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January 25, 2021

Submission Request
National Comprehensive Cancer Network Panel: Kidney Cancer

Clinical Evidence in Support of Cabozantinib in Combination with Nivolumab in Patients with Kidney Cancer

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On behalf of Exelixis, we respectfully request the NCCN Guidelines Panel for Kidney Cancer review the following data as it considers potential changes to the guidelines related to the management of patients with previously untreated advanced renal cell carcinoma (aRCC).

Specific Changes:
Exelixis requests consideration of a *Category 1, Preferred Regimen* recommendation for cabozantinib in combination with nivolumab as a first-line treatment in patients with aRCC, regardless of International Metastatic RCC Database Consortium (IMDC) risk group.

FDA Clearance:
CABOMETYX was initially approved by the US Food and Drug Administration (FDA) in April 2016 for the treatment of patients with aRCC who had received prior anti-angiogenic therapy. Results from a study that compared CABOMETYX with sunitinib as first-line therapy served as the basis of FDA approval in December 2017 for the expanded indication of treatment of patients with aRCC. On January 2019, CABOMETYX was approved for the treatment of patients with hepatocellular carcinoma who have been previously treated with sorafenib. On January 22, 2021, CABOMETYX, in combination with nivolumab, was approved for first-line treatment of patients with aRCC.

Rationale:
Cabozantinib, in combination with nivolumab, is now FDA-approved for first-line treatment of patients with aRCC.[1]

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Clinical Evidence:[1]
CheckMate 9ER, a randomized, open-label, Phase 3 study (NCT03141177), evaluated the efficacy and safety of CABOMETYX combined with nivolumab vs. sunitinib in patients with previously untreated aRCC. The primary endpoint was progression-free survival (PFS) by blinded independent central review (BICR) and secondary endpoints included the following: overall survival (OS), objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors v1.1 by BICR, and safety.

A total of 651 patients were randomized and stratified by IMDC prognostic score, PD-L1 tumor expression, and geographic region to CABOMETYX 40 mg daily with nivolumab 240 mg IV every 2 weeks (n=323) or sunitinib 50 mg daily for 4 weeks on/2 weeks off (n=328). Treatment was given until disease progression or unacceptable toxicity. Median age was 61 years, and 23% and 77% of patients had Karnofsky performance status of 70-80% and 90-100%, respectively. Patient distribution by IMDC risk categories included 22% favorable, 58% intermediate, and 20% poor.

The trial demonstrated statistically significant improvements in PFS, OS, and ORR for patients receiving CABOMETYX in combination with nivolumab vs. sunitinib (see Table 1). PFS results were consistent across the pre-specified subgroups of IMDC risk categories and PD-L1 status.

Table 1. CheckMate 9ER Efficacy Results

	CABOMETYX + Nivolumab (n=323)	**Sunitinib (n=328)**
Median PFS, months (95% CI)	16.6 (12.5-24.9)	8.3 (7.0-9.7)
	HR=0.51(95% CI: 0.41-0.64); p-value<0.0001	
Median OS, months (95% CI)	NR	NR (22.6-NR)
	HR=0.60 (98.89% CI: 0.40-0.89); p-value=0.0010	
Confirmed ORR, % (95% CI)	55.7 (50.1-61.2)	27.1 (22.4-32.3)
	p-value <0.0001	
Complete response, n (%)	26 (8.0)	15 (4.6)
Partial response, n (%)	154 (48)	74 (23)
Median DOR, months (95% CI)	20.2 (17.3-NR)	11.5 (8.3-18.4)

Abbreviations: CI=confidence interval; HR=hazard ratio; NR=not reached; ORR=objective response rate; OS=overall survival; PFS=progression-free survival.

The most common all-grade adverse reactions (ARs) reported in ≥20% of patients treated with CABOMETYX and nivolumab were diarrhea (64%), fatigue (51%), hepatotoxicity (44%), palmar-plantar erythrodysesthesia (40%), stomatitis (37%), rash (36%), hypertension (36%), hypothyroidism (34%), musculoskeletal pain (33%), decreased appetite (28%), nausea (27%), dysgeusia (24%), abdominal pain (22%), cough (20%), and upper respiratory tract infection (20%).

Serious ARs occurred in 48% of patients who received CABOMETYX with nivolumab, with the most frequent (≥2%) reported as diarrhea, pneumonia, pneumonitis, pulmonary embolism, urinary tract infection, and hyponatremia; fatal intestinal perforations occurred in 3 (0.9%) patients.

Adverse reactions leading to discontinuation of either CABOMETYX or nivolumab occurred in 20% of patients: 8% CABOMETYX only, 7% nivolumab only, and 6% both drugs due to the same AR at the same time. Adverse reaction-related dose modifications occurred in 83% of patients: 46% CABOMETYX only, 3% nivolumab only, and 21% both drugs due to the same AR at the same time, and 6% both drugs sequentially.

Reference and Enclosure:
1. CABOMETYX® (cabozantinib tablets) [package insert]. Alameda, CA. Exelixis, Inc. January 2021.