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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 bone cancer.

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 have 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:

Request that the NCCN Bone Cancer Guidelines Panel consider the inclusion of cabozantinib as a second-line systemic therapy option for osteosarcoma (relapsed/refractory or metastatic disease) and Ewing sarcoma (relapsed/refractory or metastatic disease).

Rationale:

The CABONE study, a phase 2 study evaluating the efficacy and safety of cabozantinib in patients with advanced osteosarcoma and Ewing sarcoma, met pre-defined thresholds with regard to objective response and non-progression demonstrating clinical activity.²

Clinical Evidence:

CABONE, a single-arm, phase 2 study sponsored by the National Cancer Institute and in collaboration with the French Sarcoma Group, evaluated the efficacy and safety of oral daily cabozantinib (60 mg in adults and 40 mg/m² in those ages 12-17) in patients with locally advanced (unresectable) or metastatic osteosarcoma and Ewing sarcoma. Centralized radiological reviews were performed per Response Evaluation Criteria in Solid Tumors (RECIST) v1.1.

For osteosarcoma, a composite endpoint of 6-month non-progression (CR, PR, SD) or objective response (CR, PR) by centralized radiology review was employed with a target sample size of 41 eligible and evaluable patients. For cabozantinib to be considered efficacious, 2 or more objective responses under treatment or 7 or more non-progressions had to be achieved among 21 patients in stage 1. Stage 2 required 5 or more objective responses under treatment or 16 or more non-progressions among 41 patients. With regard to Ewing sarcoma, the primary endpoint was objective response by centralized radiology review within 6 months of starting therapy. A Simon's 2-stage design with 41 eligible and evaluable patients was employed. Two or more objective responses under treatment among 21 patients in stage 1 and 5 or more objective responses under treatment among 41 patients in stage 2 were required for efficacy.²

A total of 90 patients (45 in each group) enrolled and received treatment. At the time of analysis, 42 patients with osteosarcoma and 33 patients with Ewing sarcoma were eligible and evaluable. The majority of patients were previously treated with >2 prior lines of chemotherapy (54.8% osteosarcoma; 75.8% Ewing sarcoma).²

In the analysis of the osteosarcoma group (n=42), the objective response threshold was exceeded. There were 5 objective responses yielding an objective response rate of 11.9%. The 6-month disease non-progression rate was 33.3% (n=14). Additionally, the median progression-free survival (PFS) was 6.2 months (95% CI: 5.4-8.2), median overall survival (OS) was 10.6 months (95% CI: 7.2-13.2), and 41% experienced tumor shrinkage.²

The efficacy threshold described above for the Ewing sarcoma group was exceeded at an interim analysis of 32 patients (1 patient had no tumor evaluation). Four objective responses were reported among 21 patients (19%) in stage 1 and 9 objective responses were reported among 32 patients (28.1%) in the ongoing stage 2 analysis. Additionally, the median PFS was 5.2 months (95% CI: 3.2-7.4), median OS was 9.8 months (95% CI: 7.3-13.2), and 71% experienced tumor shrinkage. Final analysis is ongoing as this group has not yet reached the accrual requirement of 41 patients; however, the objective responses achieved in 9 patients has already exceeded the pre-defined efficacy threshold of 5.²

The most commonly reported related Grade 3-4 adverse events (>5%) in a preliminary analysis of 82 evaluable patients included pneumothorax (6.1%), fatigue (4.9%), diarrhea (3.7%), oral mucositis (3.7%), palmar-plantar erythrodysesthesia (3.7%), weight loss (3.7%), and hypertension (2.4%). At the time of this analysis, of the 90 patients who received treatment, 39 in the osteosarcoma group and 34 in the Ewing sarcoma group had stopped treatment for various reasons, including but not limited to, adverse events, death, and progressive disease.²

References

- ¹ CABOMETYX[®] (cabozantinib tablets) [package insert]. Alameda, CA. Exelixis, Inc. January 2019.
- ² Italiano A. Cabozantinib in patients with advanced osteosarcomas and Ewing sarcomas. Oral Presentation. Presented at the Connective Tissue Oncology Society (CTOS) Annual Meeting; November 14-17, 2018; Rome, Italy.

Enclosure

Italiano A. Cabozantinib in patients with advanced osteosarcomas and Ewing sarcomas. Oral Presentation, CTOS 2018. (Author permission granted).