Kirk Taylor, MD
EMD Serono, Inc.
One Technology Place, Rockland, MA 02370
781-490-0455
kirk.taylor@emdserono.com

August 11, 2020

Dear NCCN Gestational Trophoblastic Neoplasia Panel Members,

On the behalf of EMD Serono, Inc, we respectfully request the NCCN Guideline Panel for Gestational Trophoblastic Neoplasia to review the enclosed information for the inclusion of avelumab, a programmed death ligand-1 (PD-L1) blocking antibody, as a monotherapy option for patients with chemotherapy-resistant gestational trophoblastic tumors (GTT).

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

- **Principles of Systemic Therapy – High Risk GTN: Therapy for Methotrexate-Resistant GTN (GTN-B 5 of 6)**:
  - **Additional agents/regimens shown to have some activity in treating multiagent chemotherapy-resistant GTN:**
    - Add Avelumab to PD-1/PD-L1 inhibitors

- **Principles of Systemic Therapy – Intermediate Trophoblastic Tumor (PSTT and ETT) (GTN-B 6 of 6)**:
  - **Additional agents/regimens shown to have some activity in treating multiagent chemotherapy-resistant GTN:**
    - Add Avelumab to PD-1/PD-L1 inhibitors

FDA Clearance[1]:
Avelumab (BAVENCIO®) is indicated for the treatment of adults and pediatric patients 12 years and older with metastatic Merkel cell carcinoma. This indication is approved under accelerated approval based on tumor response rate and duration of response. Continued approval for this indication may be contingent upon verification and description of clinical benefit in confirmatory trials.

Avelumab is also indicated for the maintenance treatment of patients with locally advanced or metastatic urothelial carcinoma (UC) that has not progressed with first-line platinum-containing chemotherapy as well as the treatment of patients with locally advanced or metastatic 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.

Avelumab in combination with axitinib is indicated for the first-line treatment of patients with advanced renal cell carcinoma.

Rationale: Avelumab, a programmed death ligand-1 (PD-L1) blocking antibody is being studied in women with gestational trophoblastic tumors (GTT) resistant to chemotherapy as part of the TROPHIMMUN study (NCT03135769), a Phase 2, multicenter trial. Results from Cohort A (patients resistant to single-agent chemotherapy) was presented earlier this year at ASCO 2020 (Abstract #LBA 6008)[2] and recently published by You et al, in the Journal of Clinical Oncology.[3]

EMD Serono
One Technology Place
Rockland, MA 02370
Tel. +01.800.283.8088
Emdserono.com

Patients in Cohort A included women (n=15) between the ages of 23-55 years (median 34 years); with 53.3% stage I disease and 46.7% stage III disease (lung); and with the following FIGO scores – 0-4 (33.3%), 5-6 (46.7%), and ≥7 (20%). 27% of patients had a baseline hCG > 1000 IU/L, 100% of patients had received prior methotrexate, and one patient (7%) also received prior actinomycin D.

At data cutoff (May 2020), the median duration of follow-up was 25 months and the median number of avelumab cycles administered was 8 (range 2-11). In these patients, 46.7% of patients had hCG normalization during avelumab treatment and one additional patient subsequently had a normalized hCG level after discontinuing avelumab.

After a median follow-up of 29 months, no patient whose hCG level was normalized had a relapse after avelumab was discontinued. There was no impact of baseline FIGO score, baseline hCG, or disease stage on the likelihood of hCG normalization. One patient subsequently had a successful pregnancy. Median resistance-free survival (RFS) has not been reached (95% CI, 1.9 months to not reached) with a 4-month-RFS of 73.3% (95% CI, 43.6-89.0) and no deaths occured during this study.

Treatment-related adverse events occured in 93.3% of population (any grade) and the most common TRAEs were fatigue (33.3%), nausea/vomiting (33.3%) and infusion-related reactions (26.7%). Two patients (13.3%) had a serious AE: grade 2 ovarian cyst and grade 3 uterine bleeding, which were both determined to be unrelated to treatment. Immune-related AEs of any grade occured in 3 patients (20%): hyperthyroidism (13.3%) and hypothyroidism (6.7%). No patient had an avelumab dose reduction or delay for >48 hours, and no patient discontinued avelumab because of toxicity.

Given the need for new and innovative treatments in GTN, in particular treatments that may allow patients to minimize the toxic effects of chemotherapy without compromising efficacy, we greatly appreciate the Panel's thorough consideration of the data for avelumab as a potential treatment option as monotherapy for chemotherapy-resistant GTN patients.

Sincerely,

DocuSigned by:
Kirk Taylor
7A5185F85F374AB...

Kirk Taylor, MD
Senior Vice President, North America Medical Affairs
EMD Serono, Inc.

References (**enclosed**):

1. BAVENCIO™ (avelumab) prescribing information. EMD Serono, Inc. https://www.emdserono.com/us-en/pi/bavencio-pi.pdf (accessed on July 27, 2020)
2. You et al. Avelumab in patients with gestational trophoblastic tumors resistant to monochemotherapy: Final outcomes of TROPHIMMUN phase II trial, cohort A.J Clin Oncol 38: 2020 (suppl; abstr LBA6008).
3. You et al. Avelumab in Patients with Gestational Trophoblastic Tumors with Resistance to Single-Agent Chemotherapy: Cohort A of the TROPHIMMUN Phase II Trial. DOI: 10.1200/JCO.20.00803 *Journal of Clinical Oncology.* Published online July 27, 2020.