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SYSTEMIC THERAPIES IN COLORECTAL CANCER (RD KIM, SECTION EDITOR)

Novel Targets in Advanced Colorectal Cancer

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Abstract

Purpose of Review Although current guidelines suggest only testing for RAS and BRAF mutations as well as MMR deficiency in metastatic colon cancer, there are many other promising therapeutic targets that are being studied. We aim to review the recent literature and evidence behind some of these novel targets.

Recent Findings Many of these targets such as NTRK, ROS, ALK, and HER2 are being studied in current clinical trials and hold great potential in changing the treatment landscape for metastatic colorectal cancer.

Summary Current molecular testing algorithms may need to be expanded to allow better target discovery and for patients to benefit from more therapeutic options.

Keywords Colon cancer · Rectal cancer · Targeted therapy · Oncogenic gene fusions · Immunotherapy · Microbiome

Introduction

Colorectal cancer is the third most commonly diagnosed cancer in the world and the fourth leading cause of cancer death [1]. In many developed countries, despite an increasing incidence, mortality rates have decreased and overall survival has improved. This is in part due to increasing screening rates and earlier detection. In addition, the armamentarium of systemic treatment options for metastatic disease has also increased with more cytotoxic agents as well as targeted therapies being approved in recent years [2]. Current NCCN guidelines suggest testing for somatic mutations in *RAS* (*KRAS* and *NRAS*) and *BRAF* in patients with metastatic colorectal cancer as well as for microsatellite instability (MSI) or mismatch repair (MMR) deficiency in all colorectal cancer patients regardless of stage [3]. In addition to these however, there are also several other genes which have been recently shown to be of interest in colorectal cancer, some of which are potentially targetable. Many of these are oncogenic gene fusions, which have been described in approximately 2.5% of colorectal cancers [4] (Table 1). These occur more frequently in elderly patient and are usually found in *BRAF* wild-type and *RAS* wild-type microsatellite stable right-sided tumors, and tend to be associated with more aggressive disease and a shorter overall survival [4]. Many of these gene fusions are actionable with some showing great promise to date.

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Human Epidermal Growth Factor Receptor 2 (HER2) and 3 (HER3)

The HER receptors, namely EGFR, HER2, HER3, and HER4, and their downstream pathways are key oncogenic pathways in various tumor types. In colorectal cancer, the use of the anti-EGFR antibodies cetuximab and panitumumab are well accepted as standard of care treatment in patients who do not have a RAS mutation [3].

One of the emerging targets in colorectal cancer is human epidermal growth factor receptor 2 (HER2). The use of anti-HER2-directed treatment is already well known in breast and gastroesophageal cancers, and recent evidence suggests that targeting HER2 in colorectal cancer may have efficacy as well. There are no known HER2 ligands and activation of the HER2 receptor that require heterodimerization with other ligand-bound receptors of the same family, such as HER3, with the heterodimer then activating intracellular signaling.

The HERACLES-A trial showed that the prevalence of HER2 amplification in KRAS exon 2 wild-type colorectal

cancer patients was about 5%. Dual anti-HER2 blockade with a combination of intravenous trastuzumab and oral lapatinib among this groups of patients with HER2-amplified tumours refractory to standard of care treatment options yielded an impressive response rate of 30% [5]. A similar response rate of 37.5% was reported from the preliminary data from MyPathway study with a response rate of 37.5% with the use of pertuzumab and trastuzumab in a similarly selected HER2-amplified colorectal cancer population [6]. The presence of HER2 amplification may also be predictive for resistance to anti-EGFR therapies [7].

There are currently many clinical trials ongoing that test anti-HER-directed therapy in HER2-amplified colorectal cancer, some in combination with cytotoxic agents or other targeted therapies. Of note, the definition for HER2 positivity varies between different trials' eligibility criteria.

HER2 amplification and increased autocrine expression of neuregulin (NRG1), the ligand for HER3, have been reported as potential mechanisms of resistance after use of anti-EGFR antibodies [8]. HER3, unlike HER2, does not have an intracellular kinase domain, and requires heterodimerization with another HER receptor to activate downstream signaling. HER3 expression has been reported to be associated with poorer prognosis [9]. Increased HER3 expression is also postulated to be a mechanism for resistance to anti-EGFR antibody use by allowing for an escape pathway to downstream signaling [10].

The FOCUS4-D trial, testing AZD8931, an oral inhibitor of EGFR, HER2, and HER3, was also terminated early after the first preplanned interim analysis suggesting no activity of the drug over placebo in patients with newly diagnosed advanced colorectal cancer that was wild-type for BRAF, PIK3CA, KRAS, and NRAS [11]. A phase II study of the dual EGFR/HER2 inhibitor duligotuzumab in combination with FOLFIRI (5-fluorouracil and irinotecan) also did not show any improvement in progression-free survival or overall survival compared to cetuximab with FOLFIRI in the second-line setting in patients with KRAS exon 2 wild-type metastatic colorectal cancer [12].

However, given the biological rationale of targeting human epidermal growth factor family, optimization of anti-Her-targeting agents and their combinations with other systemic drugs may need to improved outcome in a selected group of metastatic colorectal cancer patients.

Neutrotrophic Receptor Tyrosine Kinase

Another promising new target in colorectal cancer is neutrotrophic receptor tyrosine kinase (NTRK) family of the genes. The tropomyosin receptor kinase (TRK) proteins TRKA, TRKB, and TRKC are encoded by the genes *NTRK1*, *NTRK2*, and *NTRK3*, respectively. TRK expression is mainly limited to the nervous system, where they function in the regulation of pain, proprioception, appetite, and memory [13]. Recurrent chromosomal fusion events between TRK and various partners have been identified across diverse childhood and adult cancer types [14]. These fusions lead to ligand-independent constitutionally activated downstream intracellular signaling, and has been shown to be implicated in up to 1% of all solid tumors. In colon cancer, rearrangement of NTRK is believed to be a late event in the adenoma-carcinoma sequence in view of the absence of NTRK1 rearrangement in adenomas [15]. The prevalence of NTRK1 fusions has been estimated to be about 0.5% of colon cancers [15].

Data from the first 55 patients treated with the phase 1 adult trial, the phase 2 trial (NAVIGATE), and the phase 1/2 pediatric trial recruiting patients with TRK fusion-positive cancers treated with larotrectinib was recently published. Larotrectinib, the first oral selective TRK inhibitor, showed an impressive overall response rate of 75% according to independent review and 80% according to investigator assessment, with median duration of response and progression-free survival not reached after a median follow-up of 9.4 months. Eighty-six percent of patients with response were continuing treatment or had undergone surgery that was intended to be curative. Adverse events were predominantly of grade 1, and no grade 3 or 4 adverse event related with larotrectinib occurred in more than 5% of patients. In this study, four of the 55 patients had colon cancer, of which all four had disease control, with two patients achieving stable disease and two patients attaining partial response [16•]. Overall, the drug was well tolerated with few grade 3 or 4 adverse events.

An ongoing global multicenter phase 2 basket trial STARTRK-2 (NCT02568267) is similarly studying the activity of entrectinib, another TRK inhibitor, which also has activity against ROS1 and ALK. In the corresponding phase 1 study, a high response rate of 79% was observed in patients with solid tumors associated with NTRK, ROS1, or *ALK* rearrangements. These responses were seen in a number of tumor types including a patient with NTRK-rearrangement colorectal cancer, and another with ALK-rearranged colorectal cancer [17]. Entrectinib was granted orphan drug designation for the treatment of NTRK fusion-positive solid tumors by the United States Food and Drug Administration (FDA) in light of the above results, while larotrectinib is undergoing priority review.

A second-generation TRK inhibitor, LOXO-195, was developed to targeted acquired resistance to TRK inhibitors by recurrent kinase domain mutations such as solvent front mutations [18]. The drug is currently being evaluated in a phase 1/2 trial in patients that have progressed after receiving larotrectinib or other anti-TRK inhibitors (NCT03215511).

Another drug, TPX-0005 (repotrectinib), has also been shown to have TRK, ROS1, and ALK inhibitor activity and is similarly being tested in a phase 1/2 basket trial of

molecularly selected patients (NCT03093116). Preliminary data suggests that the drug may also have activity against tumors that have a solvent front TRK mutation as well as those who have acquired mutations in the pre-treated *ALK* fusion cohort [19].

Anaplastic Lymphoma Kinase

Chromosomal translocations in the anaplastic lymphoma kinase (*ALK*) gene were first described in anaplastic lymphoma and subsequently reported in several other tumor types, the most well known being that of lung adenocarcinoma. The *ALK* gene encodes for a receptor tyrosine kinase that is thought to drive cellular proliferation and differentiation. The roles of various *ALK* inhibitors such as ceretinib, crizotinib, and alectinib have been well established as standard of care in non-small-cell lung adenocarcinomas harboring *ALK* fusions [20]. In recent past, *ALK* fusions have also been reported in several cases of colorectal cancer and appear to be clinically correlated with an aggressive disease course [21].

In a case series, one patient with colon cancer harboring an *ALK* fusion was shown to have partial response of 9 months on treatment with the ALK inhibitor ceretinib [21]. One patient with colon cancer harboring an ALK fusion also had a partial response in the phase 1b study of crizotinib in ALK-positive tumors excluding non-small-cell lung cancers [22]. As mentioned above, a patient with ALK-rearranged colorectal cancer also showed response to entrectinib [17].

Rearranged during Transfection (RET)

RET is a proto-oncogene that encodes a transmembrane receptor with a tyrosine kinase domain. Mutations or rearrangements in *RET* can lead to constitutional kinase activation and increased downstream activation of signaling pathways such as RAS/MAPK and PI3K/AKT that lead to tumor growth and cell survival. *RET* aberrations have been described in up to 2% of all solid neoplasms, with mutations and fusions each accounting for about one third of abnormalities. *RET* alternations are seen most commonly and best described in thyroid carcinomas, being present in up to 80% of cases. They are much less frequent in other solid tumors. Mutations and fusions have been described in lung adenocarcinomas, ovarian epithelial carcinomas, and salivary gland adenocarcinomas. Recently, *RET* fusions have also been described albeit at a much lower frequency in advanced colorectal cancers [23]. *RET* rearrangements were more commonly found in right-sided cancers, and are usually associated with tumors that lack mutations in *RAS* and *BRAF*. They are also more commonly found in MSI-high tumors. When considering all these established clinical and molecular markers together, an MSI-high right-sided *RAS* and *BRAF* wild-type colon cancer is estimated to have a two third chance of harboring a *RET* rearrangement [24]. Similar to lung adenocarcinomas, it has been observed clinically and suggested that RET fusions may occur more commonly in those who have never smoked [23]. The presence of a *RET* fusion was also independently associated with a poorer prognosis [24].

In preclinical models of RAS and BRAF wild-type colorectal cancer, *RET* overexpression has been associated with primary resistance to anti-EGFR agents, but has been shown to respond to regorafenib [23] and vandetanib [25] in RET-rearranged colon cancers. There is hence interest in studying *RET* inhibitors in this group of patients, including in combination with immunotherapy in those with both *RET* fusion-positive and MSI-high. The phase 1/2 global basket study LIBRETTO-001 of LOXO-292, a drug designed to inhibit both native RET signaling and as well as anticipated acquired resistance mechanisms [26], is currently undergoing in patients with advanced RET fusion-positive solid tumors (NCT03157128).

R-spondin

The family of *R-spondin* (*RSPO*) genes encodes proteins that potentiate the Wnt signaling pathway and functions as stem cell growth factors. RSPO proteins do so through the binding of leucine-rich repeat containing G protein–coupled receptor (LGR) proteins to cause the sequestration of the E3 ubiquitin ligases RNF43 and ZNRF3, which act as negative feedback regulators of the Wnt signaling [27, 28].

Recurrent gene fusions involving the *RSPO* family members *RSPO2* and *RSPO3* have been described to occur in up to 10% of colon tumors. These fusion events appear to be mutually exclusive with APC mutations in all reported cases to date [29], suggesting that RSPO rearrangements may be a key genetic driver in CRC. These tumors are hence likely to be dependent on the Wnt signaling pathway, and preclinical studies have shown that inhibition of Wnt secretion can result in rapid tumor clearance [30].

Wnt signaling activation can also occur through RNF43 mutations, which are more frequent in colorectal cancer cells and which lead to a loss of function of the ubiquitin E3 ligase [31].

A phase 1 clinical trial enrolling patients with *BRAF V600E*–mutated colorectal cancer with either RNF43 mutations or RSPO fusions for treatment with a triple combination of a Wnt inhibitor WNT974, a BRAF inhibitor encorafenib (LGX818) and cetuximab has completed recruitment, and results are pending (NCT02278133). ETC-159, a selective small molecular inhibitor of porcupine, an enzyme required for secretion of Wnt ligands, was studied in a phase I study and shown to have on-target effects through pharmacodynamics monitoring (NCT02521844) [32]. Another Wnt pathway

inhibitor, LGK974, also acting through the inhibition of porcupine [33], a Wnt-specific actyltransferase, is also being studied as monotherapy in one of the arms of a phase 1 dose-escalation study in a similarly molecularly selected colorectal cancer population (NCT01351103).

Microbiome

There is significant interest in recent years in studying the microbiome and its effect and contribution to mutagenesis and cancer progression, particularly in colorectal cancer. The microbiome and the tumor microenvironment comprise myriad human and non-human cells including micro-organisms such as bacteria and fungus. While the exact contribution by the various micro-organisms and non-malignant human cells to mutagenesis and cancer progression is not known, there are multiple studies demonstrating their interaction and potential impact on colorectal cancer progression. A recent publication demonstrated that in an in vivo model, the use of therapy directed against local colonized bacteria had an impact on cancer cell growth. In this study, *Fusobacterium nucleatum* was shown to be among the most prevalent bacterial species in colorectal cancer tissues. The colononization of human colorectal cancers with *Fusobacterium* and its associated microbiome has been shown to be maintained in paired distal metastasis samples. Use of the antibiotic metronidazole in mice bearing a colon cancer xenograft was shown to reduce *Fusobacterium* load, cancer cell proliferation, and overall tumor growth [34]. This provides early proof of concept on the viability of this strategy of targeting or altering the microbiome in mitigating colorectal cancer progression and outcomes. .

Immunotherapy

Immunotherapy in the form of immune checkpoint inhibitors has revolutionalized the treatment of many cancers such as melanoma, lung cancer, and bladder cancer. In colorectal cancer, PD-1 inhibitors have been approved for use in the subset of microsatellite instability-high (MSI-H)/mismatch repair deficient (dMMR) tumors [35•]. Recently, the combination of an anti-PD1 inhibitor (nivolumab) and a CTLA-4 inhibitor (ipilimumab) was also approved for these patients, following impressive results showing a response rate of 49% in the CheckMate-142 study [36]. There are also many ongoing clinical trials exploring the role of immunotherapy, both alone and in combination with other systemic treatments, in microsatellite-unstable colorectal cancer. This subset of MSI-H/MMR-deficient colorectal cancers however makes up only a small minority of metastatic colorectal cancer patients. Immune checkpoint inhibitors in their current form have negligible effect on the vast majority (> 95%) of advanced colorectal patients, i.e., those with microsatellite stable (MSS) disease. This is also the group of patients where further research into the immune landscape and biological rationale for its general refractoriness to immunotherapy is most urgently needed.

Many of the novel approaches and studies involve evaluating combinations of PD1 inhibitors together with other agents that seek to enhance tumor-infiltrating lymphocyte (TIL) responses and immunogenicity of the tumor. One previously attempted approach was the use of the PD-L1 inhibitor atezolizumab together with the MEK inhibitor cobimentinib in MSS colorectal cancer. Despite encouraging findings in the phase I study [37], the randomized phase III trial comparing the atezolumab/cobimetinib combination against atezolizumab alone, or regorafenib, failed to show an improvement in progression-free survival or overall response rate. Current ongoing efforts include studying the use of PD1 inhibitors with systemic chemotherapy, the use of PD1 inhibitors with other immune checkpoint inhibitors such as LAG3 or TIM-3, and the use of immune checkpoint inhibitors in combination with cancer vaccines.

Tumor mutation burden (TMB) is also being explored as a complementary biomarker in addition to microsatellite testing as a predictor for patients who may response to immune checkpoint inhibition. An estimate of 3% of patients with MSS colorectal cancer may have high-TMB and may still benefit from immune checkpoint inhibition, expanding its potential indication [38].

Ongoing efforts to understand and map the immune landscape and tumor microenvironment in microsatellite stable colorectal cancers are being undertaken by many groups worldwide. It is anticipated that this knowledge can help inform immune treatment strategies and drug combinations for this group of patients subsequent.

Cancer Stem Cell/Stemness Inhibition

Cancer stem cells or stem-like cells are thought to have self-renewal and differentiation ability. One of the proposed hypotheses regarding the failure of conventional chemotherapy is the failure of these agents to eradicate these stem/stem-like cells. Inhibition of gene transcription driven by STAT3 has been show to inhibit these groups of cancer cells and reduce relapse and metastasis in mouse models [39]. A phase I/II study in patients with advanced colorectal cancer treated with napabucasin (BBI-608) in combination with FOLFIRI, a first-in-class cancer stemness inhibitor, showed promising activity with a disease control rate of 93% [40]. A phase III clinical trial testing the same combination of napabucasin and FOLFIRI in patients with metastatic colorectal cancer is currently in progress (NCT02753127) [41].

Table 1 Ongoing studies on novel molecular targets in colorectal cancer

HER2		
Metastatic colorectal cancer stratified by HER2 stable	Study of neratinib + trastuzumab or neratinib + cetuximab in patients with KRAS/NRAS/BRAF/PIK3CA wild-type metastatic colorectal cancer by HER2 status[a] NCT03457896	Phase 2 study recruiting
HER2-positive metastatic colorectal cancer	Study of trastuzumab emtansine in patients with HER2-positive metastatic colorectal cancer progressing after trastuzumab and lapatinib (RESCUE) NCT03418558	Phase 2 study recruiting
HER2-positive metastatic colorectal cancer	Evaluation of trastuzumab in combination with lapatinib or pertuzumab in combination with trastuzumab emtansine to treat patients with HER2-positive metastatic colorectal cancer (HERACLES) NCT03225937	Phase 2 sequential cohorts study recruiting
Locally advanced or metastatic HER2-amplified colorectal cancer	Trastuzumab and pertuzumab or cetuximab and irinotecan hydrochloride in treating patients with locally advanced or metastatic HER2/neu-amplified colorectal cancer that cannot be removed by surgery NCT03365882	Randomized phase 2 study recruiting
Unresectable or metastatic HER2-expressing colorectal cancer	DS-8201a in human epidermal growth factor receptor2 (HER2)-expressing colorectal cancer[b] NCT03384940	Phase 2 sequential cohort study recruiting
Relapsed/refractory HER2-expressing/amplified cancers	Study of A166 in patients with relapsed/refractory cancers expressing HER2 antigen or having amplified HER2 gene[c] NCT03602079	Phase 1/2 first-in human study recruiting
NTRK, ROS, and ALK		
NTRK 1/2/3 fusion cancers	Study of LOXO-101 (larotrectinib) in subjects with NTRK fusion-positive solid tumors (NAVIGATE) NCT02576431	Phase 2 basket study recruiting
NTRK 1/2/3, ROS1 or ALK gene rearrangements	Basket study of entrectinib (RXDX-101) for the treatment of patients with solid tumors harboring NTRK 1/2/3 (Trk A/B/C), ROS1, or ALK gene rearrangements (fusions) (STARTRK-2) NCT02568267	Phase 2 basket study recruiting
NTRK fusion cancers after prior treatment with TRK inhibitor	Phase 1/2 study of LOXO-195 in patients with previously treated NTRK fusion cancers NCT03215511	Phase 1/2 basket study recruiting
NTRK 1/2/3, ROS1 or ALK gene rearrangements	A study of TPX-0005 in patients with advanced solid tumors harboring ALK, ROS1, or NTRK1-3 rearrangements (TRIDENT-1) NCT03093116	Phase 1/2 basket study recruiting
RET		
RET fusion cancers	Phase 1/2 study of LOXO-292 in patients with advanced solid tumors, RET fusion-positive solid tumors, and medullary thyroid cancer (LIBRETTO-001) NCT03157128	Phase 1/2 basket study recruiting
RNF43 and RSPO		
BRAF mutant + RNF43 and/or RSPO fusion	Study of WNT974 in combination with LGX818 and cetuximab in patients with BRAF-mutant metastatic colorectal cancer (mCRC) and Wnt pathway mutations NCT02278133	Phase 1 study completed recruitment
BRAF mutant +/− RFN43 and/or RSPO fusion	A study of LGK974 in patients with malignancies dependent on Wnt ligands NCT01351103	Phase 1 dose-escalation study recruiting

[a] Neratinib is a HER2 receptor tyrosine kinase inhibitor

[b] DS-8201a is a HER2 antibody drug conjugate

[c] A166 is a HER2 antibody drug conjugate

Metabolic Targets

The Warburg effect describes the increased use of anaerobic glycolysis in cancer cells to increase bioenergetics for tumor growth [42]. This phenomenon is believed to result from several mechanisms including the overexpression of glucose transporters and glycolytic enzymes, as well as changes in gene expression regulating tumor angiogenesis and resistance

to oxidative stress. Targeting cancer cell metabolism, either through energy restriction or by attempting to shift tumor cell metabolism from anaerobic glycolysis to glucose oxidation, is ongoing in preclinical and early phase human studies [43].

Conclusions

Many of these novel targets are being addressed in ongoing studies and show great promise in changing the future landscape of treatment of advanced colorectal cancer. While many of these targets are relevant only in a small proportion of colorectal cancer patients, taken collectively, treatment strategies against these novel targets can potentially benefit a sizeable number of patients. Beyond what is current standard of care, we should work towards a more comprehensive molecular profiling of colorectal cancers and, where available, the active enrolment of suitable patients into clinical trials. As the discovery of further novel targets and potential companion therapeutics increase the repertoire and improve the accuracy of treatment options in colorectal cancer patients, we can work towards delivering truly personalized treatment. Current molecular testing algorithms may also need to be reassessed and to be expanded for this group of patients.

Compliance with Ethical Standards

Conflict of Interest Joycelyn Jie Xin Lee declares that she has no conflict of interest.

Su Pin Choo has received honoraria from Bristol-Myers Squibb, Novartis, Sirtex, Eisai, and Ipsen for service as a consultant.

Clarinda Chua declares that she has no conflict of interest.

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.

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