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Date of Request: 22 September 2015
Guidelines Panel: Colon and Rectal Cancers

Re: Request for NCCN Guidelines Colon and Rectal Cancer Panel to consider review of data for trifluridine and tipiracil (*Lonsurf®*) for treatment of metastatic colorectal cancer

On behalf of Taiho Oncology, Inc., I respectfully request the NCCN Colon and Rectal Cancer Panels to review the enclosed data for inclusion of trifluridine and tipiracil (*Lonsurf®*) for treatment of metastatic colorectal cancer, in the NCCN Guidelines and Compendium.

Lonsurf® was approved by the FDA on 22 September 2015. It is a combination of trifluridine (FTD), a nucleoside metabolic inhibitor, and tipiracil (TPI), a thymidine phosphorylase inhibitor. FTD incorporation into DNA is to be the primary mechanism of anti-tumor activity with oral administration. This mechanism of action of FTD/TPI differentiates it from conventional fluoropyrimidines, which are uracil-based, and primarily act via thymidylate synthase (TS) inhibition. The differing primary mechanism of action allows FTD/TPI to potentially overcome resistance to conventional fluoropyrimidines.[1,2] In addition, clinical trial data suggests that FTD/TPI is the first dThd-based antitumor agent whose main mechanism is the inhibition of DNA incorporation itself.[3]

[1] *Lonsurf®* prescribing information. Taiho Oncology, Inc., 9/15.
[2] Lenz HJ, et al. TAS-102, a novel antitumor agent: a review of the mechanism of action. *Cancer Treatment Reviews* (accepted manuscript); DOI: http://dx.doi.org/10.1016/j.ctrv.2015.06.001.
[3] Sakamoto K, et al. Crucial roles of thymidine kinase 1 and deoxyUTPase in incorporating the antineoplastic nucleosides trifluridine and 2'-deoxy-5-fluorouridine into DNA. *Int J Oncol* 2015 Apr 20; 2327-34. DOI: 10.3892/ijo.2015.2974

Specific Request:

Specific changes: Review of trifluridine and tipiracil as treatment of metastatic colorectal cancer, and addition to the NCCN Guidelines and Compendium for colon and rectal cancers, to fulfill an unmet medical need.

FDA Clearance: Trifluridine and tipiracil is FDA-cleared for the treatment of patients with metastatic colorectal cancer 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.

Rationale: The FDA, phase II, and phase III clinical trials document support of trifluridine and tipiracil for the treatment of patients refractory to standard metastatic colorectal cancer therapies, based on significant improvement in overall survival and progression-free survival compared with placebo, unique mechanism of action, and an acceptable safety profile.

The following references are submitted in support of this proposed change. We would like to acknowledge the contributions of NCCN panel members who are also co-authors or co-contributors of these publications.

1. NDA 207981 - approval letter and press release <<http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm463650.htm>>.

2. *Lonsurf®* prescribing information. Taiho Pharmaceutical Co., Ltd., 9/15 <<www.taihooncology.com/us/prescribing-information.pdf>>.

3. Mayer RJ, et al. Randomized Trial of TAS-102 for Refractory Metastatic Colorectal Cancer (RECOURSE). *N Engl J Med* 2015; 372:1909-19. DOI: http://dx.doi.org/10.1056/NEJMoa1414325.

4. Yoshino T, et al. TAS-102 monotherapy for pretreated metastatic colorectal cancer: A double, randomized, placebo-controlled phase II trial. *Lancet Oncol* 2012; 13: 993-1001.

5. Lenz HJ, et al. TAS-102, a novel antitumor agent: a review of the mechanism of action. *Cancer Treatment Reviews* (accepted manuscript); DOI: http://dx.doi.org/10.1016/j.ctrv.2015.06.001.

6. Sakamoto K, et al. Crucial roles of thymidine kinase 1 and deoxyUTPase in incorporating the antineoplastic nucleosides trifluridine and 2'-deoxy-5-fluorouridine into DNA. *Int J Oncol* 2015 Apr 20; 2327-34. DOI: 10.3892/ijo.2015.2974.

If you have any questions or require additional information, please do not hesitate to contact me.

Sincerely,
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Taiho Oncology, Inc.