Review Article

Update on systemic therapy for colorectal cancer: biologics take sides

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Abstract: Over the last decade, progress in the management of metastatic colorectal cancer (CRC) has focused on the development of biologic therapy in addition to the back bone of combination chemotherapy. Anti-epidermal growth factor receptor (EGFR) antibodies and agents targeting angiogenesis are widely used in the clinic, and more recently, in a subset of patients with mismatch repair (MMR) deficient cancer, immunotherapy with immune check point inhibitors have been integrated into clinical practice. The major challenge with the use of these biologic therapies is determining predictive biomarkers to optimize patient selection. In this review, we discuss the most recent updates in the use of biologic therapy in CRC. We review data on the role of primary tumor location (PTL) (sidedness) as predictive biomarker and recent advances in treatment of CRC with BRAF mutation.

Keywords: Biologics; colorectal cancer (CRC); epidermal growth factor receptor (EGFR); immunotherapy; mismatch repair deficiency (MMR deficiency); sidedness

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Introduction

Fearon and Vogelstein, in their seminal study of a 'genetic model for colorectal tumorigenesis' laid out a vision for the deployment of targeted therapeutic agents against alterations associated with the initiation and promotion of colorectal cancer (CRC). They hypothesized that 'some agents might be sought that would selectively inactivate mutated genes (e.g., ras); others might be obtained that could mimic or restore the normal biologic action of suppressor genes.' (1). This was an aspirational forecasting of the present era of biologic and targeted therapy. At the time, there was a paucity of effective systemic treatment options, and drug development was focused on traditional chemotherapy. 5-fluorouracil (5FU) modified by leucovorin (LV) delivered significant improvements in overall survival (OS) in the metastatic setting, and the addition of oxaliplatin (OX) as FOLFOX or irinotecan (IRI) as IFL/FOLFIRI to this base also resulted in a doubling of the OS benefit (20 months) compared to 5FU/LV which had been associated with an OS of 11 months (2-4). More recent clinical trials of the triple regimen of active agents - FOLFOXIRI have only shown a marginal improvement in OS, with a tradeoff of increased toxicity (5,6). It is clear that development of chemotherapy for CRC has reached a plateau. On the other hand, biologic targeted therapy development is in ascent and the peak is still far from sight.

The development of targeted therapies in CRC kicked off just after the turn of the 21st century with the investigation of monoclonal antibodies (Moab) targeted at vascular endothelial growth factor (VEGF) and the epidermal growth factor receptor (EGFR). Major improvements in our understanding of immunology led to another

class of Moab targeting the immune microenvironment. Antiangiogenic agents (bevacizumab, ramucirumab, ziv-aflibercept and regorafenib) and immune check point inhibitors (pembrolizumab, nivolumab and ipilimumab) are now licensed for the management of metastatic CRC. The benefit of the addition of biologic therapy; specifically, EGFR Moab and antiangiogenic agents to chemotherapy is modest but real and a median OS of between 29 and 36 months is now expected with metastatic CRC (7,8). Accordingly, efforts to develop novel agents for other vulnerabilities in CRC, and to better define factors that predict response to currently available biologics continue. The aim of this review is to provide an update on recent clinically relevant advances in the development of biologic therapy for CRC, with a focus on biomarkers guiding the use of these agents.

Immunotherapy finds a niche

May your road be rough: immune checkpoint inhibitors to the rescue

The classic adenoma-carcinoma sequence, with multistep accumulation of genomic alterations in APC, RAS and DCC is a useful model for conceptualizing CRC development, the majority of which arises from a premalignant polyp. However, 2–3% of patients with hereditary non-polyposis colorectal cancer (HNPCC)/Lynch syndrome do not fall into this category. HNPCC is characterized by microsatellite instability; a by-product of germline mutations in genes that encode mismatch repair (MMR) proteins—MLH1, MSH2, MSH6 and PMS2. Furthermore, 15–20% of patients with sporadic CRC (depending on stage) display a microsatellite instability profile, secondary mainly to hypermethylation of MLH1. Microsatellites are regions of the genome with multiple short DNA repeats 15–25 bp long. These repeats are prone to deletion/insertion errors and frameshift mutations during DNA replication. These errors are corrected by DNA polymerase activity and the MMR proteins. Defective DNA repair therefore allows accumulation of deleterious DNA mutations and subsequent CRC initiation and progression.

The other feature of MMR deficient (MMR-D) CRC pertinent to this discussion is the presence of a lymphocyte-rich tumor infiltrate. Tumor infiltrating lymphocytes (TIL) are part of an immune response to the relatively high burden of neoantigens that occur presumably because of multiple errors in cells with MMR-D (9). In contrast to MMR proficient (MMR-P) CRC with a microsatellite stable (MSS) or microsatellite instability-low (MSI-L) phenotype, the TIL in MMR-D, microsatellite instability high (MSI-H) CRC have an activated profile (10). Interestingly, cytotoxic CD8+ T cells from the peripheral blood of unaffected family members of patients with HNPCC were active against CRC cells (11). Despite this tumor microenvironment that may foster tumor control and better outcomes in early stages, prognosis is poor in patients with more advanced and metastatic MSI-H CRC (12-14). The progression of CRC in this immunogenic background therefore points to the success of immune evasive mechanisms in MSI-H CRC. One evasive maneuver of these tumors is the upregulation of immune check-point inhibitors, including the programmed death ligand-1 (PDL-1) on tumor cells and TIL, which can dampen the activity of activated T-cells (15,16).

Based on the above, it is clear why microsatellite instability would be a logical predictive biomarker for immune check point inhibitor therapy (immunotherapy) in CRC. In an early pilot study of ipilimumab (an anti-CTLA4 monoclonal antibody) in treatment refractory malignancies, there was no response among the 3 patients with CRC (17). Pembrolizumab, an anti-PD-1 monoclonal antibody did not fare better, with no response among 18 unselected CRC patients (18). The KEYNOTE-028 trial was a phase Ib trial designed to assess the safety of pembrolizumab in up to 20 different cohorts of patients with advanced solid tumors. This trial in addition explored the role of PDL-1 as a predictive biomarker for immunotherapy. In the CRC group, 24% of 137 patients' tumor samples were positive for PD-L1 expression by immunohistochemistry (membrane staining in at least 1% of scorable cells). There was only 1 partial response (PR) among 23 patients with PD-L1 positive CRC (ORR of 4%) treated with pembrolizumab. This response was prolonged, lasting more than 2 years. This patient had MSI-H phenotype and investigators hypothesized that this was a predictive marker for response (19). Simultaneously (and based on the hypothesis that MMR-D CRC would more likely respond to checkpoint inhibition), Le and colleagues recruited 41 patients with metastatic cancer; 11 with MMR-D CRC, 21 with MMR-P CRC and 9 with MMR-D non-CRC. They reported an ORR of 40% in the patients with MMR-D CRC and 0% for MRR-P CRC. The ORR of 71% reported for MMR-D non-colorectal tumors was similar to the number for

MMR-D CRC, supporting the role of MMR status as a predictive marker of response to immunotherapy regardless of tumor histology. In addition, pembrolizumab treatment was associated with a disease control rate (DCR) of 90%, and after a median follow up of 36 weeks, median duration of response had not yet been reached in MMR-D patients (20). This study (combined with others) led to the approval of pembrolizumab in the 2nd line for MSI-H CRC, and also contributed to the 'tumor agnostic' approval for pembrolizumab in MMR-D/MSI-H malignancies (21). The development of nivolumab, another anti PD-1 antibody in metastatic CRC followed a similar path (22-24). In addition, following the trend of immunotherapy trials, the additive/synergistic effect of anti-PD1 and anti CTLA-4 therapy has been tested in MSI-H CRC. In the CheckMate-142 trial, 119 patients with MMR-D/MSI-H metastatic CRC cancer received the combination of nivolumab and ipilimumab. The ORR was 55% and median progression free survival (PFS) was 71% at 12 months. The OS rate at 12 months was 85% which is quite impressive in a cohort where 76% of patients had received at least 2 lines of systemic therapy (25). This has also led to the approval of nivolumab and ipilimumab for MSI-H CRC in the 2nd line setting. An important concern with this combination is the severity of immune related toxicities especially colitis. Although majority of the patients (73%) had an adverse event (AE), Grade 3 and 4 toxicities were reported in 27% and 5% of patients respectively. Only 3% of patients had grade 3–4 colitis. Among 16 patients with treatment related adverse events (TRAE) leading to discontinuation of therapy, efficacy results were not different from the overall population.

A potential criticism of the approach to the development and licensing of immune check point inhibitors in CRC is the lack of a control arm and a relatively short follow-up period for OS. While randomization and blinding are the gold-standard for clinical trial design, the limitations of this approach for small numbers of patients with a particular biomarker to drive drug development needs to be recognized. The impact of a pragmatic trial design that compares patients with MSI-H CRC to those with MSS CRC and yields impressive response rates and PFS cannot be minimized. Efforts for multi-institutional and international collaborations to allow relatively large randomized trials should continue apace those focused on further delineating new biomarkers for response to immunotherapy in CRC, especially in MSS CRC.

Other biomarkers: tumor mutation burden (TMB) and DNA polymerase mutations

Using microsatellite instability as a predictive biomarker for immunotherapy in CRC limits the use of these agents to less than 5% of the metastatic CRC population, and investments to uncover other important biomarkers are critical. MMR deficiency is one of several mechanisms that may contribute to genomic instability, and accumulation of tumor mutations that foster an immune response to cancer antigens. Ultraviolet (UV) radiation and cigarette smoking cause genomic instability and a high TMB in melanoma and non-small cell lung cancer respectively. Chalmers *et al.* explored the correlation between TMB and microsatellite instability across cancer types. Based on analysis of about 62,000 samples, they found that MSI-H cancers were a subset of high TMB cancers (defined as 20 non-synonymous mutations/megabase). In that analysis, 83% of MSI-H samples had a high TMB, while only 16% of high TMB samples displayed microsatellite instability (26).

It has thus been hypothesized that it is high TMB, regardless of the underlying cause, that facilitates an immune response that can be augmented/activated by immunotherapy. In melanoma, >100 non-synonymous mutations per exome was associated with an improved RR and survival in response to anti-CTLA4 therapy, and similar findings have been described with anti-PD1 therapy in NSCLC (27,28).

Only few studies have evaluated the role of TMB specifically in CRC (when separated from MMR-D). A retrospective analysis of patients' samples from the Quick and Simple and Reliable 2 (QUASAR 2) trial of patients with high-risk stage II and III CRC suggested that independent of microsatellite instability, TMB was associated with OS (29). The use of TMB as a biomarker in MSS CRC, so far has been based on extrapolation of data from the melanoma and NSCLC literature. There have been case reports of prolonged response to immunotherapy in this scenario, making further investigation necessary (30,31). Twenty-three percent (of 30 patient samples) with 'hypermutated' CRC analyzed in the cancer genome atlas (TCGA) did not have microsatellite instability, and about 3% (of 5,702) MSS CRC samples had a high TMB in another analysis (31,32). Interestingly, alterations in DNA polymerase (*POLE*)—and a failure of its proofreading function—are the apparent cause of many of these MSS/high TMB cases. DNA polymerase alterations are present in 1–2% of CRC, and there are suggestions that these

alterations may be a marker of poor prognosis but improved immune response, similar to MMR deficiency (33). Given the small numbers of patients with MSS and high TMB, it will be difficult to perform large studies to determine the veracity of TMB and DNA polymerase mutations as bona fide predictive biomarkers markers in MSS CRC. However, the growing adoption of next generation sequencing in clinical practice may allow collaborative efforts to pool individual data that may shed more light.

The future remains bright for immunotherapy in CRC with active trials ongoing to establish the role of immunotherapy in the first line either as a stand-alone modality or in combination with chemotherapy. Given the very good prognosis of patients with stage II MSI-H CRC, it is unlikely that immunotherapy would provide a clinically meaningful benefit in the adjuvant setting in this cohort. Already, a pilot study has reported a 100% pathologic complete response (pCR) to neoadjuvant immunotherapy in stage II MSI-H CRC and there is now an ongoing randomized study exploring immunotherapy in addition to chemotherapy for stage III MSI-H CRC. The big challenge is to expand immunotherapy in metastatic MSS CRC, and we anticipate that more work will continue to be done to achieve this goal.

Antiangiogenic and EGFR therapy: extended ras testing and the tale of two colons

Extended ras testing

Cetuximab and panitumumab are the two anti-EGFR monoclonal antibodies (EGFR Moab) approved for use in metastatic CRC. Following initial development for EGFR expressing CRC (which turned out not to be predictive), their use was restricted to Kirsten Rous Sarcoma Virus wild type (KRAS WT) CRC as it became clear that a KRAS mutation (KRAS MT) was associated with lack of response to this class of therapy. In an analysis of patients enrolled into the CO.17 study of cetuximab *vs.* best supportive care, among 198 patients who received cetuximab, only 1 of the 81 patients (1.2%) with KRAS MT CRC responded to cetuximab compared to a 12.8% ORR among 117 patients with KRAS WT CRC. Furthermore, there was improvement in both PFS (3.7 *vs.* 1.8 months, P<0.001) and OS (9.5 *vs.* 4.5 months, P=0.01) in KRAS WT CRC compared to KRAS MT CRC. Correspondingly, there was no significant difference in PFS (1.8 months, HR 0.99, 95% CI: 0.73–1.35, P=0.96) or OS (4.5 *vs.* 4.6 months, HR 0.98, 95% CI: 0.7–1.37, P=0.89) between cetuximab and BSC in KRAS MT CRC (34). Similar outcomes were reported with panitumumab (35), and these analyses led to an American Society of Clinical Oncology recommendation for KRAS testing prior to administration of EGFR Moab therapy and the restriction treatment to patients with KRAS WT CRC (36).

Initial studies in this domain focused on KRAS exon 2 (codon 13 and 14) mutations, which are the most common KRAS mutations, present in approximately 40% of metastatic CRC. Considering the low response (10–20%) to EGFR Moab therapy eve. in KRAS WT CRC, it is clear that a substantial number of patients with CRC were still being exposed to potentially ineffective therapy. Efforts to uncover more biomarkers that may predict response (or a lack thereof) to EGFR Moab have continued to focus on the EGFR signaling pathway (37,38). Among 60 pre-treated patients with supposedly KRAS exon 2 WT CRC, Andre and colleagues examined less common mutations in exon 3 (codon 59 and 61) KRAS mutations in 6.6% (4 patients) of samples analyzed. They also reported 5 NRAS exon 2 and 3 mutations (8.3%) and 4 BRAF V600E mutations (4.4%). In all, they identified 19 patients with KRAS (including 6 with exon 2, codon 12 mutations), NRAS and BRAF mutations, and reported no response to cetuximab and IRI. The ORR to cetuximab was 46.3% among the patients who were wildtype for all the mutations studied (39). These results were validated in a retrospective review of the PRIME study which compared FOLFOX and panitumumab to FOLFOX alone in the first line setting in KRAS exon 2 WT CRC. In this analysis, KRAS testing was extended to include exons 3 and 4, NRAS exons 2, 3 and 4 and BRAF exon 15 (BRAFV600E). This larger analysis uncovered other RAS mutations in 17% of patients (for a total of around 50%). The OS was worse in patients with so-called 'extended RAS mutations' and it was concluded that additional RAS mutations were associated with a negative response to panitumumab. In addition, the combination of panitumumab with FOLFOX was associated with worse PFS and OS compared to FOLFOX only in CRC with RAS mutations suggesting that panitumumab may be harmful in this group. BRAF mutation (discussed further below) carried major prognostic significance but did not appear predictive of outcome relative to panitumumab (40). Along similar lines, investigators uncovered an expanded set of *ras* family mutations in 14% of 460 patients with KRAS exon 2 WT CRC treated with cetuximab and FOLFIRI versus FOLFIRI in the CRYSTAL study. Cetuximab did not

provide any additional benefit to chemotherapy in patients with these other mutations (41). Based on these findings, and several systematic reviews of the existing literature, the ASCO in 2015 updated its provisional clinical opinion, and recommended extended *ras* testing in CRC patients considered for EGFR Moab therapy. At present, this is best accomplished by sequencing the entire KRAS and NRAS genes.

While the impact of RAS mutations on response to EGFR Moab is clear, the results of findings from other proteins involved in EGFR signaling, particularly BRAF and PIK3CA remain controversial. Systematic reviews and meta-analysis have reported association between mutations in these genes and a lack of response to EGFR Moab, but there are no large prospective trials specifically investigating patients with these mutations (42,43). For instance, the BRAF V600E mutation is associated with poor prognosis in metastatic CRC (44), but its role in predicting response to therapy is still unclear. Early studies had suggested a reduced ORR and survival with EGFR Moab in KRAS WT/BRAF MT CRC, but these studies lacked a control arm. Analysis of the larger, randomized CRYSTAL and PRIME studies failed to confirm or rebut these findings but reinforced the poor prognosis associated with BRAF V600E mutation (40,45).

A tale of two colons

The clinical development of biologic therapy targeting angiogenesis has moved in parallel with EGFR Moab development. The FDA approved Bevacizumab for the management of metastatic CRC in 2004, just before cetuximab was approved. Critically, this approval was not biomarker based. Since then, a number of anti-angiogenic biologic agents including monoclonal antibodies (ramucirumab, ziv-aflibercept) and small molecules (regorafenib) have shown activity in metastatic CRC and are used in the 2nd line and beyond in metastatic CRC. To date, there is still no clinically relevant biomarker to guide the use of bevacizumab. Since EGFR Moab is administered exclusively to patients with RAS WT CRC, the natural question to ask was 'what is the optimal approach to first line biologic therapy in RAS WT CRC?'

The FIRE-3 study was one of several large studies designed to answer this question (7,46). FIRE-3 randomized 600 patients with KRAS (exon 2) WT metastatic CRC to FOLFIRI and cetuximab or FOLFIRI and bevacizumab. The study was unusual for one of its size in that radiographic response was the primary endpoint of the study. In fact, there was no difference in ORR (62% *vs.* 58%, odds ratio 1.18, 95% CI: 0.85–1.64; P=0.18) or PFS (10 *vs.* 10. 3 months, HR 1.06, 95% CI: 0.88–1.26; P=0.55) between the 2 groups. However, OS was 28.7 (95% CI: 24.0–36.6) months in the cetuximab arm compared to 25 (95% CI: 22.7–27.6) months with bevacizumab (HR 0.77, 95% CI: 0.62–0.96, P=0.0017). This complimented the findings of a Phase II trial that randomized patients to FOLFOX and panitumumab or bevacizumab in KRAS (exon 2) WT CRC (47). An OS advantage, in the absence of a PFS benefit with EGFR Moab was puzzling especially as the survival curves appeared to separate sometime after the expected end of first-line therapy. CALBG/SWOG was a significantly larger randomized trial (powered for OS), that did not show a difference in PFS (10.5 *vs.* 10.6 months, HR 0.95, 95% CI: 0.84–1.08; P=0.45) or OS (30 *vs.* 29.6 months, HR 0.88, 95% CI: 0.77–1.01; P=0.08) with the addition of cetuximab *vs.* bevacizumab to chemotherapy (FOLFOX or FOLFIRI) (8) in patients who were WT for KRAS (exon 2) mutation.

In any case, deeper exploration of the results of the above studies uncovered one of the more intriguing concepts in metastatic CRC in the last few years, vis the impact of the primary tumor location (PTL) on the response to biologic therapy. The concept of 2 distinct colons has been around for decades (48), founded on the disparate embryologic origins of the colon. The ascending colon up to the proximal two-thirds of the transverse colon arises from the midgut, while the distal third of the transverse colon, up to the rectum are derived from the hindgut endoderm. The two colons also have different blood supplies, and there is significant evidence of distinct microbiome populations between the two colons. In addition, key clinical and biologic features are described in right sided colon cancer (RCC) compared to left sided colon cancer (LCC). In summary, RCC is commoner among women and affects an older population. RCC tumorigenesis is characterized by a CpG island methylator phenotype (CIMP) and development from serrated polyps. Consequently, there is a higher proportion of MSI-high and BRAF mutations. LCC on the other hand is more likely to be associated with chromosomal instability, KRAS, TP53 and SMAD4 mutations, and development following the classical adenoma-carcinoma sequence. The prognostic impact of PTL is also established and although some investigators have questioned the dogma, several studies support the tenet that RCC carries a worse prognosis than LCC (48,49).

In a study involving about 17,000 patients with mainly operable colon cancer, patients with RCC were older and were more likely to be women. RCC was associated with a worse OS (OR 1.12) (50). In the metastatic setting, an analysis of 3 studies involving bevacizumab in addition to chemotherapy also showed that LCC was associated with a more favorable prognosis (51).

Post-hoc analysis of several randomized studies has showed an association between PTL and response to EGFR Moab in KRAS WT CRC. In the Phase III CALGB/SWOG study (that again showed similar PFS and OS with chemotherapy and cetuximab or bevacizumab), further analysis revealed a 10-month improvement in OS favoring 1st line cetuximab compared to bevacizumab in LCC. There was no difference in OS between either treatment regimen for RCC. In addition, in a retrospective analysis of 2 1st line cetuximab and chemotherapy studies (CRYSTAL and FIRE-3), patients with right sided KRAS WT RCC did not seem to benefit from the addition of cetuximab, and multivariate analysis revealed a significant interaction between PTL and OS with respect to cetuximab treatment (52).

While the exact reasons for a lack of benefit with EGFR Moab for KRAS WT RCC are still not clear, it may be that EGFR signaling is not an important driver of RCC, and other alterations may be compensating for EGFR signaling blockade. As one example, promoter methylation appears to lead to lower levels of EGFR ligands amphiregulin and epiregulin. By extension, the increased expression of EGFR and its ligands in LCC has been proposed as a reason for EGFR Moab efficacy in this cohort (53). Based on the above, there is a consensus that EGFR Moab should only be offered to the left sided KRAS WT CRC (at least in the first line of therapy). By extension, the clinical decision making on the use of bevacizumab in the first line setting is guided by PTL and RAS mutation status.

Developments in CRC with BRAF mutation: a raft for BRAF

CRC with a BRAF mutation (BRAF MT) represents a distinct clinical entity characterized by CpG island hypermethylation phenotype (CIMP) and development from serrated polyps (54,55). There is significant overlap with RCC and the associated poor prognosis (56). Indeed, the poor prognosis ascribed to RCC is thought to be driven at least in part by the preponderance of aggressive BRAF MT tumors. Mutations in BRAF occur in 10–15% of metastatic CRC, and the most common mutation (>90%) involves an exon 15, T1779A transversion that leads to substitution of glutamic acid for valine (BRAF V600E) in the BRAF kinase domain. This gain of function mutation instigates ligand independent BRAF activation and signaling (57). Because BRAF signals downstream of KRAS, and KRAS MT CRC is associated with resistance to EGFR Moab therapy, it is reasonable to hypothesize that the BRAF V600E mutation would convey a similar association.

This has been difficult to establish, principally because of the small numbers of BRAF MT CRC. However, given the undeniably poor prognosis of this subtype of CRC, significant effort is underway to improve treatment options. The BRAF V600E mutation is present in about 60% of melanoma, and vemurafenib, a potent inhibitor of oncogenic BRAF yielded an ORR of 53% in previously treated melanoma (58,59). Studies of vemurafenib in chemotherapy refractory BRAF MT CRC however failed to replicate these findings. In one attempt, among 21 patients with BRAF V600E CRC, the ORR was only 5% (60). This disappointing result can be explained by the differences in the biology of both tumors. Prahallad *et al.*, in preclinical studies showed a feedback activation of EGFR and compensatory non-MAPK signaling following BRAF inhibition. They postulated that this was not an active resistance mechanism in melanoma as melanoma cells do not express EGFR to a significant degree. Furthermore, they demonstrated synergistic activity of combined EGFR blockade (with erlotinib or cetuximab) and BRAF (V600E) inhibition (61). In support of this hypothesis, Hyman and colleagues reported a better DCR of 73% (1 PR and 18 stable disease) among 27 patients treated with cetuximab and vemurafenib compared to a DCR of 50% (0 PR and 5 stable disease) in 10 patients treated with vemurafenib only (62). Similar results have been described with the combination of vemurafenib and panitumumab and with combined BRAF and MEK inhibition (63,64). *Table 1* summarizes the results of single agent and combination therapy approaches to BRAF MT CRC management. Overall, the preliminary results from the BEACON CRC study represent the most exciting developments in this area thus far. In this ongoing phase 3 trial (NCT02928224), patients are being randomized to a triple regimen of cetuximab, encorafenib and binimetinib (a MEK inhibitor) *vs.* combination cetuximab and encorafenib or IRI (or FOLFIRI) and cetuximab. Of the 29 patients recruited to the safety lead-in for the triplet combination, a complete response was reported in 1 patient and a PR in 11, adding

Table 1 Single agent and combination therapeutic approaches in metastatic colorectal cancer with BRAF mutation

Authors	Trial design	Intervention	N	OR (%)	PFS (months)
Gomez-Roca *et al.* (65)	Phase I, dose expansion	Encorafenib	18	0	4
Kopetz *et al.* (60)	Phase II, pilot study	Vemurafenib	21	5	2.1
Yaeger *et al.* (63)	Phase I/II, pilot study	Vemurafenib + panitumumab	15	13	3.2
Corcoran *et al.* (64)	Phase I/II	Dabrafenib + trametinib	43	12	3.5
Hong *et al.* (66)	Phase Ib	Vemurafenib + cetuximab + CPT11	19	35	7.7
Tabernero *et al.* (67)	Phase Ib/II, randomized	Encorafenib + cetuximab + alpelisib *vs.* encorafenib + cetuximab	52 *vs.* 50	–	5.4 *vs.* 4.2
Van Geel *et al.* (68)	Phase Ib, dose escalation	Encorafenib (E) + cetuximab (C) + alpelisib *vs.* EC	28 *vs.* 26	18 *vs.* 19	4.2 *vs.* 3.7
Kopetz *et al.* (69)	Phase II	Irinotecan (I) and cetuximab (IC) *vs.* IC + vemurafenib	52 *vs.* 54	4 *vs.* 16	2 *vs.* 4.4

N, number of patients; OR, objective response; PFS, progression free survival.

up to an ORR of 41%. In addition, 31% of patients had stable disease that lasted up to 9 months (70).

The activation of PI3K/AKT pathway is another resistance mechanism exploited by BRAF MT CRC both *de novo* and following exposure to BRAF V600E targeting agents (71). However, a phase Ib study designed to assess the safety of combining alpelisib (a PI3K alpha inhibitor), to cetuximab and encorafenib reported a response rate of 19% (n=28) which was similar to the 18% response rate among 29 patients treated with encorafenib and cetuximab in the same trial (68). This, in addition to the worse AE profile, has dampened the enthusiasm for the development of PI3K inhibitors in this setting. Nevertheless, the encouraging results from the BEACON CRC trial and preclinical work uncovering more resistance mechanisms leave room for optimism that definite progress will be made in the management of BRAF MT CRC in the near future.

Finding a match for HER

As noted in the sections above, abrogating EGFR signaling significantly benefits a select population of patients with metastatic CRC. EGFR belongs to a family of human epidermal growth factor receptor proteins (HER) which also includes HER2, HER3 and HER4. Studies in CRC have focused on the clinical impact of HER2 and HER3 alterations. In contrast to EGFR (HER1) which can be activated by several growth promoting ligands; including amphiregulin, heregulin and other EGF related ligands, HER2 has no known ligands, while HER3 lacks an activating kinase domain. Signal transduction via these receptors proceeds via heterodimerization (HER1/HER2, HER2/HER3) and ligand independent homodimerization (HER2/HER2) in instances of HER2 overexpression. Proliferative and survival signals can therefore be transmitted through these other receptor tyrosine kinases even after EGFR blockade. Accordingly, HER2 (and HER3) overexpression have been suggested as potential *de novo* resistance and escape mechanisms to EGFR Moab (72,73). For example, in a CRC xenograft model, HER2 overexpression was reported in 18% of KRAS (exon 2) WT CRC who failed to respond to EGFR Moab, whereas none of the 14 cetuximab sensitive KRAS WT CRC showed HER2 overexpression (74). Furthermore, combination treatment with pertuzumab (a humanized IgG1 monoclonal antibody that interferes with HER2 dimerization) and lapatinib (a small molecule EGFR and HER2 tyrosine kinase inhibitor) achieved better tumor control than either agent alone, or in combination with cetuximab in this pre-clinical model. This study supported the hypothesis that HER2 overexpression is a worthy therapeutic target in CRC.

An important challenge in developing HER2 directed targeted therapy is determining the appropriate discriminatory level of HER2 that would allow response to such therapy. Investigators in the HER2 Amplification for Colorectal Cancer Enhanced Stratification (HERACLES) program, formulated consensus criteria for HER2

overexpression in CRC by adapting the criteria already in use in breast and gastric cancer. They defined HER2 overexpression as intense membrane staining of >50% of cells (3+) or ERBB2 gene amplification, captured by *in situ* hybridization (ISH) at an ERBB2/CEN17 signal ratio equal to or greater than 2 (75). Based on these criteria, HER2 overexpression is reported in 2–3% of unselected CRC with a higher prevalence in the KRAS WT population where the numbers approach 5% (75,76). Investigators in an early phase II trial of trastuzumab and IRI lamented the low prevalence of HER2 in unselected CRC (4%) and identified this as an obstacle to drug development (77). However, given the high prevalence of CRC in the United States and worldwide, the absolute number of appropriately selected patients who may benefit from HER2 targeted therapy is quite substantial and well-designed multi-institutional and international trials are ongoing to move this field forward.

The HERACLES program mentioned above is a multicohort open label Phase II trial of different HER2 targeted therapeutics in chemotherapy and EGFR Moab resistant, RAS WT, HER2 overexpressing CRC. The first cohort testing the combination of trastuzumab and lapatinib showed impressive objective response rate of 30% (1 CR and 7 PR) among 27 enrolled patients. There were no grade 4 or 5 toxicities and grade 3 toxicities reported in 22% of patients were manageable (78). A 2nd cohort, the HERACLES-RESCUE trial is administering T-DM1 (trastuzumab emtasine) to patients who progressed on trastuzumab and lapatinib (NCT03418558). Similarly, in another open-label Phase II basket trial (MyPathway) an ORR of 38% (14 PR) was reported among 37 patients with HER2 overexpressing CRC treated with trastuzumab and pertuzumab (79).

The critical role of HER2 expression as a biomarker for HER2 targeted therapy was highlighted by the UK FOCUS-4D trial. In this randomized phase 2–3 trial, patients with RAS, BRAF and PIK3CA WT CRC were randomized, after stable disease with first-line chemotherapy to maintenance therapy with AZD8931, a pan-HER family kinase inhibitor. HER2 overexpression was not a prerequisite and the trial failed to achieve its primary endpoints. PFS was lower among patients randomized to the trial drug (2.96 *vs.* 3.48 months, HR 1.1, 95% CI: 0.47–3.57, P=0.95) (80). The HERACLES and MyPathway reports have given rise to justifiable enthusiasm for HER2 targeted therapy in this population. However, it is clear that more work still needs to be done. ORR is around the 30% mark and a substantial proportion of patients are resistant to this therapy. In addition, while current trials are focused on HER2 overexpression, up to 1.5% of unselected CRC may harbor a HER2 mutation (81). It is not clear that the data derived from HER2 overexpressing CRC can be applied to this population. Furthermore, in an ongoing open label Phase II basket trial of neratinib in multiple solid tumors with HER2/3 mutations, there was no response among 12 patients with CRC (NCT01953926). CRC with HER2/3 mutation therefore represents an area for more research.

Future perspectives

In spite of progress that has been made in deploying biologic therapy in CRC, drug development has only so far resulted primarily in defining a target population based on specific alterations rather than targeting the alteration directly (with BRAF and increasingly HER2 perhaps being the exceptions). The latter goal is lofty, but an appreciation of the complex biology of CRC means that clinically relevant druggable driver alterations will occur in only a small proportion of patients with CRC as described with alterations in HER2/3. Arguably, the more clinically impactful challenge is to continue to refine populations that benefit from particular biologic agents (e.g., bevacizumab) while defining novel therapeutic combinations for others like MSS CRC and right sided CRC that are currently underserved with targeted biologic therapy.

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Footnote

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