



Submitted by:

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NCCN Kidney Cancer Panel

Re: Request for review of clinical data and recommendation to add Avelumab plus Axitinib in the NCCN Clinical Practice Guidelines in Oncology® - Kidney Cancer

On behalf of EMD Serono, Inc. and Pfizer Inc., I respectfully request the NCCN Kidney Cancer Panel to consider addition of avelumab plus axitinib as a potential preferred first-line (1L) treatment regimen for kidney cancer (Category 1) based on the first interim read-out of the phase 3 randomized JAVELIN Renal 101 study.¹⁻²

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

- **KID-3**
 - **First-Line Therapy (alphabetically by category and preference)**
 - Add Avelumab+Axitinib

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.³

Rationale: Simultaneous inhibition of the PD-1/PD-L1 and VEGFR/VEGF pathways had synergistic antitumor effects in a preclinical model.⁴ In addition, in the phase 1b JAVELIN Renal 100 (NCT02493751) study, avelumab, a programmed death ligand-1 (PD-L1) blocking antibody, in combination with axitinib, a VEGFR TKI, produced an objective response rate (ORR) of 58% (95% CI: 44.1%-71.3%) and disease control rate of 78% as a 1L treatment in patients with advanced renal cell carcinoma (aRCC, n=55).⁵

In ongoing phase 3 JAVELIN Renal 101 study, 886 aRCC patients were randomized to receive either avelumab+axitinib (ave+axi, n=442, 270 PD-L1+) or sunitinib (n=444, 290 PD-L1+).¹ Primary endpoints were PFS (as assessed by Independent Review Committee, IRC) and OS among patients with PD-L1+ tumors, defined as ≥1% immune cells (ICs). Key secondary end points were PFS and OS in the overall population, ORR, and safety. The trial accrued mostly in the North America and Western Europe (58%) with potential access to immunotherapy in the 2L setting, mimicking real-world treatment patterns faced by aRCC patients in the US.¹⁻² In



the overall population, other pertinent characteristics were male gender (72% in ave+axi & 78% in sunitinib), prior nephrectomy (80% in each arm), ECOG status of 0 (63% in each arm) and IMDC prognostic classification of either intermediate or poor risk (78% in each arm).¹

At the pre-planned interim analysis (data cut-off: June 20, 2018), there were 253 PFS events in PD-L1+ patients (396 in all-comers).¹ Median PFS for ave+axi arm were 13.8 months (11.1-NE) and 7.2 months in sunitinib arm (5.7-9.7) in PD-L1+ patients, yielding HR of 0.61 (95% CI: 0.475-0.790, p<0.001).¹ In the overall population, irrespective of the PD-L1 status, the median PFS was 13.8 months vs 8.4 months, respectively (HR: 0.69, 95% CI: 0.563-0.840, p<0.001).¹ PFS improved for ave+axi patients across all categories of IMDC risk classification, BMI or smoking status.¹ Median PFS2 (per investigator assessment) was not reached in ave+axi arm (19.9-NE) vs 18.4 months in sunitinib arm (15.7-23.6) yielding HR of 0.56 (95% CI: 0.421-0.735).² At the time of first interim analyses, overall survival data were immature with neither arm reaching median OS at the time of data cut-off (HR: 0.78, 95% CI: 0.554-1.08), indicating potentially significant impact of subsequent 2L therapies on OS.^{1,2} Moreover, survival rates based on all-cause death rates were 85.7% and 83.1% for ave+axi (median f/u of 12 months) and sunitinib (median f/u of 11.5 months), respectively.¹ Second-line use of PD-1/PD-L1 therapy in 66.7% (69.8% for all IOs) of patients in the sunitinib arm, high percentage of intermediate/poor risk by IMDC criteria and majority of enrollment in North America and Western Europe might have impacted survival rates.²

ORR (per IRC) in the all-comers population was 51.4% in ave+axi arm (46.6-56.1%) vs 25.7% in sunitinib arm (21.7-30%).¹ Response rates were 55.2% and 25.5% in PD-L1+ patients, respectively, with 4.4% patients in ave+axi achieving complete response over median follow-up (f/u) of 12 months. Median time-to-response was 2.6 months (range: 1.2-13.8 months) in ave+axi patients.¹

Treatment-related adverse events (TRAEs, any grade) occurred in 95% of ave+axi arm and 96% in sunitinib arm.² Serious TRAEs with grade 3+ occurred in 4% and 7% of patients enrolled in ave+axi and sunitinib arm, respectively.² TRAEs leading to discontinuation occurred in 4% and 8% of patients in ave+axi and sunitinib arms, respectively.² Immune-related adverse events occurred in 38.2% of ave+axi arm of which 9% of grade ≥3.¹ Infusion-related reactions occurred in 12.2%, with grade 3+ occurring in 1.6% of patients.¹

In summary, significant PFS benefit regardless of PD-L1 status or IMDC classification, markedly improved ORR and manageable safety profile make avelumab+axitinib a potentially preferred 1L therapeutic regimen (category 1) for aRCC patients.

Sincerely,

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On the behalf of

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References (enclosed):

1. Motzer R, Penkov K, Haanen J et al. Avelumab plus Axitinib versus Sunitinib for Advanced Renal Cell Carcinoma. *New Engl J med*, 2019; DOI: 10.1056/NEJMoa1816047 (accessed on February 20, 2019).
2. Choueiri T, Motzer R, Campbell M et al. Subgroup Analyses from Javelin Renal 101: Outcomes for Avelumab plus Axitinib versus Sunitinib in Advanced Renal Cell Carcinoma. <https://meetinglibrary.asco.org/record/169448/abstract> (accessed on February 20, 2019)
3. BAVENCIO™ (avelumab) prescribing information. EMD Serono, Inc. https://www.bavencio.com/en_US/document/Prescribing-Information.pdf (accessed on February 20, 2019)
4. Yasuda S, Sho M, Yamato I et al. Simultaneous blockade of programmed death 1 and vascular endothelial growth factor receptor 2 (VEGFR2) induces synergistic anti-tumour effect in vivo. *Clin Exp Immunol*. 2013 Jun; 172(3): 500–506.
5. Choueiri TK, Larkin J, Oya M et al. Preliminary results for avelumab plus axitinib as first-line therapy in patients with advanced clear-cell renal-cell carcinoma (JAVELIN Renal 100): an open-label, dose-finding and dose-expansion, phase 1b trial. *Lancet Oncology* 2018, 19: 451-60

