Summary Minutes of the
Oncologic Drugs Advisory Committee
July 20, 2010
Location: Hilton Washington DC North/Gaithersburg, The Ballrooms, 620 Perry Parkway, Gaithersburg, MD.

All external requests for the meeting transcripts should be submitted to the CDER, Freedom of Information office.

These summary minutes for the July 20, 2010 Meeting of the Oncologic Drugs Advisory Committee of the Food and Drug Administration were approved on _September 2, 2010_____.

I certify that I attended the July 20, 2010 meeting of the Oncologic Drugs Advisory Committee of the Food and Drug Administration and that these minutes accurately reflect what transpired.

___**/s/**_____	_____**/s/**_____
Nicole Vesely, Pharm.D.	Wyndham Wilson, M.D., Ph.D.
Designated Federal Official, ODAC	Committee Chair

The Oncologic Drugs Advisory Committee of the Food and Drug Administration, Center for Drug Evaluation and Research met on July 20, 2010 at the Hilton Washington DC North/Gaithersburg, The Ballrooms, 620 Perry Parkway, Gaithersburg, Maryland. Prior to the meeting, members and invited consultants were provided copies of the background material from the FDA and the sponsor. The meeting was called to order by Wyndham Wilson, M.D., Ph.D. (Committee Chair); the conflict of interest statement was read into the record by Nicole Vesely, Pharm.D. (Designated Federal Official). There were approximately 200 persons in attendance. There were six (3) speakers for the Open Public Hearing session.

Issue: On July 20, 2010 the committee met to discuss supplemental biologics license applications (sBLAs) 125085/191 and 192 for AVASTIN (bevacizumab), manufactured by Genentech, Inc. The two proposed indications (uses) for this product are: (1) first-line treatment of a subgroup of women with metastatic breast cancer known as HER2-negative breast cancer, in combination with the chemotherapy drug docetaxel; and (2) first-line treatment of HER2-negative metastatic breast cancer in combination with one of two classes of chemotherapy drugs, known as taxanes and anthracyclines, or with the chemotherapy drug, capecitabine. In addition to the discussion of these two indications, the committee will also consider the impact of the submitted studies on the conversion from accelerated to regular approval of the indication for the treatment, in combination with the chemotherapy drug paclitaxel, of patients who have not received chemotherapy for their locally recurrent or metastatic HER2 negative breast cancer.

Attendance:

Oncologic Drug Advisory Committee Members Present (Voting):
Ralph Freedman, M.D., Ph.D., Jean Grem, M.D., F.A.C.P., Patrick Loehrer, Sr., M.D., Brent Logan, Ph.D., Virginia Mason, R.N. (Consumer Representative), Mikkael Sekeres, M.D., M.S., Wyndham Wilson, M.D., Ph.D.

Special Government Employee Consultants (Temporary Voting Members):
Aman Buzdar, M.D., Ralph D'Agostino, Ph.D., Gary Lyman, M.D., M.P.H., Joanne Mortimer, M.D., Natalie Compagni Portis, Psy.D. (Patient Representative), Ronald Richardson, M.D.

Non-voting Participants:
Gregory Curt, M.D. (Industry Representative)

Oncologic Drugs Advisory Committee Members Not Present:
William Kelly, D.O.
Margaret Tempero, M.D.

FDA Participants (Non-Voting):
Richard Pazdur, M.D., Patricia Keegan, M.D., Lee Pai-Scherf, M.D., Laura Lu, Ph.D., Kyung Yul Lee, Ph.D.

Designated Federal Official:
Nicole Vesely, Pharm.D.

Open Public Hearing Speakers:
Paul Brown, Government Relations Manager, National Research Center for Women & Families/Cancer Prevention and Treatment Fund
Patricia Howard
Roberta Gelb, Member of SHARELeaderes

The agenda was as follows:

Call to Order Introduction of Committee	**Wyndham Wilson, M.D., Ph.D.** Chair, ODAC
Conflict of Interest Statement	**Nicole Vesely, Pharm.D.** Designated Federal Official, ODAC
Opening Remarks	**Richard Pazdur, M.D.** Director, Office of Oncology Drug Products (OODP), Office of New Drugs (OND), CDER, FDA
Sponsor Presentation Introduction	**Genentech, Inc.** **Sandra Horning, M.D.** Senior Vice President, Hematology/Oncology Genentech, Inc., A Member of the Roche Group
Efficacy and Safety Results	**See Phan, M.D.** Senior Medical Director, BioOncology Genentech, Inc., A Member of the Roche Group
Measures and Magnitude of Avastin Progression Free Survival (PFS) Benefit	**James Reimann, Ph.D.** Director, Oncology Biostatistics Genentech, Inc., A Member of the Roche Group
HER2-Negative Metastatic Breast Cancer and Avastin	**Gabriel Hortobagyi, M.D.** Professor and Chairman, Department of Breast Medical Oncology The University of Texas, MD Anderson Cancer Center
Concluding Remarks	**Sandra Horning, M.D.** Senior Vice President, Hematology/Oncology Genentech, Inc., A Member of the Roche Group
FDA Presentation	**Lee Pai-Scherf, M.D.** Medical Officer, Division of Biologic Oncology Products (DBOP), OODP, OND, CDER, FDA
Questions to the Presenters	
Open Public Hearing	
Questions to the ODAC and ODAC Discussion	

QUESTION # 1 (voting)

STN 125085\191 – AVADO study

The proposed new labeling claim requested in this application is for use of bevacizumab (15 mg/kg) in combination with docetaxel for the initial treatment of HER2-negative metastatic breast cancer (MBC). The proposed claim is supported by the results of the AVADO study, a randomized (1:1:1), double-blind, placebo-controlled, three-arm trial of docetaxel plus placebo, docetaxel plus bevacizumab at 7.5mg/kg every 3 weeks, and docetaxel plus bevacizumab at 15 mg/kg every 3 weeks that enrolled 736 patients. The treatment benefits and risks resulting from the addition of bevacizumab to single agent docetaxel are summarized below:

Benefits

As compared to docetaxel alone, the bevacizumab-containing arms demonstrated

- An improvement in progression-free survival (PFS) [hazard ratio (HR) = 0.7 (bevacizumab 7.5 mg/kg); HR=0.62 (bevacizumab 15 mg/kg)] with an increase of 0.80-month (bevacizumab 7.5 mg/kg) and 0.88 month (bevacizumab 15 mg/kg) in median PFS
- An incremental increase in the overall response rate by 10.8% (bevacizumab 7.5 mg/kg) and by 18.7% (bevacizumab 15 mg/kg)

Risks

As compared to those receiving docetaxel alone, patients in the bevacizumab-containing arms experienced

- A higher incidence of serious adverse events (requiring medical intervention, hospitalization or resulting in death)
- A higher incidence of NCI CTC grade 3 through 5 adverse events
- Unique adverse events attributable to bevacizumab (e.g., hypertension, proteinuria)
- 0.8 % bevacizumab related death (bevacizumab 15 mg/kg)
- A higher incidence of treatment delays and dose reduction of docetaxel
- No improvement in overall survival, with the hazard ratio favoring placebo arm

VOTE:

1. **Does the addition of bevacizumab to docetaxel represent a favorable risk/benefit analysis for the initial treatment of patients with metastatic breast cancer?**

   Vote : ***Yes=0*** ***No = 13*** ***Abstain = 0***

   - The Committee felt that the mature data in the confirmatory studies showed a statistically significant benefit in Progression Free Survival (PFS), however felt that the magnitude of the effect was marginal and not clinically meaningful and did not confirm the results of the E2100 trial that was discussed at the December 5, 2007 Oncologic Drugs Advisory Committee (ODAC) meeting in which a larger magnitude of effect was seen for PFS. The Committee also noted that no Overall Survival (OS) benefit was seen as well as no Quality of Life (QOL) benefit. The Committee was interested in seeing QOL data that the Sponsor presented, however it was noted by FDA that analysis of these secondary endpoints were not discussed and agreed-upon for use as efficacy claims and FDA noted concerns with missing data, including a concern that the QOL study may be driven by those not progressing on Avastin since data for those progressing are generally missing just prior to drop out. The Committee was concerned over the toxicity profile in light of the marginal magnitude of PFS with members noting that the toxicity profile is well known, however with the small magnitude of effect for PFS, questioned whether patients should accept this safety profile as deaths did occur on study as a result of Avastin use.

Please see the transcript for detailed discussion.

QUESTION # 2 (voting)

STN 125085\192 – RIBBON1 study
The proposed new labeling claim requested in this application is for use of bevacizumab in combination with taxanes, anthracyclines, or capecitabine for the initial treatment of HER2-negative metastatic breast cancer. The proposed claim is supported by the RIBBON 1 study, a randomized (2:1), double-blind, placebo-controlled, two-arm trial of chemotherapy plus placebo versus chemotherapy plus bevacizumab at 15 mg/kg every 3 weeks. Randomization was stratified by intended chemotherapy regimen (anthracycline vs. taxane vs. capecitabine). Results in the taxane/anthracycline cohort and in the capecitabine cohort were powered for separate analyses of efficacy in each cohort. The treatment benefits and risks resulting from the addition of bevacizumab to anthracycline, taxanes, or capecitabine are summarized below:

Benefit
As compared to chemotherapy alone, the bevacizumab-containing arms demonstrated

- An improvement in PFS [HR=0.64 (taxane/anthracycline); HR=0.69 (capecitabine)] with an increase of 1.2 months and 2.9 months in median PFS respectively
- An incremental increase in overall response rate by 13.5% (taxane/anthracycline cohort) and by 11.8% (capecitabine cohort)

Risks
As compared to those receiving docetaxel alone, patients in the bevacizumab-containing arms experienced

- A higher incidence of serious adverse events (requiring medical intervention, hospitalization or resulting in death)
- A higher incidence of NCI CTC grade 3 through 5 adverse events
- Unique adverse events attributable to bevacizumab (e.g., hypertension, proteinuria)
- 1.2 % bevacizumab related death for taxane/anthracycline and capecitabine cohorts
- No improvement in overall survival, with the hazard ratio favoring placebo arm for the taxane/anthracycline cohort

VOTE:

2. **Does the addition of bevacizumab to taxanes, anthracyclines or capecitabine represent a favorable risk/benefit analysis for the initial treatment of patients with metastatic breast cancer?**

Vote : ***Yes=1*** ***No = 12*** ***Abstain = 0***

- It was stated into the record by the Chair: "There is a correction to the text on Question #2 under Risks, the first sentence, it states as compared to those receiving docetaxel alone, the correction is that it should be as compared to those receiving chemotherapy alone because this trial involved more chemotherapy agents other than docetaxel alone."

- The Committee questioned whether the increase in PFS was clinically meaningful with most voting that the increase was not clinically meaningful. Committee members also were concerned over the 1.2% treatment-related deaths and felt that the risk/benefit ratio was not favorable, especially in 1st line treatment as is the setting.

- The one member who voted yes felt that the PFS improvement may have reached the clinically meaningful threshold in the capecitabine cohort; this member also noted that the trials were powered independently and therefore was not pleased with the way the question was written.

Please see the transcript for detailed discussion.

QUESTION # 3 (voting)

Avastin, in combination with paclitaxel, received accelerated approval for the first-line treatment of patients with HER2-negative, metastatic breast cancer on February 22, 2008, based on the results of the E2100 study, a randomized, multicenter, open-label trial of bevacizumab with paclitaxel or paclitaxel alone. The addition of bevacizumab to paclitaxel resulted in a 52% increase in progression-free survival [HR 0.48, (95% CI 0.39, 0.61); $p < 0.0001$] with an observed increase in median PFS time of 5.5 months, based on an independent radiographic review. There was no significant difference in overall survival between the two treatment arms, although the hazard ratio (0.87) favored the treatment arm. The tumor response rate was higher with bevacizumab plus paclitaxel as compared to paclitaxel alone (48.9% versus 22.2%).

As a condition of the accelerated approval, Genentech was required to submit data from two ongoing, placebo-controlled trials (AVADO and RIBBON1) to provide verification of the treatment effect on PFS and to provide additional information on the effects on overall survival. FDA's assessment of these two trials and results are summarized below:

- The AVADO and RIBBON 1 trials were well-conducted, placebo-controlled, double-blind trials.

- The improvement in PFS, as measured by the hazard ratio and as reflected in the differences in the median PFS between study arms in the AVADO and RIBBON 1 trials failed to confirm the magnitude of PFS improvement observed in the E2100 trial.

- The magnitude of treatment effect is clinically important because it is felt to be a measure of the delay in time to development of symptoms from tumor progression, which has to be weighed against drug toxicity that is present for the duration of treatment.

- The addition of bevacizumab to chemotherapy led to an increase in the incidence of serious adverse events, the incidence of NCI CTC grade 3-5 adverse events, and the development of unique toxicities of bevacizumab. Death related to bevacizumab was observed in 0.8 and 1.2% of the patients in the chemotherapy plus bevacizumab arm.

- No improvement in overall survival was observed. The hazard ratio for survival comparisons favors the placebo arm in the AVADO study and the taxane/anthracycline cohort of the RIBBON1 study.

VOTE:

3. Taking into consideration the totality of findings, and the responses to Questions 1 and 2 above, do the AVADO and RIBBON1 results provide confirmatory evidence of clinical benefit of bevacizumab in combination with paclitaxel for the initial treatment of MBC?

Vote : Yes=0 No = 13 Abstain = 0

- The Committee felt that data in the confirmatory studies was not compelling and did not confirm the results from the E2100 study. Committee members also noted that there may have been data

collection issues in the E2100 study and that there was discordance in the interpretation of radiographs. The one member who voted Yes for Question 2, felt that the data for capecitabine was more impressive than the data for paclitaxel and Avastin.

Please see the transcript for detailed discussion.

QUESTION # 4 (voting)

Accelerated approval regulation (21 CFR 601.40-46) requires that the Applicant conduct adequate and well-controlled studies to further define the degree of clinical benefit to patients. If the Applicant fails to meet these requirements, the Agency may, following a hearing, withdraw or modify approval.

The INDICATONS AND USAGE section of the Avastin package insert states:

> **"Metastatic Breast Cancer (MBC)**
> Avastin is indicated for the treatment of patients who have not received chemotherapy for metastatic HER2-negative breast cancer in combination with paclitaxel.
>
> The effectiveness of Avastin in HER2-negative, metastatic breast cancer was based on an improvement in progression free survival. There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin.
>
> Avastin is not indicated for patients with breast cancer that has progressed following anthracycline and taxane chemotherapy administered for metastatic disease."

If any Committee member answered "No" to question 3, then:

VOTE:

4. Should the indication for treatment of metastatic breast cancer be removed from the Avastin label?

Vote : ***Yes=12*** ***No = 1*** ***Abstain = 0***

- Committee members reiterated what had been previously stated in responses to Questions 1-3. The Committee felt that the confirmatory trials did not show a benefit in OS and the small benefit in PFS was not clinically meaningful. Members were also concerned over data collection and discordance in radiograph reading in the E2100 study.

- It was discussed that moving from Accelerated Approval to Regular Approval required a high bar to be met and this was not met.

- A few members felt that Avastin has activity in breast cancer in a subset population and that in the future, it should be determined which patients are benefiting and only these patients should be treated.

- The one member who voted no, expressed that language in the Avastin label "The effectiveness of Avastin in HER2-negative, metastatic breast cancer was based on an improvement in

progression free survival. There are no data demonstrating an improvement in disease-related symptoms or increased survival with Avastin" was sufficient to provide healthcare providers and patients with an understanding of benefits such that an informed choice could be made.

- It was also mentioned that the Sponsor should be commended for completing confirmatory studies.

Please see the transcript for detailed discussion.

QUESTION # 5 (discussion)

If any Committee member answered "No" to question 4, then:

DISCUSS:

5. **Please discuss what additional trials should be performed to verify the clinical benefit of Avastin in the treatment of HER2-negative, metastatic breast cancer.**

This question was not addressed.

Please see the transcript for detailed discussion

The meeting adjourned @ approximately 3:15 p.m.