ESMO Open
Cancer Horizons

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

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To cite: Alsina M, Smyth EC. Extension of the European Medicines Agency (EMA) approval of trifluridine/tipiracil for gastric cancer. *ESMO Open* 2019;**4**:e000591. doi:10.1136/esmoopen-2019-000591

Received 9 September 2019
Revised 16 September 2019
Accepted 18 September 2019

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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 its 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 phase III clinical trials.[2 3]

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 prodrug 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 CRC[6 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*

Gastric Cancer Trial,[8] a randomised phase III trial which randomised in a 2:1 ratio 507 patients with GC refractory to at least two lines of chemotherapy to receive either best supportive care (BSC) plus trifluridine/tipiracil (35 mg/m^2 twice daily on days 1–5 and days 8–12 every 28 days) or BSC plus placebo. Randomisation was stratified by region (Japan vs rest of the world), Eastern Cooperative Oncology Group (ECOG) performance status (0 vs 1) and previous treatment with ramucirumab (yes vs no). Both patients and investigators were masked to treatment allocation, and the primary endpoint was the median overall survival (OS) in the intention-to-treat population. Median OS was 5.7 months in the trifluridine/tipiracil group and 3.6 months in the placebo group (HR 0.69, 95% CI 0.56 to 0.85; p<0.001). The efficacy of trifluridine/tipiracil was maintained after adjusting for prognostic factors (ECOG performance status, age, number of previous chemotherapy regiments, number of metastatic sites and HER-2 status). Trifluridine/tipiracil offered a relatively low objective response rate (ORR), although with a good disease control rate (DCR) (ORR and DCR of 4% and 44%, respectively, in patients receiving trifluridine/tipiracil, vs 2% and 14% in the placebo group). Although a higher number of adverse events (AE) were observed in trifluridine/tipiracil-treated patients (grade ≥3 events in 80% of the patients in the trifluridine/tipiracil group vs 58% in the placebo group), most of AEs were mainly non-complicated haematological AEs. The tolerability of trifluridine/tipiracil is demonstrated by the low rate of treatment discontinuation due to AEs (11% in the trifluridine/tipiracil group vs 13% in the placebo group). Notably, patient QoL remained stable for most functional and symptom scales in both arms, and a positive trend towards a lower risk of the QoL deterioration was reported for the patients receiving trifluridine/tipiracil.[9]

Use of combination regimens of fluoropyrimidines with other chemotherapeutic agents (ie, 5-FU, leucovorin and oxaliplatin) and/or molecularly targeted agents has lengthened survival time in patients with metastatic CRC and GC, compared with earlier treatment with 5-FU alone. For this reason, the combination of trifluridine/tipiracil with other anticancer agents could have the potential to enhance its efficacy. Clinical trials are now underway evaluating the combination of trifluridine/tipiracil with other chemotherapies (oxaliplatin and irinotecan), targeted therapies (vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) inhibitors) and immunotherapies (programmed cell death protein-1/programmed death ligand-1 inhibitors).[10] In particular, early results combining trifluridine/tipiracil with anti-VEGF and anti-EGFR antibodies in colon cancer have shown promise.[10] Having established trifluridine/tipiracil as a standard in refractory GI cancers, it is hoped that moving this novel compound into earlier lines of therapy will continue to improve survival for patients with GC.

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,[8] 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.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests MA declares scientific consultancy and/or speaking honoraria from Amgen, BMS, Lilly, MSD, Roche and Servier. ECS declares honoraria from Astellas, BMS, Celgene, Five Prime Therapeutics, Servier and Gritstone Oncology.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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