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NCCN Guidelines® Panel: Kidney Cancer

Dear Panel Members,

On behalf of Bristol-Myers Squibb Company, I respectfully request the NCCN Kidney Cancer Guidelines Panel to review the enclosed data for inclusion of OPDIVO® (nivolumab) for the treatment of advanced renal cell carcinoma (RCC) in patients who received prior systemic therapy. These data are being submitted in response to the standing request from NCCN for new clinical data.

Specific Changes: Please consider adding nivolumab to the list of subsequent therapies for the treatment of patients with relapsed or Stage IV and surgically unresectable, predominantly clear cell RCC.

FDA Clearance: The FDA has granted Breakthrough Therapy Designation to nivolumab for the potential indication of advanced or metastatic RCC.[1] Currently, nivolumab monotherapy has been approved in two solid tumor types: unresectable or metastatic melanoma (accelerated approval) and squamous non-small cell lung cancer (complete indications provided in the enclosed prescribing information).[2]

Rationale: A phase 3 trial in patients with advanced RCC was stopped because an assessment conducted by the independent Data Monitoring Committee concluded that the study met its primary endpoint, demonstrating superior overall survival (OS) in patients receiving OPDIVO compared to the control arm, everolimus. Findings from this phase 3 study were published in the New England Journal of Medicine and presented at the 2015 European Cancer Congress and are summarized below.[3] In addition, long term survival from Phase 1 and 2 studies in patients with advanced RCC are described below.[4,5]

Phase 3 BMS Study CA209-025: This is a phase 3, randomized (1:1), open-label study in patients with advanced or metastatic RCC (clear-cell component), previously treated with 1 to 2 antiangiogenic therapies (no more than 3 prior systemic therapies). Nivolumab 3mg/kg IV was administered every 2 weeks (N=406) and everolimus was administered as a daily dose of 10mg (N=397). The primary endpoint was OS; secondary endpoints included ORR, PFS, association of OS with PD-L1 tumor expression, and incidence of AEs. Demographic and clinical characteristics were balanced between treatment arms; the majority of patients (72%) received one prior antiangiogenic therapy for advanced RCC.[3]

Efficacy findings, highlights[3]:

- Median OS: 25 months (95% confidence interval [CI]: 21.8, not estimable) in the nivolumab arm, and 19.6 months (95% CI: 17.6, 23.1) in the everolimus arm (hazard ratio, 0.73; 98.5% CI: 0.57, 0.93; $P = .002$).
  - Median OS (95% CI) in the nivolumab arm: 21.8 (16.5, 28.1) months in patients with ≥1% PD-L1 expression (n=94), and 27.4 (21.4, not estimable) months in patients with <1% PD-L1 expression (n=276).
- ORR: 25% for nivolumab and 5% for everolimus (odds ratio 5.98; 95% CI: 3.68, 9.72; $P < .001$).
  - Partial responses were observed in 99 (24%), and 20 (5%) patients treated with nivolumab and everolimus, respectively. Complete responses were observed in 4 (1%) and 2 patients (<1%) patients treated with nivolumab and everolimus, respectively.
- Median PFS: 4.6 months (95% CI: 3.7, 5.4) for nivolumab and 4.4 months (95% CI, 3.7, 5.5) for everolimus (hazard ratio, 0.88; 95% CI: 0.75, 1.03; $P = .11$).

Safety findings, highlights[3]:

- Treatment-related AEs of any grade were reported in 79% (319/406) and 88% (349/397) of patients in the nivolumab and everolimus arms, respectively.
- Grade 3 or 4 treatment-related AEs were reported in 19% (76/406) of patients in the nivolumab arm, fatigue being the most common (2%); and 37% (145/397) of patients in the everolimus arm, anemia being the most common (8%).
- Discontinuations due to treatment-related AEs were reported in 8% (31/406) and 13% (52/397) of patients in the nivolumab and everolimus arms, respectively.
- No deaths from study-drug toxicity were reported in the nivolumab arm, and 2 deaths were reported in the everolimus arm.

Phase 2 BMS Study CA209-010[4]

A Phase 2 study in 168 patients with RCC (clear cell component) previously treated with 1-3 prior therapies (one of which was anti-angiogenic therapy) demonstrated 3-year survival rates (80% CI), of 33% (26, 41), 40% (32, 49), 33% (25, 41), in the nivolumab 0.3-, 2-, and 10 mg/kg treatment arms, respectively. In total, 73% of patients experienced treatment-related AEs, of which 7%, 17%, and 17% of patients in the 0.3-, 2-, and 10 mg/kg arms, respectively, were Grade 3. No Grade 4 treatment-related AEs, or deaths were reported.

Phase 1 BMS Study CA209-003[5]

A Phase 1 cohort expansion study which included 34 patients with treatment-refractory RCC (with clear-cell component), 45% of whom had received 3 or more prior systemic therapies, showed durable responses (median duration of response, 12.9 months) and 1-, 2-, and 3-year survival rates of 71%, 48%, and 44%, respectively. Grade 3-4 treatment-related AEs occurred in 18% of patients. No treatment-related deaths were reported.

The following resources are submitted in support of this proposed change. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of some of these publications/ presentations.

1. FDA Grants Opdivo Breakthrough Therapy Designation for Advanced Renal Cell Carcinoma. Bristol-Myers Squibb Company press release. 16 Sep 2015.
2. OPDIVO Prescribing Information
3. Motzer RJ, Escudier B, McDermott DF, et al. Nivolumab versus everolimus in advanced renal-cell carcinoma [published online ahead of print] September 25, 2015. *N Engl J Med*. DOI: 10.1056/NEJMoa1510665
4. Plimack ER, Hammers HJ, Rini BI et al. Updated Survival Results From a Randomized, Dose-Ranging Phase II study of Nivolumab in Metastatic Renal Cell Carcinoma. Poster presented at: 51st Annual American Society of Clinical Oncology (ASCO) Meeting; May 29-June 2, 2015; Chicago, IL, USA.
5. McDermott DF, Drake CG, Sznol M et al. Survival, Durable Response, and Long-Term Safety in Patients With Previously Treated Advanced Renal Cell Carcinoma Receiving Nivolumab. *J Clin Oncol*. 2015;33(18):2013-20.

Thank you for your consideration of this request.

Sincerely,

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Bristol-Myers Squibb Company