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NCCN Guidelines Panel: Ovarian Cancer

On behalf of Genentech, Inc., I respectfully request the NCCN Ovarian Cancer Guideline Panel to review the updated Avastin® (bevacizumab) prescribing information, which includes a new FDA-approved indication for the treatment of patients with platinum-sensitive ovarian cancer, and the enclosed label enabling OCEANS and GOG-0213 studies.

Specific Changes:

- Please consider for your updating purposes the results from the Phase III OCEANS and GOG-0213 studies and the new FDA-approved indication for Avastin in platinum-sensitive ovarian cancer.
    - Coleman RL, Brady M, Herzog T, et al. A phase III randomized controlled clinical trial of carboplatin and paclitaxel alone or in combination with bevacizumab followed by bevacizumab and secondary cytoreductive surgery in platinum-sensitive, recurrent ovarian, peritoneal primary and fallopian tube cancer (Gynecologic Oncology Group 0213). *Gynecol Oncol* 2015;137:3-4. Presented at: 46th SGO Annual Meeting on Women's Cancer; March 28–31, 2015, 2015; Chicago, IL. Abstract 3.
    - Aghajanian C, Goff B, Nycum LR, et al. Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. *Gynecol Oncol.* Oct 2015;139(1):10-16.
    - Aghajanian C, Goff B, Nycum LR, et al. Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. Gynecol Oncol. Oct 2015;139(1):10-16 [63].

FDA Clearance:

- Avastin either in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, followed by Avastin as a single agent was FDA-approved for the treatment of patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer on December 6, 2016.
- Please refer to the prescribing information for a full listing of FDA-approved indications and safety information.
    - Full Avastin® prescribing information available at: https://www.gene.com/download/pdf/avastin_prescribing.pdf

Rationale:

- The FDA approval of Avastin, either in combination with carboplatin and paclitaxel or in combination with carboplatin and gemcitabine, in patients with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer is based on results from the Phase III studies of GOG-0213 and OCEANS.
- Results from OCEANS and GOG-0213 were previously submitted.[1,2]

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- **OCEANS**
  - OCEANS is a randomized, Phase III, multicenter, double-blind, placebo-controlled trial in the patients (N=484) with platinum-sensitive recurrent epithelial ovarian, fallopian tube, or primary peritoneal cancer. The trial was designed to compare the effect of adding Avastin to carboplatin and gemcitabine followed by Avastin as a single agent until progression versus carboplatin and gemcitabine alone.
  - *Efficacy*:
    - The addition of Avastin to chemotherapy, followed by Avastin resulted in a statistically significant improvement in progression-free survival (PFS), the primary endpoint (hazard ratio [HR] 0.48, p<0.0001).
    - Median PFS for the Avastin-containing arm was 12.4 months vs 8.4 months for the chemotherapy alone arm.
    - Secondary investigator-assessed endpoints of overall response rate (ORR) (78.5% vs 57.4%) and duration of response (DoR) (10.4 months vs 7.4 months) were significantly higher in patients treated with Avastin (p<0.0001, for both).
    - Overall survival (OS) was similar in each arm of 32.9 months with chemotherapy alone and 33.6 months with the addition of Avastin.[3]
  - *Safety*:
    - Grade ≥3 adverse events in >5% of Avastin-treated patients included thrombocytopenia, non-central nervous system bleeding, hypertension, and proteinuria. Two cases of gastrointestinal perforation occurred in the Avastin-containing arm. One death was reported from intracranial hemorrhage in the Avastin treatment arm
- **GOG-0213**
  - GOG-0213 is a randomized, Phase III, multi-centered, open-label trial in patients (N=674) with platinum-sensitive, recurrent ovarian, primary peritoneal, and fallopian tube cancer. The trial was designed to (1) evaluate the efficacy and safety of adding Avastin to chemotherapy (carboplatin plus paclitaxel), followed by Avastin maintenance and (2) evaluate the effect of secondary cytoreductive surgery followed by chemotherapy.
  - *Efficacy*:
    - For overall survival, the primary endpoint, the median was approximately 42 months in the Avastin plus chemotherapy arm vs 37 months in the chemotherapy alone arm. The hazard ratio was 0.82 (0.68, 0.996), based on stratification by platinum-free interval. Stratification by treatment-free interval led to a hazard ratio of 0.84 (0.69, 1.01).
    - There was a statistically significant improvement in PFS (secondary endpoint) with the addition of Avastin to chemotherapy (HR 0.61, p<0.0001). Median PFS for the Avastin plus chemotherapy arm was 13.8 months vs 10.4 months for the chemotherapy alone arm.
  - *Safety*:
    - Grade ≥3 adverse events in >5% of patients treated with Avastin plus chemotherapy included infection, neutropenia, febrile neutropenia, hypertension, proteinuria, and joint pain. Grade ≥2 neuropathy was similar for the Avastin plus chemotherapy arm and chemotherapy alone arm (20% and 19%, respectively). Gastrointestinal perforation, fistula, or abscess of any grade occurred in 15% and of Grade ≥3 severity occurred 2% of Avastin-treated patients. There were 9 treatment-related deaths in the Avastin-treated arm, which included non-gastrointestinal infections (n=2), myelodysplasia (n=1), secondary malignancy (n=1), and unspecified (n=5).

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- In addition to OCEANS and GOG-0213, published clinical data evaluating the efficacy and safety of Avastin in patients with platinum-sensitive ovarian cancer exist. However; OCEANS and GOG-0213 support this indication.

Respectfully submitted,

Krupa Parekh, Pharm.D.

References:

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;30:2039-2045.
2. Aghajanian C, Goff B, Nycum LR, et al. Final overall survival and safety analysis of OCEANS, a phase 3 trial of chemotherapy with or without bevacizumab in patients with platinum-sensitive recurrent ovarian cancer. Gynecol Oncol. Oct 2015;139(1):10-16 [63].
3. Coleman et al. Gynecol Oncol 2015;137:3-4. Presented at: 46th SGO Annual Meeting on Women's Cancer; March 28–31, 2015, 2015; Chicago, IL. Abstract 3.

Supplemental Reference:

- Coleman RL, Brady MF, Herzog TJ, et al. Bevacizumab after bevacizumab in platinum-sensitive recurrent ovarian cancer: A subgroup analysis of GOG0213. *J Clin Oncol* 2016;34(15 suppl). Presented at: American Society of Clinical Oncology Annual Meeting; June 3–7, 2016; Chicago, IL. Abstract 5523.

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