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NCCN Guideline Panel: Gastric Cancer

On behalf of Eli Lilly and Company, I respectfully request the National Comprehensive Cancer Network (NCCN) Gastric Cancer Guideline Panel to review the enclosed information in reference to NCCN Guidelines V2.2018 for Gastric 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 gastric cancer.

**Specific changes recommended:** We respectfully request the NCCN Panel to update the Gastric Cancer Guidelines to reflect the Panel's views based on results of the T-ACT trial and provide a direct recommendation regarding the use of trastuzumab beyond progression in patients who have already received trastuzumab with chemotherapy as first-line treatment for human epidermal growth factor receptor 2 (HER2)-overexpressing metastatic gastric adenocarcinoma.

**FDA Clearance:** Trastuzumab is FDA-approved, in combination with cisplatin and capecitabine or 5-fluorouracil, for the treatment of patients with HER2-overexpressing metastatic gastric or gastro-esophageal junction (G/GEJ) adenocarcinoma who have not received prior treatment for metastatic disease. Please refer to the product prescribing information for the full FDA-approved indications and safety information.<sup>1</sup>

**Rationale:** This request is based on clinical evidence from the phase 2 T-ACT study that was recently presented at the 54th Annual Meeting of the American Society of Clinical Oncology (ASCO) from June 1-5, 2018 in Chicago, IL.<sup>2</sup>

T-ACT was a multicenter, open-label, randomized phase 2 study that compared the safety and efficacy of paclitaxel plus trastuzumab versus paclitaxel alone in patients with unresectable or metastatic HER2-positive (HER2+) G/GEJ cancer after failure of first-line chemotherapy with trastuzumab plus fluoropyrimidine plus platinum. The primary endpoint of this study was progression-free survival (PFS). Key secondary endpoints included overall survival (OS), response rate, safety, and translational biomarker research.<sup>2</sup>

### **EFFICACY**

In T-ACT, 91 patients were randomly assigned 1:1 to receive paclitaxel plus trastuzumab (n=45) or paclitaxel alone (n=46). Treatment with paclitaxel plus trastuzumab did not significantly improve PFS, OS, or response rate compared to treatment with paclitaxel alone. Median PFS was 3.68 months in the paclitaxel plus trastuzumab arm compared with 3.19 months in the paclitaxel alone arm (hazard ratio (HR) 0.906; 95% CI 0.674-1.219; p=.334). Median OS was 10.20 months in the paclitaxel plus trastuzumab arm compared with 9.95 months in the paclitaxel alone arm (HR 1.230; 95% CI 0.759-1.991; p=.199). Overall response rate in patients with measurable lesions was 33.3% in the paclitaxel plus trastuzumab arm compared with 31.6% in the paclitaxel alone arm.<sup>2</sup>

### **SAFETY**

In the paclitaxel plus trastuzumab arm, the most common adverse events reported ( $\geq 20\%$ ) of any grade included neutropenia, leucopenia, anemia, peripheral sensory neuropathy (PSN), anorexia, fatigue, diarrhea, and nausea. In the paclitaxel arm, the most common adverse events reported ( $\geq 20\%$ ) of any grade included neutropenia, PSN, leucopenia, anemia, fatigue, anorexia, diarrhea, and nausea. Grade  $\geq 3$  adverse events occurring in  $\geq 5\%$  of patients in the paclitaxel plus trastuzumab arm included leucopenia, anemia, neutropenia, and PSN. Grade  $\geq 3$  adverse events occurring in  $\geq 5\%$  of patients in the paclitaxel arm included leucopenia, anemia, neutropenia, PSN, and anorexia.<sup>2</sup>

## UNITED STATES REAL-WORLD EVIDENCE

Data were recently disclosed from a real-world study of 2035 gastric adenocarcinoma patients testing positive for HER2 overexpression treated in the United States community practice setting. Approximately one-third of patients receiving first-line chemotherapy with trastuzumab who go on to receive a further line of treatment continue to receive trastuzumab beyond progression in second- and subsequent lines of therapy in the absence of any evidence for clinical benefit.<sup>3</sup>

We appreciate the Panel's careful consideration of this request to incorporate the best available evidence regarding the use of trastuzumab beyond progression in this clinical setting.

The following references are submitted to assist the committee in their review.

1. [HERCEPTIN® \(trastuzumab\) Prescribing Information](#)
2. [Makiyama A, Sagara K, Kawada J, et al. A randomized phase II study of weekly paclitaxel ± trastuzumab in patients with HER2-positive advanced gastric or gastro-esophageal junction cancer refractory to trastuzumab combined with fluoropyrimidine and platinum: WJOG7112G \(T-ACT\). Presented as a poster at the 54th Annual Meeting of the American Society of Clinical Oncology \(ASCO\): June 1-5, 2018. Chicago, IL. Abstract #4011.](#)
3. [Janjigian YY, Hess LM, Zhu Y, et al. Treatment and testing patterns among patients with HER2+ advanced/metastatic gastric, esophageal or gastroesophageal junction \(GEJ\) adenocarcinoma in the United States. 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 P-086.](#)

Please do not hesitate to contact me with any questions.

Sincerely,

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