Editorial

The role of biomarker in later-line treatment for metastatic colorectal cancer

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Trifluridine/tipiracil (FTD/TPI) is an oral drug that inhibits thymidylate synthase, interfering with DNA synthesis (1). FTD/TPI monotherapy demonstrated efficacy for overall survival in heavily treated metastatic colorectal cancer (mCRC) in the RECOURSE trial with a hazard ratio (HR) of 0.68 [95% confidence interval (CI): 0.58–0.81] against the placebo (1). FTD/TPI is widely used as the standard later-line treatment worldwide (2-4), and its efficacy and safety have been reproduced in real-world data (RWD) (5,6). Regorafenib is also a late-line treatment option, and it remains an important clinical question whether FTD/TPI or regorafenib should be administered first. As administration of all active drugs has been shown to improve survival of mCRC (7,8), information on predictive biomarkers is helpful for patient selection and for improving prognosis.

Neutropenia is considered a predictive factor for the efficacy of FTD/TPI (9,10). However, it is difficult to identify during drug selection. In mCRC, the difference in drug response, depending on the *RAS*/*BRAF*/microsatellite instability (MSI) status, as well as primary tumor location, is an area of interest. FTD/TPI has shown similar antitumor effects regardless of the *KRAS* mutation status (11). There are few reports that evaluate the effect of each *BRAF* mutation and MSI status in a large number of patients, including those with RWD. In the article of Martínez-Pérez *et al.* (12), the *BRAF* V600E mutant was a predictive biomarker and microsatellite stable (MSS) was a prognostic factor, in addition to the previously reported biomarkers. As for the MSI status, FTD/TPI has shown antitumor effects regardless of MSI status in preclinical models (13). It is interesting that the antitumor effects of FTD/TPI differed depending on the MSI status in RWD. However, the number of MSI-H patients in the present study was small, and future analysis in a larger cohort is needed.

Recently, later-line treatment for mCRC has been further advanced. The addition of bevacizumab to FTD/TPI showed good treatment efficacy in several phase 2 trials (14-16) and in a randomized phase 2 trial (17). Moreover, the SUNLIGHT trial demonstrated that the addition of bevacizumab to FTD/TPI significantly prolonged overall survival compared with FTD/TPI monotherapy (18,19). The FRESCO-2 study also showed the superiority of fruquintinib monotherapy compared with the best supportive care with a HR of 0.662 (95% CI: 0.549–0.8000) (20,21). Randomized phase 3 clinical trials of the combination therapy, with immune checkpoint inhibitors targeting MSS mCRC, are ongoing (*Table 1*). Biomarkers will become increasingly beneficial in the near future as more treatment options are expected to become available.

Table 1 List of the ongoing randomized phase 3 clinical trials for the combination therapy with immune checkpoint inhibitors targeting MSS mCRC

Checkpoint inhibitor	Study treatment groups	Primary endpoint	Trial identifier
Pembrolizumab	Pembrolizumab + lenvatinib versus SOC (regorafenib or FTD/TPI)	OS	NCT04776148 (LEAP-017)
Favezelimab/pembrolizumab	Favezelimab/pembrolizumab versus SOC (regorafenib or FTD/TPI)	OS	NCT05064059 (MK-4280A-007)
Nivolumab/relatlimab FDC	Nivolumab/relatlimab FDC versus SOC (regorafenib or FTD/TPI)	OS	NCT05328908 (RELATIVITY-123)

MSS, microsatellite stable; mCRC, metastatic colorectal cancer; SOC, standard of care; FTD/TPI, trifluridine/tipiracil; OS, overall survival; FDC, fixed dose combination.

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