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NCCN Guideline Panel: Hepatobiliary Cancer

On behalf of Eli Lilly and Company, I respectfully request the National Comprehensive Cancer Network (NCCN) Hepatobiliary Cancer Guideline Panel to review the enclosed information for CYRAMZA® (ramucirumab) in reference to NCCN Guidelines V1.2018 for Hepatobiliary Cancers.

These data are being submitted in response to a request from the NCCN for new data to be submitted no less than 21 days prior to the standing meeting for hepatobiliary cancers.

Specific changes recommended: We respectfully request that ramucirumab be recommended as a second-line treatment for patients with advanced hepatocellular carcinoma (HCC) who have an elevated baseline alpha-fetoprotein (AFP) following treatment with first-line sorafenib (Category 1), following full FDA approval for the use of ramucirumab in this setting.

FDA Clearance: Ramucirumab is not FDA-approved for treatment of HCC. Please refer to the product prescribing information for the full FDA-approved indications and safety information.¹

Rationale: This request is based on clinical evidence from REACH-2, a randomized, double-blinded, placebo-controlled, phase 3 study that compared ramucirumab plus best supportive care (BSC) and placebo plus BSC in patients with HCC and elevated baseline AFP after intolerance to or progression on prior sorafenib.² The request is further supported by clinical evidence from a prespecified pooled analysis that combined patients from the REACH-2 study with the subgroup of patients with elevated baseline AFP from the REACH study.^{3,4} The pooled analysis was pre-specified prior to the REACH-2 database lock.³ REACH-2 and REACH were both global phase 3 clinical studies of ramucirumab versus placebo in patients with advanced HCC who had progressed following first-line treatment with sorafenib.^{2,5} The results of REACH-2 were recently presented as an oral presentation at the 54th Annual Meeting of the American Society of Clinical Oncology (ASCO): June 1-5, 2018; Chicago, IL.² The results of the pooled analysis were recently presented as an oral presentation at the 20th Annual Meeting of the European Society for Medical Oncology (ESMO) World Congress on Gastrointestinal Cancer: June 20-23, 2018; Barcelona, Spain.^{3,4}

EFFICACY RESULTS

In REACH-2, patients were randomly assigned 2:1 to receive ramucirumab 8 mg/kg plus BSC (n=197) or placebo plus BSC (n=95) until disease progression or unacceptable toxicity. The primary endpoint of this study was overall survival (OS). At the time of data cutoff, 221 OS events had occurred (76% OS maturity) in the intent-to-treat analysis for OS. Treatment with ramucirumab significantly improved both OS and progression-free survival (PFS) compared with placebo, with improvement observed across predefined subgroups of interest.² Efficacy results from REACH-2 are summarized below.

- Median OS was 8.5 months in the ramucirumab arm compared with 7.3 months in the placebo arm (Hazard ratio (HR) 0.710; 95% CI 0.531-0.949; p=.0199).²
- Median PFS was 2.8 months for the ramucirumab arm compared with 1.6 months for the placebo arm (HR 0.452; 95% CI 0.339-0.603; p<.0001).²

A pooled analysis of patients from REACH-2 and REACH with baseline AFP ≥ 400 ng/mL (N=542; n=316 ramucirumab, n=226 placebo) was also performed. In the pooled analysis, patients who received ramucirumab had clinically significant improvement in OS in all subgroups compared with patients who received placebo. PFS was

also significantly improved for patients who received ramucirumab versus patients who received placebo.³ Efficacy results are summarized below.

- Median OS was 8.1 months in the ramucirumab arm compared with 5.0 months in the placebo arm (HR 0.694; 95% CI 0.571-0.842; p=.0002).^{3,4}
- Median PFS was 2.8 months in the ramucirumab arm compared with 1.5 months in the placebo arm (HR 0.572; 95% CI 0.472-0.694; p<.0001).^{3,4}

SAFETY RESULTS

In REACH-2, ramucirumab was generally well-tolerated, with a safety profile consistent with single-agent ramucirumab. No new safety signals were identified. In the ramucirumab arm, the most common treatment-emergent adverse events (TEAEs) reported ($\geq 20\%$) of any grade included proteinuria, decreased appetite, hypertension, peripheral edema, and fatigue. Hypertension was the only grade ≥ 3 TEAE which occurred in $\geq 5\%$ of patients and at a higher rate in the ramucirumab arm than in the placebo arm. Treatment discontinuation rates due to related adverse events (AEs) were 10.7% in the ramucirumab arm versus 3.2% in the placebo arm.²

The safety results from the pooled analysis were consistent with safety profile observed in REACH-2. In the ramucirumab arm, the most common TEAEs reported ($\geq 20\%$) of any grade included hypertension, ascites, decreased appetite, fatigue, and peripheral edema. Grade ≥ 3 hypertension occurred in $\geq 5\%$ of patients and at a higher rate in the ramucirumab arm than in the placebo arm. Treatment discontinuation rates due to related AEs were 9.5% in the ramucirumab arm versus 3.6% in the placebo arm.⁴

The following references are submitted to assist the committee in their review. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or contributors of some of these publications and presentations.

1. [CYRAMZA® \(ramucirumab\) Prescribing Information](#)
2. Zhu AX, Kang Y-C, Yen C-J, et al. REACH-2: A randomized, double-blind, placebo-controlled phase 3 study of ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma (HCC) and elevated baseline alpha-fetoprotein (AFP) following first-line sorafenib. Presented as an oral presentation at the 54th Annual Meeting of the American Society of Clinical Oncology (ASCO): June 1-5, 2018. Chicago, IL. Abstract #4003. <https://meetinglibrary.asco.org/record/159169/abstract>.
3. Zhu AX, Finn RS, Galle PR, et al. Ramucirumab as second-line treatment in patients with advanced hepatocellular carcinoma (HCC) and elevated alpha-fetoprotein (AFP) following first-line sorafenib: Pooled efficacy and safety across two global randomized Phase 3 studies (REACH-2 and REACH). Presented as an oral presentation at the 20th Annual Meeting of the European Society for Medical Oncology (ESMO) World Congress on Gastrointestinal Cancer: June 20-23, 2018. Barcelona, Spain.
4. Zhu AX, Finn RS, Galle PR, et al. Ramucirumab as second-line treatment in patients with advanced hepatocellular carcinoma (HCC) and elevated alpha-fetoprotein (AFP) following first-line sorafenib: Pooled efficacy and safety across two global randomized Phase 3 studies (REACH-2 and REACH). Presented as a poster at the 20th Annual Meeting of the European Society for Medical Oncology (ESMO) World Congress on Gastrointestinal Cancer: June 20-23, 2018. Barcelona, Spain. Poster #LBA-001 https://www.postersessiononline.eu/pr/aula_poster.asp?congreso=519481837&direccion_posters=Seleccion&pagina_posters=1
5. [Zhu AX, Park JO, Ryoo BY, et al. Ramucirumab versus placebo as second-line treatment in patients with advanced hepatocellular carcinoma following first-line therapy with sorafenib \(REACH\): a randomised, double-blind, multicentre, phase 3 trial. *Lancet Oncol*. 2015;16\(7\):859-870.](#)

Sincerely,

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