."

Dr. Bowden pointed to what he called "a high level of confidence" in the trial results:

- E2100 was conducted by independent U.S. cooperative groups and, thus, provides assurance the results are applicable to U.S. practice.
- There was a high level of consistency across subsets and agreement between the IRF and investigators.
- The sensitivity analyses were consistent.

PUBLIC WITNESSES

There were only two public witnesses. No patients testified. Maria Carolina Hinestrosa, executive vice president for programs and planning at the National Breast Cancer Coalition, told the panel that this was due to an oversight, "The absence of testimonials can be a statement in itself…but the reason we weren't here was we didn't know (about the

meeting) and weren't prepared. We care deeply about this issue, and we urge the committee to set the highest bar always in breast cancer for this or any other medication…We ask you to really look at ultimately what is the value of this or any medication you are considering."

Dr. Robert Erwin, co-founder, president, and director of the Marti Nelson Cancer Foundation and a member of the Research Committee of the American Society of Clinical Oncology (ASCO), told the panel, "The application should not be approved if it means lowering the bar for approvals."

Dr. Erwin made several points and posed a number of questions:

1. **Time to action on Avastin.** "Has the year-plus delay (in Avastin first-line MBC approval) made any difference? Has it added benefit in the overall process? The complete response letter was never made public, but the (panel) briefing documents provide insights. The year delay is valuable if the following is achieved: Reconfirmation and reestablishment of a new bar at the FDA for new drug approvals, and by a high bar I mean the quality of data used in the review, the reliability and believability, and also the performance and safety required for a product to be approved."

2. **National Cancer Institute (NCI).** "Should the NCI essentially be the CRO (contract research organization) for industry? I would argue no, it should not. However, NCI and industry should cooperate on the advancement of the field of oncology, and, in general, I think they do. It is extremely important that its (NCI's) integrity be maintained, and in part that requires open and non-confidential disclosure."

3. **Genentech.** "Why did Genentech ignore the FDA's requests for an IRF in 2005? It is obviously done now, and the results are extremely interesting."

4. **TTP/PFS.** "In 1999 I was opposed to TTP. I have modified that on PFS. There is no question that PFS is meaningful personally and clinically, but can you capture that in a large body of data? A person taking a drug hoping to obtain an expectation of PFS, particularly in this case, faces the possibility of early death, and that shouldn't be taken lightly. But in this study, there are individuals who received substantial benefit, and those people can't be taken lightly either…So, in evaluating this application and looking at the importance of PFS, I think that it's pretty clear that PFS is clinically meaningful. The question is how do you deal with this data and endpoint when you have problems with concordance, which to me says as much about the state of the art in radiology as about the competence of the clinical trialists or the people running the study."

5. **Deaths.** "Five of the six deaths were people over the age of 65, and one was age 64. What if the trial were only designed for patients younger than 65? Would we be looking at a different outcome?"

PANEL DISCUSSION

Before taking any vote, panel members had a number of questions for Genentech as well as a few for the FDA. These included:

The early interim analysis suggested a survival benefit. What changed that?

- *Dr. Miller:* She said the interim overall survival data were extremely premature, and even though the p-value was 0.01, it would not have been statistically significant as a primary endpoint. She said, "We had long and contentious debates on whether we should show those (survival) curves knowing they were very premature and subject to change…We ultimately decided it was better to show all the information we had at that interim time point and let (people) make their own decisions about the weight of that interim data…The release from the data monitoring committee had no impact on the curves at that point…On the effect of later treatments on overall survival, the reality is we don't know. We didn't collect data on subsequent therapies received."
- *Panel member Dr. Ralph D'Agostino, a statistician from Boston University:* "The bottom line is we have significant results in PFS but not a significant result for overall survival."
- *Dr. Miller responded:* "That is indeed the bottom line… We saw no systematic bias at all."

There was a high incidence of ER negative patients in the E2100 trial. Is there a signal for triple negative breast cancer patients doing better with Avastin than ER+ patients? Genentech's Dr. Bowden said 65% of patients in the trial were ER+, but in the subset analysis for PFS, the triple negative patients did have a treatment effect with Avastin.

Did the difference in the percent of patients with measurable disease in the two arms of E2100 affect the results?

- *Panel member Dr. Aman Buzdar, an oncologist from MD Anderson Cancer Center who specializes in breast cancer*, pointed out that >20% of patients had evaluable but not measurable disease, estimating that there was about a 9% absolute difference between the two arms, which he speculated "could be partly responsible for the differences in interpretation." He said, "There is a 9% absolute difference between the group with evaluable disease vs. the other group, and I think that could bias (the results)."
- *Genentech's Dr. Bowden:* "Non-measurable patients were assessed in the same manner as patients with measurable disease. The subset for PFS demonstrated a treatment effect in both measurable and non-measurable subsets."

- *Dr. Miller:* "I doubt any of us look at women with only bone disease and say, 'Sorry, Mrs. Smith, I can't treat you because you don't have measurable disease.' There is a slight imbalance in measurable and non-measurable disease patients, but I think it is highly unlikely that those differences account for the differences we see…I'm quite proud of this study, including those patients who otherwise are excluded from clinical trials."

How was progression in bone defined? Dr. Miller said, "Evaluating response in bone is difficult…There are patients with a flare response that can complicate that…We didn't have a specific definition for bone, per se…Patients had to have unequivocal progression – a clearly identified new lesion. Worsening on a scan is (variable)…We looked for that bias and could find no evidence of it."

Did the timing of the assessments "cushion" the PFS results? Dr. Miller answered, "We looked at the number of cycles…but most of those occurred later in patients…If treatment was delayed, those were missed and not made up…ECOG statisticians did other studies to see if there was ascertainment bias (and there wasn't)…We also looked at non-scheduled assessments, which was about a third of patients, and they were within 1% of being identical in the two arms. Then, we looked at progression at a non-scheduled assessment time and moved that forward to the next scheduled time point, and that didn't have any impact on our results… We absolutely acknowledge that including non-measurable patients does bring with it some potential for subjectivity and bias, and we looked very hard to find any impact of that on our results, and we simply couldn't find that had any impact."

How can the "terrific" performance of the control group in terms of survival be explained? Dr. Winer said, "In the end this is why we do randomized clinical trials – because comparing across trials is problematic. This group of patients did not include any HER2+ patients, and many of the older trials did include ~20%-30% of HER2+ disease…and two-thirds of these patients had ER+ disease, and we know that…they have a more favorable outcome…~2% of patients had HER2+ disease (in E2100)."

Is the toxicity with Avastin a stand-alone issue, or did Avastin control disease longer so there was more opportunity for patients to develop adverse events (in E2100)?

- *Panel member Dr. Gary Lyman, an oncologist from Duke University:* "ODAC has not weighed in on legitimacy of PFS for labeling approval for 1st line MBC, but if we do favorably, then the real issue comes down to the toxicity signals, and clearly the data show a 20% increase in Grade 3-5 adverse events in the bevacizumab group."
- *Genentech's Dr. Bowden:* "On toxicity, we did look at time and neuropathy, and time does look to be an issue. On the other side effects, we did not do a time-on-treatment analysis…The vast majority (of Avastin-related adverse events) was manageable."
- *Dr. Miller:* "Some of the toxicity is just due to our success...What is lost in lumping all the toxicity together is what those toxicities mean to women with MBC who are living with this disease day-to-day…Women complain of nausea, fatigue, diarrhea, hair loss, neuropathy, and myalgia. They never mention hypertension as something that limits them…Usually they (just) needed an anti-hypertensive to manage it."

What is the FDA philosophy on when PFS is adequate – as with GlaxoSmithKline's Tykerb (lapatinib) and Bristol-Myers Squibb's Ixempra (ixabepilone) – and when does the FDA want to see more of a survival advantage? The FDA's Dr. Pazdur said, "We've had numerous discussions with this and other committees in dealing with other end-points, and one of the important things that came out is that in dealing with more refractory disease, we are dealing with more symptomatic patients – hence, a delay in a symptomatic population probably has more clinical meaning than simply a radiographic delay in an asymptomatic population...That is why (we asked the committee) whether there is a different risk:benefit ratio than in a more refractory setting."

Why aren't the results the same in all the trials of Avastin in MBC?

- *Genentech's Dr. Bowden:* The EXCALIBUR study was a single-arm, Phase II trial, and that doesn't have a control, so a comparison can't be done. On AVF-2119g and E2100, please recall that there are a couple of major differences in the two trials (such as chemotherapy agent used)…(And) we did eight sensitivity analyses to study the robustness of the PFS data, and in all eight the treatment benefit on PFS was maintained."
- *Dr. Miller:* "The RIBBON-1 trial has a control arm, and we will be able to see benefit of adding Avastin in a variety of chemotherapy options. That will give us an answer to whether the chemotherapy partner has a major or minor impact on the outcome we see (with Avastin)… It is likely it has some impact, but it is hard to know the magnitude of that impact without the result of those further studies."

What is the risk:benefit profile with Avastin?

➢ *Dr. Winer made several points, including:*

- "I don't think there is any real attempt to minimize the acute or severe toxicity. I certainly – and I hope all my colleagues – take very seriously these rare but life threatening events, particularly when considering using an agent like Avastin in the adjuvant setting."
- "One of the major issues will be the long-term impact of hypertension. Is that for a year, two years, three, or forever?…I agree that Grade 3 hypertension that requires anti-hypertensive medication in the overall

picture is probably not nearly as worrisome as many of the other toxicities patients face with the treatments we have."

- "As someone who has administered a lot of Avastin…adding Avastin to chemotherapy adds far less toxicity than adding a second chemotherapy agent. So, while the toxicity has to be taken very, very seriously, what one has to come back to is what the symptom burden is on a day-to-day basis."
- "I don't know that we should be discounting PFS any more in the first-line setting than in the second- or third-line setting…Maintaining patients in a stable state without progression is something our patients want…I agree we have to be very careful in patients who don't have symptoms from their disease, and there are first-line patients without symptoms…We emphasize that when you have a patient who is asymptomatic, you are not going to make the patient feel better with any therapy…That said, I still don't understand why PFS would be a meaningful endpoint in second-line or third-line and not in first-line."
- "I do believe ixabepilone was approved second- and third-line for improvement in PFS that was <2 months. While I realize we are not supposed to compare across agents, in terms of day-to-day toxicity of adding ixabepilone to capecitabine vs. adding Avastin to paclitaxel, I'm left speechless. There is no comparison here. It is far, far easier to add Avastin to paclitaxel for 5.5 months of PFS improvement than even considering adding ixabepilone for a 6-week improvement in PFS."

➢ *Dr. Maha Hussein, the panel chair and an oncologist from the University of Michigan:* "A lot of the approved drugs in second-line – If I were the president, I would not approve them."

What does "clinically meaningful" mean?

- *Dr. Hussein, panel chair:* "There is no question that a 5.5-month improvement in PFS is meaningful. But if a patient is not living better. And you showed they are not. And if they are not living longer, and they aren't. Then, how does it translate to clinical benefit. I would argue the burden of symptoms (is a concern). These patients are terminal, and our job is to make their life better, not to say it is okay to have a stroke or it (a side effect) is manageable or that you can take a pill...Your quality of life, if anything, showed these patients' quality of life went down, not improved. Compared to baseline, their quality of life went down...So you didn't show they are living longer or better."
- *FDA's Dr. Pazdur:* "I'd like to underscore we don't have a blinded trial here. We have one trial. We didn't capture other symptomatic measures perhaps given to these patients…God knows if they were uneven. Measuring quality of life in an unblinded trial is highly problematic…We do have new (FDA) guidance on quality of life claims…But this type of study in this submission doesn't come close to a credible claim for any improvement in quality of life."
- *Genentech's Dr. Bowden:* "Genentech doesn't see the quality of life data as submissible for a claim...but the (quality of life) curves are better for Avastin...There is less decline in quality of life with Avastin."
- *Dr. Pazdur:* "With all due respect, I disagree…What we are talking about is substantial evidence or regulatory evidence…So, some degree of substantial evidence should be demonstrated on that endpoint."

How much discordance on the dates of progression was there in the E2100 trial? The FDA's Dr. Lu said, "Discordance was any difference in progression date – even one or two days, but that was rare."

What was the primary endpoint for the approval of Lilly's Gemzar (gemcitabine) + paclitaxel for first-line treatment? Was overall survival the primary determinant there?

- *FDA official:* "The primary endpoint was positive TTP, but that was supported by a strong trend to improved survival."
- *FDA's Dr. Pazdur:* "We were looking at the totality of the data and looking at a survival benefit."
- *Panel member Dr. Lyman:* "Are you suggesting it wouldn't have been approved without a survival benefit?" Dr. Pazdur said he couldn't address that.

Was the lost to follow-up balanced across the E2100 arms? A Genentech biostatistician indicated it was relatively balanced.

Did the more frequent assessment in the AVF-2119g trial than in the E2100 trial account, at least partly, for the longer PFS in E2100?

- *Dr. Patricia Keegan, director of the FDA's Division of Biologic Oncology Products, CDER:* "In one trial we (FDA) had input, and in the other we didn't, so it is very difficult for us to justify the E2100 development period. We didn't have an opportunity to get good input on it."
- *Genentech biostatistician:* "The issue of timing of assessments is important…and we do need to keep a high bar for PFS…Certainly, it is true that when assessing less frequently you have less precision to detect small differences…Having a three-month interval gave us less precision (in E2100) than in the AVF-2119g setting, but the good news is it didn't matter here…What we are really talking about with frequent assessment is we would smooth out the bumps (in the curves)...but I think we can be really confident that the magnitude of benefit wouldn't be sensitive to that."

- *Panel statistician Dr. D'Agostino:* He pointed out that more frequent assessments would have actually worked in favor of Avastin, if anything.

Other interesting panel member/FDA comments included:

- *Dr. Michael Link, a pediatric oncologist from Stanford:* "If you (Genentech) showed a survival advantage, we wouldn't be having this discussion."
- *Dr. Lyman:* "One of the concerning things to me is…the breakdown in communication not only with the sponsor but with ECOG and NCI…Having been a member of ECOG and having done a number of cooperative studies, this troubles me…This is concerning."
- *Natalie Portis, the patient advocate:* "I am concerned about incomplete and missing data…I agree we need meaningful treatments for MBC. To me that means overall survival and quality of life. There is a significant increase in Grade 3-5 adverse events, and yet the sponsor says quality of life is not impacted. I'm concerned the toxicity is being minimized…I think this is a very serious issue. Just because an adverse event is expected or in the package insert doesn't mean it is acceptable to patients… We have real data on toxic effects…and severe toxic effects and deaths...And that can't be overlooked."
- *Dr. D'Agostino, statistician:* "I'm not surprised by the consistency of the subsets...but I was hoping the sponsor has no intention of looking for subsets where survival looks good."

PANEL CONSIDERATION OF FDA QUESTIONS AND VOTE

QUESTION 1. In the E2100 study, PFS is not a surrogate endpoint for overall survival in first-line breast cancer. Please discuss whether PFS alone without a demonstrated survival advantage, should be considered a measure of direct clinical benefit in the initial treatment of metastatic breast cancer.

This was a discussion point only; there was no vote, and the chair did not summarize the consensus of panel members. Panel member comments included:

- *Dr. D'Agostino, statistician:* "If PFS is not a surrogate for overall survival, then what is it? What we are hearing is we have no way of saying how it translates into quality of life. We don't have anything beyond that it is a measure that has shown some improvement, but nothing to say what it means...so I would think it is serious in this first-line treatment that we don't buy into PFS…What is the clinical benefit beyond PFS? Shouldn't we have a list of why we think PFS has some clinical benefit? (Avastin) doesn't lead to improved quality of life, and it doesn't improve survival."
- *Dr. Lyman made several points, including:*
  - "Clinically, I think there is no question that PFS is clinically meaningful…Having said that, it challenges how much and again the safety and toxicity side….Raising the bar for first-line to an unequivocal overall survival difference (is wrong), given the difficulty in many cases of documenting, monitoring, and standardizing subsequent therapies. Many of my patients, after first-line, go thru 5, 6, or 7 different therapies, and that adds noise and clouds the survival benefit of a first-line regimen. When we see differences in PFS of a certain level – and I think this may have done that – one has to wonder if survival differences aren't being clouded by perhaps multiple treatments done subsequently. And we don't know because those data weren't collected. The differences in managing first-line MBC and second- and third-line disease has become very, very cloudy as well."
  - "(Patients) come fairly extensively treated – in the adjuvant setting – before I see them for first-line MBC, and I'm not sure that is any different from the patient who comes back after first-line MBC. I would suggest setting different rules for different malignancies, but from a breast cancer management perspective, I find PFS fairly compelling."
  - "Women with MBC are being treated with Avastin every day in combination with chemotherapy. The real issue is whether we have an indicator that says it is safe and effective to do that first-line. I think most breast cancer oncologists and most breast cancer patients would accept PFS as a reasonable endpoint."
  - "In the adjuvant setting, aromidase inhibitors and hormonal therapies were approved not on survival, which ultimately had to be looked at, but on disease-free survival…I really think we have a legitimate effect here, and we are all wrestling with if it was measured correctly and was the toxicity risk:benefit justifiable."
  - "There is no question survival is the gold standard. I think first-line MBC may be one of the most challenging things to show (a survival benefit for) vs. other diseases (GU, etc.)…So, whether it (PFS) should be applied to all settings, I have some discomfort...but in this setting I think it is clinically significant and an important endpoint…I like the suggestion of coupling it with documentation of no worsening of survival."
  - "A couple of recent studies in colorectal cancer by statisticians have demonstrated across multiple metastatic colorectal cancer trials a highly significant relationship between PFS and overall survival, so it is conceivable you will have less blurring and muddying of early treatment survival impact in that setting."

- *Dr. Joanne Mortimer, an oncologist from the University of California, San Diego, specializing in breast cancer:* "I think PFS is an important endpoint…Most of these women have been heavily pre-treated, making it harder to expect overall survival…I don't think any chemotherapy alters overall survival. I think PFS is a meaningful endpoint for second- and third-line MBC…I think we are being inconsistent here."
- *Dr. Buzdar:* "We need harder, fixed endpoints…The majority of these patients were treated in the U.S…We can't talk out of both sides of the mouth and say maybe the patients got different therapy on progression…In the U.S. most practice is very similar…That should not be the only reason we didn't see a survival advantage…I think we have to look for other reasons for a PFS advantage and no advantage in survival."
- *Dr. Hussein, panel chair, comments included:*
  - "I wonder if there is a middle of the road on approval …If I am in the clinic…and (the patients) are not progressing, there is no way to capture the clinical benefit of that…But I have come from a field where early positive indications did not translate into a survival advantage (for drugs). If anything, despite early therapy…resulted in worse survival. So, if you ignore the survival and just go by reason or PFS, you would have put harmful drugs on the market…I'm wondering if there is a way to couple approval with at least equivalence survival...So, if PFS is delayed, you (would have to show) survival data that there is no significant chance of harm."
  - "I look at the drug (Avastin), and I couldn't disregard the toxicity. A little nausea is not like a perforated gut, bleeding, etc…If you don't look at survival, you can't capture bad events after patients are removed from the study…(Genentech) showed (improved) survival in colorectal cancer, and other drugs have had the trend (to improved survival)…I would encourage sponsors in the future that as much data as possible be collected…There may be subtle harmful effects not being picked up that may explain why (Avastin) survival is not different (from control)."
  - "We have no way of measuring subtle issues of benefit….There is nothing that captures sleepless nights, nightmares, etc….I agree there is really no clinical benefit (with Avastin) in the traditional context. There isn't. But assuming the therapy is safe – and I'm not sure it is safe – patients are a nervous wreck when their disease is progressing…and there is no way to measure that."
- *FDA's Dr. Pazdur's comments included:*
  - "You have to show safety and efficacy to get a drug approved…In adjuvant breast cancer, for example, we would approve on a disease-free survival endpoint, with the sponsor submitting subsequent data to make sure there is no harm to overall survival…We want to make sure no new therapy is producing a detriment in survival."
  - "I guarantee we would demand that the sponsor provide survival data later…The question here is if you have PFS where we don't see an advantage to survival, not a survival advantage…If we saw a survival disadvantage, we would not even be here."
  - "Let me assure you that in our discussions with sponsors, when we are negotiating PFS, whether in a more refractory setting...we ask they power the trial to ensure we can look at overall survival…The reason is that obviously if we never ask a survival question, we will never see the answer."
  - "If we go on the slippery slope of smaller and smaller trials, then we are really doomed to failure…So, we would require a look at overall survival and power for overall survival…The disadvantage is that when you over-power a trial for PFS because you are powering for overall survival...the PFS benefit could be relatively marginal but highly statistically significant."
- *Patient advocate:* "I agree we have to raise the bar in terms of safety, and that is very important...There have been mistakes in the past, and they have cost people their lives…everyone wants to offer a woman with MBC hope, but we don't want to offer false hope…Because we approved things in the past, that is no reason to go forward and make a similar mistake."
- *Dr. S. Gail Eckhardt, an oncologist from the University of Colorado Health Sciences Center:* "I would be willing to say PFS is an adequate endpoint and does include a clinical benefit…What I am struggling with is the measurement in these kinds of studies. That is something that has to be decided going forward. In this trial it was something that started out as a non-pivotal trial. There were a lot of variabilities, including 30% lack of follow-up…I'd hate to throw out the whole endpoint because it was fairly difficult to apply in this setting."
- *Virginia Mason RN, the executive director of the Inflammatory Breast Cancer Research Foundation and the panel's consumer representative:* "I am also a survivor…Clearly, when you are a clinician or patient looking at the issues it is a very, very difficult place to be…There are a lot of options for MBC patients…Yet, I am also concerned about the toxicities, and there we lowered our standards more and more...There have been some comments on that…I have difficulty picking sides on this… Either way, you are making difficult decisions."

QUESTION 2. Given:

- Estimated 5.5-month improvement in median PFS claimed by Genentech.
- No improvement in overall survival.

- Increased toxicity/toxic death.
- No effect on PFS or overall survival in second- and third-line metastatic breast cancer.

Are the data provided sufficient to establish a favorable risk:benefit analysis for the use of Avastin + paclitaxel for first-line treatment of patients with metastatic breast cancer?

NO by a vote of 5 No, 4 Yes.

The nine voting members on the panel included seven oncologists (two of whom are breast cancer specialists), a consumer representative, and a patient advocate. The non-voting member was the industry representative. The no votes were: Dr. Buzdar (breast cancer specialist), Dr. D'Agostino, the patient advocate, the consumer representative, and the panel chair. The yes votes were: Dr. Mortimer (the other breast cancer specialist), Dr. Lyman, Dr. Eckhardt, and Dr. Link.

Panel member discussion included these comments:

- *Dr. Lyman:* "I do think that in this context a 5.5-month increase in PFS is clinically meaningful. It is certainly statistically significant and holds up through a variety of sensitivity analyses. It is true there is no significant difference in overall survival, but there is a trend. Statisticians don't like trends, but it at least assures me, to a large extent, that subsequent studies wouldn't show a worsening of survival. So, the relevant question in my mind, and where I have the most difficulty is the toxicity and whether we are doing any harm…How much is the advantage of Avastin and how much is because patients didn't relapse for an additional 5.5 months and stayed on study. For the neuropathy, that may completely explain the difference…There are other Avastin-specific toxicities, but they are not new. It was there when Avastin was approved for second-line and third-line therapy…Do we want to say the toxicities are unacceptable in first-line but not in second- or third-line? It is very unlikely these patients won't die of breast cancer. It is a fatal disease. If we can more than double the median survival in these patients, they will still go on to die…I am certainly not at all convinced here...but I am leaning to voting yes."
- *Dr. D'Agostino:* "There is no improvement in overall survival. If overall survival went the other way, we wouldn't be here…I don't think we can say there is a trend to improvement in survival…I think the toxicity is a real problem, and as a package, I think that our approval would rest completely on buying into PFS as an appropriate measure of efficacy, and I don't think we have that ability at the moment, given the data before us."
- *Patient advocate:* "If there isn't meaningful data to support (PFS) – and there isn't – I remain very uncomfortable…I think (the toxicity) is too high a price to pay."
- *Panel chair, Dr. Hussein:* "I was impressed by the PFS at first. Then, I saw all the data. If things were perfect, I would have voted yes…I am leaning to ***no*** because there are too many uncertainties."

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