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Submission Request
National Comprehensive Cancer Network: Panel – Soft Tissue Sarcoma

Clinical Evidence in Support of Cabozantinib in Patients with Gastrointestinal Stromal Tumors

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On behalf of Exelixis, we respectfully request that the NCCN Soft Tissue Sarcoma Guidelines Panel review the following data as it considers potential changes to the guidelines related to the management of patients with gastrointestinal stromal tumor (GIST).

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 GIST. Exelixis recommends that CABOMETYX only be used in accordance with the approved product labeling.[1]

Specific Changes:
Exelixis' request pertains to the GIST-5 algorithm located on Page 23 of the NCCN Soft Tissue Sarcoma guidelines; more specifically, it applies to GIST-D (Systemic Therapy Agents and Regimens for Unresectable or Metastatic GIST) on Page 29. Given the unmet medical need that exists among patients with multi-drug-resistant GIST, we respectfully request inclusion of cabozantinib as a third-line and fourth-line systemic therapy option as "useful in certain circumstances" for unresectable or metastatic GIST.

Rationale:
CaboGIST, a Phase 2 study evaluating the activity and safety of cabozantinib in patients with metastatic GIST who had progressed on imatinib and sunitinib, met its pre-specified primary endpoint.[2]

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Clinical Evidence:
CaboGIST was a Phase 2, multi-center, multi-national, open-label, single-arm study sponsored by the European Organisation for Research and Treatment of Cancer. The activity and safety of cabozantinib 60 mg orally daily was evaluated in patients with metastatic GIST who progressed on imatinib and sunitinib with no prior exposure to other TKIs.[2]

The primary endpoint was progression-free survival rate at 12 weeks as assessed by the local investigator based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1. An A'Hern single-stage study design was utilized. If at least 21 of 41 eligible and evaluable patients were progression-free at Week 12, the activity of cabozantinib would be considered sufficient to warrant further exploration in metastatic GIST. To allow for an adequate number of patients to be assessable for the decision rule, enrollment continued beyond 41 patients with a maximum of 50 patients. Secondary endpoints included: progression-free survival (PFS), overall survival (OS), objective response rate, disease control rate (proportion of patients achieving a complete response [CR], partial response [PR], or stable disease [SD]), total duration of treatment (including treatment beyond RECIST progression), and safety.[2]

A total of 50 eligible patients received treatment with cabozantinib and were analyzed for activity and safety. At the clinical cut-off date (September 10, 2019), four patients were still continuing therapy. The median age was 63 years (range: 35-82 years), 76% had an Eastern Cooperative Oncology Group performance status of 0, and 94% had received prior surgery for GIST. Overall, the pre-defined efficacy threshold was exceeded. Among the first 41 eligible and evaluable patients, 24 (58.5%, 95% CI: 42-74%) were progression-free at Week 12. Among all 50 treated patients, 30 (60%, 95% CI: 45-74%) were progression-free at Week 12, median PFS was 5.5 months (95% CI: 3.6-6.9 months), and median OS was 18.2 months (95% CI: 14.3-22.3 months). Additional efficacy endpoints are presented below.[2]

Table 1: Additional Efficacy Endpoints (N=50)

Best Overall Response*	**Patients, n (%)**
PR	7 (14)
SD	34 (68)
PD	8 (16)
Non-evaluable	1 (2)
Objective Response (CR + PR)	7 (14)
Disease Control (CR + PR + SD)	41 (82)

Abbreviations: CR=complete response, PD=progressive disease, PR=partial response, SD=stable disease.
*Response assessed by local investigator per Response Evaluation Criteria in Solid Tumors v1.1.

Central mutational analysis was performed based on collected archival tissue samples from 37 of 50 patients in the study. Among 37 patients, 83.8% (n=31) had *KIT* mutations, 2.7% (n=1) had a *PDGFRA* mutation, 5.4% (n=2) had *NF1* frameshift mutations, and 2.7% (n=1) had a *RBPMS-NTRK3* fusion; no driver mutation was found in 5.4% (n=2) of cases. Clinical benefit (CR, PR, and SD) was observed in 13/16 evaluable *KIT* exon 11 cases, 4/5 *KIT* exon 11 + 17 cases, in all evaluable *KIT* exon 9, 13, 17, 9 +17 and 11 + 14 cases, and all *NF1*- and *RBPMS-NTRK3*-driven GISTs in this study.[2]

The most common treatment-related Grade 3 adverse events (AEs) were as follows: hypertension (36%), diarrhea (26%), palmar-plantar erythrodysesthesia (8%), anorexia (2%), and hypothyroidism (2%). No Grade 4 treatment-related AEs (in >10% of patients) were observed, and no treatment-related deaths occurred. Dose modifications were reported in 40 patients (80%), with 32 patients (64%) receiving dose reductions and 27 patients (54%) requiring treatment interruptions.[2]

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References

[1] CABOMETYX® (cabozantinib tablets) [package insert]. Alameda, CA. Exelixis, Inc. January 2020.

[2] Schöffski P, Mir O, Kasper B, et al. Activity and safety of the multi-target tyrosine kinase inhibitor cabozantinib in patients with metastatic gastrointestinal stromal tumour after treatment with imatinib and sunitinib: European Organisation for Research and Treatment of Cancer phase II trial 1317 'CaboGIST'. Eur J Cancer. 2020;134:62-74.

Enclosure

Schöffski P, Mir O, Kasper B, et al. Activity and safety of the multi-target tyrosine kinase inhibitor cabozantinib in patients with metastatic gastrointestinal stromal tumour after treatment with imatinib and sunitinib: European Organisation for Research and Treatment of Cancer phase II trial 1317 'CaboGIST'. Eur J Cancer. 2020;134:62-74.