Submitted by:
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NCCN Non-Small Cell Lung Cancer/Malignant Pleural Mesothelioma/Thymomas and Thymic Carcinomas Panel

Re: Request for review of clinical data and recommendation to add Avelumab in the NCCN Clinical Practice Guidelines in Oncology® - Malignant Pleural Mesothelioma (MPM)

On the behalf of EMD Serono, Inc. and Pfizer Inc., I respectfully request the NCCN Non-Small Cell Lung Cancer/Malignant Pleural Mesotherlioma/Thymoma and Thymic Carcionomas Panel consider addition of Avelumab, a programmed death ligand-1 (PD-L1) blocking antibody, as a potential subsequent therapy option for MPM, based on the long-term follow-up of avelumab efficacy in MPM patient population from the JAVELIN Solid Tumor Phase Ib study led by Dr. Hassan.[1]

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

- **Principles of Systemic Therapy (MPM-A 1 of 2)**:
  - **Subsequent Therapy**
    - 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 has been studied in MPM population (histologically or cytologically confirmed mesothelioma that was unresectable and had progressed after prior platinum and pemetrexed treatment [as monotherapy or in combination]) with long-term follow-up data presented at recently-concluded ASCO 2018 (n=53, in the JAVELIN Solid Tumor trial (NCT01772004)).[1]

MPM patients included in the JAVELIN Solid Tumor trial were mostly: elderly (age≥65 years, 62.3%), had ECOG status of 1 (73.6%) and were heavily pre-treated with 37.9% receiving ≥3 prior medications with median of 2 (range:1-8). Epithelial histology was the most common (81.1%) with mixed histology observed in 11.3%. In terms of PD-L1 expression, 30.2% were deemed positive (≥5% of tumor cells) while 50.9% were deemed PD-L1 negative at that cut-off. We are reporting overall results with this submission.

In this 2L+ cohort, 53 patients were treated with avelumab over a median follow-up of 24.8 months (16.8 – 27.8 months). In these patients, avelumab demonstrated median PFS of 4.1 months (1.4-6.2 months), median OS of 10.9 months (7.5-21 months) and 12-month OS of 45.9% (31.9-58.5%).[1] ORR was 9.4% (3.1-20.7%) with disease control rate of 58.5% with a median duration of response of 15.2 months (11.1 – NE).[1] Of 48 patients evaluable for change in tumor size, 24 (50%) had a reduction in tumor size of any level.

Treatment-related adverse events (TRAEs) occured in 81.1% of population (any grade); however, grade 3+ TRAEs occured in 9.4% population comprising pneumonitis (n=2), blood creatine phosphokinase (n=1), colitis (n=1), type 1 diabetes mellitus (n=1). 12 patients (22.6%) has an immune-related TRAE of any grade and 3 out of 12 had a grade ≥3 TRAE. No treatment-related grade 5 AEs were observed in this cohort.

A manuscript of this study is in preparation for a peer-reviewed publication. Meanwhile, given the high unmet medical need in MPM population with no FDA-approved 2L+ treatment and median overall survival with 2L chemotherapy in clinical practice of approximately 5 months, we would urge the panel to consider the addition of Avelumab as a potential treatment option as a subsequent therapy for MPM patients (category 2A) whose disease has progressed despite multiple (≥1) prior lines of anticancer therapies.

Sincerely,

DocuSigned by:
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On the behalf of

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Julia Perkins Smith
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Julia Perkins Smith, MD
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Zhen Su, MD, MBA
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References (**enclosed**):

1. Hasan et al. Phase 1b Study of Avelumab in advanced previously treated mesothelioma: long-term follow-up from JAVELIN Solid Tumor. J Clin Oncol 36, 2018 (suppl; abstr 8563). http://abstracts.asco.org/214/AbstView_214_217639.html
2. BAVENCIO™ (avelumab) prescribing information. EMD Serono, Inc. https://www.bavencio.com/en_US/document/Prescribing-Information.pdf (accessed on June 11th, 2018)