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April 15, 2020

Submission Request
National Comprehensive Cancer Network: Panel – Bone Cancer

Clinical Evidence in Support of Cabozantinib in Patients with Bone Cancer

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On behalf of Exelixis, we respectfully request that the NCCN Bone Cancer Guidelines Panel review the following data as it considers potential changes to the guidelines related to the management of patients with Ewing sarcoma and osteosarcoma.

CABOMETYX® (cabozantinib tablets) Indication:
CABOMETYX is a kinase inhibitor indicated for the treatment of patients with advanced renal cell carcinoma (RCC) and patients with hepatocellular carcinoma (HCC) who have been previously treated with sorafenib.[1]

FDA Clearance:
CABOMETYX was initially approved by the U.S. Food and Drug Administration (FDA) in April 2016 for the treatment of patients with advanced RCC 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 for the expanded indication of treatment of patients with advanced RCC in December 2017. On January 14, 2019, CABOMETYX was approved for the treatment of patients with HCC who have been previously treated with sorafenib. CABOMETYX is not approved for the treatment of patients with bone cancer. Exelixis recommends that CABOMETYX only be used in accordance with the approved product labeling.[1]

Specific Changes:
Given the high unmet medical need that exists among these patients, we respectfully request that the NCCN Bone Cancer Guidelines Panel consider the inclusion of cabozantinib as a second-line systemic therapy option for Ewing sarcoma (relapsed/refractory or metastatic disease) and osteosarcoma (relapsed/refractory or metastatic disease).

Rationale:
The CABONE study, a Phase 2 study evaluating the efficacy and safety of cabozantinib in patients with advanced Ewing sarcoma or osteosarcoma, reached its primary endpoint in the Ewing sarcoma cohort as well as the osteosarcoma cohort.[2]

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Clinical Evidence:
CABONE, a multicenter, single-arm, Phase 2 study conducted by the French Sarcoma Group in collaboration with the National Cancer Institute (Cancer Therapy Evaluation Program), evaluated the efficacy and safety of oral daily cabozantinib (60 mg in adults and 40 mg/m^2 in those ages 12-15) among patients with advanced Ewing sarcoma or osteosarcoma. Tumor assessment was performed per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 at baseline and every 8 weeks until disease progression or the start of another treatment.[2]

For the Ewing sarcoma cohort, the primary endpoint was objective response within 6 months of treatment onset (6-month objective response). A Simon's 2-stage design was utilized with 41 eligible and evaluable patients. Five or more objective responses at the final stage were required for cabozantinib to be considered efficacious. For the osteosarcoma cohort, the dual-endpoint design was based on 6-month objective response and 6-month non-progression (percentage of patients with complete response, partial response [PR], or stable disease [SD] 6 months after treatment onset) as the primary endpoints. At the final stage, cabozantinib would be considered efficacious if at least 5 of 41 evaluable patients had an objective response or at least 16 patients were progression-free at 6 months.[2]

A total of 90 patients (45 in each group) were enrolled. Within the Ewing sarcoma group, 2 patients (4%) and 6 patients (13%) in the osteosarcoma group were <18 years of age. Patients primarily had an ECOG performance status of 0-1 (97% Ewing sarcoma; 96% osteosarcoma). Additionally, 67% of patients in the Ewing sarcoma cohort and 40% of patients in the osteosarcoma cohort had been previously treated with two or more lines of therapy. Six Ewing sarcoma patients and three osteosarcoma patients were not eligible for the efficacy analysis due to protocol deviations. As such, 39 patients with Ewing sarcoma and 42 patients with osteosarcoma were evaluable and comprised the efficacy population.[2]

Among the Ewing sarcoma group, the pre-defined efficacy threshold was exceeded. Of 39 evaluable patients, 10 had an objective response yielding an objective response rate (ORR) of 26% (95% CI: 13-42%; all PRs). Additionally, median progression-free survival (PFS) was 4.4 months (95% CI: 3.7-5.6 months), and median overall survival (OS) was 10.2 months (95% CI: 8.5-18.5 months). After a median follow-up of 31.3 months (95% CI: 12.4-35.4 months), 13 Ewing sarcoma patients (33%) were still alive and 3 patients (8%) were still undergoing therapy.[2]

In the osteosarcoma group, the objective response threshold was achieved. Among 42 evaluable patients, there were 5 objective responses yielding an ORR of 12% (95% CI: 4-26%; all PRs). The 6-month disease non-progression was 33% (n=14; 12 patients had SD and 2 had PRs). Additionally, median PFS was 6.7 months (95% CI: 5.4-7.9 months), and median OS was 10.6 months (95% CI: 7.4-12.5 months). After a median follow-up of 31.1 months (95% CI: 24.4-31.7 months), 10 of 42 patients (24%) with osteosarcoma were still alive and 3 patients (7%) were still undergoing treatment.[2]

Adverse events (AEs), which were evaluated among all 90 patients who received at least one dose of cabozantinib, were primarily Grade 1-2. The most common treatment-related Grade 3-4 AEs (>5% in either group) among the Ewing sarcoma and osteosarcoma patients, respectively, were as follows: hypophosphatemia (11%; 7%), neutropenia (4%; 9%), lipase increase (9%; 4%), pneumothorax (2%; 9%), palmar-plantar syndrome (7%; 4%), aspartate aminotransferase increase (4%; 7%), fatigue (7%; 2%), oral mucositis (2%; 7%), and weight loss (7%; 0%). Of 90 patients, 21% had a dose reduction due to a drug-related AE, and AEs leading to dose modification or treatment discontinuation occurred in 39% of patients. At least one serious AE occurred in 68% of patients, and no treatment-related deaths were reported.[2]

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References

[1] CABOMETYX® (cabozantinib tablets) [package insert]. Alameda, CA. Exelixis, Inc. January 2020.
[2] Italiano A, Mir O, Mathoulin-Pelissier S, et al. Cabozantinib in patients with advanced Ewing sarcoma or osteosarcoma (CABONE): a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2020;21(3):446-455.

Enclosure

Italiano A, Mir O, Mathoulin-Pelissier S, et al. Cabozantinib in patients with advanced Ewing sarcoma or osteosarcoma (CABONE): a multicentre, single-arm, phase 2 trial. Lancet Oncol. 2020;21(3):446-455.