Editorial Commentary

Angiogenesis inhibitors for metastatic colorectal cancer

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With the recent publications of two important studies, FRESCO-2 (1) and SUNLIGHT (2), we now have data from phase 3 randomized trials showing benefit of anti-angiogenic therapy across the continuum of care, from first to fourth line, in patients with metastatic colorectal cancer (mCRC).

Colorectal cancer (CRC) is the third most prevalent cancer worldwide. Every year around 1.9 million new patients were diagnosed. Approximately half of the patients will, sooner or later, be diagnosed with mCRC, either at the time of diagnosis or later, due to recurrence. Unfortunately, more than 0.9 million (almost 50% of CRC patients) die each year posing a significant challenge for the oncologist community (3).

Since the turn of the millennium, therapy of patients with mCRC has changed extensively, and a doublet or triplet combination of chemotherapy with a targeted agent is now widely used (4,5). Modern treatment strategy for patients with mCRC consists of sequential lines of different systemic therapies. However, with each treatment line, 20–50% of patients will not be candidates for further therapy. The proportion depends very much on patient selection; patients included in clinical trials more often receive further lines of therapy than those in unselected cohorts. The European Society for Medical Oncology has stated that the treatment goal is that 50% of 'fit' first-line patients should receive third-line therapy (4), however, in real-world cohorts only 25–30% of 'real-world first-line patients' are receiving third-line therapy and only 10–15% fourth-line (6,7).

First-line chemotherapy consists of a combination of 5-fluorouracil (5FU) and irinotecan followed upon progression by 5FU and oxaliplatin (or vice versa) and often a molecular-targeted drugs will be added, e.g., epidermal growth factor receptor inhibitors (for selected patients whose tumors are *RAS*wt/*BRAF*wt) or anti-angiogenic drugs which can be used in all patients independently of the molecular subtypes (4,5).

The treatment of patients with mCRC, has in general changed from 'one strategy fits all' to a more personalized approach. This strategy is, however, not yet the case for anti-angiogenic therapy due to the absence of validated predictive biomarkers. In this commentary, we will stick to the therapeutic approach in molecularly unselected patients and leave the discussion of 'druggable alterations' to others (5,8).

Angiogenesis refers to the creation of new blood vessels from already present endothelial cells. Angiogenesis plays an important part in the continued growth of malignant cells since growth beyond a few millimeters requires a blood supply (9). However, malignant blood vessels are often functionally abnormal and consist of an unbalanced network of leaky blood vessels, which result in a high intratumoral

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pressure. Folkman (10) described this dependency 50 years ago and the factor that stimulated the formation of new blood vessels was later named vascular endothelial growth factor (VEGF). This system comprises of 6 ligands and 3 receptors (VEGFR).

Targeting angiogenesis represents a key element in the overall treatment strategy and angiogenesis inhibition is in general clinically effective and has an important place in the therapeutic armamentarium of mCRC. Anti-angiogenic drugs consist of 2 main groups (9); the monoclonal antibodies (mAbs) and the small molecules, tyrosine kinase inhibitors (TKIs). The mAbs bind directly to VEGF-A or block the extracellular binding domain of the matching receptor.

Bevacizumab, a humanized mAb that targets VEGF-A and was approved in 2004, is used in combination with chemotherapy in first-line or in second-line treatment or, according to a 'beyond progression' strategy, in both first- and second-line with a change of the chemotherapy backbone. Two other anti-angiogenic drugs (aflibercept, a recombinant fusion protein and ramucirumab, a fully human mAb that exclusively targets the VEGFR-2 ligand-binding domain) are approved in combination with chemotherapy as second-line treatment (9). As monotherapy, mAbs have limited efficacy in mCRC, but in general, anti-angiogenic therapy increases efficacy of chemotherapy with a slightly additional toxicity (9).

The small molecules, TKIs, exert their anti-angiogenic effect after internalization in the cell and binding to, and inhibit the kinase domain of the various receptors involved in the angiogenesis. Despite many studies including thousands of patients—in contrast to the mAbs—no randomized study has shown a survival benefit of TKIs in combination with chemotherapy neither in first- or second-line therapy in mCRC (9). So far, only regorafenib has been implemented in the treatment sequence of mCRC patients.

As first-line therapy, bevacizumab in combination with 5FU monotherapy or IFL (an outmoded bolus regimen combining irinotecan and 5FU), substantially improved efficacy with a median overall survival (OS) benefit of 3–6 months (9). However, in combination with modern regimens (e.g., FOLFOX or CapOx), the advantage was more modest and the survival benefit was only around 1.5 months (9,11,12). As second-line therapy with non-cross resistant chemotherapy, bevacizumab (or aflibercept/or ramucirumab) prolonged median survival with about two months, also in patients who had received bevacizumab as part of first-line therapy.

Until recently, after failure of the first two subsequent lines of therapy, treatment possibilities for patients with molecularly unselected mCRC were limited to two orally administered drugs: regorafenib (13) and trifluridine–tipiracil (FTD/TPI) (14).

Regorafenib is an oral multikinase inhibitor that blocks numerous protein kinases including VEGFR1. Compared to placebo, regorafenib prolonged median OS with 1.4 months (from 5.0 to 6.4 months). The most common grade 3 or more symptomatic adverse events were hand-foot skin reaction (17%), fatigue (10%), diarrhea (7%), and rash (6%). In 2012, regorafenib was approved as third-line monotherapy in unselected patients with chemo-refractory mCRC.

FTD/TPI consists of an antineoplastic thymidine-based nucleoside analogue, trifluridine, and a thymidine phosphorylase inhibitor, tipiracil hydrochloride, which prevents the rapid breakdown of trifluridine. Compared to placebo, FTD/TPI prolonged median OS with 1.8 months (from 5.3 to 7.1 months) with limited toxicity. In 2015, FTD/TPI was approved as a third-line monotherapy option in unselected patients with chemo-refractory mCRC.

However, angiogenesis received renewed interest after the publication of SUNLIGHT and FRESCO-2 trials, showing benefit of anti-angiogenic therapy across all lines of therapy (1,2).

A Danish randomized trial including 93 patients with mCRC showed a median survival benefit of 2.7 months [from 6.7 to 9.4 months; hazard ratio (HR) =0.55, P=0.028] for the combination of bevacizumab with FTD/TPI compared to FTD/TPI with a comparable benefit across patient subgroups, including prior treatment with bevacizumab in the immediate past line of therapy (15). These promising results were recently confirmed by data from the large SUNLIGHT study which had a similar design.

SUNLIGHT was an international, randomized phase 3 study, including 492 patients with metastatic colorectal adenocarcinoma. Patients should have received a maximum of two prior lines of systemic treatment including all current standard approved therapies (5FU, oxaliplatin, irinotecan, anti-EGFR (only for *RAS*wt), and anti-VEGF mAb). The combination of bevacizumab with FTD/TPI prolonged median OS with 3.3 months from 7.5 to 10.8 months (HR =0.61; P<0.001). The progression-free survival (PFS) was prolonged from 2.4 to 5.6 months in the combination group (HR =0.44; P<0.001). In both groups, most common adverse events were hematological toxicities (neutropenia and anemia), hypertension, and nausea.

Consequently, in June 2023, the European Medicines Agency (EMA) and in August 2023 the U.S. Food and Drug Administration (FDA) adopted a positive opinion recommending a change to the terms of the marketing authorisation for FTD/TPI (Lonsurf) to: Lonsurf is indicated in combination with bevacizumab for the treatment of adult patients with mCRC who have received two prior anticancer treatment regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents.

The importance of VEGFR is paramount in tumor angiogenesis and progression. The new pan-VEGFR inhibitor fruquintinib was developed to enhance kinase selectivity resulting in improved efficacy and better tolerability. Fruquintinib demonstrated a favorable toxicity profile as monotherapy and is currently investigated in combination with other drugs in clinical trials. Based on data from the FRESCO trial, fruquintinib has been approved in China (16). The FRESCO trial was a Chinese phase 3 trial including 416 patients with chemo-refractory mCRC and patients were randomized to fruquintinib or placebo. Treatment with fruquintinib prolonged median OS with 2.7 months (from 6.6 to 9.3 months, HR =0.65; P<0.001).

FRESCO-2 was an international, randomized, placebo-controlled study conducted in 14 countries and in less than 16 months, including 691 patients with mCRC (1). Patients had received all current standard approved therapies (5FU, oxaliplatin, irinotecan, anti-EGFR (only for *RAS*wt), and bevacizumab) and patients should be resistant or intolerant to FTD/TPI, or regorafenib (or both). FRESCO-2 included more heavily pretreated patients than SUNLIGHT.

The primary endpoint of the FRESCO-2 study, OS was 7.4 months in the fruquintinib arm *vs.* 4.8 months with placebo arm (HR =0.66, 95% CI: 0.55–0.80; P<0.0001). Fruquintinib also improved PFS from a median of 1.8 to 3.7 months (HR =0.32; P<0.0001). At 6 months, 24% of patients in the fruquintinib group versus 1% in the placebo group had no sign of progressive disease. Fruquintinib improved OS and PFS across all patient subgroups, including prior treatment with FTD/TPI or regorafenib. Only 25 patients had not received prior VEGF inhibitors and in this small group the advantage was extensive (HR =0.19), but also prior anti-VEGF treated patients benefitted (HR =0.68). Common symptomatic grade ≥3 adverse events were), asthenia (8%) and hand-foot syndrome (6%). Treatment discontinuation due to adverse events occurred in 20% and 21% of the patients receiving fruquintinib *vs.* placebo, respectively.

Currently, a New Drug Application for fruquintinib undergoes priority review by the FDA for mCRC indication in line with the FRESCO-2 inclusion criteria.

As third line therapy in unselected patients with mCRC, the combination of FTD/TPI with bevacizumab will be the new standard of care in mCRC and fruquintinib will probably be the standard of care in patients progressing to FTD/TPI and bevacizumab even though only few patients in FRESCO-2 study did receive the FTD/TPI and bevacizumab combination immediately prior starting fruquintinib. In the FRESCO-2 study, all subgroups seemed to benefit from fruquintinib but it would be interesting to see if patients receiving bevacizumab in the immediate prior line before starting fruquintinib do benefit to the same extent from this new fascinating anti-angiogenic therapy.

The results of the SUNLIGHT and the FRESCO-2 studies support the use of anti-angiogenic therapy in the continuum of care for patients with chemo-refractory mCRC. A significant number of ongoing and planned phase 2 and 3 trials, mainly Chinese, are testing promising and interesting combinations of fruquintinib with chemotherapy (including FTD/TPI), targeted agents, and immunotherapy, also in earlier lines of therapy. Results from these trials will hopefully guide to the best clinical practice and establish the place of emerging treatment options in the continuum of care for patients with mCRC.

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aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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