

Submitted by:

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NCCN Guidelines Panel: Ovarian Cancer

On behalf of Genentech, I respectfully request the NCCN Ovarian Cancer Guideline Panel to review the enclosed data for the use of Avastin® (Bevacizumab) in women with recurrent ovarian, primary peritoneal, or fallopian tube cancer.

Specific Changes: Consider updating page MS-14 which currently states "Several trials are assessing combination therapy with bevacizumab for recurrent ovarian cancer (i.e., OCEANS, AURELIA)." as results from these trials are now available. Consider data from the OCEANS and AURELIA trials for updates to Acceptable Recurrence Therapies on page OV-E.

FDA Clearance: FDA has not approved Avastin in combination with chemotherapy for the treatment of either ovarian, primary peritoneal, or fallopian tube cancers. Please refer to the enclosed prescribing information for the full FDA-approved indications and safety information.¹

Rationale: Results of the OCEANS and AURELIA Phase III trials were recently published and/or presented at the American Society of Clinical Oncology (ASCO) Annual Meeting held June 1-5, 2012.

OCEANS: platinum-sensitive recurrent ovarian cancer

Results of OCEANS, a randomized, double-blind, placebo-controlled Phase III trial of chemotherapy with or without Avastin in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer, have been published and an updated safety analysis was recently presented at the ASCO annual meeting.^{2,3} The study met its primary endpoint of significantly improving median progression free survival (PFS) in patients treated with Avastin in combination with gemcitabine and carboplatin versus placebo in combination with gemcitabine and carboplatin, respectively.² Grade ≥ 3 adverse events included neutropenia, hypertension, proteinuria, arterial/venous thromboembolic events (ATEs), non-central nervous system bleeding, congestive heart failure, and wound healing complications. No GI perforations were noted in either arm during treatment, but 2 GI perforations occurred 69 days after the last Avastin dose in the Avastin-containing arm. The updated safety analysis added 11 months of follow-up and safety findings were similar to that seen at the time of the original PFS analysis.³

AURELIA: platinum-resistant, recurrent ovarian cancer

AURELIA is a randomized Phase III trial evaluating Avastin combined with chemotherapy for platinum-resistant recurrent ovarian, primary peritoneal, or fallopian tube cancer. The study met the primary endpoint of PFS improvement in favor of Avastin + chemotherapy versus chemotherapy alone.⁴ Grade ≥ 3 adverse events that occurred more frequently in the Avastin arm compared with the chemotherapy alone arm included hypertension, proteinuria, GI perforation, fistula formation, and ATEs. In addition, Grade ≥ 3 peripheral sensory neuropathy and hand-foot syndrome occurred at a higher incidence in the Avastin arm.

Additional Phase II studies (N ≥ 25) of Avastin in recurrent ovarian cancer are cited for your reference.⁵⁻¹⁴

Respectfully submitted,



Cited and Enclosed References(copyright-paid where applicable):

1. Aghajanian C, Blank SV, Goff BA, et al. OCEANS: a randomized, double-blind, placebo-controlled Phase III trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent epithelial ovarian, primary peritoneal, or fallopian tube cancer. *J Clin Oncol* 2012;30(17):2039-2045.
2. Aghajanian C, Blank SV, Goff B, et al. An updated safety analysis of OCEANS, a randomized, double-blind, phase III trial of gemcitabine (G) and carboplatin (C) with bevacizumab (BV) or placebo (PL) followed by BV or PL to disease progression (PD) in patients with platinum-sensitive (Plat-S) recurrent ovarian cancer.. Presented at the American Society of Clinical Oncology 2012 Annual Meeting in Chicago, IL; June 1-5, 2012. ASCO poster presentation #LBA5054.
3. Pujade-Lauraine E, Hilpert F, Weber B, et al. AURELIA: a randomized Phase III trial evaluating bevacizumab combined with chemotherapy for platinum-resistant recurrent ovarian cancer. Presented at the American Society of Clinical Oncology 2012 Annual Meeting in Chicago, IL; June 1-5, 2012. ASCO Oral presentation #LBA5002.
4. Avastin® Prescribing Information

Additional Phase II studies (N≥25)

5. Burger RA, Sill MW, Monk BJ, et al. Phase II trial of bevacizumab in persistent or recurrent epithelial ovarian cancer or primary peritoneal cancer: a Gynecologic Oncology Group Study. *J Clin Oncol* 2007;25:5165-5171.
6. Cannistra SA, Matulonis UA, Penson RT, et al. Phase II study of bevacizumab in patients with platinum-resistant ovarian cancer or peritoneal serous cancer. *J Clin Oncol* 2007;25:5180-5186.
7. Chambers SK, Clouser MC, Baker AF, et al. Overexpression of tumor vascular endothelial growth factor A may portend an increased likelihood of progression in a phase II trial of bevacizumab and erlotinib in resistant ovarian cancer. *Clin Cancer Res* 2010;16:5320-5328.
8. Eisenhauer E, Zanagnolo V, Cohn D, et al. A Phase II study of gemcitabine, carboplatin and bevacizumab for the treatment of platinum-sensitive recurrent ovarian cancer. Presented at the 42nd Annual Meeting of the Society of Gynecologic Oncologists in Orlando, Florida; March 6-9, 2011. SGO Abstract and Poster #69.
9. Garcia AA, Hirte H, Fleming G, et al. Phase II clinical trial of bevacizumab and low-dose metronomic oral cyclophosphamide in recurrent ovarian cancer: a trial of the California, Chicago, and Princess Margaret Hospital phase II consortia. *J Clin Oncol* 2008;26:76-82.
10. Kohn EC, Lee J, Annunziata CM, et al. A Phase II study of intermittent sorafenib with bevacizumab in bevacizumab-naïve epithelial ovarian cancer (EOC) patients. *J Clin Oncol* 2011;29.ASCO Abstract #5019.
11. McGonigle KF, Muntz HG, Vuky J, et al. Combined weekly topotecan and biweekly bevacizumab in women with platinum-resistant ovarian, peritoneal, or fallopian tube cancer. *Cancer* 2011;117:3731-3740.
12. Morgan R, Oza AM, Qin R, et al. A Phase II trial of temsirolimus and bevacizumab in patients with endometrial, ovarian, hepatocellular carcinoma, carcinoid, or islet cell cancer: ovarian cancer (OC) subset-a study of the Princess Margaret, Mayo, Southeast Phase II, and California cancer (CCCP) N01 Consortia NCI#8233. *J Clin Oncol* 2011;29.ASCO Abstract #5015.
13. Tillmanns TD, Lowe MP, Schwartzberg LS, et al. A Phase 2 study of bevacizumab with nab-paclitaxel in patients with recurrent, platinum-resistant primary epithelial ovarian or primary peritoneal carcinoma. Presented at the 46th Annual Meeting of the American Society of Clinical Oncology in Chicago, IL; June 4-8, 2010. ASCO Abstract and Poster #5009.
14. Wenham R, LaPolla J, Hui-Yi L, et al. Phase II trial of docetaxel and bevacizumab in recurrent ovarian cancer within 12 months of prior platinum-based chemotherapy. *Gynecol Oncol* 2011;120(suppl 1):S83-S84. SGO Abstract #192.