Extension of the European Medicines Agency (EMA) approval of trifluridine/tipiracil for gastric cancer

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The European Medicines Agency’s (EMA) Committee for Medicinal Products for Human Use has recommended an extension to the indication of trifluridine/tipiracil. Previously, trifluridine/tipiracil had been approved as a later line treatment in colorectal cancer (CRC). Now, a positive opinion for the use of trifluridine/tipiracil as monotherapy for the treatment of adult patients with metastatic gastric cancer including adenocarcinoma of the gastro-oesophageal junction, who have been previously treated with at least two prior systemic treatment regimens for advanced disease, has been given on 25 July 2019 with full EMA approval on 6 September 2019.

Gastric and gastro-oesophageal junction cancer (GC) represents a significant worldwide problem, being the sixth most common malignancy and the fifth most common cause of cancer death.1 Due to its critical location, patients with GC normally present with symptoms which can impact on their performance status. This fact, linked with the inherent aggressiveness of this tumour, makes GC as one of the most difficult neoplasias to manage. In the metastatic setting, first-line and second-line chemotherapy treatment improve survival and quality of life (QoL) of patients with GC.2 Only two targeted agents have demonstrated their efficacy in GC; trastuzumab in the first-line setting for patients with human epidermal growth factor receptor-2 (HER-2)-positive GC tumours, and ramucirumab in the second-line setting. The lack of an adequate biomarker selection, together with the intrinsic heterogeneity of GC, has challenged the development of many other targeted agents that have been tested in clinical trials including trastuzumab in the second-line setting.

Trifluridine/tipiracil is an orally active chemotherapy agent which comprises a nucleoside analogue consisting of a thymidine base (trifluridine) and a thymidine phosphorylase (TP) inhibitor (tipiracil). Trifluridine/tipiracil has a unique mechanism of action with antitumor activity based primarily via the trifluridine incorporation into replicating DNA strands, resulting in the inhibition of cell proliferation and tumour growth. Trifluridine also inhibits thymidine synthetase (TS) which is necessary for DNA synthesis, but this is believed to play a minor role in its antitumor effects. Tipiracil is an inhibitor of the TP, which inhibits trifluridine degradation and consequently increases its availability. Trifluridine/tipiracil had been previously approved for patients with refractory CRC, based on the results of the phase III RECOURSE trial,4 and had demonstrated preliminary efficacy in Japanese patients with GC (EPOC1201 trial).5 Fluoropyrimidines (fluorouracil (5-FU), capecitabine and S-1, a prodrg of 5-FU) are the most extensively used chemotherapeutic agents in gastrointestinal (GI) cancers. Indeed, they constitute the backbone of the combination therapies for these cancers, being recommended for first-line and second-line treatment of metastatic CRC6 7 and first-line metastatic GC, as well as perioperative and adjuvant therapy.2 The cytotoxic mechanism of action of the fluoropyrimidines is primarily mediated via the inhibition of TS by one of its metabolites thereby impeding DNA synthesis. Antitumor activity is also achieved through the misincorporation of 5-FU metabolites into DNA and RNA. The primary difference in the mechanism of action of trifluridine compared with fluoropyrimidines enables trifluridine/tipiracil to overcome acquired resistance to these standard therapies. Preclinical data demonstrating activity of trifluridine/tipiracil in 5-FU-resistant and other fluoropyrimidine-resistant cell lines and in fluoropyrimidine-refractory patients have been validated in clinical trials including in chemorefractory CRC where it is a standard of care.4 8

The approval for trifluridine/tipiracil in GC is based on the results of the Trifluridine/Tipiracil vs Placebo in Patients with Advanced...
In conclusion, in a chemorefractory patient population affected by GC, trifluridine/tipiracil has demonstrated to offer a clinically meaningful and statistically significant improvement in the median OS with an increase of 2.1 months compared with placebo, with a good tolerability and a trend towards patient QoL improvement. Thus, the benefit of trifluridine/tipiracil to overcome fluoropyrimidine resistance has been clearly established. Ongoing research evaluating different combinations with trifluridine/tipiracil will determine its potential role as the chemotherapeutic backbone for the continuum of care for GC in the future.

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**REFERENCES**

1. Bray F, Ferlay J, Soerjomataram I, et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 2018;68(6):394–424.
2. Smyth EC, Verheij M, Allum W, et al. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27(suppl 5):v38–49.
3. Alsina M, Miquel JM, Diez M, et al. Gastric cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2016;27(suppl 5):v38–49.
4. Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med 2015;372:1909–19.
5. Bando H, Doi T, Muro K, et al. A multicenter phase II study of TAS-102 monotherapy in patients with pre-treated advanced gastric cancer (EPOC1201). Eur J Cancer 2016;62:46–53.
6. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. Ann Oncol 2016;27:1386–422.
7. Yoshino T, Arnold D, Taniguchi H, et al. Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: a JSMO-ESMO initiative endorsed by CSCO, KACC, mos, Sso and TOS. Ann Oncol 2018;29:44–70.
8. 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(9):1437–48.
9. Alsina M, Tabernero J, Shitara K, et al. Analysis of symptoms and functional HRQoL scales in TAGS, a phase III trial of trifluridine/tipiracil (FTD/TPI) in metastatic gastric cancer (mGC). JCO 2019;37(15_suppl):4043.
10. Peeters M, Cervantes A, Moreno Vera S, et al. Trifluridine/tipiracil: an emerging strategy for the management of gastrointestinal cancers. Future Oncology 2018;14(14):1629–45.