

Dual HER2 inhibition strategies in the management of treatment-refractory metastatic colorectal cancer: History and status

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Abstract

Human epidermal growth factor receptor 2 (HER2) signaling pathway activation has been identified as a contributor to de novo or acquired resistance to epidermal growth factor receptor (EGFR) inhibitors in a small subset of patients with metastatic colorectal cancer (mCRC). Dual anti-HER2-targeted treatment exhibits strong antitumor activity in preclinical models of HER2-positive mCRC, supporting its testing in clinical trials. The HERACLES trial at four Italian academic cancer centers has confirmed the effectiveness of dual blockage of HER2 with trastuzumab plus lapatinib in patients with heavily pretreated HER2-positive mCRC, refractory to the anti-EGFR antibodies cetuximab or panitumumab. Here, we reviewed the preclinical studies exploring the role of HER2 signaling in the development of anti-EGFR therapy resistance and discussed the status of clinical trials assessing the activity of HER2 inhibitors in this setting.

Key words: Epidermal growth factor receptor; Cetuximab; Panitumumab; Human epidermal growth factor receptor 2; Anti-epidermal growth factor receptor resistance; Trastuzumab; Dual inhibition

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Core tip: We reviewed the preclinical studies exploring the role of human epidermal growth factor receptor 2 (HER2) signaling in the development of anti-epidermal growth factor receptor therapy resistance in metastatic colorectal cancer and discussed the status of clinical trials assessing the activity of HER2 inhibitors in this setting.

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INTRODUCTION

The occurrence of distant metastases is an unfortunate but common event during the clinical course of colorectal cancer (CRC). Approximately three-quarters of patients with CRC present with unresectable stage IV disease at initial diagnosis or at follow up^[1]. These patients usually benefit from modern systemic therapies, including chemotherapy alone or in combination with targeted therapy. However, in the treatment decision-making process, clinicians should consider various patient (age, performance status, comorbidity, and life expectancy) and tumor characteristics [location (*i.e.*, right-sided vs left-sided), mutation profile (*i.e.*, RAS mutated vs RAS wild-type), disease extent, and possibility of secondary resection] that may influence the treatment effectiveness and morbidity outcomes.

Patients with metastatic CRC (mCRC) who have poor performance status and very extensive disease are mostly managed by a palliative care approach. Expectedly, the administration of chemotherapy may create tolerability issues in elderly patients. Therefore, single-agent chemotherapy (fluoropyrimidine or irinotecan) is generally preferred to classical combination regimens in elderly patients. Otherwise, all physically fit patients with mCRC, particularly those who have a greater chance for salvage surgical resection following systemic therapy, should be aggressively treated to obtain better clinical outcomes. In the modern clinical practice, epidermal growth factor receptor (EGFR, also known as HER1) pathway inhibition in CRC cells using EGFR-targeting monoclonal antibodies (cetuximab and panitumumab) is an important component of this aggressive approach to treatment^[2].

Because of their mechanism of action, anti-EGFR antibodies should be administered only in patients with CRC whose tumors do not contain activating mutations in one of their RAS genes (K-, N-, and H-RAS)^[3,4]. Briefly, these drugs specifically bind to the extracellular portion of EGFRs in cancer cells to prevent triggering their activation by endogenous ligands, such as epidermal growth factor and transforming growth factor alpha^[5] (Figure 1). Therefore, anti-EGFR antibodies successfully inhibit ligand-induced dimerization of EGFR with itself and with another HER family member (HER2, HER3, and HER4). This causes deactivation of intracellular mitogenic signaling pathways including the RAS-RAF-MEK-ERK and PI3K-AKT-mTOR cascades, leading to G1 phase cell cycle arrest and apoptosis in cancer cells^[5,6].

Conversely, in tumors harboring RAS mutations, the RAS-RAF-MEK-ERK pathway remains consecutively

active, independent of the canonical EGFR signaling^[7]. In this case, anti-EGFR antibodies are completely inactive and sometimes detrimental^[8].

EGFR inhibitors are preferentially administered together with oxaliplatin-based (*i.e.*, 5-fluorouracil, leucovorin, and oxaliplatin) and irinotecan-based (*i.e.*, 5-fluorouracil, leucovorin, and irinotecan) doublet chemotherapy regimens, or intensified chemotherapy regimens such as FOLFOXIRI (5-fluorouracil, leucovorin, oxaliplatin, and irinotecan). Recent retrospective evidence revealed the relatively impaired antitumor activity of cetuximab in the frontline treatment of patients with mCRC whose tumors arise from the right side of the colon. Despite this finding, EGFR inhibitors are still important in both chemo-naïve and carefully selected chemo-refractory cases^[9-13]. Notably, a recent phase 2 study comparing panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) with the antiangiogenic drug bevacizumab plus mFOLFOX6 in patients with previously untreated RAS wild-type mCRC reported a median survival time exceeding 40 mo for patients receiving panitumumab^[14].

Wild-type RAS status does not guarantee a response to anti-EGFR drugs, and these drugs cannot induce any tumor shrinkage in a significant proportion of patients (30%–50%) with RAS wild-type mCRC. Numerous studies have elucidated the underlying mechanisms of anti-EGFR treatment refractoriness (*de novo* or primary resistance) in these patients. These studies consistently revealed that the presence of other genetic alterations in tumor cells potentiating the RAS-RAF-MEK-ERK and PI3K-AKT-mTOR signaling, such as BRAF (V600E) mutation, PI3KCA (exon 20) mutation, and PTEN loss, can at least partially account for unresponsiveness^[15-19]. In patients with these mutations, the use of angiogenesis inhibitors instead of EGFR inhibitors or the administration of intensified chemotherapy backbone such as FOLFOXIRI along with anti-EGFR agents are reasonable treatment strategies^[20].

Additionally, almost all patients with mCRC who initially respond to EGFR inhibitors become resistant to the treatment over time (secondary or acquired resistance). The identification of compensatory cellular mechanisms leading to treatment failure is crucial to determine effective salvage pharmacological interventions that can re-induce tumor regression.

Over the last few years, studies have shown that despite its rarity, HER2 signaling pathway activation in cancer cells, primarily due to HER2 overexpression and gene amplification may play an important role in the development of primary and secondary resistance to anti-EGFR therapies in patients with mCRC^[21,22].

HER2-POSITIVE COLORECTAL CANCER AS A NEW CLINICAL ENTITY

In contrast to other proteins in the HER family, HER2 has no endogenous ligand and is considered an example of an orphan receptor that is functionally incomplete^[23]. It has

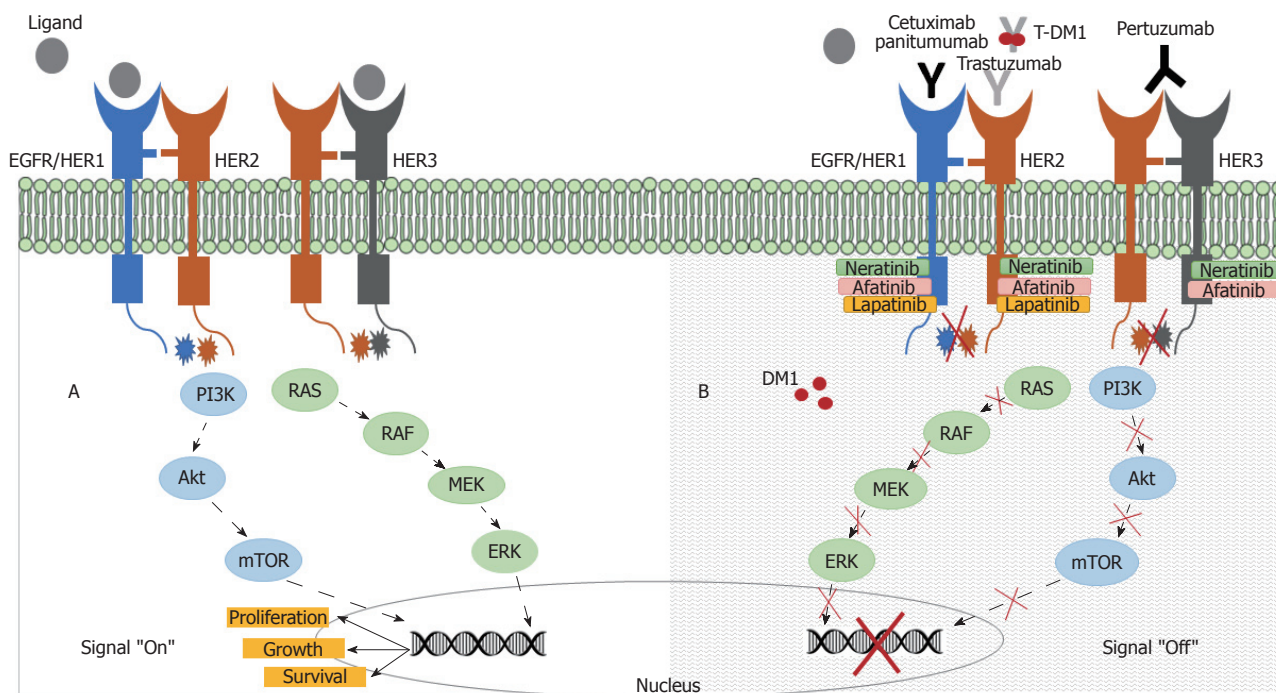


Figure 1 Epidermal growth factor receptor-related signaling pathways and anti-epidermal growth factor receptor and anti-human epidermal growth factor receptor 2 targeted drugs in colorectal cancer. A: Following ligand binding, the epidermal growth factor receptor (EGFR) (HER1) forms active homo- or heterodimers, resulting in the autophosphorylation of tyrosine residues within the cytoplasmic domain of the receptors. This triggers the RAS/RAF/MEK/ERK and PI3K/AKT/mTOR pathways that transmit mitogenic signals to the nucleus; B: Dimerization of the receptors can be inhibited by EGFR-targeted (cetuximab or panitumumab) or HER2-targeted antibodies (trastuzumab or pertuzumab). Small molecule tyrosine kinase inhibitors (neratinib, afatinib, or lapatinib) can block EGFR and HER2 signaling by preventing adenosine triphosphate binding to the catalytic domain of protein kinases.

the strongest catalytic tyrosine kinase activity; therefore, it is a preferable dimerization partner, particularly for EGFR and HER3^[23,24]. HER2 overexpression leads to increased EGFR membrane expression and activity^[25]. HER2 overexpressing cells have significantly prolonged the activation of mitogen-activated protein kinase (originally called extracellular signal-regulated kinase, ERK) and c-Jun N-terminal kinase downstream signaling pathways following stimulation with EGFR or HER3 ligands compared with HER2-low expressing cells^[26]. HER3 is considered an obligate dimerization partner in HER2-induced tumor cell proliferation^[27,28]. HER2 overexpression is associated with enhanced HER3 phosphorylation and increased PI3K/Akt pathway activation^[27,28].

The clinical and biological significance of HER2 signal activation in CRC has become an important research topic after the identification of *HER* gene amplification as a potential mechanism of anti-EGFR treatment resistance in patient-derived xenograft models and cell lines^[21,22]. Bertotti *et al.*^[21] produced a large patient-derived xenograft platform using tumor samples from patients with CRC undergoing liver metastasectomy. They found that only a small portion (2%–3%) of genetically unselected xenopatient models showed *HER2* gene amplification. However, in xenopatient models whose tumors were KRAS wild-type and cetuximab-resistant, the frequency of *HER2* gene amplification increased to 13.6%. Furthermore, in a subset of xenopatient models with cetuximab-refractory KRAS/NRAS/BRAF/PIK3CA wild-type CRC,

its frequency increased to 36%. This suggested that HER2 amplification could be a key driver of anti-EGFR resistance in CRC, and anti-HER2 therapy could be an option in selected patients. Therefore, the effects of anti-EGFR and anti-HER2 therapies in cetuximab-resistant, HER2-amplified mCRC xenopatient models were investigated. Dual EGFR/HER2 inhibition with pertuzumab (an anti-HER2 monoclonal antibody that blocks HER2/HER3 dimerization) plus lapatinib (a small molecule dual inhibitor of EGFR and HER2 receptor tyrosine kinases) caused significant tumor regression. A combination of lapatinib and cetuximab also significantly reduced tumor volume, but to a lesser extent than pertuzumab plus lapatinib.

Yonesaka *et al.*^[22] found that the activation of HER2 signaling either by *HER2* gene amplification or HER3-activating heregulin ligand overproduction led to de novo or acquired resistance to cetuximab in human CRC cell lines by increasing activation of ERK 1/2 signal pathway. Treatment of these cetuximab-resistant cell lines with HER2 small interfering RNA (siRNA) and inhibition of HER2/HER3 dimerization using lapatinib and pertuzumab could restore cetuximab sensitivity both in vitro and in vivo. These preclinical findings were further confirmed by the authors in a cohort of patients with mCRC exhibiting de novo or acquired resistance to cetuximab-based therapy. In these patients, *HER2* gene amplification in tumor specimens or high levels of circulating heregulin in patient plasma samples was detected.

Using HER2-amplified patient-derived tumor grafts,

Leto *et al.*^[29] confirmed the necessity of dual HER2 inhibition to induce effective tumor shrinkage in patients with CRC. They indicated that trastuzumab plus lapatinib or irreversible pan-HER inhibitor afatinib alone have higher antitumor activity than lapatinib monotherapy in HER2-amplified patient-derived CRC and gastric cancer cell-line xenografts. Delayed reactivation of HER3 and EGFR during lapatinib treatment has been proposed as a reason for its reduced effectiveness.

Kavuri *et al.*^[30] revealed that HER2 somatic mutations (S310F, L755S, V77L, V842I, and L866M) can activate the HER2 signaling pathway and cause panitumumab and cetuximab resistance in CRC cell lines, irrespective of the presence of HER2 amplification or overexpression. In addition, the *HER2* gene was sequenced in 48 CRC PDX samples that were cetuximab-resistant and wild-type for KRAS, NRAS, BRAF, and PIK3CA. Only four (8.3%) PDXs were found to have HER2-activating mutations. Treatment of mice carrying these HER2 mutant xenografts with dual HER2-targeted therapy with either trastuzumab plus neratinib (an irreversible pan-HER tyrosine kinase inhibitor) or trastuzumab plus lapatinib led to sustained tumor regression. These data suggest that a small number of patients with anti-EGFR therapy-refractory mCRC can have HER2 activating mutations, and these patients may benefit from dual HER2 blockage.

CLINICAL RELEVANCE OF HER2 EXPRESSION IN METASTATIC COLORECTAL CANCER

Studies have shown that HER2 overexpression seems to have no prognostic value in CRC. Richman *et al.*^[31] investigated the relationship between HER2 overexpression and survival in 1342 patients with mCRC who were previously enrolled in the FOCUS and PICCOLO cancer therapy trials. Among them, HER2 overexpression by fluorescence in situ hybridization (FISH) and/or immunohistochemistry (IHC) was identified in 29 (2.2%) patients but was not predictive of disease-free and overall survival (OS). Seo *et al.*^[32] found that *HER2* gene amplification was associated with tumor location and was more frequently detected in tumors originating in the rectum than those originating in the right and left colon. However, they did not see a relationship between HER2 overexpression and several aggressive clinicopathological features of CRC, including infiltrative tumor border, invasion depth, perineural invasion, lymph node metastasis, and distant metastasis.

Tu *et al.*^[33] reported HER2 overexpression in 102 (11.6%) of 878 Chinese patients with CRC. HER2 overexpression was more frequent in patients with early-stage CRC compared to patients with advanced stage CRC. HER2 overexpression was associated with gender, age, histological type, tumor location, and other prognostic indicators such as tumor grade, depth of invasion, lymph node metastases, and distant metastases. Again, it was

not a significant predictor of survival. All these findings were confirmed by a meta-analysis of 18 studies comprising 2867 patients with CRC^[34].

Conversely, several studies found that HER2 overexpression or amplification was predictive of resistance to EGFR inhibitors in patients with mCRC. Jeong *et al.*^[35] identified HER2 amplification in seven (4.9%) of 142 patients with mCRC with RAS and BRAF wild-type tumors. These 142 patients were treated with cetuximab after failure of oxaliplatin, irinotecan, and fluoropyrimidine. The patients with HER amplification had significantly shorter progression-free survival (PFS) than did those without HER2 amplification [median, 3.1 mo vs 5.6 mo; hazard ratio (HR) 2.73, $P = 0.019$]. In addition, there was a trend for poor OS in patients with HER2-amplified tumors (10.1 mo vs 13.5 mo, HR 1.31; $P = 0.488$).

Martin *et al.*^[36] evaluated the *HER2* gene status by FISH in 170 patients with KRAS wild-type mCRC receiving cetuximab or panitumumab alone or in combination with chemotherapy for first- or second-line treatment. Among these patients, seven (4%) had *HER2* gene amplification in 90% of tumor cells and were classified as HER2-all-A patients. Sixty-one percent of the patients had HER2 overexpression due to polysomy or gene amplification in minor clones (HER2-FISH+ cases), and 35% of patients had slight or no HER2 gain (HER2-FISH-cases). Patients who were classified as HER-all-A had worse outcomes than those designated as HER2-FISH+ and HER2-FISH- in terms of response rate ($P = 0.0006$), PFS ($P < 0.0001$), and OS ($P < 0.0001$). These findings suggest that that tumor HER2 copy numbers may predict the response to anti-EGFR treatment in patients with KRAS wild-type mCRC.

CLINICAL TRIALS USING ANTI-HER2 AGENTS IN METASTATIC COLORECTAL CANCER

Early studies that investigated the effectiveness of using the anti-HER2 antibody trastuzumab in combination with irinotecan- and oxaliplatin-based chemotherapy in previously treated patients with mCRC revealed promising antitumor activity^[37,38]. Since these studies were conducted in unselected patients, they did not provide useful information on the clinical activity of this therapeutic approach.

Some studies investigated whether HER2 inhibition could restore sensitivity to EGFR inhibitors in unselected patients with mCRC (Table 1). In a phase I / II trial, Rubinson *et al.*^[39] evaluated the efficacy and tolerability of a combination of pertuzumab and cetuximab in patients with cetuximab-refractory KRAS wild-type metastatic CRC. The study was terminated early following the enrollment of 13 patients due to intolerable side effects such as diarrhea, skin rash, and mucositis. Only seven patients were evaluable for response, with one

Table 1 Summary of completed and ongoing clinical trials of anti-human epidermal growth factor receptor 2 agents in metastatic colorectal cancer

Study	Phase	Treatment	Number of patients	Patient population	RR	mPFS	mOS
Rubinson ^[39]	I / II	Cetuximab + pertuzumab	7	Chemo- and cetuximab-refractory	14%	2.1 mo	3.7 mo
Sartore-Bianchi (HERACLES) ^[40]	II	Trastuzumab + lapatinib	27	Chemo- and cetuximab/ panitumumab-refractory	30%	21 wk	46 wk
Hainsworth (MyPathway) ^[44]	II	Trastuzumab + pertuzumab	34	Chemo-refractory	35%	NR	NR
Siena (HERACLES-RESCUE) ^[42]	II	Trastuzumab- emtansine	Recruiting	Chemo- and cetuximab/ panitumumab and trastuzumab plus lapatinib-refractory			
NCT03457896	II	Neratinib + trastuzumab or cetuximab	Recruiting	Cetuximab and/or chemo- refractory			
MOUNTAINEER ^[45]	II	Tucatinib + trastuzumab	Recruiting	Chemo- and bevacizumab- refractory			

RR: Response rate; mPFS: Median progression-free survival; mOS: Median overall survival; Chemo: Chemotherapy; NR: Not reported.

(14%) patient showing a partial response lasting more than six months, and two (29%) patients achieving stable disease. These results suggested that the use of dual HER2 inhibitors with minimally overlapping toxicities could be a promising option to overcome cetuximab resistance in mCRC.

The seminal HERACLES (HER2 Amplification for Colorectal Cancer Enhanced Stratification) phase 2 trial conducted by Italian researchers tested the activity of dual-targeted trastuzumab and lapatinib therapy in patients with treatment-refractory, KRAS codon 12/13 wild-type and HER2-positive mCRC^[40]. The rationale for this therapeutic approach was primarily based on the above-mentioned preclinical data suggesting promising activity for dual anti-HER2 blockade in this setting. Before patient enrollment, the authors screened 914 patients with KRAS exon 2 (codons 12 and 13) wild-type mCRC and identified 48 (5%) patients who had HER-positive tumors according to the HERACLES Diagnostic Criteria for colorectal cancer (tumors with 3+ HER2 score in more than 50% of cells by IHC or with 2+ HER2 score and a HER2:CEP17 ratio higher than 2.0 in more than 50% of cells by FISH)^[41]. Of these 48 patients, 27 were eligible for the study. Twenty (74%) patients had previously received at least four treatment regimens, including the anti-angiogenesis drugs bevacizumab, regorafenib, or aflibercept, and all patients had been previously treated with the anti-EGFR antibodies cetuximab or panitumumab. Trastuzumab was given intravenously (initial loading dose 4 mg/kg followed by 2 mg/kg weekly), and lapatinib was given orally (1000 mg/d). The treatment was continued until disease progression or until withdrawal of treatment because of an adverse event. The primary endpoint was objective response rate (complete plus partial response). The secondary endpoints were PFS and safety. All 27 patients were evaluable for response. One had a complete response, and seven had a partial response with an overall objective response rate of 30%. Twelve (44%) patients

achieved disease stabilization longer than 16 wk. Median PFS was 21 wk (95%CI: 16-32), and 12 (45%) patients were alive at one year. Treatment was mostly well tolerated. Six of 27 patients (22%) experienced grade 3 adverse events consisting of fatigue, skin rash, and increased bilirubin concentration. The study authors also investigated the molecular determinants of response, and they found that patients with a high *HER2* gene copy number (> 9.45 copies/cell) had significantly longer PFS compared with patients whose tumors had a lower gene copy number (median, 29 wk vs 16 wk, $P = 0.0001$). Patients who had a gene copy number higher than 9.45 were also more likely than patients with a gene copy number lower than 9.45 (44% vs 0%, $P = 0.02$) to have a response to treatment. These results showed that the combination of trastuzumab and lapatinib is safe and effective in treating patients with HER2-positive mCRC resistant to chemotherapy and anti-EGFR agents.

The HERACLES-RESCUE clinical study is currently investigating the activity of trastuzumab-emtansine (T-DM1), an antibody-drug conjugate consisting of trastuzumab linked to the cytotoxic agent emtansine, in patients with HER2-positive mCRC progressing after trastuzumab plus lapatinib^[42]. The rationale for the selection of T-DM1 in this study resulted from testing in patient-derived xenograft models of CRC generated from patients with acquired resistance to trastuzumab and lapatinib in the HERACLES study. These models were found to have high levels of HER2 expression, and treatment with T-DM1 resulted in significant tumor regression, whereas no response was observed in animals treated with pertuzumab alone. Another relevant study, the HERACLES cohort B trial is evaluating the clinical activity of lapatinib or pertuzumab in combination with T-DM1 in patients who are HER2-therapy-naïve and have HER2-positive mCRC^[43].

The MyPathway phase II trial is investigating the efficacy and safety of pertuzumab plus trastuzumab in patients with treatment-refractory mCRC showing

overexpression or amplification of HER2 by gene sequencing and/or by FISH or IHC^[44]. The interim efficacy data reflects initial results from 34 patients. Twelve patients have achieved partial response, and three have achieved stable disease for longer than four months. The median duration of response is 11.1 mo.

Another interesting phase II trial (NCT03457896) is examining the efficacy of pan-HER inhibitor neratinib plus trastuzumab or neratinib plus cetuximab in patients with quadruple wild-type (KRAS/NRAS/BRAF/PIK3CA wild-type) HER2-amplified, HER2-nonamplified (wild-type), or HER2-mutated mCRC. In this trial, patients with HER2-amplified CRC with prior anti-EGFR therapy and/or HER2-mutated CRC with or without prior anti-EGFR therapy will be treated with trastuzumab plus neratinib until disease progression. Patients with HER2 wild-type or HER2-amplified CRC with no prior anti-EGFR therapy will receive cetuximab plus neratinib until disease progression.

The MOUNTAINEER study will test the combination of tucatinib and trastuzumab in patients with HER2 positive, anti-HER2 targeting therapy-naïve, and RAS wild-type mCRC who have been previously treated with chemotherapy and an antiangiogenic drug^[45]. Tucatinib is a very potent and highly selective small molecule inhibitor of HER2 receptor. In HER2 positive xenograft models of CRC, it has shown substantial antitumor activity^[46].

CONCLUSION

Extensive preclinical efforts have identified HER2 amplification or overexpression as a distinct and druggable molecular target in patients with mCRC who exhibit poor sensitivity to anti-EGFR. The ever-expanding clinical experience reveals that dual HER2 blockade may be an effective therapeutic strategy to overcome or reverse tumor resistance in this setting. Moreover, some case examples suggest that sequential HER2 blockade may provide long-term clinical benefit without causing significant class-specific adverse effects in patients with molecularly selected and treatment-refractory mCRC^[47]. The initial results of the HERACLES-RESCUE study will most likely clarify this issue.

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