Submitted by:
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NCCN Neuroendocrine and Adrenocortical Tumors Panel

Re: Request for review of clinical data and recommendation to add Avelumab in the NCCN Clinical Practice Guidelines in Oncology® - Neuroendocrine and Adrenocortical Tumors Panel

On behalf of EMD Serono, Inc. and Pfizer Inc., I respectfully request the NCCN Neuroendocrine and Adrenocortical Tumor Panel to consider addition of Avelumab, a programmed death ligand-1 (PD-L1) blocking antibody, as a treatment option for previously treated metastatic adrenocortical cancer patients based on the results of the JAVELIN Solid Tumor Trial (NCT01772004).[1]

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

- **AGT-5**
  - **Metastatic disease - treatments**
    - 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: adrenocortical cancer is a rare Neuroendocrine tumor with poor treatment options comprising cytotoxic treatments often associated with limited efficacy and high toxicity.[1] Avelumab, with or without concurrent use of mitotane, was investigated as a potential therapeutic option in previously treated metastatic adrenocortical cancer (mACC) patients as a part of the JAVELIN Solid Tumor phase 1b dose expansion cohort (n=50).[1]

Median age of these patients was 50 years (range: 21-71years). Most of these patients were heavily pre-treated with median number of prior lines of systemic therapies being 2 (range1-6) and 74% receiving at least 2 systemic therapies before enrollment in the expansion cohort. Median time since last progression was 0.92 months (range:0.33 months – 8.61 months). Median duration of avelumab treatment was 3.4 months (range, 0.5 to 24.8 months), and median follow-up was 16.5 months (range, 11.7 to 27.6 months).

Overall response rate was 6.0% (n=3. 95% CI, 1.3%-16.5%) in this heavily pre-treated population with a disease control rate of 48.0% (n=24). In patients who had received 1 (n=13), 2 (n=18), or≥3 (n=19) prior lines of systemic therapy since diagnosis, ORR was 15.4%, 5.6%, and 0%, respectively. Results were similar irrespective of the use of concomitant mitotane, which occurred in 50% of the cohort.

Median PFS was 2.6 months (95% CI, 1.4 to 4.0), and PFS rates at 6 months and 1 year were 20.9% (95% CI, 10.6% to 33.5%) and 8.7% (95% CI, 2.6% to 19.6%), respectively. Using immune-related criteria, median PFS was 3.8 months (95% CI, 2.4 to 5.5). Median OS was 10.6 months (95% CI, 7.4 to 15.0), and the 1-year OS rate was 43.4% (95% CI, 27.9% to 57.9%).

PD-L1 expression was evaluable in tumor samples from 42 patients (84%). At a 5% PD-L1 expression cutoff using Dako PD-L1 IHC 73-10 assay (Dako, Carpinteria, CA), ORR (95% CI) was 16.7% (2.1% to 48.4%) in PD-L1+ patients (n=12) vs 3.3% (0.1% to 17.2%) in PD-L1- patients (n=30), median PFS was 5.5 months (1.3 to 8.2) in PD-L1+ vs 1.7 months (1.4 to 4.0) in PD-L1- patients. Median OS was 14.4 (7.4 to 14.4) vs 10.6 (7.3 to NE) months, respectively. Findings were similar based on analyses of PD-L1 expression using a 1% cutoff.

All 50 patients (100.0%) had an AE of any grade; 41 patients (82.0%) had a treatment-related AE (TRAE). The most common TRAEs of any grade were nausea (n = 10; 20.0%), fatigue (n=9; 18.0%), hypothyroidism (n=7; 14.0%), and pyrexia (n=7; 14.0%). Five patients (10%) had an infusion-related reaction; all were grade 1 or 2. Eight patients (16.0%) had a grade 3 TRAE and no patient had a grade 4 or 5 TRAE. Reasons for treatment discontinuation (80%) were disease progression (n = 32 [64.0%]), AE (n = 5 [10.0%]), death (n = 3 [6.0%]).

In summary, in previously treated patients with metastatic ACC, avelumab demonstrated activity with acceptable safety profile as either a monotherapy or in combination with mitotane. Higher activity was demonstrated in patients with PD-L1+ tumors or with 1-2 prior lines of systemic therapies. We respectfully request the panel to consider addition of avelumab, with or without mitotane, as a potential treatment option in previously treated patients with metastatic adrenocortical cancer.

Sincerely,

DocuSigned by:
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On the behalf of

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References (**enclosed**):

1. Le Tourneau C, Hoimes C, Zarwan C et al. Avelumab in patients with previously treated metastatic adrenocortical carcinoma: phase 1b results from the JAVELIN solid tumor trial. Journal for ImmunoTherapy of Cancer; 2018;6:111. https://doi.org/10.1186/s40425-018-0424-9
2. BAVENCIO™ (avelumab) prescribing information. EMD Serono, Inc. https://www.bavencio.com/en_US/document/Prescribing-Information.pdf (accessed on February 22, 2019)