Current Colorectal Cancer Reports (2022) 18:27–37
https://doi.org/10.1007/s11888-022-00475-0

SYSTEMIC THERAPIES IN COLORECTAL CANCER (SM KAZMI, SECTION EDITOR)

Current Updates on HER2–Directed Therapies in Metastatic Colorectal Cancer

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Accepted: 27 January 2022 / Published online: 9 April 2022

Abstract

Purpose of Review Colorectal cancer is the third most common malignancy in the USA with 20% of patients presenting with metastatic disease. While first line agents include cytotoxic chemotherapy regimens, targeted therapies have an increasing role in the management of metastatic colorectal cancer (mCRC). Next Generation Sequencing (NGS) has expanded the ability to identify HER2 variations and is crucial to the next steps in personalized medicine.

Recent Findings Anti-HER2 therapies provide a promising treatment option for patients who have exhausted traditional regimens including those who have failed prior anti-HER2 therapy. This is in accordance with the 2021 addition of trastuzumab-deruxtecan to the National Comprehensive Cancer Center Guidelines as a subsequent therapy in eligible patients based on the results of the DESTINY-CRC01 trial.

Summary Various anti-HER2 therapies are approved alone or in combination for patients with mCRC and HER2–amplified tumors. Further investigation into the role of HER2–directed therapy in mutated mCRC is an unmet need, as is the wider use of NGS and ctDNA to explore mechanisms of resistance.

Keywords Colorectal cancer · Targeted oncologic therapy · Next Generation Sequencing · Anti-HER2 therapy

Introduction

As of 2020, colorectal cancer is the third most commonly diagnosed cancer worldwide and is second only to lung cancer in cancer-related mortality [1]. An estimated 20% of patients have evidence of metastatic disease at presentation and those with stage four disease have a 5-year survival rate of 14% [2] despite the advent of personalized medicine. First-line therapy for metastatic colorectal cancer (mCRC) typically includes systemic chemotherapy, but may also include other systemic therapies, surgery, and radiation therapy depending on tumor-related symptoms, tumor resectability, location, and genetic markers [3]. Current National Comprehensive Cancer Network (NCCN) [3] chemotherapy guidelines for patients with mCRC are based on side effect profile. Preferred initial therapies [3] include oxaliplatin-based regimens including combinations with 5-fluorouracil (5-FU)/leucovorin (FOLFOX) [4], capecitabine (CAPEOX) [5], or FOLFOX combined with irinotecan (FOLFOXIRI) [6], the latter of which is only recommended for patients with superior performance status. Additionally, the irinotecan-based regimen FOLFIRI [7] is available to appropriate patients. Capecitabine or 5-FU/leucovorin monotherapy is reserved for patients unable to tolerate oxaliplatin or irinotecan-based therapies and in the maintenance setting after combination therapy [3]. Chemotherapeutic regimens FOLFOX, FOLFOXFIRI, and FOLFIRI may be combined with bevacizumab or either cetuximab/panitumumab as first-line treatment of mCRC [3]. Bevacizumab is a direct vascular endothelial growth factor inhibitor (VEGF) [8, 9] that selectively binds to circulating VEGF and prevents it from binding to the endothelial cell surface, preventing VEGF–directed stimulation of microvascular tumor growth

This article is part of the Topical Collection on *Systemic Therapies in Colorectal Cancer*

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[8]. Both cetuximab and panitumumab are endothelial growth factor receptor (EGFR) inhibitors, and are treatment options for patients with RAS wild-type tumors. Tumors with RAS mutations exhibit well-documented resistance to EGFR inhibitors and evidence from the FIRE3 [10] trial suggested that the addition of cetuximab likely has a detrimental impact on overall survival (OS) in these patients.

Unfortunately, many patients are either non-responders to these biologic therapies as a result of pre-existing mutations or develop resistance over time [11], and efforts are ongoing to identify these patients from the outset. The PERMAD [11] trial utilized advanced bioinformatics to establish a cancer-associated fibroblasts (CAF) marker combination to better predict anti-VEGF resistance in treatment naïve patients receiving FOLFOX and bevacizumab up to 3 months before evidence of radiological progression on imaging. Patients who fail standard chemotherapeutic regimens are candidates for regorafenib, a small molecule inhibitor targeting multiple angiogenic processes which significantly increased OS by 1.4 months in the phase III CORRECT [12] trial and 2.5 months in the phase III CONCUR [13] trial compared with placebo. Additionally, trifluridine, a cytotoxic thymidine analog, and tipiracil, a thymidine phosphorylase inhibitor, are available as oral combination therapy trifluridine-tipiracil (TAS-102). The RECOURSE [14] trial, a double-blind, randomized, controlled phase III trial investigating TAS-102 in comparison to placebo, demonstrated an increase in OS from 5.3 months to 7.1 months (HR, 0.68; 95% *CI*, 0.58–0.81; $p < 0.001$) with TAS-102. These results held up in a sub-group analysis regardless of KRAS mutation status [14]. Additionally, trifluridine-tipiracil in combination with bevacizumab showed an improved progression free survival (PFS) of 4.6 months compared to 2.6 months with TAS-102 alone in patients with and without prior treatment with regorafenib and anti-VEGF therapy [15]. The modest improvements in PFS and OS seen with both regorafenib and TAS-102 make precision medicine–based approaches and active participation in clinical trials preferred in appropriate patient populations.

Tumor Molecular Profiling

Next Generation Sequencing (NGS) has revolutionized the oncology field by allowing for the molecular characterization of tumors more efficiently than traditional Sanger sequencing, albeit at a higher cost [16]. Examples of NGS include targeted gene sequencing (TGS), whole exome sequencing (WGS), and comprehensive genomic sequencing (CGS) [17]. Targeted gene panels are most commonly utilized in clinical medicine and focus on a set number of relevant genes with a sequencing depth of 10,000 × or higher [17]. Tumor biopsy specimens are often of insufficient quantity, or have poor DNA quality, making the high sequencing depth of TGS useful [17]. The high sequencing depth of TGS is also helpful in identifying rare mutations in sub-clonal cell populations which may play a substantial role in discovering new therapeutic targets [17]. The approval of the FoundationOne® companion diagnostic by the US Food and Drug Administration (FDA) marked a huge step forward in personalized medicine, with information regarding over 300 genes available in as little as 2 weeks [17]. Additional tumor molecular profiling platforms are either under development or in routine use in clinical practice. Alternatively, circulating tumor DNA (ctDNA) or "liquid biopsy" offers a non-invasive means of extracting tumor-specific genetic information from the plasma of patients when traditional biopsy is not feasible or portends high clinical risk [18]. Additionally, ctDNA has the potential to be utilized as a marker of a tumor's genomic evolution over time to gauge response to therapy and guide future treatment decisions [18]. The usefulness of ctDNA as a diagnostic tool is currently being investigated. For example, a study comparing concordance rates of human epidermal growth factor receptor 2 (HER2)/ERBB2 amplification as detected by ctDNA versus the gold standard of immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) determined a 66.7% concordance rate between methods [18]. Despite this low concordance rate, the use of ctDNA represents a promising means of detecting genomic alterations in patients without adequate tumor tissue samples [2], and for disease monitoring. Further advancements in ctDNA technology are needed before establishing a role for ctDNA in determining progression on targeted therapy in routine clinical practice [18].

Molecular Targets in Metastatic CRC

With the broader application of NGS, many CRC-relevant genomic alterations have been identified, including those in the BRAF, KRAS, NRAS, NTRK, MMR, and HER2 genes, many of which have clinical implications [19]. In fact, NGS is now indicated [3] for all patients with mCRC to evaluate for RAS (NRAS and KRAS) and BRAF mutations, which are mutually exclusive [20]. The presence of a BRAF mutation is associated with poorer PFS [20] and OS [20] than BRAF wild-type tumors and confers poor response to anti-EGFR therapies [20]. The V600E BRAF mutation is found in 10% of mCRC and acts as both a mechanism of resistance and a therapeutic target [19]. The BRAF V600E mutation confers resistance to anti-EGFR therapies, but also provides an immunotherapy target: encorafenib plus cetuximab was approved as second-line therapy based on the results of the BEACON trial which demonstrated improved OS, PFS, and overall response rates [19]. Similarly, RAS mutations constitutively activate the RAS-RAF-MAPK pathway downstream

of the transmembrane EGFR protein, effectively negating any clinical benefit of these therapies in RAS mutant tumors [19].

The presence of MSI-H/dMMR tumors is a prognostic indicator that predicts a poor response to 5-FU-based chemotherapy given the inherent high burden of DNA mutations associated with deficient mismatch repair mechanisms [19]. However, these same mutations have proved beneficial because of their ability to attract T lymphocytes to the tumor, magnifying the impact of programed death-1 (PD-1) inhibition [19, 21]. The KEYNOTE177 trial [22], comparing pembrolizumab vs. chemotherapy (± bevacizumab or cetuximab) as first line therapy for MSI high metastatic CRC demonstrated a longer media PFS of 16.5 months vs. 8.2 months (*HR* 0.60; *CI*, 0.45–0.80). This trial led to the subsequent approval [19] of pembrolizumab as first-line monotherapy for patients with MSI-I/dMMR mCRC and provided an alternative to chemotherapy in these patients. Next generation sequencing continues to provide both prognostic information and opportunities to identify new therapeutic targets in mCRC.

Molecular Targets: HER2

The HER2/neu/ErbB2 gene [2] is located on the long arm of chromosome 17 and encodes a transmembrane tyrosine kinase receptor (TKR) [2, 23]. This TKR is an orphan receptor that does not require an endogenous ligand for activation, but rather relies on homodimerization, and more often, higher potency heterodimerization with other EGFR family receptors including HER3 and EGFR for activation [23, 24]. Dimerization of the HER2 receptor activates downstream signaling through pathways such as the MAPK and PI3K/AKT/mTOR signaling pathways [2, 23]. The resultant activation of these pathways allows for tumor proliferation and differentiation, angiogenesis, and inhibition of apoptosis, all of which are essential aspects of carcinogenesis [2, 23].

HER2 receptor gene amplification and mutations are two mechanisms of constitutive pathway activation with predictive and prognostic significance. The prevalence of HER2 amplification in advanced CRC is not well-defined due to variations in scoring systems [2, 23] and small sample sizes [23]. Best estimates indicate HER2 amplification is found in 2.5–7.4% of patients with advanced CRC [2, 25]. However, the prevalence of HER2 amplification increases with co-occurring BRAF/RAS wild-type mutations to an estimated 5–14% [3]. Although the significance of gene amplification is better understood, activating mutations are playing an increasingly important role as therapeutic targets [2, 26•]. In fact, it has made it to the NCCN guidelines to test routinely. Current NCCN guidelines [3] recommend all patients with advanced or mCRC should undergo testing to determine HER2 receptor status either individually utilizing IHC and FISH with positivity as defined by the HERACLES criteria or through NGS. Testing for HER2 mutations is not indicated in known KRAS/NRAS or BRAF mutated tumors [3]. The prevalence of HER2 mutations has been estimated at 2.8% through the large scale efforts of the Cancer Genome Atlas [27].

HER2 positivity is associated with other known gene alterations well-described in CRC [26•, 31]. The co-occurrence of other alterations such as KRAS mutations and an MSI-high genotype in HER2 positive tumors depends on whether the overexpression of HER2 is due to HER2 amplification or mutation [26•]. A study by Ross et al. [26•] of 569 mCRC tumors positive for ERBB2/ERBB3 with either amplification, short variant alterations, or a combination were analyzed [26•]. ERBB3 mutant tumor samples were associated with an increased likelihood of MSI, in contrast to HER2–amplified tumors, none of which demonstrated microsatellite instability [26•]. Similarly, the HOLIC [31] study found MSI was rarely associated with HER2 amplification [31]. HER2 amplification is also rarely associated with KRAS mutations, with Ross et al. [26•] finding that only 27% of HER2 tumors co-expressed KRAS mutations compared to 52% of wild-type tumors. Interestingly, 49% of HER2 short variant mutated tumors co-expressed KRAS mutations, similar to the 52% observed in the wild-type population [26•]. The reverse is true for TP53 alterations, which are more common in HER2–amplified samples (87–92%) than HER2 short variant samples (64%–72%) [26•]. This study also determined that HER2 amplification is strongly correlated with a lack of BRAF mutations [26•].

Clinicopathologic Features and Prognostic Implications of HER2 in mCRC

The clinicopathologic characteristics and prognostic implications of HER2 overexpression and mutation in advanced/metastatic CRC are not as well-defined as in other cancers such as breast and gastric tumors [2, 23, 24, 26•]. One of the major difficulties encountered in assessing the implications of HER2 positivity in mCRC is the lack of a well-defined scoring system and low prevalence of HER2 alterations as alluded to above [2]. The HERACLES trial attempted to address this by proposing uniform criteria for assessing HER2 positivity in CRC. Most previous studies utilized the gastroesophageal adenocarcinoma (GEA) criteria, developed for assessment of HER2 positivity in gastroesophageal carcinomas [2]. Criteria for HER2 positivity are defined in Fig. 1.

However, a 2015 meta-analysis of 2867 CRC patients demonstrated HER2 overexpression was not associated with clinicopathologic features such as sex, tumor location, grade of differentiation, or tumor node metastasis

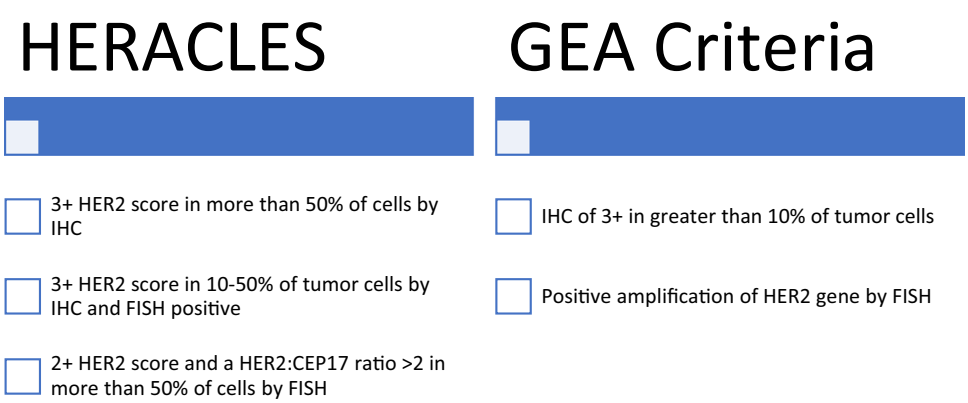

Fig. 1 Comparison of the HERACLES and GEA criteria for HER2 positivity. The more conservative HERACLES criteria require any one of the three criteria for HER2 positivity [23]

(TNM) stage [32]. In addition, this study reported no relationship between HER2 overexpression and prognosis [32]. This was also demonstrated in a pooled analysis of patients from the QUASAR stages II and III trials and the stage IV FOCUS and PICCOLO trials, which demonstrated no significant association between HER2 overexpression and OS [33].

Contrarily, some studies have suggested HER2 positivity is a poor prognostic indicator. An analysis by Huang et al. [34] aiming to address the prognostic value of HER2 in stage IV CRC determined that HER2 positivity is an independent risk factor for worse PFS and OS. In 2017, the HOLIC [31] study, a large-scale retrospective study of 160 Asian patients with HER2 positive CRC, demonstrated an association with poor prognosis secondary to aggressive tumor behavior defined as increased rates of perineural and vascular invasion, more frequent lymph node positivity, and higher TNM stage at diagnosis. Furthermore, a younger age at presentation (< 60 years) was found in patients with mCRC with associated HER2 amplification [26•, 31] or mutation [26•]. Lastly, the presence of HER2 alterations does have predictive significance. As previously eluded to, HER2–positive patients have documented resistance to the standard anti-EGFR antibody treatments cetuximab and panitumumab, which limits available lines of therapy and may also contribute to an overall worse prognosis [35••, 36]. Specifically, median PFS was significantly shortened in HER2–amplified versus non-amplified tumors (2.8 vs. 8.1 months, respectively; hazard ratio, 7.05; 95% *CI* 3.4 to 14.9) [36].

HER2–Directed Therapy in CRC

The success of HER2–directed therapy in both breast and gastric cancer led to the HERACLES A study [30], the first trial investigating combination of HER2–directed therapy in mCRC with a combination of the anti-HER2 monoclonal antibody trastuzumab, and the HER2 tyrosine kinase inhibitor (TKI) lapatinib. Other studies have investigated other anti-HER2 monoclonal antibodies and combinations, including pertuzumab in combination with trastuzumab, pertuzumab and trastuzumab-emantansine, trastuzumab and tucatinib, and trastuzumab deruxtecan. The rationale for the combination of lapatinib and trastuzumab stemmed from xenograft models demonstrating the ability of trastuzumab to prevent paradoxical phosphorylation of HER3, an undesired effect of long-term lapatinib therapy, secondary to compensatory HER3 transcriptional upregulation [30]. Trastuzumab and pertuzumab were investigated in combination originally in breast cancer trials, based on the rationale that the combination of these two monoclonal antibodies against the extracellular domain of HER2 results in synergism due to many proposed mechanisms related to non-overlapping functions of the antibodies in cancer cells and enhanced binding affinity to HER2 by cooperative interaction [37]. Other combinations including pertuzumab and trastuzumab emtansine (T-DM1) investigated in the HERACLES B trial and trastuzumab with tucatinib investigated in the MOUNTAINEER trial were based on the same rationales. Finally, most recently, the Destiny CRC01 trial demonstrated the efficacy of trastuzumab deruxtecan, a humanized anti-HER2 antibody drug conjugated with a topoisomerase I inhibitor in patients who have failed prior HER2–directed therapy [35••]. The aforementioned trials predominately focused on tumors with HER2 amplification or overexpression. The utility of these therapies in HER2 activating mutations is an ongoing area of investigation.

Clinical Trials of HER2–Directed Therapy in CRC

HERACLES A and HERACLES B Trials

The HERACLES A [30] trial laid the foundation for the use of anti-HER2 therapy in patients with refractory,

HER2–altered CRC. In this proof-of-concept, multicenter, open-label, phase II trial, 27 heavily pre-treated patients with KRAS wild-type, HER2–amplified mCRC that had failed prior anti-EGFR therapy were treated with a combination of trastuzumab and lapatinib [30]. Patients received treatment with intravenous trastuzumab as a 4-mg/kg loading dose followed by 2 mg/kg once weekly as well as oral lapatinib 1000 mg by mouth daily until either disease progression or treatment toxicity [30]. The primary endpoint of this trial was the proportion of patients achieving a complete or partial objective response by RECIST criteria. The combination yielded responses in 30% of patients (8/27), with one patient displaying a complete response [30]. The patient with a complete response was a 63-year-old woman with chemo-resistant HER2–positive mCRC who sustained a complete clinical response and continued to tolerate her HER2 therapy after 7 years of follow-up [38]. Disease stabilization was noted in 44% of patients [30]. These results are particularly encouraging given 74% of the patients had failed at least 4 prior lines of therapy [30]. Furthermore, this trial suggested uniform criteria for assessing HER2–positivity in CRC, as discussed above.

Long-term follow-up data [38] from the HERACLES A trial at a median of 6.7 years after combination therapy was available for 32 of 35 patients [38]. At follow-up, 25% of patients displayed a partial response, 44% had stable disease, and as stated previously there was one complete response [38]. Median PFS was 4.7 months and median OS was 10 months [38]. Unfortunately, 19% of patients had experienced progression in the central nervous system (CNS), a rate 4 × higher than previously reported in patients with mCRC [38]. Increased CNS involvement is well-described in HER2–amplified breast and gastric cancers [38]. Tosi et al. [38] suggested several possible hypotheses for the high rates of CNS involvement seen, including limited penetration of the blood brain barrier, increased likelihood of progression in rare anatomic sites secondary to an improvement in OS, and tropism of ERBB2–amplified cells for the CNS. This increased propensity for CNS progression in patients treated with trastuzumab and lapatinib warrants brain imaging at therapy initiation and for ongoing tumor assessment during treatment [38].

HERACLES B [39] was a single-arm, phase II trial investigating the combination of pertuzumab (840 mg IV loading dose followed by 420 mg IV every 3 weeks) and trastuzumab-emtansine (T-DM1) (3.6 mg/kg every 3 weeks) in 31 patients with histologically confirmed chemorefractory RAS/BRAF wild-type, HER2–amplified mCRC. The primary end point of this trial was objective response rate (ORR) and secondary endpoints were PFS and safety [39]. This trial did not reach its pre-planned primary endpoint of ≥ 30% ORR or 7 objective responses, rather, the ORR was 9.7% at the time of data cutoff [39]. Despite not meeting the primary endpoint, disease control was observed in 77% of patients [39]. Additionally, the median PFS was 4.1 months, similar to the HERACLES A study where mPFS was 4.2 months with trastuzumab and lapatinib, and the MyPathway [25] trial discussed below (5.3 months; trastuzumab and pertuzumab) [39]. Evidence of an overall response or stable disease of 4 months duration was significantly associated with higher HER2 IHC scores (3 + versus 2 +) [39]. Furthermore, overall the toxicity profile of pertuzumab and T-DM1 was favorable and provided disease control with few adverse effects [39].

MyPathway

The MyPathway [25] trial is an ongoing, multicenter, non-randomized, open-label, phase 2a multiple basket study evaluating the efficacy of appropriately matched, non-indicated targeted therapies in advanced solid tumors that investigated the combination of trastuzumab (8 mg/kg IV loading dose, then 6 mg/kg every 3 weeks) and pertuzumab (840 mg IV loading dose, followed by 420 mg every 3 weeks) in patients with HER2–amplified mCRC. The ORR was 32% (18/57) with one complete response [25]. Stratification by both KRAS and PIK3CA mutation status revealed differing response rates [25]. An ORR of 40% was observed in KRAS wild-type tumors compared to a decreased ORR of 8% in 23% of patients harboring a KRAS mutation [25]. A lower ORR of 13% was also observed in patients with PIK3CA mutations compared to an ORR of 43% in PIK3CA wild-type tumors, though this was a small subset of the patient population ($n = 8$) and further investigation is warranted to determine the clinical relevance of this finding [25]. The MyPathway trial [25] corroborated previous findings that right-sided tumors are associated with worse outcomes by demonstrating a decreased ORR and clinical benefit rate (CBR, defined as the percentage of patients with an objective response or stable disease for > 4 months), as well as shorter PFS and OS than either left-sided or rectal tumors. The association between tumor location and prognosis is suggestive, however may be related to other factors such as molecular features, given 50% of the right-sided tumors were also KRAS–mutated compared to only 30% of rectal tumors and 4% of left-sided tumors [25]. The impact of tumor location as a prognostic indicator independent of KRAS status in this group also requires further investigation [25].

MOUNTAINEER

The MOUNTAINEER [40] trial, an open-label, phase II study, evaluated the efficacy and safety of combination therapy with tucatinib and trastuzumab in patients with HER2–amplified, RAS wild- type mCRC refractory to standard therapy. Tucatinib is an oral, highly selective

TKI with little inhibition of EGFR. Tucatinib was recently approved for the treatment of HER2–positive metastatic breast cancer including in patients with brain metastases with continued disease progression after the use of multiple HER2–directed therapies [41]. The basis for this approval comes from the HER2Climb [42] trial, which demonstrated that the addition of tucatinib to trastuzumab and capecitabine led to increased OS (21.9 months vs. 17.4 months) and PFS at 1 year (33.1% vs. 12.3%) compared with the addition of placebo in patients with metastatic breast cancer. Progression-free survival at 1 year was 24.9% in patients with brain metastases that received tucatinib combination therapy compared to 0% who received placebo [42]. This trial formed the basis for the MOUNTAINEER trial in mCRC, which on interim analysis demonstrated a 52% ORR in the first 23 patients, as well as a median PFS of 8.1 months, and a median OS of 18.7 months [40]. The trial was expanded based on these preliminary results and will further evaluate ORR and therapeutic safety [40]. Further investigation into PFS in patients with brain metastases and mCRC is warranted given the increased number of patients with brain metastases identified on long-term follow-up of the HERACLES A trial discussed above.

TAPUR and TRIUMPH

The phase III basket TAPUR [43] study evaluated the combination of pertuzumab and trastuzumab in mCRC using NGS to identify patients with ERBB2 amplification and specific ERBB2 mutations. Of the 28 patients enrolled, 27 had an ERBB2 amplification and one patient had concurrent HER2 amplification/mutation [43]. The majority of patients were male (64%) and (77%) received 1–2 lines of therapy and 9% received three or more lines of therapy prior to treatment initiation [43]. The primary outcome measure is ORR assessed at 16 weeks of treatment and secondary endpoints are PFS and OS [43]. At follow-up, four partial responses were seen and ten patients had stable disease, for an ORR of 14% (*CI* 4%–33%) and a disease control rate (DCR) of 50% (*CI* 36%–60%) [43]. Median PFS was 17.2 weeks (*CI* 11.1–27.4) and the 1-year OS was 27 months, with a 1-year survival rate of 58% [43]. Grade 3 adverse events or severe adverse events potentially related to the combination were reported in two patients, including left ventricular dysfunction, infusion reaction, and anemia [43]. This study demonstrated that combination therapy with pertuzumab and trastuzumab has anti-tumor activity in patients with heavily pre-treated mCRC with ERBB2 amplification [43].

The TRIUMPH [44•] trial was also a phase II trial evaluating the use of trastuzumab and pertuzumab in mCRC patients with HER2 amplification as confirmed by tissue sample or ctDNA who were refractory to standard chemotherapy regimens, including anti-EGFR therapy. Patients received the same dosing regimen utilized in the MyPathway [25] trial. This trial was the first to show the efficacy of dual HER2–targeted therapy in patients identified using ctDNA [44•]. Both the cohorts of patients positive by tissue and by ctDNA met their primary endpoints [44•]. The confirmed sue (n = 27) and 28% (CI 12–49%) in the patients positive by ctDNA (n = 25) [44•]. These results were in stark contrast to the ORR of 0% in the standard of care salvage therapy cohort [44•]. Median PFS was 4 months (1.4–5.6 months) in the tissue-positive patients and 3.1 months (1.4–5.6 months) in the ctDNA patients [44•]. Overall survival was 10.1 months (4.5–16.5) in the tissue-positive cohort versus 8.8 months (4.3–12.9 months) in the ctDNA cohort [44•]. Importantly, this trial provided evidence that response to therapy was best in HER2–amplified tumors not co-expressing clonal ctDNA driver mutations in KRAS, BRAF, PIK3CA, and/or ERBB2 with an ORR of 44% (tissue positive) and 37% (ctDNA positive) vs. an ORR of 0% in both tissue and ctDNA–positive patients with a mutation in at least one of these genes [44•]. These co-occurring mutations are a marker for resistance to therapy and ctDNA has proven to be a useful tool to identify clonal mutations that may predict primary treatment resistance to anti-HER2 therapies [44•].

DESTINY-CRC01

The open label, phase II DESTINY-CRC01 [35••] trial assessed the use of trastuzumab deruxtecan in patients with treatment refractory HER2–amplified RAS/BRAFV600E wild-type mCRC who failed a median of four prior treatments. Poignantly, this was the first study to enroll patients previously treated with anti-HER2 therapy excluding trastuzumab deruxtecan [35••]. Study participants were stratified into three cohorts by HER2 expression level: cohort A (HER2–positive, immunohistochemistry [IHC] 3 + or IHC2 + and in situ hybridization [ISH]-positive), cohort B (IHC2 + and ISH-negative), or cohort C (IHC1 +) [35••]. After a median follow-up of 62.4 weeks, the ORR in cohort A was 45.3% (24/53 pts; *CI* 31.6–59.6) with 23 (43%) partial responses and one complete response [45•], the DCR was 83% (44/53 pts; *CI* 70.2–91.9), the median DOR was 7 months (*CI* 5.8–9.5), and the mPFS and mOS were 6.9 months (*CI* 4.1–8.7) and 15.5 months (8.8–20.8), respectively [45•]. Cohorts B and C had a median PFS of 2.1 months (*CI* 1.4–4.1) and 1.4 months (*CI* 1.3–2.1), and a median OS of 7.3 months (*CI* 3.0–not evaluable) and 7.7 months (*CI* 2.2–13.9), respectively [45•]. High response rates were observed in groups with and without prior exposure to HER2 therapy [45•]. Those with prior HER2 therapy exposure had a confirmed ORR of 43.8% (7/16 pts; *CI* 19.8–70.1); however, the majority of responding patients were in the IHC3 + group (57.5%, 23/40 pts; *CI* 40.9–73.0), with only 1/13 patients (7.7%) in the IHC2 + /ISH + group

Table 1 This table details ongoing clinical trials in HER2–positive mCRC

Study title/phase	Intervention	HER2 status	Primary outcome
A Clinical Study of Pyrotinib in Patients with HER2–positive Advanced Colorectal Cancer: Phase II NCT04380012	Pyrotinib Pyrotinib + trastuzumab	Amplified	ORR
Trastuzumab Deruxtecan in Participants With HER2–overexpressing Advanced or Metastatic Colorectal Cancer (DESTINY-CRC02): Phase II NCT04744831	Trastuzumab deruxtecan 5.4 mg/kg Q3W vs. 6.4 mg/kg Q3W	Amplified	ORR
Study of Neratinib + Trastuzumab or Neratinib + Cetuximab in Patients With KRAS/NRAS/BRAF/PIK3CA Wild-Type Metastatic Colorectal Cancer by HER2 Status: Phase II NCT03457896	Trastuzumab + Neratinib Cetuximab + Neratinib Diagnostic test: Guardant360 diagnostic test	Amplified, non-amplified (wild-type), mutated	PFS
A Safety and Efficacy Study of ZW25 (Zanidatamab) Plus Combination Chemotherapy in HER2–expressing Gastrointestinal Cancers, Including Gastroesophageal Adenocarcinoma, Biliary Tract Cancer, and Colorectal Cancer: Phase II NCT03929666	Zanidatamab + standard first-line chemotherapy (XELOX, FP, or mFOLFOX6 for GEA; mFOLFOX6 with or without bevacizumab for CRC; and CisGem for BTC)	HER2–expressing CRC (IHC 3 + with or without gene amplification; or IHC 0, 1 + or 2 + with gene amplification)	ORR, incidence of DLTs, AEs, lab abnormalities
Pyrotinib in Combination With Trastuzumab in Treatment-refractory, HER2–positive Metastatic Colorectal Cancer: Phase II NCT03843749	Pyrotinib + trastuzumab	HER2–positive ALK mutation (mutation, fusion, rearrangements)	ORR
MOUNTAINEER: A Phase II, Open Label Study of Tucatinib Combined With Trastuzumab in Patients With HER2 + Metastatic Colorectal Cancer: Phase II NCT03043313	Tucatinib vs. tucatinib + trastuzumab	Overexpression or amplification	ORR
S1613, 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: Phase II NCT03365882	Trastuzumab + pertuzumab vs. cetuximab + irinotecan	Amplified	PFS
A Study of Poziotinib in Patients With EGFR or HER2 Activating Mutations in Advanced Malignancies: Phase II NCT04172597	Poziotinib	Activating mutations	ORR
Phase 1/2 Expansion Cohorts Trial of Intravenous Administration of TAEK-VAC-HerBy Vaccine Alone and in Combination With HER2 and PD-1/PD-L1 Antibodies in Patients With Advanced HER2–expressing Cancer: NCT04246671	TAEK-VAC-HerBy vaccine	Amplification	DLT
Tucatinib Plus Trastuzumab and Oxaliplatin-based Chemotherapy or Pembrolizumab-containing Combinations for HER2 + Gastrointestinal Cancers: Phase I/II NCT04430738	Tucatinib + trastuzumab	HER2–positive	DLT, AE, lab abnormalities, dose alterations
Study of A166 in Patients With Relapsed/Refractory Cancers Expressing HER2 Antigen or Having Amplified HER2 Gene: Phase I/II NCT03602079	A166: antibody drug conjugate targeting HER2 expressing cancer cells	Overexpression or amplification	ORR

Table 1 (continued)

Study title/phase	Intervention	HER2 status	Primary outcome
A First-in-human Study Using BDC-1001 in Advanced HER2–Expressing Solid Tumors: Phase I/II NCT04278144	Pembrolizumab	Expression or amplification	ORR
Targeted Therapy Directed by Genetic Testing in Treating Patients With Advanced Refractory Solid Tumors, Lymphomas, or Multiple Myeloma (The MATCH Screening Trial): Phase II NCT02465060	Afatinib or pertuzumab + trastuzumab or trastuzumab emtansine	Amplification or activating mutations	ORR
MasterKey-01: A Phase 1/2, Open-label, Two-part, Multicenter Study to Assess the Safety, Tolerability, Pharmacokinetics & Antitumor Activity of BDTX-189, an Inhibitor of Allosteric ErbB Mutations, in Patients w/ Advanced Solid Malignancies: Phase I/II NCT04209465	BDTX-189	Amplification or overexpression and mutation	ORR
A Phase II, Multicenter, Open-label Study to Evaluate the Efficacy and Safety of Trastuzumab Deruxtecan (T-DXd) for the Treatment of Unresectable and/or Metastatic Solid Tumors Harboring HER2 Activating Mutations Regardless of Tumor Histology: Phase II NCT04639219	Trastuzumab deruxtecan	Activating mutations	ORR

ORR, objective response rate; *PFS*, progression free survival; *AE*, adverse events; *DLT*, dose limiting toxicity; *FP*, 5-flurouracil + cisplatin

responding [45•]. Grade 3 or higher treatment-related adverse events occurred in 65.1% of patients, the majority of which were gastrointestinal or hematologic events [45•]. Treatment-related adverse events led 13 patients (15.1%) to discontinue therapy [45•]. Interstitial lung disease or pneumonitis occurred in 8 patients (9.3%) and was the cause of three treatment-related deaths [45•]. Close monitoring of patients for the above pulmonary complications is essential during treatment [45•].

Ongoing Clinical Trials in HER2–Positive mCRC

The multi-center, non-randomized, open-label phase II trial NSABP FC-11 [46] is currently underway, investigating the efficacy of neratinib plus trastuzumab versus neratinib plus cetuximab in quadruple wild-type (KRAS/NRAS/BRAF/PIK3CA) mCRC based on HER2 status (amplified, non-amplified (wild type), and/or mutated). Neratinib is an irreversible TKI that binds intracellularly to signaling domains (HER1, HER2, HER3, HER4) as well as EGFR, and inhibits downstream pathways [38]. Intracellular inhibition by neratinib is believed to overcome tumor escape mechanisms currently plaguing other HER2–directed therapies [47]. The primary outcome for the study is 6-month PFS, and secondary outcomes include ORR, CBR (from initiation of study to disease progression), and frequency of adverse events [46]. This study is still ongoing and will allow a better understanding of the response of HER2–mutated CRCs. Ongoing phase I/II and above clinical trials are listed in (Table 1).

Conclusion

Therapy with anti-HER2 agents is an ongoing and active area of research in the treatment of mCRC. Increasing use of NGS has facilitated the discovery of new targets including HER2–activating mutations. Anti-HER2 therapies provide a promising treatment option for patients who have exhausted traditional regimens and in certain populations may supplant the need for chemotherapy. Promising results from phase II studies led the NCCN to include combination therapy with trastuzumab paired with either lapatinib or pertuzumab in HER2–amplified mCRC [3]. Heavily pre-treated patients who fail prior HER2 treatments may derive benefit from the antibody drug conjugate trastuzumab deruxtecan, albeit with a higher risk of pulmonary complications [45•]. Further investigation into the role of HER2–directed therapy in mutated mCRC is an unmet need, as is the wider use of NGS and ctDNA to explore mechanisms of resistance.

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•• Of major importance

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