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REVIEW

Refractory Metastatic Colorectal Cancer: Current Challenges and Future Prospects

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Abstract: Despite advances, patients with metastatic colorectal cancer (mCRC) still have poor long-term survival. Identification of molecular subtypes is important to guide therapy through standard treatment pathways and holds promise for the development of new treatments. Following standard first- and second-line chemotherapy plus targeted agents, many patients retain a reasonable performance status, and thus are seeking further effective treatment to extend life and maintain symptom control. The challenge lies in selecting the most appropriate therapy in the third- and fourth-line settings, from a range of options including the relatively new oral agents TAS-102 and regorafenib, or rechallenge with previous chemotherapy or anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibodies (mAB). Beyond this, therapy consists of trials involving novel agents and new combinations of treatments with theoretical synergy and/or non-overlapping toxicity. There is a great focus on enhancing immunogenicity in mCRC, to reflect the impressive results of immunotherapy drugs in the small cohort with mismatch repair deficient (dMMR) mCRC. Rare molecular subtypes of mCRC are increasingly being identified, including *Her2*-positive disease, *NTRK* fusions and others. Clinical trials exploring the efficacy of immunomodulatory and precision agents are plentiful and will hopefully yield clinically meaningful results that can be rapidly translated into routine care.

Keywords: molecular targets, genomic profiling, immunotherapy, precision medicine

Introduction

Colorectal cancer (CRC) is a major global health issue, being the third most commonly diagnosed malignancy with an estimated global incidence of over 1.8 million in 2018, predicted to increase to 2.2 million in 2030.[1,2] CRC is the second commonest cause of global cancer mortality with 0.5 million deaths in 2018, predicted to increase to 1.1 million by 2030.[1,2] Twenty percent of patients have metastatic colorectal cancer (mCRC) at presentation, whilst up to 50% of the patients who present with early-stage disease relapse later, despite curative-intent surgery, (neo)adjuvant chemotherapy and/or radiotherapy.

Over the last decade, clinical outcomes in mCRC have improved significantly, largely due to the identification of molecular subtypes. The median overall survival (OS) now approximates 30 months in clinical trial populations and two years in the general population.[3] Molecular profiling of tumors is now routinely performed, to identify the approximately 40% that are *RAS* wild type (WT) that are susceptible to anti-epidermal growth factor receptor (anti-EGFR) monoclonal antibody (mAB) therapy;[4] tumors with deficiencies in mismatch repair genes (dMMR) which are highly responsive to immune checkpoint inhibitors; targeted antibodies (AB) for

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tumors with *Her2* amplification or mutation; combination therapy for tumors with *BRAF* mutations; and other rarer subtypes.

After two lines of chemotherapy, 44–50% of the patients may retain a good performance status and be suitable to receive further therapy to improve quantity and quality of life.[5] Understanding the mechanisms that drive treatment resistance is essential in guiding the development of new therapies in this refractory stage. This manuscript provides an overview of currently available agents, and emerging options after failure of standard treatment.

Initial Therapy of Metastatic Colorectal Cancer

For more than 50 years, fluoropyrimidine therapy with 5-fluorouracil (5-FU) administered as an infusional agent or an oral form, capecitabine, has been the cornerstone of treatment for mCRC. Standard combinations include oxaliplatin, irinotecan or both (regimens such as "FOLFOX", "FOLFIRI", and "FOLFOXIRI") plus either the anti-vascular endothelial growth factor (anti-VEGF) mAB bevacizumab, or one of the anti-EGFR mABs in patients with no tumor mutations in *RAS* genes, ie wild type (WT). Alternative anti-VEGF mABs that can be used in the second-line setting include ramucirumab or aflibercept, with efficacy demonstrated in the "RAISE" and "VELOUR" phase 3 trials, respectively, when used with "FOLFIRI".[6,7] The treatment pathway usually includes a de-escalation or maintenance phase. In this article, patients whose disease has progressed beyond these therapies are defined as refractory.

Although there is Level 1 evidence for third- and fourth-line treatment, not all are globally available. Options include Trifluridine/Tipiracil (TAS-102); regorafenib; rechallenge with oxaliplatin; or single-agent anti-EGFR mAB in *RAS* WT disease. Older regimens such as Mitomycin C plus 5-FU are rarely prescribed due to low efficacy.[8]

Treatment of Chemorefractory mCRC

Trifluridine/Tipiracil (TAS-102)

TAS-102 is an orally administered combination of trifluridine, a cytotoxic nucleic acid analogue, and tipiracil, a thymidine phosphorylase inhibitor that prevents enzymatic breakdown of the active compound.[9] TAS-102 became a standard of care option based on the multicenter randomized phase 3 "RECOURSE" trial (n=800) of TAS-102 compared to placebo for mCRC patients who had received all prior chemotherapy plus anti-VEGF therapy and/or anti-EGFR mAB for *RAS* WT mCRC.[9] The primary endpoint was met, with median OS 7.1 versus (v) 5.3 months (m) [hazard ratio (HR) 0.68; 95% confidence interval (CI) 0.58–0.81; p<0.001], and small improvement in median progression-free survival (PFS) [2.0 v 1.7 m; HR 0.48; p<0.001].[7] Of note, 17–20% of the patients had received regorafenib.[9] Grade 3 or higher adverse effects (AEs) were reported in 69% of the patients; neutropenia was the most frequent although only 4% experienced febrile neutropenia.[9] Interestingly, a post-hoc association between TAS-102-induced neutropenia and efficacy has been demonstrated, suggesting that dose incrementing to neutropenia may be of value.[10,11]

Due to concern regarding ethnic variation in pharmacogenomics, the "TERRA" trial was undertaken in a similar Asian population, but with no requirement for previous anti-VEGF or anti-EGFR therapy. There was similar improvement in median OS [7.8 v 7.1 m; HR 0.79; 95% CI; p=0.035] and PFS [2 vs 1.8 m; HR 0.43; p<0.001].[12]

In an effort to improve efficacy and harness potential synergy, TAS-102 is being trialed in a number of combinations. TAS-102 plus bevacizumab for refractory mCRC is supported by pre-clinical and early trial evidence; a phase 1/2 single-arm study ("C-TASK FORCE") reported a PFS rate of 42.9% at 16 weeks, with median PFS 3.7 m and median OS 11.4 m in the primary analysis.[13] A subsequent phase 2 study (n=93) reached the primary endpoint of improved median PFS for the combination compared to TAS-102 alone [4.6 v 2.6 m; HR 0.45; 95% CI 0.29–0.72; p=0.0015]; median OS was also improved [9.4 v 6.7 m; HR 0.55; 95% CI 0.32–0.94; p=0.028].[14] Ramucirumab, another anti-VEGF mAB, is being combined with TAS-102 in the "REMETY" phase 1 study which reported a disease control rate (DCR) at 8 weeks of 58.3%, with PFS and OS data awaited.[15] A phase 2b study using the combination is ongoing.[16]

Oxaliplatin plus TAS-102 is being investigated in a phase 2 trial, consequent to a phase 1 study demonstrating a DCR of 67% at 8 weeks and no dose-limiting toxicities.[17] Despite supportive preclinical data, a phase 1/2 trial of TAS-102 plus panitumumab in 56 patients with *RAS* WT mCRC (with no prior anti-EGFR or regorafenib) reported a 33.3% PFS rate at 6 m, below the prespecified threshold for activity.[18] With regard to immunotherapy, a phase 2 study of TAS-102 plus nivolumab in patients with proficient MMR (pMMR) refractory mCRC was disappointing, with no observed responses and median PFS of 2.8 m.[19]

Regorafenib

Regorafenib is an oral inhibitor of multiple oncogenic kinases, including VEGF receptors.[20] The United States Food and Drug Administration (FDA) granted approval for regorafenib in 2012 for use in patients with refractory mCRC based on results of the phase 3 "CORRECT" trial (n=760) comparing regorafenib to placebo. The primary end point was met, with improved median OS [6.4 v 5.0 m; HR 0.77; 95% CI 0.64–0.94; p=0.0052] and small improvement in PFS [1.9 v 1.7 m, HR 0.49; p<0.0001].[21] Similar to TAS-102, the small PFS gain would not be clinically meaningful in the absence of the OS benefit. The DCR was significant [41% v 15%, p<0.0001], although ORR was 1%.[21]

In the Asian population, the "CONCUR" study was similar but did not require prior anti-VEGF or anti-EGFR therapy. This demonstrated an improved median OS [8.8 v 6.3 m; HR 0.55; 95% CI 0.4–0.77, p=0.00016] and median PFS [3.2 v 1.7 m; HR 0.31; p<0.0001].[22]

The rate of adverse effects with regorafenib at the trial dose of 160mg daily for 21 days of a 28-day cycle was concerningly high. Over 50% of the patients had Grade 3 or higher toxicity; most commonly palmar-plantar erythrodysesthesia (PPE), hypertension, fatigue and diarrhea; dose modification was required in over 70% of the patients.[21,22]

To address this, the "ReDOS" phase 2 trial investigated an alternative dosing schedule, by commencing at 80mg daily and titrating up by 40mg per week to 160mg. On this schedule, more patients initiated cycle 3 of treatment compared to standard dosing.[23] However, progression occurred prior to cycle 3 in 47% of the patients on the modified schedule arm v 37% with standard dosing, raising concerns about the utility of this strategy, although OS and PFS were not statistically significantly different.[23] The dose escalation strategy is still used in clinical practice, particularly for patients with more indolent disease. This overall poor tolerability has limited regorafenib use in the real-world mCRC setting.

Rechallenge Strategies

Given the limited options, re-introducing oxaliplatin is an attractive strategy. In selected patients with previous oxaliplatin response (defined in this article as a PFS interval of at least 6 months), the "RE-OPEN", "RE-OX" and a similar Korean trial demonstrated disease control rates of 39–68%, with OS ranging from 14.5 to 18.5 m.[24–26] Grade 1–2 oxaliplatin-induced neuropathy (OIN) occurred in 53% of the patients in "RE-OPEN", and grade 2–3 in 14.5% of the patients in the Korean study.

Patients who ceased oxaliplatin because of OIN without concurrent disease progression present a challenging clinical scenario.[27] A retrospective analysis of 106 patients demonstrated feasibility with close toxicity monitoring, although one-third of patients developed worsening neuropathy.[28] The clinical decision must balance the impact of worsening OIN on quality of life for patients already with a short prognosis.

Rechallenge with the anti-EGFR mABs cetuximab or panitumumab despite prior progression is based on data demonstrating the dynamic nature of clonal populations with EGFR resistance mutations which are now well defined, measured by circulating tumor deoxyribonucleic acid (ctDNA).[29] Ct-DNA-detected *KRAS* mutant clones were shown to rise during anti-EGFR therapy as a selection pressure phenomenon, with a decay half-life of 4.4 m after drug cessation, leading to the strategy of interval dosing.[30,31] A retrospective review demonstrated non-statistically significant trends towards improved median PFS and overall response rate (ORR) as the time intervals between anti-EGFR cycles increased [ORR 32% for >2 half-lives v 20% <1 half-life].[31]

Monitoring of *RAS*-resistant mutations using ct-DNA was taken forward in the "CRICKET" study.[32] This examined rechallenge with cetuximab plus irinotecan in the third-line setting in patients with previous response to cetuximab-containing therapy. An ORR of 21% [95% CI 10–40%] and DCR of 54% [95% CI 36–70%] were observed.[32] Patients with *RAS* WT ctDNA had a longer PFS than those with ctDNA-detected *RAS* mutations [median PFS 4.0 v 1.9 m; HR 0.44; 95% CI 0.18–0.98; p=0.03].[32]

A 2019 systematic review supported anti-EGFR mAB rechallenge after evaluating 26 studies of retreatment.[33] An ongoing prospective trial utilizing ctDNA monitoring will provide definitive proof.[34]

Choosing Between Currently Available Therapy

TAS-102 and regorafenib have not been compared head-to-head but appear to have similar efficacy in two meta-analyses, with regorafenib having higher toxicity of any grade.[35,36] The clinical decision regarding choice and order of use should be based on matching the side effect profile with each patient's comorbidities and pace of disease (Table 1).

Table 1 Currently Available Therapies for Refractory mCRC

Name	Class	Key Trials	Main Toxicities	Patient Population
Trifluridine/tipiracil (TAS-102)	Oral nucleic acid analogue/thymidine phosphorylase inhibitor	RECOURSE[5] TERRA[9]	Neutropenia	Refractory mCRC[a]
Regorafenib	Oral multikinase inhibitor	CORRECT[21] CONCUR[22] ReDOS[23]	PPE Hypertension Fatigue Diarrhea	Refractory mCRC[a]
Oxaliplatin reintroduction	Cytotoxic	RE-OX[16] RE-OPEN[26]	Peripheral neuropathy	Oxaliplatin response[b]
Anti-EGFR mAB reintroduction	mAB	CRICKET[34]	Acneiform rash	*RAS* WT, anti-EGFR response[b]

Notes: [a]Prior second-line chemotherapy with or without anti-EGFR; [b]PFS duration greater than 6 months.

Emerging Therapies

Anti-VEGF Strategies

Two novel oral agents are in clinical trials. Fruquitinib, a selective inhibitor of VEGF receptors 1, 2 and 3, is being investigated in the "FRESCO" phase 3 trial in a Chinese refractory mCRC population naive to anti-VEGF therapy.[37,38] This is based on phase 2 data where fruquintinib improved median OS to 9.3 m, v 6.6 m with placebo [HR 0.65; 95% CI 0.51–0.83; p<0.001].[38] The "FRESCO-2" trial is being conducted in a similar population but allows previous treatment with anti-VEGF mAB, TAS-102 or regorafenib.[39]

Famitinib is an oral tyrosine kinase inhibitor (TKI) with activity that includes inhibition of c-kit, VEGF receptors 2 and 3, platelet-derived growth factor receptor, and FMS-like tyrosine kinases.[40] This agent was compared to placebo in a phase 2 trial in refractory mCRC. The primary end point was met, with improved median PFS 2.8 v 1.5 m [HR 0.60; 95% CI 0.41–0.86; p=0.004] with OS data awaited.[41] The most common Grade 3–4 AEs included PPE, thrombocytopenia and neutropenia.[41]

Targeting Her2

Based on success in breast and gastric cancer, agents have been used with the hope of similar responses in patients with mCRC containing *Her2* aberrations. *Her2* amplification is found in around 5% of patients with *KRAS/BRAF* WT mCRC, and around 1% with *RAS* mutant tumors.[42] Amplifications are notably more prevalent in Chinese populations; around 14% of patients with *KRAS/BRAF* WT mCRC and 4.4% with *RAS* mutant disease.[43] An analysis of patients from the "FOCUS" and "PICCOLO" studies (n=1342) in mCRC demonstrated that *Her2* amplification confers resistance to anti-EGFR treatment.[42,44]

Her2 activating mutations, which are also rare in breast and gastric cancer, are found in around 2% of mCRC; these will not be identified by immunohistochemistry.[45]

The combination of the anti-*Her2* mABs trastuzumab and pertuzumab was investigated in the phase 2 "TRIUMPH" study of 19 patients with *Her2*-amplified, *RAS* WT refractory mCRC.[46] *Her2* amplification was confirmed on tumor tissue and/or ctDNA, with analysis of ORR reported by detection method. Both had similar ORR, around 33–35%.[46] Combined median PFS was 4 months. Interestingly, the patients who had disease progression had baseline ct-DNA-detected *KRAS, BRAF, PIK3CA* or *Her2* activating mutations.[46]

In the phase 2 "MOUNTAINEER" trial, 22 patients with *RAS* WT, *Her2* amplified refractory mCRC received trastuzumab plus tucatinib, an oral TKI that inhibits the *Her2* receptor.[47] The ORR was 55%, median PFS was 6.2 m [95% CI 3.5-NE] with median duration of response not reached at a median 10.6 m of follow up; median OS was 17.3 m [95% CI 12.3-NE].[47]

Trastuzumab plus the oral dual-target TKI, lapatinib, appears to be an efficacious combination in mCRC based on the phase 2 "HERACLES" trial.[48] In the heavily pretreated cohort, the median PFS was 21 weeks [95% CI 16–32] and median OS 46 weeks [95% CI 33–68 weeks].[49] The primary endpoint was met with ORR 30.3% [95% CI 17–47%] and DCR 70% [95% CI 52–82%].[50] The combination was chosen due to efficacy not seen with either single agent in preclinical models. Although this regimen is now standard for refractory

disease, these drugs are not universally funded by health schemes, and the cost and efficiency of screening many patients must be considered. However, trials examining utility in earlier lines of therapy are in progress. *Her2* activating mutations also confer susceptibility to trastuzumab and lapatinib in xenograft models.[51]

The phase 2 trial "HERACLES-B" (n=30) investigated pertuzumab and trastuzumab-emtansine (TDM1) in a similar population.[52] However, with an ORR of 10% [95% CI 0–28%], the trial did not meet its primary endpoint.[52] Notably, the DCR was 80% [24 of 30; stable disease (SD) in 70%] and median PFS was 4.8 m [95% CI 3.6–5.8].[52]

Single-agent TDM1 is being investigated in a phase 2 trial after progression on trastuzumab and lapatinib.[53] A novel *Her2*-targeted AB-drug conjugate, trastuzumab deruxtecan, is being investigated in a similar population.[54] A phase 2 study (n=35) is investigating neratinib plus trastuzumab v neratinib plus cetuximab.[55]

In the "MyPathway" study, an ongoing phase 2a multi-basket trial for *Her2*-amplified cancers, 57 patients with refractory CRC received trastuzumab and pertuzumab.[56] In an updated report, the objective response rate was 32% [95% CI 20–45%].[54] The follow-on randomized phase 2 study "CETIRI" is comparing trastuzumab plus pertuzumab to cetuximab and irinotecan (in the second or later line).[57]

Neurotrophin Tropomyosin Receptor Kinase (NTRK) Fusions

NTRK fusions are reported at a prevalence of 0.2–2.4% in CRC, but 4% with dMMR present.[58] Current drugs exploiting this target are the first-generation tropomyosin kinase (TRK) inhibitors larotrectinib and entrectinib; and the next-generation agents selitrectinib (LOXO-195) and repotrectinib.

Larotrectinib and entrectinib both inhibit TRK A, B and C; entrectinib is a multikinase inhibitor (MKI) with activity also against *ALK* and *ROS1*.[59] They demonstrated ORR of 75–79% and 57% respectively in a number of solid tumor basket studies, where 5% of the patients had mCRC.[60–63] Larotrectinib was well tolerated, with 93% of AEs being Grade 1, and no treatment-related Grade 3–4 events.[60] Entrectinib was associated with neurotoxic AEs including cognitive disorder, cerebellar ataxia, paresthesia and peripheral sensory neuropathy; the most common Grade 3 or higher AEs were weight gain and anemia.[63] Both drugs were granted accelerated FDA approval within the last two years for *TRK* fusion-positive cancers. Although the number of mCRC patients in these studies was small, it would appear larotrectinib is preferred due to a better toxicity profile, particularly lack of neurotoxic AEs.

Resistance to *TRK* inhibitors has been shown via development of *TRK* mutations, amongst other mechanisms.[64] Selitrectinib was specifically designed to overcome resistance mutations. Data from phase 1 and expanded access programs in patients with previous *TRK* inhibitor therapy have shown tolerability and an ORR of 34%; ORR was 45% in patients who developed mutations whilst on a *TRK* inhibitor.[64] Common AEs included dizziness, nausea and vomiting, anemia, abdominal pain and fatigue.[64] A second drug, repotrectinib, has activity in patients with resistance to first-generation *TRK* inhibitors due to acquired *TRK, ALK* or *ROS1* mutations.[65,66]

Targeting BRAF Mutations

BRAF mutations occur in approximately 6–9% of mCRC, with 95% comprising a point mutation in the V600E allele.[6,67,68] These tumors have aggressive biology and an unusual pattern of metastases (lung, brain, bone and peritoneum, with less liver involvement). Their poor prognosis (median OS around 12 m) means that only a third of patients are suitable for second-line therapy.[67] About 12% of *BRAF*-mutant patients are concurrently dMMR, almost always due to a sporadic intra-tumoral mutation; they have a similarly poor prognosis.[67,69]

BRAF-mutant tumors respond poorly to standard therapy. The triplet regimen "FOLFOXIRI" plus or minus bevacizumab appears more active and is often the regimen of choice in the first-line setting.[70,71] In the second line, *BRAF* inhibitor monotherapy failed to demonstrate activity, unlike melanoma. A proposed mechanism is EGFR-mediated rapid reactivation of ERK, after initial phospho-ERK inhibition.[72] Anti-EGFR mABs were subsequently trialed also as monotherapy; however, two meta-analyses found no benefit.[73,74] This resistance mechanism was overcome by combining BRAF and EGFR inhibitor therapy in preclinical studies.[72] The combination has been taken forward in a number of trials (Table 2).

Current NCCN guidelines suggest encorafenib plus anti-EGFR with or without binimetinib, or dabrafenib plus trametinib plus anti-EGFR as second-line therapy in patients with *BRAF* V600E mutations.[75] The phase 3 "BEACON" trial suggested an OS benefit for triplet over doublet therapy [HR 0.79; 95% CI 0.59–1.06] but was not powered for this comparison.[76] Notably, 62% of the patients

Table 2 Clinical Trials of Agents Targeting *BRAF* V600E Mutations in Advanced CRC

Clinical Trial	Treatment Arms	PFS or OS (m)	ORR
SWOG 1406[105] (n=106)	A: irinotecan+cetuximab +vemurafenib B: irinotecan+cetuximab	PFS 4.4 v 2.0[a]	ORR 16% v 4% DCR 67% v 22%
EViCT[106] (n=23)	Vemurafenib+erlotinib	Not available	Interim ORR 39% [b]
BEACON[76] (n=665)	A: encorafenib +binimetinib+cetuximab B: encorafenib +cetuximab C: cetuximab +irinotecan/FOLFIRI	OS 9.0 v 8.4 v 4.0[c]	Not available
Phase 1b[107] (n=142)	A: dabrafenib+trametinib +panitumumab B: dabrafenib +panitumumab C: trametinib +panitumumab	Estimated OS 13.2 v 9.1 v 8.2[d]	21% v 10% v 0%
Phase 1b[108] (n=54)	A: encorafenib +cetuximab+alpelisib[e] B: encorafenib +cetuximab	PFS 4.2 v 3.7	19% v 18%

Notes: [a]HR 0.42; 95% CI 0.26–0.66; P<0.001; [b][95% CI 20–61%], [c]Triplet v control: HR 0.52; 95% CI 0.39–0.70; p<0.0001; doublet v control: HR 0.6; 95% CI 0.45–0.79; p=0.0003, [d]13.2 [95% CI 6.7–22] v 9.2 [95% CI 7.6–20] v 8.2 [95% CI, 6.5–9.4], [e]phosphatidylinositol kinase-alpha inhibitor.

receiving triplet therapy had Grade 3 diarrhea, compared to 33% with the doublet, making a clinical argument for the latter for many patients.[76]

Immune Checkpoint Inhibitors

Immune checkpoint inhibition (ICI) with anti-programmed death (PD-1 or PD-ligand-1) mAB therapy has proven highly effective in many cancers, but in mCRC patients only benefits those with microsatellite instability-high (MSI-H) or the correlative dMMR tumors.[77] In patients with refractory mCRC, interim results from two phase 2 studies ("KEYNOTE-016" using pembrolizumab and "Checkmate-142" using nivolumab) demonstrated response rates of 40% and 31% respectively in patients with dMMR mCRC, but no response in patients with pMMR tumors.[77,78] PD-1 expression did not appear to predict ICI response.[77] A current phase 3 study is evaluating dual checkpoint blockade combining ipilimumab, a cytotoxic T-lymphocyte-associated protein 4 (CLTA-4) inhibitor, with nivolumab.[79] ICI is currently approved by the FDA for use in the second line or later for dMMR mCRC, although recent data show dramatic benefit in the neoadjuvant and first-line setting.[80]

Concurrent *BRAF* or *RAS* mutations in dMMR mCRC are associated with a slightly lower response rate to single-agent anti-PD-1 compared to the WT (25–27% v 41%); however, the DCR was not statistically different.[78] With dual checkpoint inhibition, ORR and DCR were similar whether *BRAF* was mutant or WT, in the presence of dMMR.[81]

Improving Tumor Immunogenicity in pMMR CRC

Using Known Agents

Combining ICI with an agent that causes tumor cell apoptosis and antigen presentation to induce an antitumor immune response, such as chemotherapy, radiation, or targeted therapy, seems the most promising next step in making ICI effective in pMMR mCRC. Standard cytotoxic chemotherapy has been shown to increase antigen presentation and the ratio of cytotoxic to regulatory T-cells, with resulting increased PD-1 expression.[82] In mouse CRC models, both 5-FU and oxaliplatin increased PDL-1 expression, and when followed by an anti-PD1 agent improved OS.[82,83] Irinotecan and anti-PD1 demonstrated an additive effect on tumor regression in mice.[84] Multiple clinical trials, mainly in the refractory setting, are now examining combinations with ICI (Table 3). The risk of increased toxicity and impact on quality of life is paramount to document.

Using Novel Agents

A phase 1b trial of the anti-CD20 mAB obinutuzumab followed by cibisatamab (a mAB with bispecificity for tumor CarcinoEmbryonic Antigen (CEA) and T-cell CD3) aims to promote cytotoxic immune cell recruitment, and is being combined with atezolizumab.[85] The innate immune system is another targetable pathway, with autologous infusions of universal donor natural killer cells being tested with a cytokine support agent, ALT803.[86] Another trial is using an injectable vaccine to promote secretion of donor granulocyte macrophage colony-stimulating factor (GM-CSF).[87] Indoleamine 2,3 dehydrogenase (IDO) inhibitors are being combined with anti-OX40 AB (promoting cytotoxic T-cells) and a bifunctional anti-PD-L1/TGFβ fusion mAB in a phase 1 trial.[88]

Antitumor vaccines aim to stimulate presentation of tumor-associated antigens by antigen-presenting cells (APCs) to cytotoxic and memory T-cells. A phase 1b

Table 3 Trials Using Combination Therapy with ICI

Clinical Trial/Phase	Patient Population	Treatment Arms	Class of Agents
Phase2[109]	pMMR mCRC	Nivolumab+regorafenib	MKI
Phase 1b[110]	Refractory solid tumors	Nivolumab+cisplatin+CPB501	Calmodulin binding peptide
Phase 1b[111]	2nd line or more mCRC	Pembrolizumab+MK8353	*ERK*1/2 inhibitor
Phase 1/2[112]	pMMR, *BRAF* V600E mutant mCRC	Nivolumab+encorafenib+cetuximab	*BRAF*+EGFR inhibitors
Phase 1/2[113]	pMMR, *BRAF* V600E mutant mCRC	Encorafenib+binimetinib+nivolumab	*BRAF*+*MEK* inhibitors
Phase 1a/1b[89]	Refractory solid tumors	Atezolizumab+regorafenib	MKI
"Morpheus-CRC" (Phase 1b/2)[114]	2nd or 3rd line mCRC	Control arm: regorafenib A: atezolizumab+imprime PGG+ bevacizumab B: atezolizumab+isatuximab C: atezolizumab+selicrelumab+ bevacizumab D: atezolizumab+idasanutlin E: atezolizumab+regorafenib F: atezolizumab+regorafenib+AB928	A: DRA+anti-VEGF mAB B: anti-CD38 mAB C: anti-CD40 mAB + anti-*VEGF* mAB D: *MDM2* smA E: MKI F: MKI + A2A/A2B ARA

Abbreviations: MKI, multikinase inhibitor; DRA, dectin receptor agonist; smA, small molecule antagonist; ARA, adenosine receptor antagonist.

basket trial using the personalised tumor vaccine RO7198457 in combination with atezolizumab is currently underway, as well as an Australian phase 1 trial using the TetMYB vaccine together with tiselizumab, an anti-PD1 agent.[89,90] An anti-*Her2* tumor vaccine is being examined in a phase 1 trial for *Her2*-amplified mCRC.[91]

Novel Targeted Therapy and Drug Delivery Vehicles

mABs against CEA, a membrane-anchored glycoprotein, such as labetuzumab, aim to target payloads to tissue CEA which is overexpressed in over 90% of CRC.[92] Such payloads include targeted photodynamic therapy, radio-guided surgery, and radioimmunotherapy for peritoneal metastases.[93–95] A phase 1/2 trial using the payload govitecan (a liposomal irinotecan metabolite) demonstrated tumor response in 38% of the 72 patients enrolled, with SD in 48%.[96] Diarrhea and cytopenias were the major toxicities (7–16% of patients) and phase 2 of the trial is ongoing.[96]

Another focus is loco-regional cytotoxic delivery, using nanomedicines. Alginate microcapsules prevented the degradation of anti-CD44 agents in the gastrointestinal tract, with accumulation of the micelles in CD44-positive colorectal tumors.[97] Targeted micelles may provide improved drug delivery to poorly vascularized tumors.

Engineered viruses with inherent tropism for cancer cells are also being investigated as a targeting method. In mouse mCRC models, TG6002 with 5-fluorocytosine and intraperitoneal vaccines have improved survival.[98,99] Direct intra-tumoral injection of talimogene laherparepvec (TVEC), an oncolytic herpes virus with activity in melanoma, is currently in phase 1b/2 trials.[100]

CAR-T Cell Therapy

Individualized chimeric antigen receptor T-cells (CAR-T cells) have been developed with success mainly in hematological malignancy, with focus turning to solid tumors. Intraperitoneal delivery of anti-CEA CAR-T cells induced distal tumor response and prevented peritoneal reseeding in murine models.[101] A phase 1 study using hepatic arterial injection of the same CAR-T cells met safety targets, with tumor necrosis seen in 4 of 6 patients.[102]

Supportive Care

Early integration of palliative care is shown to reduce in-hospital deaths and end-of-life healthcare costs and prolong overall survival in mCRC patients.[103,104] Maximal symptom control to maintain good quality of life requires excellent holistic care. Patients with mCRC have particular, complex end-of-life issues, including nutrition, stomal complications, recurrent ascites and bowel obstructions due to peritoneal disease.

Conclusion

Increasing numbers of patients with mCRC maintain good performance status even with disease progression, and seek active anti-cancer treatment in the third- and fourth-line setting and beyond. There have been relatively few advances in chemotherapy and only a handful of new agents entering standard practice. Benefit from immunotherapy is currently restricted to the small number of patients with tumors harboring deficient mismatch repair genes. Multiple new agents are in clinical trials at various stages, with combinations of therapy aimed at overcoming innate and acquired resistance. Toxicity and costs to both the patient and healthcare systems are important factors to weigh against modest gains in treatment efficacy. Biomarkers to guide patient selection for refractory therapies are eagerly sought. It is hoped that the next decade brings significant advances in this area of great need.

Disclosure

Prof. Dr Eva Segelov reports personal fees from Merck, outside the submitted work. The authors report no other conflicts of interest in this work.

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