

# Advances in Colon Cancer Therapy

DOI: 10.36000/HBT.OH.2022.14.088

De Dosso S. Advances in Colon Cancer Therapy. *healthbook TIMES Onco Hema.* 2022;14(4):xx-xx.



**PD Dr Sara De Dosso**  
Deputy Head of Medical Oncology  
Oncology Institute of  
Southern Switzerland (IOSI)  
Bellinzona, Switzerland

### Neoadjuvant therapy in colon cancer

Neoadjuvant therapy in the management of colon cancer is an underdeveloped field<sup>1</sup> and surgical resection followed by adjuvant chemotherapy is currently the only treatment option available to Swiss clinicians. Neoadjuvant therapies have shown many positive impacts in upper gastrointestinal cancers; these benefits could be potentially translated in colon cancer such as the early treatment of systemic micro-metastases, the downsizing of tumors by increasing R0 resection, as well as testing the response to treatment on an individual basis.

The phase III FOxTROT trial evaluated the efficacy and safety of neoadjuvant chemotherapy versus surgery followed by chemotherapy in patients with locally advanced colon cancer.<sup>2</sup> Previously presented data showed that the primary endpoint of disease-free survival (DFS) was not met, despite a trend towards DFS improvement. Although not practice-changing, the trial demonstrated a significantly lower response ( $p<0.001$ ) in patients with mismatch repair deficient (dMMR) compared with mismatch repair proficient (pMMR) tumors. Notably, about 10–15% of colon cancers are dMMR, a third of which are associated with Lynch syndrome. Stage III dMMR colorectal cancer (CRC) has a relatively high rate of recurrence at 20–40% and is known to be less responsive to conventional chemotherapy compared with pMMR CRCs in both the adjuvant setting and metastatic disease. Of interest, a proof-of-concept trial on programmed cell death protein 1 (PD-1) blockade as curative intent therapy in dMMR locally advanced rectal cancer showed that dostarlimab treatment for 6 months resulted in clinical complete remission rate of 100%, as presented at this year's ASCO Annual Meeting.<sup>3,4</sup>

### NICHE-2: Major pathological response in nearly all patients with dMMR tumors treated with nivolumab and ipilimumab

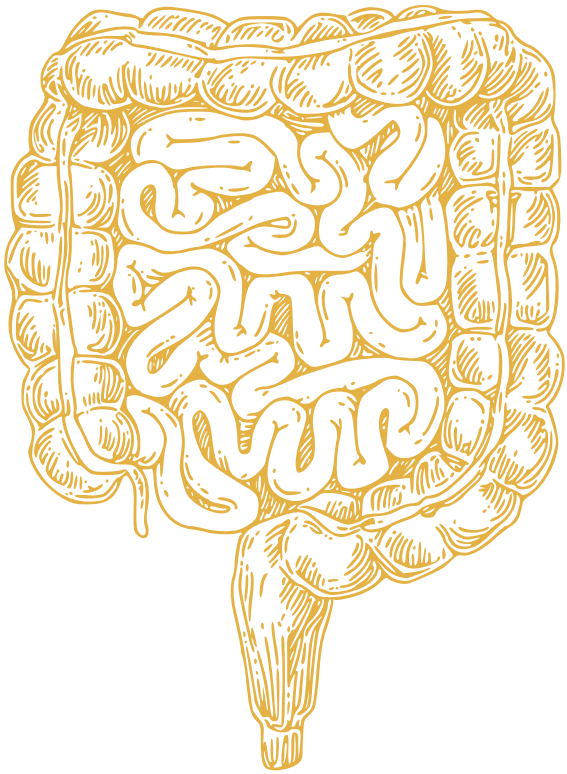
The proof-of-concept NICHE-1 study showed that neoadjuvant immune checkpoint blockade is highly effective in non-metastatic dMMR colon cancers, with 100% of patients ( $n=20$ ) achieving a pathologic response and 60% a complete response.<sup>5</sup> This formed the rationale for the non-randomized multicenter NICHE-2 trial,

in which patients with non-metastatic and previously untreated dMMR colon cancer received nivolumab (3 mg/kg, cycles 1 and 2) and ipilimumab (1 mg/kg, cycle 1) followed by surgery within 6 weeks of therapy initiation.<sup>6</sup> The co-primary endpoints were safety and feasibility, and 3-year DFS; secondary endpoints included major and complete pathologic response rates (MPR and pCR, respectively) and circulating tumor DNA dynamics. Importantly, high-risk stage III disease was seen in 74% of patients in the intention-to-treat (ITT) population ( $n=112$ ). Addressing safety, the incidence of grade  $\geq 3$  immune-related adverse events (AEs) was very low at 4%. A total of 98% of patients underwent timely surgery, therefore meeting the safety and feasibility primary endpoint, which was set at 95%. MPR was achieved in 95% of patients and pCR was achieved in 67% of patients. In addition, an exploratory analysis of pCRs among patients with Lynch syndrome versus sporadic tumors indicated that Lynch syndrome was associated with a higher response rate to neoadjuvant immunotherapy ( $n=97$ , 78% vs 58%;  $p=0.056$ ). Given the size of the test population, the results require further confirmation. These results are not immediately practice-changing and the upcoming 3-year DFS data will provide a clearer understanding of the use of neoadjuvant immunotherapy in dMMR colon cancers.

In general, a neoadjuvant approach in locally advanced colon cancer must be carefully considered, as decision-making is based on radiological tumor assessment which is particularly difficult in this setting and might result in more aggressive treatment than needed. A neoadjuvant immunotherapy could be considered in case of locally advanced tumors, with infiltration of the other abdominal organs, in order to facilitate a more conservative surgery.

### CAIRO5: Neoadjuvant approach for CRC patients with initially unresectable liver metastases and left-sided primary tumors

First-line treatment strategies combining chemotherapy and targeted therapy have been under investigation in patients with primarily unresectable liver metastasis were randomized to receive either doublet (FOLFOX or FOLFIRI) or triplet (FOLFOXIRI)



chemotherapy plus bevacizumab in case of right-sided primary tumors and/or RAS/BRAF V600E-mutated. Furthermore, patients with left-sided and RAS/BRAF V600E wild-type primary tumors were randomized to receive doublet chemotherapy plus either bevacizumab (anti-vascular endothelial growth factor [VEGF] antibody) or panitumumab (anti-epidermal growth factor receptor [EGFR] antibody).<sup>7,8</sup> The primary endpoint was progression-free survival (PFS); secondary endpoints included overall survival (OS), overall response rate (ORR), toxicity, R0/1 resection rates and postoperative morbidity. Results from patients with right-sided and/or RAS/BRAF V600E-mutated primary tumors were presented at the ASCO Annual Meeting 2022 and showed a clinical benefit of the triplet combination regimen in this patient population.<sup>8</sup> At the ESMO Congress 2022, data from patients with left-sided and RAS/BRAF V600E wild-type primary tumors were reported.<sup>7</sup> At a median follow-up of 44 months, there was no difference in median PFS between the

bevacizumab ( $n=114$ ) and panitumumab ( $n=116$ ) arms (10.8 months vs 10.4 months, HR: 1.12 [95% CI: 0.83–1.52];  $p=0.45$ ). Panitumumab versus bevacizumab plus chemotherapy improved ORRs (76% vs 52%;  $p<0.001$ ) and depth of response (49% vs 33%;  $p<0.001$ ); however, this did not translate into a higher resection/ablation rate (67% vs 68%;  $p=1$ ). The awaited OS data would be valuable for clinical practice guidelines.

### FRESCO-2: Significant PFS benefit with fruquintinib for patients with refractory metastatic colorectal cancer

Fruquintinib is a highly selective and potent oral tyrosine kinase inhibitor of VEGF receptors 1, 2 and 3<sup>9,10</sup> and was approved in China based on positive data from the phase III FRESCO study in Chinese patients with mCRC and progression after  $\geq 2$  prior lines of therapy.<sup>11,12</sup> The follow-up global, phase III FRESCO-2 trial enrolled patients with mCRC and prior treatment with fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy if RAS wild-type; prior exposure to TAS-102 and/or regorafenib; prior treatment with an immune checkpoint inhibitor or BRAF inhibitor if indicated.<sup>13</sup> Patients were randomized 2:1 to receive best supportive care (BSC) plus either fruquintinib (5 mg, daily; 3 weeks on, 1 week off) ( $n=458$ ) or placebo ( $n=229$ ). The primary endpoint was OS. PFS, objective response rate (ORR), disease control rate (DCR) and safety were secondary objectives. Fruquintinib plus BSC significantly prolonged median OS by 2.6 months (7.4 months vs 4.8 months, HR: 0.662 [95% CI: 0.549–0.800];  $p<0.001$ ). OS favored fruquintinib plus BSC in most key subgroups, including patients with prior VEGF inhibitor and prior EGFR inhibitor therapy (HR  $<0.7$  for both). Furthermore, the addition of fruquintinib to BSC significantly improved PFS (median, 3.7 months vs 1.8 months, HR: 0.321 [95% CI: 0.267–0.386];  $p<0.001$ ). The DCR was 55.5% with fruquintinib and 16.1% with placebo ( $p<0.001$ ), with a confirmed ORR of 1.5% versus 0%, respectively. Regarding safety, 62.7% of patients in the fruquintinib arm experienced grade  $\geq 3$  AEs compared with 50.4% in the placebo arm, with the most common being hypertension (13.6% and 0.9%). In conclusion, fruquintinib provides a possible new treatment option with a meaningful survival benefit in heavily pretreated patients with mCRC.

1. Roth MT, Eng C. Neoadjuvant Chemotherapy for Colon Cancer. *Cancers (Basel)*. 2020;12(9):2368. doi:10.3390/cancers12092368.

2. Seymour MT and Morton D. FOxTROT: an international randomised controlled trial in 1052 patients (pts) evaluating neoadjuvant chemotherapy (NAC) for colon cancer. Presented at: 2019 ASCO Annual Meeting I; 31 May–4 June 2019. Abstract 3504.

3. Cercek A, Lumish M, Sinopoli J, et al. PD-1 Blockade in Mismatch Repair-Deficient, Locally Advanced Rectal Cancer. Presented at: 2022 ASCO Annual Meeting; 3–7 June 2022. Chicago, IL, USA. Abstract 16.

4. Cercek A, Lumish M, Sinopoli J, et al. PD-1 Blockade in Mismatch Repair-Deficient, Locally Advanced Rectal Cancer. *N Engl J Med*. 2022;386(25):2363–2376. doi:10.1056/NEJMoa2201445

5. Chalabi M, Fanchi LF, Dijkstra KK, et al. Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers. *Nature Medicine*. 2020;26(4):566–576. doi:10.1038/s41591-020-0805-8

6. Chalabi M, Verschoor YL, van den Berg J et al. Neoadjuvant immune checkpoint inhibition in locally advanced MMR-deficient colon cancer: The NICHE-2 study. Presented at: 2022 ESMO Congress; 9–13 September 2022. Paris, France. Oral presentation LBA7.

7. Bond MJ, Bolhuis K, Loosveld OJL, et al. FOLFOX/FOLFIRI plus either bevacizumab or panitumumab in patients with initially unresectable colorectal liver metastases (CRLM) and left-sided and RAS/BRAFV600E wild-type tumour: Phase III CAIRO5 study of the Dutch Colorectal Cancer Group. Presented at: 2022 ESMO Congress; 9–13 September 2022. Paris, France. Oral presentation LBA21.

8. Punt CJA, Bond MJG, Bolhuis K, et al. FOLFOXIRI + bevacizumab versus FOLFOX/FOLFIRI + bevacizumab in patients with initially unresectable colorectal liver metastases (CRLM) and right-sided and/or RAS/BRAFV600E-mutated primary tumor: Phase III CAIRO5 study of the Dutch Colorectal Cancer Group. Presented at: 2022 ASCO Annual Meeting; 3–7 June 2022. Chicago, IL, USA. Oral presentation LBA3506.

9. Hicklin DJ, Ellis LM. Role of the vascular endothelial growth factor pathway in tumor growth and angiogenesis. *J Clin Oncol*. 2005;23(5):1011–1027.

10. Sun Q, Zhou J, Zhang Z, et al. Discovery of fruquintinib, a potent and highly selective small molecule inhibitor of VEGFR 1, 2, 3 tyrosine kinases for cancer therapy. *Cancer Biol Ther*. 2014;15(12):1635–1645.

11. Li J, Qin S, Xu RH, et al. Effect of Fruquintinib vs Placebo on Overall Survival in Patients With Previously Treated Metastatic Colorectal Cancer: The FRESCO Randomized Clinical Trial. *Jama*. 2018;319(24):2486–2496. doi:10.1001/jama.2018.7855

12. HUTCHMED Announces that Fruquintinib Global Phase III FRESCO-2 Study Has Met Its Primary Endpoint in Metastatic Colorectal Cancer. [Accessed November 2022]. Available from: <https://www.hutchmed.com/fresco-2-met-primary-endpoint/>.

13. Dasari NA, Lonardi S, Garcia-Carbonero R, et al. FRESCO-2: A global phase III multiregional clinical trial (MRCT) evaluating the efficacy and safety of fruquintinib in patients with refractory metastatic colorectal cancer. Presented at: 2022 ESMO Congress; 9–13 September 2022. Paris, France. Oral presentation LBA25.