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Promising New Agents for Colorectal Cancer

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Summary

There are many exciting new therapies being developed for mCRC patients. Beyond adding to existing combination backbones of chemotherapy with oxaliplatin and irinotecan, subsets of mCRC patients have been identified who may benefit from novel treatments such as immune checkpoint blockade, HER2 inhibition, and MAPK blockade through targeting *RAS* and *RAF* based on genomic profiling from NGS. Other patients have demonstrated responses with developmental therapeutics including cytotoxic-conjugated antibodies targeting CEA, bi-specific antibodies drawing CD3 expressing T cells to tumor cells, metabolic modifiers to increase T cell proliferation at the tumor interface and epigenetic modulators preventing export of key tumor suppressor proteins. How to sequence these new options and determine where they fit into the framework of existing treatments remain major questions whose answers we hope to determine through ongoing clinical trials.

Keywords

Metastatic colorectal cancer; Therapeutics; Microsatellite instability; RAS; BRAF; HER2

Introduction

Outcomes of patients with mCRC have dramatically improved over the last decade. Overall survival (OS) has increased from 14.2 months with 5-fluorouracil (5FU)-based monotherapy

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Conflict of Interest

Satya Das declares that he has no conflict of interest.

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Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

to near 30 months with targeted agent combinations with FOLFOX- or FOLFIRI-based chemotherapy [1]. Factors that further contribute to this OS gain include better surgical techniques that permit surgeons to resect oligometastatic disease (primarily in liver or lung), a more nuanced understanding of tumor biology (sidedness, *RAS*, and MSI status) and integration of biologic agents. Despite this progress, five-year survival rates remain < 15% for patients with stage IV disease [2]. The identification of new treatment options remains a priority for patients with advanced mCRC who have progressed through FOLFOX- and FOLFIRI-based therapies but who are still excellent candidates to receive further therapy based on their desire for additional treatment and a robust performance status. While single-agent therapy with either regorafenib or TAS-102 is approved in the USA as options after progression on initial infusion-based regimens, they each have only modest OS benefits compared with best supportive care [3, 4]. In the following paragraphs, we will focus on promising new therapeutics and treatment approaches that may positively influence outcomes for mCRC patients. Some of the most exciting of these include immunotherapy for patients with MSI-H/dMMR tumors, targeted agents for molecular subsets of mCRC patients (Table 1), CEA-seeking cytotoxic-conjugated antibodies and metabolic inhibitors which generate immunogenicity.

Novel therapeutic options

Immunotherapy

- Checkpoint inhibitors have recently garnered approval in MSI-H, chemotherapy refractory mCRC patients. Both single-agent nivolumab and pembrolizumab are now FDA-approved for mCRC patients after disease progression on oxaliplatin- and irinotecan-based regimens. The Checkmate 142 study demonstrated the benefit of nivolumab in this setting and was a single-arm phase II study with ORR as the primary endpoint [5•]. In this study, 74 patients with recurrent or mCRC were treated with nivolumab 3 mg/kg (mg/kg) every 2 weeks. The ORR was 31%, while disease control rate (DCR) was 69%. DCR for more than 4 months was achieved in 69% of patients.
- Pembrolizumab's efficacy was shown in the single-arm Keynote 164 phase II trial [6]. In this study, 61 patients with mCRC (90% with at least two prior lines of therapy) were treated with pembrolizumab 200 mg every 3 weeks. The primary endpoint for this study was overall response rate (ORR) and was 26%. DCR was demonstrated in 51% of patients, and median duration of response was not reached.
- Given the success of single-agent therapy, immunotherapy combinations are also being explored in both MSI-H and microsatellite stable (MSS) refractory mCRC patients. In the Checkmate 142 study described above, other arms included nivolumab 3 mg/kg plus ipilimumab 1 mg/kg $\times$ four doses (N3/I1) in MSI-H patients and nivolumab 1 mg/kg plus ipilimumab 3 mg/kg (N1/I3) and N3/I1 in MSS patients. In MSI-H patients, the combination resulted in ORR of 55%, DCR of 80%, and median PFS and OS which were not reached [7•]. In the MSS group, the N3/I1 combination produced an ORR of 0%, PFS of 1.3 months and

median OS of 3.73 months. The N1/I3 combination produced an ORR of 10%, PFS of 2.3 months, and OS of 11.3 months in the MSS patient cohort.

- Immunotherapy agents are also being combined with other agents in the mCRC setting. Hochster et al. presented findings from a phase 1b study looking at the combination of the PD-L1 inhibitor atezolizumab plus bevacizumab in MSI-H mCRC patients [8]. A total of 10 patients were given both atezolizumab 1200 mg and bevacizumab 15 mg/kg every 3 weeks. The combination was safe and produced an ORR of 30% with a DCR of 90%. Median OS after 11 months of follow-up has not yet been reached.
- Given that only about 4% of patients with mCRC have tumors that are MSI-H, there naturally remains a great interest in translating immune-oncologic benefits to MSS patients. Bendell et al. presented findings from a phase I study looking at the combination of cobimetinib (20–60 mg oral daily) and atezolizumab (800 mg every 2 weeks) in MSS CRC patients [9]. Out of the 23 patients enrolled in the trial, 22 had tumors that were KRAS mutant. The combination was well tolerated at the maximum tolerated dose (MTD) of 60 mg for cobimetinib and 800 mg for atezolizumab with no observed DLTs. ORR was 17% and DCR was 39%; three responses were ongoing at the time of data reporting. A phase III trial with this combination has completed accrual and the expectation is that results will be forthcoming soon.
- POLE and POLD-1 mutations in DNA polymerase genes can occur as germline [10] or tumor mutations in patients with CRC [11]. POLE/POLD-1 mutations invariably are associated with a high tumor mutational burden and are usually not associated with a MSI-high state. They appear to occur in 1–3% of CRC although the incidence may be lower in mCRC. Case reports have shown responses to pembrolizumab [12].

BRAF V600E inhibition

- Among the 5–10% of mCRC patients with BRAF mutations, 90% have BRAF V600E mutations. Patients who have tumors with this specific BRAF mutation generally have a poorer prognosis. Unfortunately, unlike in BRAF V600E mutant patients with melanoma where BRAF inhibition with single agents such as dabrafenib or vemurafenib produces significant benefits in ORR, PFS and OS, this approach has not been successful in CRC patients. Sundar et al. demonstrated that melanoma cells exhibit minimal rebound in EGFR signaling, while CRC cell lines demonstrate rapid negative feedback upregulation and signaling through EGFR when exposed to BRAF inhibitors [13].
- Several exploratory approaches that combine agents which target the RAF pathway have shown promise in these patients, including triplet therapy with BRAF, MEK and EGFR inhibition, and BRAF and EGFR inhibitors plus irinotecan.
- Atreya et al. first reported results from the triplet combination in 2015 [14]. A total of 35 mCRC patients with BRAF V600E mutations received dabrafenib 150

mg twice daily, trametinib 2 mg daily and panitumumab 6 mg/kg every 2 weeks. ORR for this combination was 26% and DCR was 83%; median duration of response was 5.4 months. In contrast, in patients on the study who received dabrafenib twice daily and panitumumab every 2 weeks, ORR was 10%. Phosphorylated ERK levels between pre-treatment and on-treatment biopsies were more profoundly reduced in the triplet regimen than in the doublet regimen. This suggests that the strategy of hitting multiple targets within the pathway may overcome drug resistance in this group of patients.

- The combination of vemurafenib, cetuximab, and irinotecan was initially reported by Kopetz et al. in a phase II trial in 2017 [15]. In this study, mCRC patients whose tumors harbored BRAF V600E mutations and who had received up to two prior lines of therapy were randomized to irinotecan 180 mg/m² every 14 days, cetuximab 500 mg/m² every 14 days and vemurafenib 960 mg twice daily, or irinotecan and cetuximab at the same dosages. Median PFS in the triplet arm was 4.4 months compared to 2.0 months in the doublet arm. ORR was 16% and DCR was 67% in the triplet arm compared to 4 and 22%, respectively, in the doublet arm. A total of 50% of patients in the doublet arm crossed over at the time of progression.
- The BEACON-CRC trial is an ongoing three arm phase III study assessing the efficacy of encorafenib 300 mg daily, binimetinib 45 mg twice daily, and cetuximab 250 mg/m² weekly versus encorafenib and cetuximab versus irinotecan or FOLFIRI and cetuximab in patients with BRAF V600E mutant CRC. Early results from the trial were presented in abstract form in 2018 by Van Cutsem et al. [16]. Of the initial 29 patients treated on the encorafenib, binimetinib, and cetuximab arm, ORR was 41%, DCR was 72%, and median time on treatment was 5.6 months.
- Another triplet combination that has shown promise in BRAF V600E mutant mCRC patients is the combination of encorafenib 200 mg daily, cetuximab 500 mg/m² every 2 weeks and the PI3K inhibitor alpelisib 300 mg daily [17]. Tabernero et al. reported findings from a randomized phase II study in which 102 BRAF V600E mutant CRC patients were randomized in the third line setting to the triplet regimen versus encorafenib and cetuximab. Median PFS and ORR with the triplet regimen was 5.4 months and 27% compared to 4.2 months and 22%, respectively, with the doublet.

HER2 inhibition

- HER2 amplification occurs in 3–5% of colorectal tumors. In the preclinical setting, HER2-amplified xenografts were not inhibited by single-agent trastuzumab or lapatinib. The combination, however, appears to overcome single-agent tumor resistance. These observations have given rise to three therapeutic trials under the HERACLES moniker [18].
- In the proof-of-concept phase II HERACLES study from Sartore-Bianchi et al., 27 heavily pre-treated patients whose tumors were HER2 amplified (IHC 2+

with FISH confirmation, or 3+ by IHC) and who had previously been treated with an average of four prior lines of therapy were treated with oral lapatinib 1000 mg daily and trastuzumab 2 mg/kg weekly [19]. Seventy-four percent of patients achieved DCR, while 30% of patients achieved ORR. In the B-cohort of the HERACLES trial, patients with HER2-amplified CRC were treated with pertuzumab and T-DM1. Preliminary results suggest seven of eight evaluable patients have received clinical benefit.

- The MOUNTAINEER study is an ongoing single arm phase II study of tucatinib, an oral selective small molecule inhibitor of HER2, 300 mg daily combined with trastuzumab 6 mg/kg every 3 weeks in patients with HER2-amplified (IHC 3+ or amplified by FISH) mCRC. Strickler et al. presented the framework of the trial in 2017 but results have not yet been reported [20].

Tropomyosin receptor kinases fusion inhibition

- Tropomyosin receptor kinases (TRK) proteins are encoded by the neurotrophic receptor tyrosine kinase genes NTRK1, NTRK2, and NTRK3. Recurrent TRK fusions with different upstream partner proteins create oncogene addicted cancers across diverse sites; these mutations are found in 0.2–2.4% of mCRC patients. Inhibition of tumors expressing these fusion proteins with selective small molecule inhibitors such as larotrectinib has become an area of interest due to remarkable responses seen with monotherapy.
- Results with larotrectinib were recently reported as an aggregate of three trials (a phase I, phase I/II and phase II) by Drilon et al. [21]. Fifty-five patients, four of whom had mCRC, with 17 unique TRK fusions confirmed by NGS were treated with larotrectinib 100 mg twice daily in adults or 100 mg/m² in pediatric patients with a BSA ≥ 1 m² in the phase II studies. ORR was 75% with 13% of patients demonstrating CR and 62% demonstrating PR; DCR was 88%. Median duration of response after 8.3 months of follow-up has not been reached, while median PFS after 9.9 months of follow-up has not been reached. Response was reported on three of the four CRC patients; two achieved a partial response (PR) while one achieved stable disease (SD).

Antibody-conjugated chemotherapy agents

- Labetuzumab govitecan (IMMU-130) is an antibody conjugated chemotherapy agent which targets carcinoembryonic antigen-related cell adhesion molecule 5 (CEACAM). This molecule is expressed in over 80% of colorectal cancers. Upon binding to its target, the agent releases SN-38, the active metabolite of irinotecan, into the cancer cell, creating targeted cytotoxicity. Furthermore, much higher doses of SN-38 are deposited into the tumor with reduced serum levels of glucuronidated SN-38, a factor that can reduce the drug's propensity to cause diarrhea [22].
- Results from a phase I/II study with IMMU-130 were recently published by Dotan et al. [23•]. In this study, 86 mCRC patients who had been exposed to a

median of five prior therapies received labetuzumab govitecan. Four dose-expanded cohorts (8 mg/kg weekly, 10 mg/kg weekly, 4 mg/kg bi-weekly, and 6 mg/kg bi-weekly every two out of 3 weeks) were determined based on DLTs experienced during the dose escalation portion of the study. In this study, 50% of all patients achieved DCR, with most patients demonstrating SD with the treatment. Thirty-three of patients had SD for at least 4 months.

Bi-specific T cell engagers

- CEA-CD3 TCB (T cell bispecific) (RG7802) is an antibody which binds to both CEA on tumor cells and the CD3 receptor on T cells. Its Fc region was designed specifically to reduce inadvertent binding to complement elements or Fc gamma receptors. This therapeutic strategy is based on the premise that increasing T cell infiltration into tumors improves clinical outcome of patients with multiple tumor types, including CRC [24]. Combination of this agent with PD-1 or PD-L1 inhibitors in tumors that are not MSI-H is an appealing therapeutic strategy.
- In two separate ongoing studies reported in 2017, mCRC patients were given RG7802 alone weekly or in combination with the PD-L1 inhibitor atezolizumab at a dose of 1200 mg every 3 weeks [25•]. In the patients receiving RG7802 monotherapy, doses up to 600 mg were tolerated with minimal dose-limiting toxicities (DLT). Single-agent DCR in mCRC patients was 9%. In the combination study, doses up to 160 mg of RG7802 were tolerated well with only one noted DLT of liver function test elevation. Increased efficacy was suggested with a DCR of 25% in mCRC patients. Updated data from both trials are pending.

Targeting RAS mutant disease

- The prognostic influence of RAS mutations in mCRC patients is controversial, although some studies suggest worse outcomes in patients with RAS mutated tumors. However, RAS mutations are clearly predictive biomarkers for resistance to anti-EGFR therapies. The prevalence of RAS mutations in CRC patients has been estimated as high as 40–50%, and therefore this family of genes is a target of high interest [26].
- RAS targeting agents have been very difficult to develop due to cross talk and redundancy within the MAPK pathway that appears to allow tumors to evade susceptibility to single agents. Many compounds targeting MAPK escape pathway mediators such as PI3K and mTOR have failed to show efficacy in early phase settings [27] (Fig. 1).
- MEK inhibition plus BCL-XL inhibition with navitoclax (ABT-263) and CDK4/6 inhibition represent approaches that appear promising preclinically. Corcoran et al. identified the anti-apoptotic BCL-XL gene as a potential target to combine with MEK inhibition in KRAS mutant CRC cell lines through shRNA screening [28]. Navitoclax plus selumetinib caused significantly higher levels of apoptosis than either agent alone in RAS mutant cell lines than in RAS wild-type

cell lines. Navitoclax plus the MEK inhibitor trametinib is being investigated in a phase I/II trial in patients with KRAS or NRAS mutant advanced solid tumors [NCT02079740].

- The CDK4/6 inhibitor palbociclib has been investigated as monotherapy in a phase II trial in CRC patients with tumors harboring KRAS mutations [29]. From O'Hara et al., 36 patients with KRAS mutant tumors were screened for Rb expression and 35 were found to be Rb positive. Of these patients, 15 were treated with palbociclib at 125 mg for 21 out of every 28 days. In this study, DCR was 33%. Nine patients underwent pre-treatment and post-cycle one FLT-PET scans as an imaging correlate, and six of the nine demonstrated metabolic response as measured by decrease uptake in visualized lesions.
- Reolysin® is a ubiquitous reovirus which selectively replicates in KRAS mutant cells, resulting in lysis and cell death. Single-agent Reolysin® was shown to be safe in KRAS mutant CRC patients and prompted a subsequent chemotherapy combination trial [30]. Ocean et al. treated 21 CRC patients whose tumors had KRAS mutations with FOLFIRI plus Reolysin® [31]. Two patients experienced a DLT of neutropenia and thus the RP2D was determined to be 150 mg/m² of irinotecan in conjunction with Reolysin® 3 × 10¹⁰ tissue culture infectious dose (TCID₅₀) D1-D5 every 28 days. Median PFS in FOLFIRI-naïve patients (9/21) was 7.4 months, while median PFS was not reached in prior FOLFIRI (12/21)-treated patients. The results from a randomized phase II study of FOLFOX plus bevacizumab plus Reolysin® versus FOLFOX plus bevacizumab alone are pending [NCT01622543].

Modified fluoropyrimidine (NUC-3373)

- Fluoropyrimidines have been long been a cornerstone of therapy for mCRC patients, both as monotherapy or in combination with other agents. Resistance to 5FU and capecitabine is stimulated by thymidine kinase inhibition, thymidine phosphorylase overexpression, and membrane transporter inhibition [31].
- NUC-3373 is a novel fluoropyrimidine whose levels are unaffected by the enzyme dihydropyrimidine dehydrogenase (DPD) in vitro. Furthermore, the NUC-3373 compound generated 363-fold higher concentrations of the toxic metabolite F-dUMP intracellularly. In CRC xenografts, NUC-3373 delivered at equimolar doses to 5FU generated significantly greater tumor growth inhibition than 5FU (47% versus 25%) and generated lower levels of the toxic metabolite dihydroflurouracil [32].
- These preclinical findings inspired a phase I trial looking at NUC-3373 in patients with refractory advanced solid tumors. Interim PK and PD data from this trial was presented in 2017 at the European Society for Medical Oncology (ESMO) meeting and demonstrated rapid intra-cellular concentrations of the active metabolite F-dUMP without the generation of key toxic metabolites [NCT02723240].

Glutaminase inhibitor (CB-839)

- Mitochondrial glutaminase (GLS), the enzyme responsible for converting glutamine to glutamate, is overexpressed in many tumor types, including CRC. GLS expression has been correlated with adverse clinicopathologic features in CRC patients and was found to be associated with higher T stage and the presence of distant metastases. In vitro inhibition of GLS in the colon cancer cell lines HT29 and SW480 resulted in growth suppression and increased apoptosis [33]. Additionally, because glutamine can stimulate T cell activation, raising its levels through GLS inhibition can promote late stages of T cell activation resulting in an immunogenic microenvironment [34].
- CB-839 is a potent and selective inhibitor of glutaminase and is being explored in a myriad of early phase studies. At Case Western, a study in metastatic CRC patients with tumors that are fluoropyrimidine-resistant are receiving CB-839 plus capecitabine. The phase I portion of the study is a traditional dose escalation study, while the phase II portion is a dose expansion in patients with tumors that exhibit a PIK3CA mutation [NCT02861300]. At Vanderbilt, CB-839 plus panitumumab and irinotecan is being explored in a phase I study in patients with RAS WT tumors. The phase II portion of this trial will look at CB-839 plus panitumumab in patients previously treated with EGFR inhibitors [NCT03263429].

SINE inhibitors

- SINE inhibitors represent a class of agents which are selective inhibitors of nuclear export proteins. Tumor suppressor genes can be inactivated by export proteins, rendering them unable to carry out their normal regulatory function in the nuclei of cancer cells. Furthermore, resistance to DNA damaging agents such as irinotecan can be mediated through nuclear export proteins such as CRM1 [35].
- Preclinically, treatment of cell lines with the SINE inhibitor KPT-251 demonstrated nuclear sequestration of the protein topoisomerase 1 (Top1). Top1 is the target enzyme of irinotecan. Dramatic synergism between KPT-251 and CPT-11 was demonstrated in cell lines from both topoisomerase sensitive and refractory patients, suggesting the mechanism of action of KPT-251 stems from inhibition of CRM1 mediated Top1 export [36].
- A phase I expansion trial of KPT-330 (selinexor), an XPO-1 nuclear export protein inhibitor, in CRC patients was reported in abstract form in 2014. From Mau-Sorensen et al., 27 mCRC patients with an average of four prior lines of therapy were treated with KPT-330. In this trial, 28% of patients achieved DCR, with three patients demonstrating SD for at least 6 months. Pre- and post-treatment biopsies from patients demonstrated the restoration of nuclear localization of tumor suppressor proteins [37].

- A second-generation XPO-1 inhibitor, KPT-8602, is being investigated in a phase I/II trial in patients with refractory solid tumors, including CRC [NCT02649790].

WNT pathway inhibitors

- The WNT pathway is dysregulated in many CRCs and as such, is a potentially promising therapeutic target. A growing body of research links this pathway with cancer cells expressing a CRC stem cell phenotype. The stem cell phenotype is associated with tumor chemoresistance through the upregulation of transporters involved in drug efflux [38].
- There are numerous ongoing clinical trials targeting various members of this pathway, including B-catenin, which is a mediator of the classical WNT pathway. Some of these inhibitors include Foxy-5, LGK-974, vantictumab, PRI-724, and BBI-608 [39].
- Napabucasin (BBI-608) represents a first-in-class inhibitor of STAT-driven gene transcription in CRC stem cells. Preclinically, it has also demonstrated ability to sensitize CRC cell lines to chemotherapeutic agents such as irinotecan and 5-FU. The agent has exhibited promise in mCRC model systems along with cell cultures of tumors derived from other gastrointestinal malignancies [40].
- In the initial phase I study, napabucasin was well tolerated, with a recommended phase II dose (R2PD) of 500 mg BID. Findings from a phase II expansion cohort of *KRAS* WT colorectal cancer patients were reported in 2017 in abstract form [41]. Out of 48 patients who received napabucasin plus bi-weekly panitumumab (85% who had received at least three lines of therapy), DCR was achieved in 52%. In 31 patients previously treated with anti-EGFR directed therapy, the DCR was 48% compared with 59% in anti-EGFR treatment-naïve patients. Another phase I/II study from Bendell et al. looked at the combination of FOLFIRI ± bevacizumab and napabucasin in pre-treated mCRC patients [42•]. Of 82 enrolled patients, 32 had already manifested progressive disease on FOLFIRI ± bevacizumab. There were no DLTs and ORR was 22%, while DCR was 83%. In 27 patients who were previously exposed to FOLFIRI, DCR was 81% and ORR was 21%. This was nearly identical to patients who were FOLFIRI-naïve. The promising findings from this study have spawned the CanStem303C trial, a phase III randomized study of napabucasin plus FOLFIRI versus FOLFIRI alone in second line mCRC patients. Enrollment is currently underway [43].

New approaches with old agents

- The results from the REVERCE study were presented in 2018 by Shitara et al. [44•]. In this trial, 101 patients with *KRAS* exon two wild-type colorectal adenocarcinomas with disease progression on prior 5FU-, oxaliplatin- and irinotecan-based therapies were randomized to regorafenib followed by cetuximab with or without irinotecan or cetuximab with or without irinotecan followed by regorafenib. The primary endpoint was OS, while secondary

endpoints included PFS with first (PFS1) and second (PFS2) treatments. Sequential treatment was completed in 86% of patients and after 29 months of follow-up, median OS in the therapy arm where regorafenib was initiated first was 17.4 months compared to 11.6 months in the cetuximab first arm (HR 0.61). There was no statistically significant difference between PFS1 between the arms; however, interestingly there was a difference in PFS2 with a HR of 0.29 for the regorafenib first treatment arm. No statistically significant differences in adverse events were seen in either arm.

- Results from the ReDOS study were also presented in 2018 by Bekaii-Saab et al. [45]. In this randomized phase II study, mCRC patients were randomized between a weekly dose escalation arm (80 mg for 1 week, then dose escalation as tolerated of 40 mg per week up to 160 mg; final tolerated dose given for 21 of 28 days per cycle) and a standard dose arm (160 mg daily for 21 of 28 days per cycle) of regorafenib. The primary endpoint was the percentage of patients who completed 2 cycles of therapy and started on a third cycle. Secondary endpoints included OS and PFS. Forty-three percent of patients in the experimental arm versus 25% of patients in the standard treatment arm were able to receive a third cycle of regorafenib ($p = .028$). Median OS was 9 months in the experimental arm and 5.9 months in the standard treatment arm (not statistically significant). Overall rates for G3/G4 toxicity were more favorable in patients treated with the experimental regimen with lower rates of hand-foot syndrome, fatigue, and hypertension. This trial suggests rapid weekly dose escalation is the optimal way to administer regorafenib for mCRC patients.

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Opinion statement

Choosing the optimal treatment approach for patients with metastatic colorectal cancer (mCRC) demands that oncologists assess both clinical and genomic variables and individualize care based upon the findings. Clinically, choices depend on assessing the side of the colon in which the primary tumor originates, the sites and burden of metastatic disease, the patient's performance status, and their individual comorbidities. Genomic assessment of the tumor to discern the mutational status of genes such as RAS/RAF, HER2, and TRK, as well as assessing whether tumors have defective mismatch repair (dMMR) or high microsatellite instability (MSI-H), all factor in to potential treatment options and can determine clinical trial eligibility. Metastasectomy may be an option for patients with a low burden of disease and accessible liver- or lung-limited metastases. In some unresectable cases, systemic therapy with a FOLFOX- or FOLFIRI- based regimen with or without a biologic agent can lead to sufficient disease reduction to make a patient eligible for resection of metastatic disease. Tumor sidedness and *RAS* mutational status guide which biologic we add to the initial chemotherapy backbone, with patients with left-sided, *RAS* wild-type (WT) tumors receiving anti-epidermal growth factor receptor (EGFR)-directed therapy and patients with right-sided tumors or those with *RAS* mutations receiving bevacizumab. In patients with tumors that manifest microsatellite instability or deficient mismatch repair, we typically administer checkpoint inhibitors such as pembrolizumab or nivolumab after progression on irinotecan- or oxaliplatin-based therapies. In patients with progressive disease, we routinely send tumor tissue for next generation sequencing (NGS) to assess for the presence of actionable genomic alterations such as *HER2*, *BRAF*, and *TRK* fusions and offer them the option of enrollment on clinical trials with agents targeting those or other identified alterations.

Fig. 1. Schema of multiple pathway targets in CRC described in the review. Also illustrated is the T cell and its multiple points of interaction with CRC cells which can be exploited therapeutically. Arrows refer to agonistic binding while the “—|” symbols refer to inhibition.

Frequency of commonly found genomic mutations, targeted agents toward those mutations and ongoing trials in mCRC patients

Table 1.

Genomic alteration	Frequency	Agents	Phase of study
MSI-H/dMMR	4%	Nivolumab [*]	II
		Nivolumab and ipilimumab	II
		Pembrolizumab [*]	II
BRAF V600E mutation	5–10%	Dabrafenib, trametinib, and panitumumab	I/II
		Vemurafenib, cetuximab, and irinotecan	II
		Encorafenib, binimetinib, and cetuximab	III
HER2 mmplification	3–5%	Lapatinib and trastuzumab	II
		Pertuzumab and T-DM1	II
		Tucantinitib and trastuzumab	II
TRK fusions	0.2–2.4%	Larotrectinib	I/II
RAS mutation	40–50%	Navitoclax and trametinib	I/II
		Palbociclib	II
		FOLFIRI and Reolysin®	I
		FOLFOX and Reolysin®	II

^{*} Gained accelerated FDA approval for MSI-H/dMMR cancer in 2017