Summary Review for Regulatory Action

Date	August 14, 2014
From	Amna Ibrahim MD
Subject	Division Director Summary Review
BLA # **Supplement #**	125085 301
Applicant Name	Genentech, Inc.
Date of Submission	April 24, 2014
PDUFA Goal Date	October 24, 2014
Proprietary Name / **Established (USAN) Name**	Avastin ® bevacizumab
Dosage Forms / Strength	Intravenous/ 100 mg/4 mL, single use vial; 400 mg/16 mL, single use vial
Proposed Indication(s)	Treatment of recurrent, persistent, or metastatic carcinoma of the cervix
Action/Recommended Action	Approval

Material Reviewed/Consulted OND Action Package, including:	Names of discipline reviewers
Medical Officer Review	Prowell, Tanya M
Statistical Review	Tang, Shenghui
Pharmacology Toxicology Review	NA
CMC Review/OBP Review	NA
Microbiology Review	NA
Clinical Pharmacology Review	NA
DDMAC	Toscano, Marybeth
DSI	NA
CDTL Review	McKee, Amy E
OSE/DMEPA	NA
OSE/DDRE	NA
OSE/DRISK	NA
Other	NA

OND=Office of New Drugs
DDMAC=Division of Drug Marketing, Advertising and Communication
OSE= Office of Surveillance and Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis
DSI=Division of Scientific Investigations
DDRE= Division of Drug Risk Evaluation
DRISK=Division of Risk Management
CDTL=Cross-Discipline Team Leader

1. Introduction

Avastin, BLA 125085, initially approved in 2004, has been approved for multiple other indications as a single agent or in combination with other chemotherapeutic agents. Other malignancies for which Avastin is approved are metastatic colorectal cancer, non-small cell lung cancer, glioblastoma, and metastatic renal cell cancer. It also received an accelerated approval for metastatic breast cancer but this indication was later withdrawn due to lack of confirmation of clinical benefit.

This sBLA includes data from Study GOG-0240, for Avastin in the treatment of women with persistent, recurrent, or metastatic carcinoma of the cervix.

2. Background

Patients with metastatic or recurrent cervical cancer have a relatively short survival. Cisplatin is one of the more active and most used agents for cervical cancer, but not all patients are able to receive it due to its expected toxicity. Topotecan and paclitaxel are some of the other active agents in the treatment of cervical cancer. In the submitted trial, two chemotherapy regimen, cisplatin plus paclitaxel; and topotecan plus paclitaxel were studied in an add-on design with Avastin (see details of design in section 7). An improvement of 3.9 months in median overall survival (OS) was observed in Study GOG-0240, which was conducted mainly in the US.

3. CMC/Device

No data was submitted. Applicant's request regarding the categorical exclusion from an Environmental Assessment was approved.

4. Nonclinical Pharmacology/Toxicology

No data was submitted.

5. Clinical Pharmacology/Biopharmaceutics

No data was submitted.

6. Clinical Microbiology

No data submitted.

7. Clinical/Statistical-Efficacy

The findings from the multicenter Study GOG 0240 form the basis of this supplement. This phase III, randomized, open-label, multicenter study in patients with persistent, recurrent, or stage IVB carcinoma of the cervix was designed to evaluate the following efficacy parameters:

- To determine whether the addition of bevacizumab to chemotherapy improves OS
- To determine whether the regimen of topotecan and paclitaxel (non-platinum) improves OS in comparison with the standard cisplatin and paclitaxel regimen

Eligible patients had persistent, recurrent, or Stage IVB carcinoma of the cervix, with no prior chemotherapy (other than as a sensitizer with radiation) or anti-VEGF treatment. A total of 452 patients were randomized (1:1:1:1) to receive one of the following regimens:

- paclitaxel and cisplatin
- paclitaxel and cisplatin with Avastin
- paclitaxel and topotecan
- paclitaxel and topotecan with Avastin.

The primary endpoint was overall survival for both comparisons. There was an absolute improvement of 3.9 months [Hazard Ratio (HR) 0.74 (95% CI 0.58; 0.94)] in median overall survival in the Avastin + chemotherapy group when compared to chemotherapy alone for the first comparison. Please see table 1. The response rates were also improved.

Table 1: Efficacy Results: Chemotherapy versus Chemotherapy + Avastin

	Chemotherapy (n=225)	Chemotherapy + Avastin (n=227)
Overall Survival		
Median (months)[a]	12.9	16.8
Hazard ratio [95% CI]	0.74 [0.58;0.94] (p-value[b] = 0.0132)	

[a] Kaplan-Meier estimates.
[b] log-rank test (stratified).

For the other efficacy comparison, the superiority of the non-platinum regimen was not demonstrated. The results for the comparison of the topotecan-containing regimen to the platinum-containing regimen are noted. The HR was 1.15 [0.91, 1.46] p-value=0.23, favoring the cisplatin-containing regimen. Please see table 2.

Table 2: Efficacy Results: Platinum Doublet versus Nonplatinum Doublet

	Topotecan + Paclitaxel +/- Avastin (n=223)	Cisplatin + Paclitaxel +/- Avastin (n=229)
Overall Survival		
Median (months)[a]	13.3	15.5
Hazard ratio [95% CI]	1.15 [0.91, 1.46] p-value=0.23	

[a] Kaplan-Meier estimates

The HRs for the two chemotherapy (topotecan-containing regimen and the cisplatin-containing) regimens compared to chemotherapy with Avastin added on, were similar. Tatiana Prowell MD, concluded in her medical officer review that the paclitaxel/topotecan plus Avastin regimen may provide a reasonable alternative to platinum-based treatment for advanced cervical cancer patients who are platinum-intolerant.

In the statistical review signed by Shenghui Tang, PhD, it is stated that "The results from the GOG-0240 trial support the applicant's efficacy claims of bevacizumab. Data from the GOG-0240 trial indicates that there is a significant survival benefit in patients treated with bevacizumab plus chemotherapy compared to those treated with the chemotherapy alone. There is evidence of this benefit in subgroups that make up important prognostic factors. The final decision on the benefit-risk evaluation of bevacizumab in treatment of the proposed indication is deferred to the clinical review team." No major statistical issues were identified.

The clinical and statistics reviewers recommend approval of this sBLA.

8. Safety

Avastin initially approved in 2004, has been used extensively previously and the safety profile is well known. The adverse reaction profile seen in Study GOG 0240 was generally similar to that observed previously. Dr. Prowell states in her review "The adverse event profile is comparable to what has been observed with Avastin in other disease settings with the notable exception of: a) a more striking increase in GI perforation/fistula and non-GI fistula/abscess that likely reflects the additive risk of Avastin in the setting of prior radiotherapy for advanced cervical cancer; and b) an increased incidence of venous thromboembolic events for which patients with advanced pelvic malignancies are already at increased risk." Gastro-intestinal-vaginal fistulae were reported in 8.2% of Avastin-treated patients and 0.9% in control patients, all of whom had a history of prior pelvic radiation. This fistulae event rate is much higher than that seen in patients with other disease who were treated with Avastin. For example, an incidence of up to 2% gastrointestinal fistulae was reported in patients with metastatic colorectal cancer.

Deaths were fewer but grade 3 and 4 toxicity was increased on the Avastin-containing arms. Hemorrhage, hypertension, proteinuria, and wound healing complications are some of the

more serious complications of treatment with Avastin. There is an existing Boxed Warning in the label as well as additional Warnings and Precautions. Please see the label for details.

9. Advisory Committee Meeting

Not conducted.

10. Pediatrics

A full waiver has been granted because pediatric studies would be impossible or highly impracticable in this disease.

11. Other Relevant Regulatory Issues

- DSI Audits: Given the small number of patients at each site, nature of the primary endpoint, the magnitude of benefit and known safety profile of the drug, inspections were not recommended.
- Financial Disclosure: Per Dr. Prowell, "Disclosure of financial arrangements were requested from all clinical investigators who participated in GOG-0240. Off 255 investigators, 98.4% of investigators (251 out of 255) had no disclosable financial interest. Given the large number of clinical investigators who participated in the GOG-0240 trial, the potential bias resulting from patients enrolled by these 4 investigators (1.6%) who disclosed financial interests is unlikely to have substantially altered the findings of the trial or the regulatory risk/benefit assessment."
- OPDP reviewer Marybeth Toscano had no comments.

There are no other unresolved relevant regulatory issues

12. Labeling

Includes:

- Proprietary name: not applicable
- Physician labeling: all major issues were resolved during labeling meetings.
- Carton and immediate container labels: not applicable
- Patient labeling/Medication guide: not applicable

13. Decision/Action/Risk Benefit Assessment

- Regulatory Action:

Approval

- Risk Benefit Assessment

  The CDTL, Amy McKee MD, stated in her review that "This application demonstrated an improvement in overall survival, a highly objective and clinically meaningful outcome measure, as the primary endpoint, particularly in a disease with a historical median overall survival of less than 12 months and a treatment that is known to be associated with substantial, and at times fatal, toxicity". I agree with Dr. McKee's assessment. There are no unresolved issues.

- Recommendation for Postmarketing Risk Evaluation and Mitigation Strategies

  None.

- Recommendation for other Postmarketing Requirements and Commitments

  None.

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/s/

AMNA IBRAHIM
08/14/2014