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NCCN Ovarian Cancer Panel

Re: Request for review of clinical data and recommendation to add Avelumab in the NCCN Clinical Practice Guidelines in Oncology® - Ovarian Cancer including Fallopian Tube Cancer and Primary Peritoneal Cancer (OC)

On the behalf of EMD Serono, Inc. and Pfizer Inc., I respectfully request the NCCN Ovarian Cancer Panel to consider addition of Avelumab, a programmed death ligand-1 (PD-L1) blocking antibody, as a potential treatment option for recurrent/refractory Ovarian Cancer, based on results from the JAVELIN Solid Tumor Phase Ib study led by Dr. Disis.[1]

Suggested Changes: We respectfully ask the NCCN Panel to consider the following additions:

- **Principles of Systemic Therapy**:
  - **"Acceptable Recurrence Therapies for Epithelial Ovarian Cancer (including LCOH)/Fallopian Tube/Primary Peritoneal Cancer" (5 of 8)**
    - **Under Platinum-Resistant Disease**
      - Add Avelumab (please note that this is not a cytotoxic therapy)
  - **"Acceptable Recurrence Therapies for Epithelial Ovarian Cancer (including LCOH)/Fallopian Tube/Primary Peritoneal Cancer" (6 of 8)**
    - **Immunotherapy (new category recommended)**
      - Add Avelumab

FDA Clearance: Avelumab (BAVENCIO®) is approved by the FDA for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma (MCC) and for the treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy. These indications are approved under accelerated approval based on tumor response rate and duration of response. Continued approval for these indications may be contingent upon verification and description of clinical benefit in confirmatory trials.[2]

Rationale: Avelumab, a programmed death ligand-1 (PD-L1) blocking antibody, was recently investigated in heavily pre-treated recurrent/refractory (R/R) stage III and IV Ovarian Cancer patients whose disease had progressed within 6 months of platinum-based therapy or after subsequent therapy in previously relapsed patients (n=124, in the JAVELIN Solid Tumor trial (NCT01772004)).[1]

In the largest immunotherapy-treated OC cohort to date, 124 R/R ovarian cancer patients fulfilling the above-mentioned criteria received avelumab intravenously at a dose of 10 mg/kg over 60 min every two weeks.[1] Patient enrollment was not based on PD-L1 expression, histology, BRCA mutation status or CA 125 concentration. Most of these patients were heavily pre-treated, with 65.3% receiving ≥3 prior anticancer therapies.[1] Median duration of treatment was 12 weeks and median follow-up was 12.4 months. Approximately 13.7% of patients were still on the treatment at the time of analysis.[1]

Primary objective of this study was to assess safety and tolerability of Avelumab; secondary objectives included best overall response by RECIST v1.1, progression-free survival (PFS), and overall survival (OS).[1] Efficacy analyses indicated that 9.7% (5.1% – 16.3%) of patients achieved an objective response and disease control rate (DCR) was 54%.[1] At the time of data cut-off, 50% of the responses were ongoing (median follow-up: 12.4 months).[1] Median OS was 10.8 months (6.7 – 16.1) and OS rate at 12 months was 44.3% (31.5% – 56.4%).[1] Treatment-related adverse events (TRAE) occurred in 66.1% of patients, including 6.5% with Grade ≥3 TRAEs. The most common TRAEs (all grades) in R/R ovarian cancer patients were fatigue (13.7%), infusion-related reactions (12.1%) and nausea (9.7%).[1] There were two grade 4 TRAEs with increased lipase (n=1) and hyperglycemia (n=1) at the time of data cut-off.[1] Ten patients (8.1%) discontinued treatment due to a TRAE. Three patients (2.4%) had grade ≥3 immune-mediated TRAEs including arthritis, colitis and myositis.[1]

A manuscript of this study is in preparation for a peer-reviewed publication.

Avelumab is also currently being investigated in two pivotal Phase III studies for Ovarian Cancer: a) relapsed/refractory OC population (n=546, NCT02580058) and b) frontline/newly diagnosed OC population (n=951, NCT02718417). Meanwhile, given the high unmet medical need in relpased/refractory OC population and gap in time between study read-outs, we would urge the panel to consider the addition of Avelumab as a potential treatment option for R/R OC patients whose disease has progressed despite multiple (≥1) prior lines of anticancer therapies for locally advanced/metastatic disease.

Sincerely,

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On the behalf of

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Julia Perkins Smith, MD
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References (**enclosed**):

1. Disis ML, et al. Avelumab (MSB0010718C; anti-PD-L1) in patients with recurrent/refractory ovarian cancer from the Javelin Solid Tumor phase Ib trial: safety and clinical activity. DOI: 10.1200/JCO.2016.34.15_suppl.5533 Journal of Clinical Oncology 34, no. 15_suppl (May 2016) 5533-5533.
2. BAVENCIO™ (avelumab) prescribing information. EMD Serono, Inc. https://www.bavencio.com/en_US/document/Prescribing-Information.pdf
3.