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Submitted by:
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Takashi Harada
Director, Medical Affairs PMO
Taiho Pharmaceutical Co., Ltd.
Date of request: July 26, 2021

Dear NCCN Clinical Practice Guidelines Gastric and Esophageal/Esophagogastric Junction Cancers Panels,

On behalf of Taiho Oncology, Inc. and Taiho Pharmaceutical, Co., Ltd., we respectfully request the NCCN Gastric and Esophageal and Esophagogastric Junction Cancer Panels review the enclosed data from an open-label, phase 2 study of trifluridine and tipiracil (FTD/TPI) in combination with ramucirumab in metastatic gastric cancer (mGC), in support of the inclusion of FTD/TPI in combination with ramucirumab in the NCCN guidelines for gastric cancers.

Specific Changes:

Recommend the NCCN Clinical Practice Guidelines include FTD/TPI in combination with ramucirumab as a second-line or subsequent therapy option in systemic therapy for unresectable locally advanced, recurrent, or metastatic disease GAST-F, 4 of 16 and ESOPH-F, 4 of 16.

FDA Clearance:

The combination of FTD/TPI with ramucirumab is not indicated in mGC. As a monotherapy FTD/TPI is approved for the treatment of adult patients with metastatic gastric or gastroesophageal junction adenocarcinoma (mGEJC) who have been previously treated with at least two prior lines of chemotherapy that included a fluoropyrimidine, a platinum, either a taxane or irinotecan, and if appropriate, HER2/neu-targeted therapy.[1]

Ramucirumab as a single agent or in combination with paclitaxel is indicated for the treatment of patients with advanced or metastatic, gastric or gastro-esophageal junction adenocarcinoma with disease progression on or after prior fluoropyrimidine- or platinum-containing chemotherapy.[2]

Rationale:

The TAGS study, FTD/TPI and best supportive care (BSC) vs. placebo and BSC in patients with heavily pretreated mGC and mGEJC, showed a statistically significant improvement in median overall survival by 2.1 months (mos) (5.7 vs 3.6 mos) corresponding to a 31% reduction in the risk of death (hazard ratio 0.69; 95% Confidence Interval [CI]: 0.56-0.85; one-sided p=0.00029.[3] Most common adverse events ≥10% in incidence were neutropenia, anemia, nausea, decreased appetite, thrombocytopenia, vomiting, and diarrhea.[1] Based on the result of TAGS, FTD/TPI monotherapy was recommended as third line treatment on the NCCN guidelines for gastric cancer and esophageal and esophagogastric junction cancers.

The clinical benefit associated with FTD/TPI has led to the exploration of potential combination regimens with other agents in gastrointestinal cancer. FTD/TPI plus DC-101 (ramucirumab murine version) showed efficacy in KRAS mutant murine colorectal cancer CT26 syngeneic model compared with either drug alone.[4] An open-label, single-arm, two-cohort, phase 2 study of FTD/TPI in combination with ramucirumab was conducted in

patients with mGC refractory or intolerant to standard chemotherapies.[5] The primary endpoint was disease control rate, assessed by investigators. A total of 64 patients previously treated with one line of chemotherapy without ramucirumab (cohort A, n=33) or previously treated with two to four lines of chemotherapy, including ramucirumab (cohort B, n=31), were enrolled. The disease control rate in cohort A and B were 85% (95% CI: 68-95) and 77% (59-90), respectively. Median progression free survival in cohort A and B were 5.9 (95% CI: 4.2–7.9) mos and 5.3 (2.8–6.0) mos, respectively. Common treatment-related adverse events of grade ≥ 3 were neutrophil count decreased (27 [82%] in cohort A and 23 [74%] in cohort B), white blood cell count decreased (8 [24%] and 7 [23%]), and platelet count decreased (8 [24%] and 4 [13%]).[5]

The combination of FTD/TPI and ramucirumab has demonstrated efficacy with a manageable safety profile in mGC and mGEJC patients. We respectfully request the NCCN to consider adding FTD/TPI in combination with ramucirumab as an option for second line treatment of patients with mGC and mGEJC.

In support of the proposed change, we submit the supportive data referenced below:

1. LONSURF® (trifluridine and tipiracil) tablets [prescribing information]. Princeton, NJ: Taiho Oncology, Inc. 12/2019.
2. CYRAMZA® (ramucirumab) [prescribing information]. Indianapolis, IN: Eli Lilly and Company. 6/2021.
3. Shitara K, Doi T, Dvorkin M, et al. Trifluridine/tipiracil versus placebo in patients with heavily pretreated metastatic gastric cancer (TAGS): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2018; 19: 1437-1448.
4. Tsunekuni K, Kawakami H, Mastuoka K, et al. Efficacy of combination chemotherapy using a novel oral chemotherapeutic agent, FTD/TPI, with ramucirumab murine version DC101 in a mouse syngeneic cancer transplantation model. *J Clin Med*. 2020; 9: 4050.
5. Kawazoe A, Ando T, Hosaka H, et al. Safety and activity of trifluridine/tipiracil and ramucirumab in previously treated advanced gastric cancer: an open-label, single-arm, phase 2 trial. *Lancet Gastroenterol Hepatol*. 2021; 6: 209-217.

Sincerely,

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Karin Blakolmer (Jul 26, 2021 14:57 EDT)

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Jul, 28, 2021

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