Editorial Commentary

Negative hyperselection beyond RAS: is a key tool for choosing the optimal maintenance treatment in metastatic colorectal cancer?

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Colorectal cancer is the third most prevalent global cancer and is also the second most common cause of cancer deaths (1). In Europe, colorectal cancer also represents the second leading cause of cancer deaths in 2018. However, recent years have seen a decline in mortality rates (2). In middle to high-income countries this decline can be attributed to effective screening and early detection programmes, along with advancements in therapeutic approaches such as systemic therapies, the integration of biomarkers, surgical procedures and ablative treatment of metastases. These interventions have resulted in improved disease management, prolonged control and, in some cases, even cure. It is important to note that approximately 20–25% of patients initially present with metastases, while 25–50% of those with localized disease will eventually develop distant disease, presenting a significant health challenge (2).

For patients diagnosed with unresectable RAS wild-type (WT) microsatellite stable metastatic colorectal cancer (mCRC), a combination of chemotherapy with a monoclonal antibody-drug is usually considered the standard first-line treatment. Moreover, chemotherapy is combined either with an anti-vascular endothelial growth factor (VEGF) antibody (such as bevacizumab) or an anti-epidermal growth factor receptor (EGFR) antibody (such as cetuximab or panitumumab). The choice of second-line treatment depends on the first-line therapy and biomarker status, including RAS and BRAF mutations, and also mismatch repair (MMR) and human epidermal growth factor receptor 2 (HER2) status.

Second-line treatment usually includes chemotherapy combined with anti-VEGF antibody, such as aflibercept, bevacizumab or ramucirumab, or an anti-EGFR antibody. Moreover, the combination of encorafenib and cetuximab is recommended for BRAF V600E-mutated mCRC patients as the preferred treatment option in second line setting. Immunotherapy is advised for deficient MMR tumors. In the third line setting, trifluridine-tipiracil plus bevacizumab is an effective treatment option for patients with refractory mCRC (3-6).

The phase 3 PARADIGM trial evaluated unresectable RAS WT mCRC patients and demonstrated a better overall survival (OS) with first-line mFOLFOX6 plus panitumumab compared with mFOLFOX6 plus bevacizumab in left-sided CRC tumors. Among patients with left-sided tumors receiving anti-EGFR based treatment, the median OS was 37.9 months, whereas those treated with anti-VEGF therapy had a median overall survival (mOS) of 34.3 months [hazard ratio (HR) =0.82; 95% CI: 0.68–0.99; P=0.03] (7).

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Furthermore, a prognostic analysis stratified by measurable biomarkers in clinical practice and by tumor side was performed. Its results support the use of panitumumab plus mFOLFOX6 as a first-line treatment for patients diagnosed with left-sided, microsatellite stable, RAS/BRAF WT tumors (8).

Exploratory analyses reported worse survival (around 22 months) among patients with right-sided CRC tumors. All these results are in line with those previously reported in several meta-analyses (9).

Maintenance treatment as a concept holds importance for patients dealing with a disease not suitable for locoregional treatment or surgery. The concept involves de-escalation of the therapeutic approach to improve tolerability and enhance quality of life, without substantially compromising therapeutic efficacy and disease control. Moreover, the OPTIMOX1 trial suggested that avoiding oxaliplatin after induction treatment could be considered as a maintenance strategy. In addition, the OPTIMOX2 trial evaluated a fluoropyrimidine maintenance treatment compared to a chemotherapy-free period of time, and reported that fluoropyrimidine maintenance treatment did better in terms of survival and disease control rate (10).

While evidence for anti-EGFR maintenance therapy lacks support from phase III data, phase II randomized trials support maintenance therapy with an anti-EGFR targeted agent plus 5-fluorouracil (5-FU) compared to either anti-EGFR or fluoropyrimidine monotherapy (11,12).

According to European, American and Asian Guidelines, anti-EGFR treatment use is determined by primary tumor location, RAS and RAF mutational status as well as assessment of MMR status (3,4,13).

Beyond these established biomarkers, less common molecular alterations have been associated with primary resistance to anti-EGFR agents. These include mutations in EGFR extracellular domain, PTEN, fusions of ALK, NTRK1 and RET, and amplifications of MET and HER2 (14).

The collection of tumor-derived biomarkers from blood or other body fluids, known as liquid biopsy, allows for circulating tumor DNA (ctDNA) analysis and enables the assessment of real-time tumor-associated genomic changes. Additionally, ctDNA monitoring can guide treatment selection in mCRC. The CHRONOS prospective clinical trial demonstrated that ctDNA-analysis is an effective strategy for identifying patients who could benefit from rechallenge with an anti-EGFR targeted agent. Furthermore, ctDNA analysis helps to identify rare genomic alterations (15). Negative hyperselection of these uncommon molecular alterations associated to resistance to EGFR inhibitors, along with sidedness, have been predictive of treatment results in several maintenance treatment studies (16,17). However, the predictive role of negative hyperselection in the maintenance scenario was based in studies where anti-EGFR treatment was not randomized.

Moreover, Stahler *et al.* conducted a pre-specified biomarker analysis of the randomized maintenance treatment PANAMA trial, where anti-EGFR treatment was randomized (18). This analysis assessed the prognostic and predictive value of negative hyperselection in RAS WT mCRC patients treated with a panitumumab-based maintenance strategy. The negative hyperselected mutation subgroup was defined by the identification of one or more pathogenic tumor point mutations of the following genes: *RAS*, *BRAF-V600E*, *AKT1*, *PTEN*, *PIK3CA-exon 9/20*, *ERBB2*, *ALK1* and or *HER2/neu* overexpression. Among the 248 patients undergoing maintenance treatment in the PANAMA trial, targeted next-generation sequencing (NGS) data was available for 202 patients (81.5%) with 162 of those patients exhibiting negative hyperselected WT tumors (representing 80.2% of the available NGS targeted data). In terms of prognosis, these negative hyperselected WT mCRC patients achieved better median progression-free survival (mPFS), mOS and higher objective response rates (ORR) compared to those patients with mutated mCRC. This observation is consistent with the results of several other studies (19,20).

Interestingly, the addition of panitumumab to maintenance therapy in the negative hyperselected WT subgroup showed significant benefits in terms of ORR (44% *vs.* 26.2%), progression-free survival (PFS) (9.2 *vs.* 6.0 months; HR =0.6), and numerically for OS as well (36.9 *vs.* 24.9 months; HR =0.91). This finding suggests a predictive value of negative hyperselection, despite the non-significant trend in OS. Nevertheless, this limited impact on OS might be attributed to the treatment setting of maintenance therapy for which the study was conducted, and also because of the limited sample size for analysis.

Stahler *et al.* also conducted subgroup analyses to evaluate the efficacy of anti-EGFR maintenance treatment regarding primary tumor sidedness and genetic biomarkers (18). Left-sided hyperselected WT patients achieved better PFS when treated with maintenance anti-EGFR + FU compared to 5−FU alone (PFS: 8.8 *vs.* 6.0 months; HR =0.65; P=0.02). Interestingly, even right-sided negative hyperselected patients also showed numerical improvement when treated with anti-EFGR based maintenance therapy (PFS: 9.2 *vs.*

5.8 months; non-significant) although the results were limited by the sample size in the analysis. Additionally, according to the recently published results of liquid biopsy testing in the PARADIGM trial, even hyperselected WT right-sided patients may benefit of the addition of anti-EGFR treatment. For 98 negative hyperselected patients, OS was prolonged with panitumumab plus mFOLFOX6 compared with bevacizumab plus mFOLFOX6 in left-sided primary tumors (42.1 *vs.* 35.5 months; HR =0.76; 95% CI: 0.61–0.95; P=0.171). Furthermore, those patients diagnosed with negative hyperselected WT right-sided primary tumors achieved a numerically better OS (38.9 *vs.* 30.9 months; HR =0.82; 95% CI: 0.50–1.35; P=0.145) suggesting that tumor sidedness may not be the sole determinant when deciding between anti-EGFR or anti-VEGF treatment. Thus, this supports the notion that primary tumor location, as well as hyperselection based on solid or liquid DNA-testing, endorse the correct identification of mCRC patients who may benefit from a combination of anti-EGFR based chemotherapy in the first-line setting (21).

Therefore, extended molecular profiling beyond recommended RAS/RAF analysis and sidedness may improve efficacy results of anti-EGFR containing maintenance regimens for our patients. Prospective validation is warranted to translate these findings into current generalized clinical practice.

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Footnote

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