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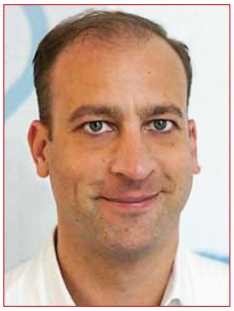
Beyond the second line of the care continuum in metastatic colorectal cancer

by G. Prager, *Austria*



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Recent stratification studies have led to the start of more efficient treatment designs, where the* RAS *mutation status, the sidedness of the primary tumor, and the subsequent sequence strategies are now considered to improve the prognosis of patients with metastatic colorectal cancer (mCRC). In this context, more patients are fit for treatment continuation, and thus, there is an increasing need for effective and well-tolerated third-line therapies. Before the recent advances in the development of novel targeted therapies that significantly improved the patients' prognosis in this setting, such as tyrosine kinase inhibitors, there had been an unmet need for well-tolerated drugs to overcome acquired treatment resistance. The introduction of trifluridine/tipiracil), an oral drug composed of trifluridine plus tipiracil hydrochloride, has improved the prognosis for heavily pretreated mCRC patients, and it has an acceptable toxicity profile to maintain the patients' performance status. The RECOURSE trial (REfractory COloREctal cancer Study), a prospective, randomized phase 3 trial, showed that this cytotoxic antimetabolite controls the disease efficiently, thereby prolonging progression-free survival and overall survival. Notably, the toxicity is manageable in pretreated mCRC patients. This paper reviews both recent phase 3 trials that are exploring the use of approved agents and early phase trials that are investigating new drugs for chemotherapy-refractory metastatic colorectal cancer.

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A better understanding of the tumor biology of colorectal cancer has led to the development and introduction of effective targeted first-line treatments for patients with metastatic colorectal cancer (mCRC). Antibodies against the epidermal growth factor receptor (EGFR) are considered to be the most effective for treating patients with *RAS* wild-type mCRC with left-sided primary tumors.[1] Patients with *BRAF*-mutated tumors seem to benefit from a double or triple combination chemotherapy containing an anti–vascular endothelial growth factor receptor (VEGF),[2] whereas microsatellite instable (MSI-high) tumors have good responses to immunotherapy.[3] However, there is an increasing need for effective and well-tolerated third and later lines of treatment.

Until novel active agents were introduced for pretreated mCRC patients, rechallenge using previous lines of treatment was the preferred treatment option.[4] Regorafenib was the first multikinase inhibitor to be approved for pretreated mCRC,[5] and although it has demonstrated clinical activity, its potential toxicity requires proactive

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management.[6] Despite these advances in treatment options, there is an increasing unmet need for pretreated mCRC patients, who frequently have sustained side effects caused from previous lines of treatment, such as polyneuropathia, diarrhea, and skin reactions, including hand-foot syndrome. In the prospective, placebo-controlled, phase 3 trial RECOURSE (REfractory COloREctal cancer Study), trifluridine/tipiracil, an oral drug consisting of trifluridine plus tipiracil hydrochloride, improved patient survival rates.[7] Trifluridine/tipiracil is currently approved in 50 countries, including the United States (US), the European Union, and Japan, for the treatment of adult patients with mCRC who have been previously treated with, or are not considered candidates for, available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents.

There is an unmet need to address the molecular drivers of an individual's disease to overcome treatment resistance. Insights from genetic studies have led to ongoing studies on novel targeted agents for the treatment of CRC. In addition, individualized treatment is required to address the molecular mechanisms for malignant transformation, tumor growth, angiogenesis, and metastasis formation.[8-10] Therefore, an extension of treatment protocols focusing on the patient's molecular profile and a combination of novel chemotherapeutic agents and biological products is needed.

This review focuses on current and future strategies in the continuum of care beyond second-line treatment in mCRC. Recent phase 3 trials are summarized in relation to the continuum of care approach for the patients' benefit.

Trifluridine/tipiracil

In 2014, a new agent, trifluridine/tipiracil, was introduced in Japan, which was followed by US Food and Drug Administration approval in the United States in 2015 and by the European Medicines Administration in Europe in 2016. Trifluridine/tipiracil has been shown to provide a significant overall survival benefit for patients with refractory mCRC. The tipiracil hydrochloride component of this oral drug improves the bioavailability of trifluridine (a reversible inhibitor that binds to the active site of thymidylate synthase) by inhibiting its catabolism by thymidine phosphorylase. The primary mode of action of trifluridine/tipiracil is to incorporate trifluridine into the DNA, which induces DNA dysfunction, including DNA strand breaks. Fluoropyrimidines, such as fluorouracil (5-FU), may also be incorporated into the DNA, but they are rapidly cleaved by uracil-DNA glycosylases, which reduces the damaging effects to the DNA. Moreover, the tipiracil hydrochloride component may enhance the durability of the response to trifluridine.[11]

SELECTED ABBREVIATIONS AND ACRONYMS

CRC	colorectal cancer
ECOG	Eastern Cooperative Oncology Group [scale]
EGFR	endothelial growth factor receptor
FOLFOXIRI	folinic acid [leucovorin]/5-fluorouracil [5-FU]/irinotecan
mCRC	metastatic colorectal cancer
MSI	microsatellite instable
Q-TWIST	quality-adjusted time without toxicity and symptoms
VEGF	vascular endothelial growth factor

In the RECOURSE trial, 800 mCRC patients were randomized 2:1 to either trifluridine/tipiracil or placebo.[7] Patients included in the trial were all resistant or intolerant to standard chemotherapies, including oxaliplatin, irinotecan, fluoropyrimidine, bevacizumab, and, in *(K)RAS* wild-type tumors, anti-EGFR antibodies. The patients had received ≥2 previous standard chemotherapy regimens. The median overall survival was 7.1 months with trifluridine/tipiracil vs 5.3 months with placebo, representing a 32% mortality risk reduction (hazard ratio [HR], 0.68; 95% confidence interval [CI], 0.58-0.81; $P<0.001$). These robust signs of clinical activity were further supported by the fact that trifluridine/tipiracil significantly reduced the risk of progression by 52% (HR, 0.48; 95% CI, 0.41-0.57; $P<0.001$). Besides its clinical activity in improving survival of heavily pretreated mCRC patients, the time to deterioration in the performance status from ECOG (Eastern Cooperative Oncology Group [scale]) 0 or 1 to ECOG 2 was significantly longer for patients treated with trifluridine/tipiracil (5.7 months vs 4.0 months; HR, 0.66; 95% CI, 0.56-0.78; $P<0.001$) *(Figure 1)*.[7,12]

These results are consistent with the manageable safety profile of the drug. Although grade 3+ adverse events were recorded in 69% of patients, most side effects were due to hematotoxicity, meaning that 38% of patients had grade 3+ neutropenia, whereas febrile neutropenia was recorded in only 3.7% of all patients treated with trifluridine/tipiracil. Routine blood cell count testing, dose delays, and/or dose reductions are likely to prevent severe adverse events. In contrast with many other active agents that are routinely used for the treatment of mCRC, trifluridine/tipiracil is very unlikely to cause polyneuropathia (0%), hand-foot syndrome (0%), skin reactions (0%), stomatitis (0.4%), diarrhea (3%), or pulmonary embolism (1.5%).[7] Due to its activity and tolerability, trifluridine/tipiracil was rapidly incorporated into the treatment recommendations from the European Society of Medical Oncology (ESMO),[13] the National Comprehensive Cancer Network (NCCN),[14] and the National Institute for Health and Care Excellence (NICE).[15]

Regorafenib

On the basis of data from the CORRECT trial (Regorafenib Monotherapy for Previously Treated Metastatic Colorectal Cancer), regorafenib was introduced in 2013 at a time when there was a clear unmet need for new treatment options. The CORRECT trial was a prospective randomized phase 3 trial, which randomized 760 CRC patients who were resistant to standard

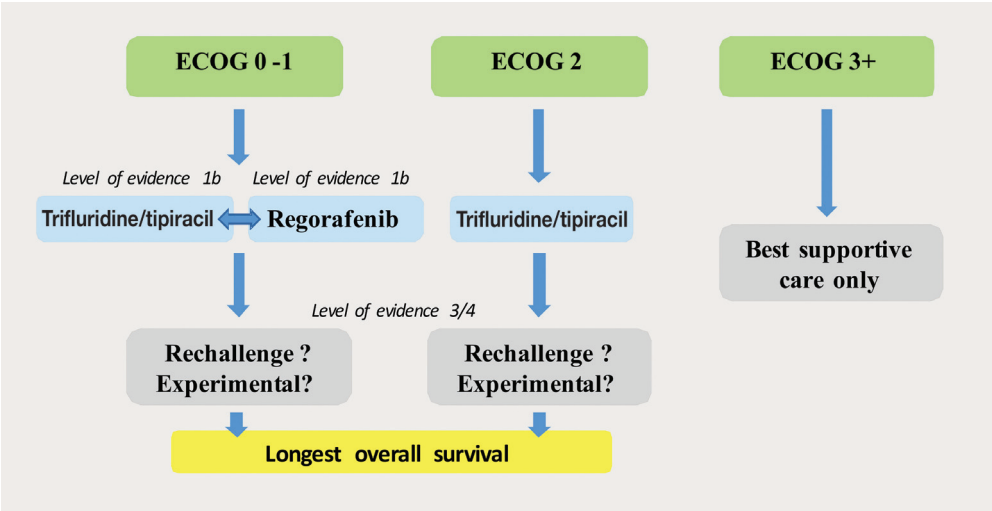

Figure 1. *Salvage treatment in metastatic colorectal cancer according to performance status after failure of fluoropyrimidine, oxaliplatin, irinotecan, anti-VEGF, and anti-EGFR (if* RAS *wild-type).*

In later lines of treatment, phase 3 trials have demonstrated clinical efficacy in improving overall survival. Due to the good tolerability of trifluridine/tipiracil, this drug might also be considered in ECOG 2 patients based on a phase 2 trial.[12] For ECOG 3+ patients, best supportive care only is the appropriate option. Although rechallenge with earlier lines of treatment is intriguing, large prospective trials are needed.
Abbreviation: *ECOG, Eastern Cooperative Oncology Group [scale].*

intravenous therapy options 2:1 to receive either the oral multikinase inhibitor regorafenib or best supportive care only.[6] Regorafenib targets both angiogenic and stromal tyrosine kinases, including tyrosine kinase with immunoglobulin-like and EGF-like domains 2, human VEGF receptor 2, fibroblast growth factor receptor 1, platelet-derived growth factor receptor, and oncogenic kinases, such as KIT, RET, and BRAF. The activity of and results with regorafenib led to its recommendation in major oncology guidelines, including those by ESMO[13] and the NCCN.[14]

In the CORRECT trial, prolongation of the median overall survival was observed in regorafenib recipients with a 23% reduction in the risk of death vs best supportive care alone (median 6.4 months for regorafenib vs 5.0 for placebo; HR, 0.77; 95% CI, 0.64-0.94; one-sided *P*=0.0052). Furthermore, the risk of progression was reduced by half with regorafenib with a median progression-free survival of 1.9 months for regorafenib and 1.7 months for placebo (HR, 0.49; 95% CI, 0.42-0.58; *P*<0.0001). Notably, patients were heavily pretreated, with half of the patients having received ≥4 treatments before regorafenib for mCRC.[6]

The CONCUR trial (Asian Subjects With Metastatic Colorectal Cancer Treated With Regorafenib or Placebo After Failure of Standard Therapy), another double-blind, placebo-controlled, phase 3 trial, showed that regorafenib is also beneficial in Asian patients.[16] This trial was exclusively performed in Asia, confirming a survival benefit in pretreated CRC patients with a median overall survival of 8.8 months for regorafenib vs 6.3 months for placebo (HR, 0.55; 95% CI, 0.40-0.77; *P*=0.00016). However, the phase 3b CONSIGN trial (Regorafenib in Subjects With Metastatic Colorectal Cancer Who Have Progressed After Standard Therapy), an open-label, expanded-access study conducted in 2872 patients, recorded the safety profile of this agent,[17] showing that 57% of patients reported treatment-related grade 3+ adverse events. The most common (>5%) grade 3+ treatment-related adverse events were hypertension (15%), hand-foot skin reaction (14%), and fatigue (13%). The safety profile was consistent with all phase 3 regorafenib trials in mCRC patients.

Rechallenge with anti-EGFR treatment

In *RAS* wild-type patients, the anti-EGFR antibodies cetuximab and panitumumab have demonstrated clinical activity when combined with chemotherapy in first- and second-line settings. Small, prospective, but not randomized, trials provided the first evidence that rechallenge with anti-EGFR antibodies after failure of second-line treatment might be effective in patients pretreated with anti-EGFR drugs in earlier lines. In a prospective phase 2 trial that analyzed the rechallenge with cetuximab in combination with an irinotecan-based chemotherapy, Santini et al[4] reported that 39 patients, who were pretreated with and benefited from an anti-EGFR containing regimen, benefited from a rechallenge with cetuximab in combination with an irinotecan-based chemotherapy. The results demonstrated a disease control rate of almost 90% and a partial or complete response rate in 53.8% of the patients. Furthermore, the activity was sustained, leading to a median progression-free survival of 6.6 months.

Our retrospective analysis of the first-line treatment trials PRIME (Panitumumab Randomized Trial In Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy) and PEAK (Panitumumab Plus mFOLFOX6 vs. Bevacizumab Plus mFOLFOX6 for First Line Treatment of Metastatic Colorectal Cancer Patients With Wild-Type KRAS Tumors) revealed that rechallenge with anti-EGFR antibodies in *RAS* wild-type mCRC patients led to a median overall survival from the start of treatment to >45 months. The patients who underwent rechallenge were healthier at baseline and had a better response to first-line treatment than those who did not undergo rechallenge.[18]

However, recent evidence suggests that anti-EGFR treatment frequently leads to acquired resistance toward anti-EGFR treat-

ment by clonal selection of preexisting clones containing a molecular mutation in the EGFR-/RAS-/RAF-/MAPK-signaling pathways. In their analysis of cell-free circulating tumor DNA from the plasma of patients, Bettegowda et al[9] found a selection of novel clones that were resistant to anti-EGFR treatment. The authors described a large number of mutations in codon 61 of either the *KRAS* or *NRAS* gene. In this particular study, 15 of 24 patients (62.5%) had at least 1 mutation in codon 61, and these mutations comprised 45% of the total mutations (n=69).

In summary, rechallenge with anti-EGFR antibodies for patients who had a benefit in earlier lines of treatment with this strategy might work for a certain subgroup of patients, but real-time molecular profiling might be required due to the unstable cancer genome. A liquid biopsy might allow for a better selection of patients who may benefit from two lines of treatment with anti-EGFR antibodies. So far, the small series of prospective rechallenge trials have provided only a low level of evidence for treatment recommendation and further studies are urged.

Future perspectives

◆ *Targeting HER-2 in mCRC*

In a molecular profile analysis of pretreated mCRC patients, a subgroup of tumors revealed amplification of the human epidermal growth factor receptor 2 (HER2/neu). HER2 overexpression is an effective target for trastuzumab in breast and gastric cancers,[19,20] but leads to resistance to anti-EGFR antibodies in mCRC. In two recent series, the rate of HER2 overexpression based on an immunohistochemistry score of 2+ or 3+ or HER2 gene amplification as assessed by cytogenetic analysis was between 1.6% and 6.3%.[21] A consensus study using CRC-specific criteria for HER2 positivity revealed that 5% of *KRAS* wild-type CRC cancers that overexpress HER2 are suitable for therapeutic targeting.[22] Missiaglia et al reported that distal carcinomas are more likely to amplify HER2 than are proximal tumors.[23]

Recently, the prospective phase 2 HERACLES trial (HER2 Amplification for ColorectaL cancer Enhanced Stratification) tested the combination of trastuzumab and lapatinib in patients with HER2-positive and *KRAS* wild-type mCRC after chemotherapy failure.[22] According to the above-mentioned criteria, of the 913 patients screened for HER2 positivity, 44 were overexpressing HER2 (4.8%) and 27 were eligible for the trial and were treated with trastuzumab plus lapatinib. Of these 27 patients, 8 (30%; 95% CI, 14-50) achieved an objective response, with 1 patient (4%; 95% CI, -3 to 11) achieving a complete response, 7 (26%; 95% CI, 9-43) achieving partial responses, and 12 (44%; 95% CI, 25-63) who had stable disease. Tolerability was manageable, with 6/27 patients with grade 3 adverse events (22%), which consisted of fatigue, skin rash, and an increase in bilirubin concentration. Notably, tumor responses were sustained for more than 1 year.

◆ BRAF *mutation in mCRC*

Constitutive B-Raf activation via mutations occurs in approximately 5% to 10% of mCRC patients. These mutations are thought to be driver mutations because they lead to intracellular signaling that can be associated with aggressive tumor behavior. This tumor cell activation is reflected by a worse prognosis, leading to a lower chance of a response and a reduction in overall survival.[2] While a subgroup analysis of larger phase 3 trials suggested that *BRAF*^{V600}-mutated CRC patients might have a benefit from aggressive folinic acid (leucovorin)/5-fluorouracil (5-FU)/irinotecan (FOLFOXIRI) plus bevacizumab treatment, a small series of prospectively observed *BRAF*^{V600}-mutated mCRC patients could confirm the efficacy of this approach.

The first approaches to target *BRAF*^{V600}-mutated tumors with B-Raf inhibitors resulted in low clinical activity. Only 5% of patients had a partial response with this strategy, and the progression-free survival was 2.1 months. In addition, a double blockage of B-Raf and its downstream signaling molecule MEK using dabrafenib plus trametinib showed a marginally higher efficacy (9% response rate) and a median progression-free survival of 3.5 months.[24] Thus, the first evidence suggested that blocking upstream EGFR was an effective strategy to overcome constitutively activated B-Raf. Subsequent phase 1/2 trials have explored the addition of anti-EGFR monoclonal antibodies to B-Raf inhibitors, with varying results; for example, a 10% relative risk and progression-free survival of 3.5 months was observed with dabrafenib-panitumumab.[25] The triple blockage of EGFR, B-Raf, and MEK has also been analyzed,[24] showing an improved efficacy with a 26% relative risk and progression-free survival of 4.1 months. Based on the data from these recent combination trials targeting B-Raf with a specific serine/threonine-protein kinase inhibitor plus upstream as well as downstream signaling inhibition using a MEK inhibitor and an anti-EGFR antibody, this triplet combination seems to be an effective approach. Currently, the large, prospective, phase 3 trial BEACON-CRC is addressing the question of the most effective way to overcome B-Raf activation (A Multicenter, Randomized, Open-label, 3-Arm Phase 3 Study of Encorafenib + Cetuximab Plus or Minus Binimetinib vs. Irinotecan/Cetuximab or Infusional 5-Fluorouracil [5-FU]/Folinic Acid [FA]/Iri-notecan [FOLFIRI]/Cetuximab With a Safety Lead-in of Encorafenib + Binimetinib + Cetuximab in Patients With BRAF V600E-mutant Metastatic Colorectal Cancer; NCT02928224).

Immunotherapies

Recently, hypermutated colorectal tumors have been treated efficiently with anti–programmed-cell-death-protein-1 (anti–PD-1) antibodies. Most of these tumors are characterized by a mismatch-repair deficiency or mutations in DNA polymerase ε (POL-E) or DNA polymerase δ (POL-D). In this context, a recent study by Le et al[3] demonstrated that pembrolizumab was effective in heavily pretreated MSI-high tumors. The im-

Parameter	First-line	Second-line	≥ Third-line
Overall risk ratio	38%-65%	5%-35%	1%-17%
Progression-free survival	9-12 months	4-7 months	2-4 months
Treatment aim	Response, PFS	PFS, OS	OS, QOL
Receiving treatment	100%	69%	44%

Table I. *Lines of treatment for metastatic colorectal cancer.*
While patients fit for an effective first-line treatment (set as 100%) can expect response rates up to 65% and progression-free survival intervals up to 12 months, expected efficacy gradually decreases with each line of treatment. In this context, the treatment aims of clinical relevance shift from response in first-line treatments to an improvement in overall survival plus maintaining quality-of-life in later lines.
Abbreviations: *OS, overall survival; PFS, progression-free survival; QOL, quality of life.*

mune-related objective response rate was seen in 4 out of 10 mismatch repair–deficient mCRC patients (40%), whereas none of the 18 mismatch repair–proficient mCRC patients (0%; 0/18 patients) had clinical activity with this strategy. The prospective, phase 2 trial Checkmate 142 (An Investigational Immunotherapy Study of Nivolumab, and Nivolumab in Combination With Other Anti-cancer Drugs, in Colon Cancer That Has Come Back or Has Spread) demonstrated that nivolumab has comparable activity in mismatch repair–deficient/MSI-high mCRC patients.[26] Thereby, the addition of the cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) inhibitor ipilimumab to nivolumab yielded an increased response rate; however, as expected, higher rates of toxicity were observed.

As only 5% to 10% of stage 4 CRC tumors are mismatch-repair deficient, it is important to understand how to enhance the immunotherapy susceptibility in patients with mismatch repair–proficient tumors. In this context, the first evidence suggests that blocking MEK alone can result in intratumoral T-cell accumulation and major histocompatibility complex (MHC I) upregulation, and synergizes with an anti–PD-L1 agent to promote durable regression of mismatch repair–proficient tumors. Data from the phase 3 trial IMblaze370 (A Study to Investigate Efficacy and Safety of Cobimetinib Plus Atezolizumab and Atezolizumab Monotherapy Versus Regorafenib in Participants With Metastatic Colorectal Adenocarcinoma; NCT02788279) were first presented at the ESMO World Congress on Gastrointestinal Cancer 2018.[27] The trial failed to show superiority compared with regorafenib.

Summary

The recent introduction of novel drugs and a better understanding for treatment-option stratification have led to a median overall survival that is greater than 30 months in mCRC patients. In first-line treatment, a deep response on the tumor load is the primary aim to improve patient prognosis; however, in later lines of treatment, quality of life and disease stabilization becomes an increasingly important, but often unmet, need *(Table I).* In this context, the introduction of the novel drug trifluridine/tipiracil accomplished both by increasing the overall survival and by maintaining performance status. Tabernero et al[28] recently demonstrated, using a quality-adjusted time without toxicity and symptoms (Q-TWIST) global score analysis, that trifluridine/tipiracil improves progression-free survival time above the time spent with treatment-related toxicity. Aside from an increase in hematotoxicity, trifluridine/tipiracil treatment has a low rate of grade 3 or higher nonhematological adverse events, thereby sparing hand-foot-skin reaction. Thus, trifluridine/tipiracil is thought to be a potential combination partner for other active drugs in mCRC treatment; this is currently being tested in clinical phase 1 to 3 trials.

Beside novel antimetabolic drugs, a deeper understanding of the underlying mechanism of the tumor's innate or acquired resistance toward anticancer drugs is a prerequisite for novel and efficient treatment strategies for CRC. As more patients are fit for a continuum of care approach, there is a need for novel and individualized therapies in the third-line setting and beyond. Modern techniques to characterize somatic mutations from tissue or cell-free tumor DNA are resulting in a reconsideration of known targets, such as MSI, HER2, and B-Raf, for individual treatment concepts. ■

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