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May 5, 2021

Clinical Evidence in Support of Cabozantinib in Patients with Endometrial Cancer

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On behalf of Exelixis, we respectfully request the NCCN Guidelines Panel for Cervical/Uterine Cancers review the following data as it considers potential changes to the guidelines related to the management of patients with endometrial carcinoma (EC).

FDA Clearance:
CABOMETYX (alone or in combination with other agents) is not approved for the treatment of patients with EC.

Specific Changes:
Exelixis' request pertains to the ENDO-D (1 of 4) algorithm located on Page 31 of the NCCN Uterine Neoplasms guidelines. Exelixis requests the inclusion of cabozantinib as a systemic therapy option for patients who have progressed following prior chemotherapy for recurrent, metastatic, or high-risk EC.

Rationale:
A multicenter Phase 2 study demonstrated the activity of cabozantinib in serous and endometrioid histology EC with response rates of 14% and 12%, respectively, and 12-week progression-free survival (PFS) rates of 67% and 56%, respectively.

Clinical Experience:
A Phase 2, multicenter, single-arm study (NCT01935934) sponsored by the National Cancer Institute evaluated the use of cabozantinib 60 mg orally once daily in 102 patients with EC who had previously received one line of chemotherapy for metastatic disease or had recurrence within a year of adjuvant, platinum-based chemotherapy.[2] Co-primary endpoints were objective response rate (ORR) per Response Evaluation Criteria in Solid Tumors v1.1 and 12-week investigator-assessed PFS. Patients with serous or endometrioid histology were enrolled in the experimental cohort while patients with rare histology EC were accrued to an exploratory cohort.

Among patients with endometrioid histology (n=36), the ORR was 14% (5 partial responses [PRs]), 12-week PFS rate was 67%, and median PFS was 4.8 months (95% CI: 4.4-6.4 months).[2] Among patients with serous EC (n=34), the ORR was 12% (4 PRs), 12-week PFS was 56%, and median PFS was 4.0 months (95% CI: 2.8-4.7 months). Among all patients who met 12-week PFS, >50% (23 of 43 patients) remained progression free at their subsequent 20-week scan. Among all 70 patients in the experimental cohort (serous and endometrioid), median PFS was 4.6 months (95% CI: 3.7 to 4.9 months).

Patients with rare histology EC (n=32) were evaluated in a parallel exploratory cohort which

consisted of the following histologies: carcinosarcoma (n=19), mixed (n=6), clear-cell (n=5), mucinous (n=1), and adenosquamous (n=1).[2] Within the exploratory cohort, the ORR was 6% (1 patient with carcinosarcoma and 1 patient with mixed histology had a PR). Fifteen patients (47%) achieved 12-week PFS, including 5 who remained progression-free at their subsequent 20-week scan. Of 19 carcinosarcoma patients, 8 patients (42%) achieved 12-week PFS. The patient with carcinosarcoma who experienced a PR had a PFS of 6.7 months. Median PFS for both the full exploratory cohort and the carcinosarcoma subgroup was 3 months.

Adverse events (AEs) were primarily Grade 1-2 in severity.[2] The most common treatment-related AEs, of all grades, were reported as follows: AST increase (n=66), fatigue (n=65), ALT increase (n=64), diarrhea (n=60), hypertension (n=52), anorexia (n=49), nausea (n=46), dysgeusia (n=42), and hand-foot syndrome (n=40). Gastrointestinal perforation/fistula occurred in 6% of serous/endometrioid patients and 16% of patients in the exploratory cohort. One death related to complications of a colonic fistula was reported, and six deaths were attributed to evidence of disease progression. Of 102 treated patients, 21 patients discontinued treatment due to an AE.

References and Enclosures:

1. CABOMETYX® (cabozantinib tablets) [package insert]. Alameda, CA. Exelixis, Inc. January 2021.
2. Dhani NC, Hirte HW, Wang L, et al. Phase II trial of cabozantinib in recurrent/metastatic endometrial cancer: A study of the Princess Margaret, Chicago, and California Consortia (NCI9322/PHL86). Clin Cancer Res. 2020;26(11):2477-2486.