May 9, 2017

Joseph Leveque, MD
EMD Serono, Inc.
One Technology Place, Rockland, MA 02370
Phone: (781) 681 2240
Email: Joseph.Leveque@emdserono.com

NCCN Bladder Cancer Panel

Re: Request for review of clinical data and recommendation for avelumab in the NCCN Clinical Practice Guidelines in Oncology® - Bladder Cancer

On behalf of EMD Serono, Inc. and Pfizer Inc, I respectfully request the NCCN Bladder Cancer Panel to review the enclosed FDA approved label[1] and clinical trial data[2,3] in support of avelumab as a systemic therapy option for locally advanced or metastatic urothelial carcinoma (mUC).

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

- **"Principles of Systemic Therapy" (BL-G 2 of 4)**:
  - **"Subsequent systemic therapy", under "Standard regimens": Add Avelumab**[1-3]

FDA Clearance: Avelumab (BAVENCIO®) is approved by the FDA for the treatment of patients with locally advanced or metastatic urothelial carcinoma (mUC) in addition to metastatic Merkel cell carcinoma.[1] Indication language specific to UC is as follows:

Patients with locally advanced or metastatic urothelial carcinoma (UC) who:
- Have disease progression during or following platinum-containing chemotherapy
- Have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy

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.

Rationale:

The efficacy and safety of BAVENCIO was demonstrated in the UC cohorts of the JAVELIN Solid Tumor trial, an open-label, single-arm, multi-center study that included 242 patients with locally advanced or metastatic UC with disease progression on or after platinum-containing chemotherapy or who had disease progression within 12 months of treatment with a platinum-containing neoadjuvant or adjuvant chemotherapy regimen.[2,3]

Of 226 patients treated with avelumab with a minimum of 13 weeks of follow-up, 44% of patients had non-bladder urothelial carcinoma including 23% of patients with upper tract disease, and 83% of patients had visceral metastases.[1] Enrolled patients received avelumab at 10mg/kg by 1-hour intravenous infusion every 2 weeks. Among patients with at least 6 months follow-up (N=161), the overall response rate (ORR) was 16.1% (95% confidence interval [CI], 10.8, 22.8), with a complete response in 5.6% of patients and a partial response in 10.6% of patients.[1] Among patients with at least 13 weeks of follow-up (N=226), the ORR was 13.3% (95% CI, 9.1, 18.4), with a complete response in 4.0% of patients and a partial response in 9.3% of patients.[1] At both follow-up time-points, median DOR was not estimable, ranging from 1.4+ to 17.4+ months.[1] Among the total 30 responding patients followed for a minimum of 13 weeks, 22 (73%) had an ongoing reponse of 6 months or longer and 4 patients (13%) had ongoing responses of 12 months or longer. Among the total 26 responding patients followed for at least 6 months, 22 (85%) had ongoing responses of 6 months or longer and 4 patients (15%) had ongoing response of 12 months or longer.[1]

Based on data presented at ASCO GU in February 2017, 17.6% of 153 patients (≥6 months of follow-up) achieved objective response, 88.9% of which was ongoing at the time of data cut-off.[2] The durable response rate (defined as a response lasting for at least 6 months) at 24 weeks was 92.0% using Kaplan-Meir estimates.[2] Median progression-free survival (PFS) was 6.4 weeks and the 24-week PFS rate was 22.6%; the 6-month OS rate was 54.5% but OS data are not mature at this point.[2]

The most common adverse reactions (≥20%) reported in the UC cohorts of the JAVELIN Solid Tumor trial were fatigue, infusion-related reaction, musculoskeletal pain, nausea, decreased appetite, and urinary tract infection. The most frequent serious adverse reactions (≥2%) were urinary tract infection/urosepsis, abdominal pain, musculoskeletal pain, creatinine increased/renal failure, dehydration, hematuria/urinary tract hemorrhage, intestinal obstruction/small intestine obstruction, and pyrexia. Avelumab was permanently discontinued for Grade 1-4 adverse reactions in 12% of patients and temporarily discontinued in 29% of patients, excluding temporary dose interruption for infusion-related reactions where infusion was restarted the same day. Six percent of patients experienced an adverse event which led to death.[1] The warnings and precautions for BAVENCIO include immune-mediated adverse reactions (such as pneumonitis, hepatitis, colitis, endocrinopathies, nephritis and renal dysfunction, and other adverse reactions), infusion-related reactions and embryo-fetal toxicity.

Treatment of locally advanced or metastatic urothelial carcinoma (mUC) represents the second accelerated approval for Bavencio in the last 6 weeks. EMD Serono and Pfizer Inc. thank the Committee for considering the importance of having BAVENCIO available as a new treatment option for UC patients.

Sincerely,

DocuSigned by:
Joseph Leveque, MD
695C6952B7DF463...

Joseph Leveque, MD
Chief Medical Officer
EMD Serono, Inc.

On the behalf of

Joseph Leveque, MD
Chief Medical Officer
EMD Serono, Inc.

Julia Perkins Smith, MD
North America Medical Affairs Lead
Pfizer Oncology

References (**enclosed**):

1. BAVENCIO® (avelumab) prescribing information. EMD Serono, Inc. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761078s000lbl.pdf (accessed on May 9, 2017)
2. Patel M, et al. Avelumab in patients with metastatic urothelial carcinoma: pooled results from two cohorts of the phase 1b JAVELIN Solid Tumor trial. Presented at: 2017 Genitourinary Cancers Symposium; February 16-18, 2017; Orlando, FL. Abstract 330.
3. Apolo AB, et al. Avelumab, an anti-programmed death-ligand 1 antibody, in patients with refractory metastatic urothelial carcinoma: results from a multicenter, phase Ib study. J Clin Oncol. 2017 Apr 4, DOI: 10.1200/JCO.2016.71.6795.