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June 10, 2015

Submission Request
National Comprehensive Cancer Network

**Re: Clinical Evidence in Support of Cabozantinib in Metastatic Non-Small Cell Lung Cancer (NSCLC) Patients Whose Tumors Lack an EGFR Activating Mutation**


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| NCCN Guidelines Panel: | Non-Small Cell Lung Cancer |


On behalf of Exelixis, I respectfully request that the NCCN NSCLC Guidelines Panel review the enclosed data for the inclusion of cabozantinib monotherapy and cabozantinib in combination with erlotinib (Tarceva®) in the NSCLC guidelines.

Specific Changes: Recommend the addition of cabozantinib monotherapy and cabozantinib in combination with erlotinib (Tarceva®) as potential treatments for patients with non-squamous, metastatic NSCLC who have received one or two prior lines of therapy and whose tumors lack an EGFR activating mutation.

FDA Clearance: COMETRIQ® (cabozantinib capsules) is approved for the treatment of patients with progressive, metastatic medullary thyroid cancer (MTC). (Approved dose is 140mg daily).

Rationale: The E1512 study, a randomized phase II study comparing cabozantinib monotherapy and cabozantinib in combination with erlotinib to erlotinib monotherapy in patients with metastatic non-squamous NSCLC whose tumors lack activating EGFR mutations, demonstrated a statistically-significant improvement of progression-free survival (PFS) and overall survival (OS) for each of the cabozantinib arms compared to the erlotinib monotherapy arm.

Clinical Evidence: E1512, an ECOG-ACRIN Cancer Research Group study, is a 3-arm randomized phase II study comparing cabozantinib (60 mg daily) and cabozantinib in combination with erlotinib (40mg daily and 150 mg daily, respectively) to erlotinib (150mg daily) in patients with metastatic non-squamous NSCLC who have received one or two prior lines of chemotherapy and whose tumors lack an EGFR activating mutation[1]. Patients were stratified based on performance status and the number of prior lines of chemotherapy. The primary endpoint was the comparison of PFS of each of the cabozantinib-containing regimens to erlotinib monotherapy. Secondary endpoints included OS, objective response rate (ORR) and safety. Between February 2013 and July 2014, the study enrolled 125 patients of whom 118 were evaluable for safety and 113 were evaluable for the efficacy endpoints. Baseline characteristics were reasonably well-balanced with the exception of a significantly greater percentage of patients with a history of mediastinal metastasis (cabozantinib monotherapy arm 56%, combination arm 50%, and erlotinib monotherapy arm 30%) and a history of treated brain metastasis (cabozantinib monotherapy arm 33%, combination arm 25%, erlotinib monotherapy arm 8%) in each

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cabozantinib arm compared with the erlotinib arm. Median follow up at the time of data analysis was 12.6 months. The study met its primary endpoint demonstrating a statistically-significant improvement of PFS for each of the cabozantinib arms compared to the erlotinib arm (Table 1). A statistically-significant improvement in OS was also demonstrated for the cabozantinib arms (Table 2).

**Table 1. Progression-Free Survival**

| | Median (months) | Hazard Ratio (vs Erlotinib) | p-value (vs Erlotinib) |
|---|---|---|---|
| Erlotinib (N=38) | 1.9 | -- | -- |
| Cabozantinib (N=39) | 4.2 | 0.38 (0.27-0.55)* | 0.0004† |
| Combination (N=36) | 4.7 | 0.35 (0.23-0.52)* | 0.0005† |

†1-sided p-value *80% confidence interval

**Table 2. Overall Survival**

| | Median (months) | Hazard Ratio (vs Erlotinib) | p-value (vs Erlotinib) |
|---|---|---|---|
| Erlotinib (N=38) | 4.1 | -- | -- |
| Cabozantinib (N=39) | 9.2 | 0.59 (0.42-0.84)* | 0.03† |
| Combination (N=36) | 13.3 | 0.44 (0.30-0.66)* | 0.004† |

†1-sided p-value *80% confidence interval

The safety profile for Grade 3 or greater treatment-related adverse events was similar between the arms with the exceptions of a significant increase of Grade 3 mucositis and hypertension in the cabozantinib monotherapy arm vs erlotinib and of Grade 3 diarrhea in the combination arm vs erlotinib. In addition, there was a significant increase in the number of patients with a worst grade of Grade 3-5 toxicity in the cabozantinib arms compared to erlotinib.

Cabozantinib Formulations: Currently COMETRIQ capsules are commercially available at 2 dose strengths (80 mg and 20 mg) supplied in blister packs. Patients prescribed a COMETRIQ dose of 60 mg take three 20 mg capsules daily. E1512 was conducted using cabozantinib tablets at a dose of 60 mg in the cabozantinib monotherapy arm and 40 mg in combination with erlotinib. The tablet formulation is currently not available commercially. In a single-dose healthy volunteer study comparing a dose of 140 mg as capsules (one 80 mg capsule + three 20 mg capsules) with 140 mg as tablets (one 100 mg tablet + two 20 mg tablets), the AUC for the tablets was 8% higher than capsules[2]. $C_{max}$ was approximately 19% higher with the tablets compared with capsules and the upper limit of the 90% CI around the ratio of least-squares means for $C_{max}$ (131.65%) was outside the 80.00%-125.00% accepted bioequivalence range. Therefore, the capsule and tablet formulations cannot be considered to be bioequivalent.

Literature Support

[1]Neal JW, Dahlberg SE, Wakelee HA et al. Cabozantinib (C), erlotinib (E) or the combination (E+C) as 2nd or 3rd line therapy in patients with EGFR wild-type (wt) NSCLC: a randomized phase 2 trial of the ECOG-ACRIN Cancer Research Group (E1512). J Clin Oncol 33, 2015 (suppl; abstr 8003).

[2]Exelixis Internal Report, Data on file.