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Submitted by:
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Dear NCCN Clinical Practice Guidelines Colon and Rectal Cancer Panels,

On behalf of Taiho Oncology, Inc., we respectfully request the NCCN Colon Cancer and Rectal Cancer Panels review the enclosed data from a randomized open-label, non-comparative, Phase 2 study of trifluridine and tipiracil (FTD/TPI) in combination with bevacizumab in metastatic colorectal cancer (mCRC) and phase 1 and 2 studies, in support of the inclusion of FTD/TPI in combination with bevacizumab in the treatment guidelines for mCRC and rectal cancer.

Specific Changes: Recommend NCCN Clinical Practice Guidelines include FTD/TPI in combination with bevacizumab as a first line treatment option in Systemic Therapy for Metastatic Colon Cancer (COL-D, 1 of 13) and Systemic Therapy for Metastatic Rectal Cancer (REC-F, 1 of 13).

FDA Clearance:
The combination of FTD/TPI with bevacizumab is not indicated in mCRC. As a monotherapy FTD/TPI is approved for the treatment of patients with mCRC who have been previously treated with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF biological therapy, and if RAS wild-type, an anti-EGFR therapy.[1]
Bevacizumab is a vascular endothelial growth factor inhibitor indicated for the treatment of mCRC, in combination with intravenous fluorouracil-based chemotherapy for first- or second-line treatment. Metastatic colorectal cancer, in combination with fluoropyrimidine-irinotecan- or fluoropyrimidine-oxaliplatin-based chemotherapy for second-line treatment in patients who have progressed on a first-line bevacizumab-containing regimen.[2]

Rationale:
RECOURSE, a randomized phase 3 trial with FTD/TPI (n= 534) vs. placebo (n=266) in patients with refractory mCRC, the median overall survival improved with FTD/TPI 7.1 mos. vs 5.3 mos. (hazard ratio [HR] 0.66; 95% confidence interval [CI]: 0.58 - 0.81; P<0.001), resulted in a 2 months survival benefit in this heavily pretreated population.[3] The clinical benefit associated with FTD/TPI has led to the exploration of potential combination regimens with other agents in mCRC. One such agent is the anti-vascular endothelial growth factor antibody bevacizumab, which improved progression-free survival (PFS) when added to first-line and second-line fluorouracil-based combination chemotherapy with other agents. FDT/TPI plus bevacizumab (FTD/TPI-B) demonstrated activity against colorectal cancer xenografts compared with either drug alone.[4] Clinical data from the phase 1/2 C-TASK FORCE study and a randomized Danish phase 2 study demonstrated that treatment with FTD/TPI-B had promising antitumor activity with manageable toxicity in a small patient population with advanced mCRC refractory or intolerant to standard therapies.[5,6]

C-TASK FORCE was a phase 1/2 investigator-initiated trial that evaluated FTD/TPI-B (n=25) in Japanese patients with previously treated mCRC. The primary endpoint of the phase 2 part was centrally assessed PFS at 16-weeks, which was 42.9% (80% CI: 27.8-59.0).[5] The most common grade ≥ 3 adverse events were neutropenia (72%), leukopenia (44%), anemia (16%), and febrile neutropenia (16%).[5] An investigator initiated randomized Danish phase 2 study compared outcomes of FTD/TPI treatment with or without bevacizumab. The median PFS was significantly improved in the arm that received FTD/TPI-B (n=46; 4.6 months) compared with the arm that received FTD/TPI alone (n=47; 2.6 mos.; HR 0.45; 95% CI: 0.29 -0.72; P=0.001).[6] In addition, the median overall survival (OS) was significantly prolonged with FTD/TPI-B vs. FTD/TPI (9.4 mos. vs. 6.7 mos., respectively; HR 0.55; 95% CI: 0.32- 0.94; P=0.028).[6] Patients receiving FTD/TPI-B had more grade 3-4 neutropenia versus FTD/TPI alone (67% vs. 38%), and 3 patients had febrile neutropenia with FTD/TPI-B

versus 1 with FTD/TPI alone.[6] Serious adverse events were observed in 21 and 19 patients in the FTD/TPI-B and FTD/TPI-alone arms, respectively.[6]

TASCO1, an open-label randomized non-comparative phase 2 European study, assessed the safety and efficacy of first-line treatment with FTD/TPI plus bevacizumab (FTD/TPI-B, n=77) and capecitabine plus bevacizumab (C-B, n=76) in untreated patients with unresectable mCRC who were not candidates for intensive oxaliplatin- or irinotecan-based chemotherapy. The primary endpoint was PFS. The main reasons for non-eligibility for intensive chemotherapy combinations as assessed by the investigator were age, tumor burden, performance status, and comorbidities. Median PFS was 9.2 mos. (95% CI: 7.6-11.6) for FTD/TPI-B and 7.8 mos. (95% CI: 5.5-10.1) for C-B. Median OS was 18 (95% CI: 15.2–NA) and 16.2 (95% CI:12.5-NA) mos., respectively. Quality of life questionnaires showed no clinically relevant changes over time for either treatment. Patients receiving FTD/TPI-B had more grade ≥3 neutropenia (47% vs. 5% with C-B). Patients receiving C-B had more grade ≥3 hand-foot syndrome (12% vs. 0% with FTF/TPI-B) and grade ≥3 diarrhea (8% vs. 1% with FTD/TPI-B). These data indicate that FTD/TPI-B provides an additional treatment option in first line for patients not eligible for intensive chemotherapy combinations.[7]

Collectively, data from C-TASK FORCE, the Danish study, and TASCO1 have shown that the combination of FTD/TPI-B demonstrated a manageable safety profile with no new safety findings. Based on the efficacy findings in TASCO1 we respectfully request NCCN to consider adding FDT/TPI-B as an option for the first line treatment of patients with mCRC not eligible for intensive combination chemotherapy.

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. AVASTIN® (bevacizumab) [prescribing information]. South San Francisco, CA: Genentech, Inc.; 2019.
3. Mayer RJ, Cutsem EV, Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic colon cancer. *N Engl J Med*. 2015; 372:1909-1919.
4. Tsukihara H, Nakagawa F, Sakamoto K, et al. Efficacy of combination chemotherapy using a novel oral chemotherapeutic agent, TAS–102, together with bevacizumab, cetuximab, or panitumumab on human colorectal cancer xenografts. *Oncol Rep* 2015; 33**:**2135–42.
5. Kuboki Y, Nishina T, Shinozaki E, et al. TAS-102 plus bevacizumab for patients with metastatic colorectal cancer refractory to standard therapies (C-TASK FORCE): an investigator-initiated, open-label, single-arm, multicentre, phase 1/2 study. *Lancet Oncol*. 2017 Jul 28. pii: S1470-2045(17)30425-4. doi: 10.1016/S1470-2045(17)30425-4.
6. Pfeiffer P, Yilmaz M, Møller S, et al. TAS-102 with or without bevacizumab in patients with chemorefractory metastatic colorectal cancer: an investigator-initiated, open label, randomised phase II trial. *Lancet Oncol.* January 27, 2020. https://doi.org/10.1016/S1470-2045(19)30827-7.
7. Van Cutsem E, Danielewicz I, Saunders MP, et al. Trifluridine/Tipiracil plus bevacizumab in patients with untreated metastatic colorectal cancer ineligible for intensive therapy: the randomized TASCO1 study. *Ann. Oncol*.2020.doi: https:// doi.org/10.1016/j.annonc.2020.05.024.


Sincerely,

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Blakolmer (Jun 10, 2020 15:42 EDT)


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