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International Journal of Molecular and Immuno Oncology

Review Article

HER2 'neu' promise for mCRC

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Received : 18 December 2022
Accepted : 08 January 2023
Published : 03 February 2023

DOI
10.25259/IJMIO_30_2022

Quick Response Code:

ABSTRACT

Following the staggering impact of anti-HER2 treatment in improving the outcomes for breast and gastric cancers, human epidermal growth factor receptor 2 (HER2 neu) has emerged as a promising new oncogenic target for metastatic colorectal carcinoma (mCRC) also. Through this article, we review the role of HER2 in mCRC as a prognostic biormarker as well as a poor predictive factor and mechanism of resistance against anti-EGFR therapy. We discuss the emergence of dual anti-HER2 blockade as effective therapeutic intervention for HER2 amplified mCRC and the advantageous role of ct-DNA in appropriate clinical setting. Furthermore, we explore the encouraging future paradigms for effectively targeting HER2 in mCRC.

Keywords: Human epidermal growth factor receptor 2, Metastatic colorectal carcinoma, Liquid biopsy, Biomarker

INTRODUCTION

Colorectal cancer harbors heterogenous molecular characteristics with primarily two genetic subgroups with distinguishable biological features: Chromosomal instability status and microsatellite instability status. The right-sided colon cancers more frequently have MSI and gene mutations in v-RAF murine sarcoma viral oncogene homolog B1 (BRAF), phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA), Phosphatase and TENsin homolog (PTEN), and ataxia-telangiectasia (ATM), which are in contrast to adenomatous polyposis oli, tumor protein 53, and human epidermal growth factor receptor 2 (HER2) aberrations found more commonly in the left-sided colorectal tumors.[1] Molecular profiling of the tumor remains the cornerstone in managing patients with metastatic colorectal cancers. At present, we use rat sarcoma viral oncogene (RAS) and BRAF testing to select patients for human epidermal growth factor receptor (anti-EGFR) therapy. However, not all patients benefit from anti-EGFR treatment, and we need to have a better understanding of the detailed mitogen-activated protein kinase (MAPK) pathway alterations to appropriately select our patients. High tumor mutation burden (TMB) and marked presence of tumor infiltrating lymphocytes and other neoantigens are some of the unique features of metastatic colorectal carcinoma (mCRC) with mismatch repair deficient (MMR-D) or microsatellite instability-high (MSI-H) which make them a hotspot for the target of immune checkpoint inhibitors that have led to the phenomenal improvement in the outcomes with pembrolizumab for MMR-D or MSI-H.[2] It is of paramount importance that efforts get directed at identifying more such oncotargets that can open new avenues for precision oncology in the mCRC. Recently, the HER2 gene has emerged as a promising new targetable genomic alteration for mCRC.

The current review focuses on the role of HER2 as a potential biomarker of resistance for the use of anti-EGFR therapy and the potential approaches to use anti-HER2 therapy efficiently to turn HER2 into an attractive biomarker in the treatment algorithm of mCRC. The spectacular

results with the effective targeting of this pathway in other malignancies such as breast cancer and gastric cancer with a substantial decrease in the mortality rates have led to the efforts being directed toward finding appropriate approaches to similarly target it in colorectal cancer too. Further, we discuss the future opportunities that may have a promising impact on the outcomes of the patients with HER2 amplified mCRC.

PREVALENCE OF HER2 IN mCRC

While HER2 over-expression is higher in breast cancer and gastric adenocarcinomas, the prevalence of HER2 in CRC is merely 1.6% in an unselected population. One of the largest attempts of HER2 testing came from the University of Kiel, where out of 1645 resected specimens of CRC, only 26 patients had HER2 over-expression (immunohistochemistry [IHC] 3+ or IHC 2+ and *in situ* hybridization [ISH]+).[3] Albeit significantly higher proportions of the resected rectal adenocarcinomas post neoadjuvant chemoradiotherapy were found to be HER2 positive (26%) in another report from the university of Frankfurt, only 12.4% of pre-treatment specimens in this study were HER2 positive, suggesting heterogenous HER2 over-expression.[4] Other studies reporting HER2 over-expression in CRC show wide differences mainly due to different methods of HER2 testing and/or small sample size. Valtorta *et al*.[5] suggested a more stringent HERACLES diagnostic criteria for CRC-specific testing for HER2 over-expression.[6] On the other hand, the MyPathway trial used the American Society of Clinical Oncology (ASCO)/College of American Pathologists guidelines to determine HER2 status as is done in breast cancer.[7] The HERACLES study considers tumor cell membranous reactivity of ≥10% but ≤50% as negative with no further testing needed, while the MyPathway study needs ISH to further characterize it. The HERACLES study considers staining in 10–50% of tumor cells as conditionally positive and further needing ISH, while the MyPathway considers both staining of 10–50% and the staining of more than 50% as positive with no need of further testing.

The studies conducted by Schrock *et al*.[8] and Takegawa *et al*.[9] investigated the role of liquid biopsy in the detection of the HER2 status. There is a reasonable concordance between next-generation sequencing (NGS) and IHC platforms for assessing HER2 positivity, although NGS may be superior as it also provides information about copy number gains which may be another biomarker altogether.[10] There has also been promising molecular concordance between the tissue sampling and plasma circulating tumour DNA (ct-DNA)-based testing, but this is not well established yet and tissue-based molecular testing still remains the gold standard.[11] Conversely, it has been observed that around 32% of HER2 aberrations can get missed out on IHC and ISH. Hence, ct-DNA (circulating tumor DNA)-based NGS must get performed in the appropriate clinical setting.[12] The role of liquid biopsy for HER2 testing is evolving and shows great promise as it bypasses the issue of tumor heterogeneity.

HER2 AS A PROGNOSTIC FACTOR

The HER2 amplification in stage II colorectal carcinoma indicates poor prognosis as found in the PETACC-8 study.[13] The HER2 positivity status in CRC is not related to the stage but the left-sided colon, especially, rectal tumors are more likely to harbor HER2 amplification. Peculiarities of metastasis in mCRC with HER2 amplification are that these tumors are biologically more aggressive with likely to have more sites of metastasis, the most common site being the lung.[14] There are more chances of brain metastasis as it is a sanctuary site for anti-HER2 therapies. It establishes HER2 amplification as an independent prognostic factor for colorectal cancer.[15]

HER2 AS A PREDICTIVE FACTOR

The activation of the HER2 pathway can be a probable bypass signaling pathway as an underlying mechanism of resistance against the anti-EGFR therapy. Furthermore, the up-regulation of heregulin can evolve as an acquired mechanism of resistance against the anti-EGFR therapy.[16] Hence, HER2 positivity is a negative predictive biomarker for the response to EGFR directed treatment as HER2 overexpression seems to hamper the efficacy of cetuximab and panitumumab.[17] Yonesaka *et al*. studied 233 patients previously treated with cetuximab to identify the mechanism of resistance to anti-EGFR other than KRAS mutation. This study revealed that the subset of HER2 negative tumors had remarkably improved disease control as compared to the HER2-amplified tumors with PFS (149 days vs. 89 days) and significantly better survival with OS (515 days vs. 307 days).[18] In a retrospective analysis by Raghav *et al*.,[19] it was observed that HER2 amplified RAS/BRAF wild type tumors treated with anti-EGFR therapy showed poorer mPFS (2.9 vs. 8.1 months) as compared to those who did not harbor HER2 aberration. Hence, it is surmised that HER2 is not just an oncogenic driver, it is also a potential mechanism of resistance against anti-EGFR therapy, and it is crucial to find competent ways to target HER2 in mCRC.

ANTI-HER2 MONOTHERAPY

The initial studies were directed at exploring the role of combing trastuzumab with the standard chemotherapy backbone for HER2 amplified mCRC, as similar approaches for breast and gastric cancer harboring HER2 aberrations have shown heartening improvement in the outcomes. In

a Phase II trial, Clark *et al*.[20] studied 21 patients of HER2 positive mCRC (IHC 2+ or 3+) who were treated with the combination of folinic acid, 5-fluorouracil, and oxaliplatin with trastuzumab. Although the study closed prematurely, it showed that approximately 1 in 4 showed response to the treatment with a median duration of disease control being 4.5 months. In another phase II study, Ramanathan *et al*.[21] assessed the response with the combination of irinotecan with trastuzumab in a similar subset of the patient (n = 9). Even though this study too had to be closed prematurely because of poor accrual, it showed that 71% of patients had an objective response that was sustained for around 6 months. These studies showed that even though anti-HER2 monotherapy showed some encouraging response for HER2+ mCRC patients, it was just modest at the best and some different approach for it was exigent that led to further studies with binate anti-HER2 agents.

EMERGENCE OF DUAL HER2 BLOCKADE

In the preclinical studies, genetically characterized patient-derived xenografts of mCRC samples were studied by Bertotti *et al*. in a proof-of-concept, multi-arm study.[22] It was observed that 2–3% xenografts of mCRC showed HER2 amplification, but the probability of having HER2 aberration can be as high as 1 in 3 in KRAS/NRAS/BRAF/PIK3CA wild type cetuximab resistant tumors. These xenopatients were found to be responsive to the treatment with pertuzumab and cetuximab when combined with lapatinib, but pertuzumab alone or if used only with anti-EGFR agent had no effect.

Through these preclinical studies, it was concluded that anti-HER2 monotherapy with either just anti-HER2 monoclonal antibodies – trastuzumab and pertuzumab or anti-HER2 tyrosine kinase inhibitor (TKI) – lapatinib would be less efficacious, whereas the combination of these two classes of agents will have superior anti-tumor activity. These studies laid the foundation for future clinical studies with the rationale of targeting HER2 in mCRC with a dual anti-HER2 blockade[Table 1].

HERACLES A

In this multicenter, open label, and phase II trial, 48 patients of HER2 amplified KRAS-WT (KRAS wild type) mCRC were studied who had been pre-treated with the standard of care therapies.[6] This cohort made up 5% of the 914 patients of KRAS-WT mCRC screened for HER2 positivity based on CRC-specific diagnostic criteria. The patients were treated with a trastuzumab and lapatinib combination. This study showed encouraging results with 30% of the patients showing partial response with one patient having an encouraging durable complete response beyond 7 months. Around 44% of the patients had stable disease and the disease control rate (DCR) was 59%. The mPFS was 5.3 months and mOS was 11.5 months with the median duration of the response being 8.7 months.[23] Based on the HERACLES diagnostic criteria, it was also observed that the patients with higher HER2 amplification derive greater advantage from the anti-HER2 treatment as HER2 IHC 3+ was noted among 88% of the responding patients as against 59% of the non-responding patients.

HERACLES B

In this single-arm phase II study, the KRAS-WT, as well as BRAF-WT mCRC patients, were included who showed HER2 positivity as per the HERACLES criteria. In this, the role of pertuzumab in combination with anti-HER2 antibody drug conjugate TDM-1 (Trastuzumab Emtansine) in combination with pertuzumab was evaluated in the second line and beyond.[24] The primary endpoint of ORR ≥30% was not achieved. With an mPFS of 4.1 months and DCR of 67.7%, 21 patients showed stable disease and three patients showed objective response among a total of 37 patients studied.

MyPathway

It is a phase II basket trial studying the patients with HER2 positive tumors among multiple solid tumors who were treated with a combination of pertuzumab and trastuzumab, to effectively target HER2 and HER3 dimerization.[25] Among 57 patients of mCRC with HER2 positive tumors subset, 30% showed partial response, 2% showed complete response with an ORR of 32%, and around four patients showed sustained response beyond a year.[7] The results obtained from the HERACLES and the MyPathway opened promising new avenues for CRC-specific HER2 testing criteria and the subsequent treatment for the mCRC with chemo refractory diseases as in contrast to dismal ORR of 1–4% with regorafenib[26] and TAS-102 (trifluridine/tipiracil),[27] the other therapeutic options available. The role of trastuzumab and pertuzumab combination was further solidified by TAPUR and TRIUMPH trials.

Targeted agent and profiling utilization registry (TAPUR)

TAPUR study by ASCO is a basket study for precision medicine to study target agents for advanced tumors not based on site but for those harboring similar genomic alterations. The preliminary results of the phase II trial for mCRC with HER2 positivity in the TAPUR study showed ORR of 14%. It also showed an encouraging DCR of 50% for approximately 4 months for 28 patients studied, establishing the safety and efficacy of this anti-HER2 combination effectively targeting HER2/HER3 heterodimerization.[28]

TRIUMPH trial

This is a proof-of-concept study that not just explored the role of a combination of trastuzumab and pertuzumab

Table 1: The clinical trials studying the role of anti-HER2 agents in HER2 positive mCRC.

	Treatment	Number of patients	Line of treatment	ORR %	mPFS (months)	mOS (months)
Clark *et al*., (2003)[20]	Trastuzumab+FOLFOX	21*	1st/3rd	24		
Ramanathan *et al*., (2004)[21]	Trastuzumab+Irinotecan	9*	1st/2nd	71		
HERACLES-A (2016)[6]	Trastuzumab+Lapatinib	27	≥2nd	30	5.3	11.5
MyPathway, (2019)[7]	Trastuzumab+Pertuzumab	37	≥2nd	32	4.6	10.3
MOUNTAINEER, (2019)[31]	Trastuzumab+Tucatinib	26**	≥2nd	52.2	8.1	18.7
HERACLES-B, (2020)[24]	Pertuzumab+TDM-1	30	≥2nd	9.7	4.1	
TRIUMPH (2021)[29]	Trastuzumab+Pertuzumab	19	≥2nd	Tissue +ve: 30 ctDNA +ve: 28	Tissue +ve: 4 ctDNA +ve: 3.1	
DESTINY-CRC01, (2021)[30]	Trastuzumab deruxtecan (T-DXd)	78	3rd	45.3	6.3	15.5
TAPUR, (2022)[28]	Trastuzumab+Pertuzumab	28	≥2nd	14	3.96	
HER2-FUSCC-G, (2022)[32]	Trastuzumab+Pyrotinib	19**	1st/2nd/3rd	45.5	7.8	14.97

HER2: Human epidermal growth factor receptor, mCRC: Metastatic Colorectal Carcinoma, FOLFOX: 5-FU, Leucovorin, Oxaliplatin, TDM-1: Trastuzumab Emtansine, ISH: *In situ* hybridization, ORR: Objective response rate, mPFS: Median Progression Free Survival, mOS: Median Overall Survival, ct-DNA: Circulating tumor DNA, *Study terminated prematurely, **Ongoing study

in the HER2+ RAS-WT mCRC, but it also explored the role of ct-DNA testing. For the 30 patients enrolled in this study, HER2 amplification was determined by either IHC/FISH or through copy number increase detected by ct-DNA-based NGS. The concordance between tissue biopsy and liquid biopsy was found to be an astounding 83%. The results observed for the patients with HER2 amplification confirmed through tissue-based testing were ORR of 30%, mPFS of 4 months, and mOS of 10.1 months. Moreover, for those having HER2 amplification confirmatory testing done through blood-based ct-DNA, ORR of 28%, mPFS of 3.1 months, and mOS of 8.8 months were noted.[12] Furthermore, a reduction in HER2 plasma copy number as tested 21 days after the commencement of the treatment showed its propitious role for monitoring the treatment response. Hence, it established ct-DNA NGS as a promising modality for diagnosis, a valid alternative testing approach in cases of limited tissue availability and as means of treatment response monitoring for HER2 amplified mCRC.[29]

DESTINY-CRC01

The DESTINY-CRC01 is an open label, phase II, and multicenter study with three cohorts that have paved the path for the heavily pre-treated HER2 amplified RAS and RAF wild type mCRC patients whose disease has also progressed on anti-HER targeted therapies like trastuzumab, pertuzumab, lapatinib, and tucatinib. Trastuzumab-deruxtecan (T-DXd), an antibody-drug conjugate with topoisomerase I inhibitor payload, was studied in this trial with the additional advantage of showing activity in the central nervous system (CNS). It has been observed that HER2 positive mCRC has a higher propensity for brain metastasis similar to the biological nature of this molecular subtype for breast cancer. In this study, Cohort-A (HER 2 IHC 3+ or IHC 2+ & ISH positive), Cohort-B (HER2 IHC 2+ ISH negative) and Cohort-C (HER2 IHC 1+) had 53, 7 and 18 patients in each, respectively. No objective response was observed for cohorts B and C, while cohort A reported a promising ORR of 45.3% and mPFS was nearly 7 months. The duration of disease control was found to be greater in the patients with IHC 3+ as compared to those with IHC 2+ and ISH-positive. When treated with T-DXd, a notable radiological response of 43.8% was observed even for the patients pre-treated with other anti-HER2 agents with an encouraging mPFS of 4.3 months.[30]

MOUNTAINEER

In this open-label single-arm phase II study, the combination of trastuzumab with tucatinib was studied for the treatment of HER2 amplified RAS-WT mCRC showing poor response to previous treatments. Tucatinib is a potent HER2-directed TKI which is US Food and Drug Administration-approved as a single agent for breast cancer. The CNS is a sanctuary site for conventional anti-Her2 therapy, but tucatinib is found to be able to penetrate BBB. The ORR was 52.2% with a durable median response period of 10.4 months with this combination in the interim preliminary analysis of this study. Among the 26 patients enrolled for the study, mPFS and mOS noted were 8.1 months and 18.7 months, respectively.[31]

HER2-FUSCC-G

It is a non-randomized, open-label, and phase II study to evaluate the role of pyrotinib, an irreversible dual pan-ERBB TKI in the HER2-positive gastrointestinal tract solid tumors. The combination of trastuzumab with pyrotinib used for 11 patients of HER2 amplified mCRC pre-treated with chemotherapy showed promising results. The interim analysis revealed an ORR of 55.6% in patients with RAS-WT mCRC as compared to 45.5% in the whole population. At a median follow-up of approximately 1.5 years, mPFS was

7.8 months and mOS was 14.9 months. It was observed that KRAS-wild type tumors fared better with mPFS of 9.9 months and mOS of 20.6 months as compared to those harboring KRAS mutation with mPFS of 7.7 months and mOS of 12.4 months, respectively.[32]

Future paradigm

The current NCCN practice guidelines recommend a combination of trastuzumab with either pertuzumab or TKI (lapatinib or tucatinib) for chemo refractory HER2 amplified mCRC. Exciting new avenues are being explored with newer agents like bispecific HER2-targeted antibody, zanidatamab.[33] Another most anticipated study is the VISTA trial that is exploring the role of binary oncolytic adenovirus in combination with autologous CAR-T cells promoting proinflammatory tumor microenvironment.[34-36] The HERACLES RESCUE aims to study the role of TDM-1 as a monotherapy.[37] The mutations in MAPK and PIK3CA pathways are a known mechanism of resistance against anti-HER2 therapy.[38] Studies are directed at circumventing these pathways too. The present studies have shown a high road for future clinical research and translational studies for treating this molecular subgroup of mCRC patients with promising results.

CONCLUSION

Appropriately targeting HER2 aberration has been shown to improve outcomes for mCRC. It is imperative that HER2 testing should be considered during the initial workup as it predicts poor response to the antibodies against EGFR. However, it is strongly recommended for the RAS and RAF wild-type mCRC patients whose disease progresses on the anti-EGFR therapy. The latter approach has been incorporated in the NCCN practice guidelines too, as HER2 amplification is found to be an acquired mechanism of resistance to EGFR-directed treatment. Even though tissue testing is preferred over liquid biopsy, in this setting, ct-DNA scores are higher as it can pick up even those aberrations that can get missed out on the conventional tissue-based IHC and ISH. The dual HER2 blockade emerged as the efficacious modality because of the weak performance of anti-HER2 agents as monotherapy for HER2-positive mCRC. T-Dxd is a promising therapeutic agent for subsequent lines even for those HER2-positive mCRC patients who fail the initial anti-HER2 treatment.

Declaration of patient consent

Patient consent not required as there are no patients in this study.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Salem ME, Weinberg BA, Xiu J, El-Deiry WS, Hwang JJ, Gatalica Z, *et al*. Comparative molecular analyses of left-sided colon, right-sided colon, and rectal cancers. Oncotarget 2017;8:86356-68.
2. Le DT, Kim TW, Van Cutsem E, Geva R, Jäger D, Hara H, *et al*. Phase II open-label study of pembrolizumab in treatment-refractory, microsatellite instability-high/mismatch repair-deficient metastatic colorectal cancer: KEYNOTE-164. J Clin Oncol 2020;38:11-9.
3. Heppner BI, Behrens HM, Balschun K, Haag J, Krüger S, Becker T, *et al*. HER2/neu testing in primary colorectal carcinoma. Br J Cancer 2014;111:1977-84.
4. Conradi LC, Styczen H, Sprenger T, Wolff HA, Rödel C, Nietert M, *et al*. Frequency of HER-2 positivity in rectal cancer and prognosis. Am J Surg Pathol 2013;37:522-31.
5. Valtorta E, Martino C, Sartore-Bianchi A, Penaullt-Llorca F, Viale G, Risio M, *et al*. Assessment of a HER2 scoring system for colorectal cancer: Results from a validation study. Mod Pathol 2015;28:1481-91.
6. Sartore-Bianchi A, Trusolino L, Martino C, Bencardino K, Lonardi S, Bergamo F, *et al*. Dual-targeted therapy with trastuzumab and lapatinib in treatment-refractory, KRAS codon 12/13 wild-type, HER2-positive metastatic colorectal cancer (HERACLES): A proof-of-concept, multicentre, open-label, phase 2 trial. Lancet Oncol 2016;17:738-46.
7. Meric-Bernstam F, Hurwitz H, Raghav KP, McWilliams RR, Fakih M, VanderWalde A, *et al*. Pertuzumab and trastuzumab for HER2-amplified metastatic colorectal cancer: An updated report from mypathway, a multicentre, open-label, phase 2a multiple basket study. Lancet Oncol 2019;20:518-30.
8. Schrock AB, Pavlick D, Klempner SJ, Chung JH, Forcier B, Welsh A, *et al*. Hybrid capture-based genomic profiling of circulating tumor DNA from patients with advanced cancers of the gastrointestinal tract or anus. Clin Cancer Res 2018;24:1881-90.
9. Takegawa N, Yonesaka K, Sakai K, Ueda H, Watanabe S, Nonagase Y, *et al*. HER2 genomic amplification in circulating tumor DNA from patients with cetuximab-resistant colorectal cancer. Oncotarget 2016;7:3453-60.
10. Cenaj O, Ligon AH, Hornick JL, Sholl LM. Detection of ERBB2 amplification by next-generation sequencing predicts HER2 expression in colorectal carcinoma. Am J Clin Pathol 2019;152:97-108.
11. Malla M, Loree JM, Kasi PM, Parikh AR. Using circulating tumor DNA in colorectal cancer: Current and evolving practices. J Clin Oncol 2022;40:2846-57.
12. Nakamura Y, Okamoto W, Kato T, Esaki T, Kato K, Komatsu Y, *et al*. Circulating tumor DNA-guided treatment with pertuzumab plus trastuzumab for HER2-amplified metastatic colorectal cancer: A phase 2 trial. Nat Med 2021;27:1899-903.
13. Laurent-Puig P, Balogoun R, Cayre A, Le Malicot K, Tabernero J, Mini E, *et al*. ERBB2 alterations a new prognostic biomarker in stage III colon cancer from a FOLFOX based adjuvant trial (PETACC8). Ann Oncol 2016;27:vi151.

14. Siravegna G, Lazzari L, Crisafulli G, Sartore-Bianchi A, Mussolin B, Cassingena A, *et al*. Radiologic and genomic evolution of individual metastases during HER2 blockade in colorectal cancer. Cancer Cell 2018;34:148-62.e7.
15. Kavanagh DO, Chambers G, O'Grady L, Barry KM, Waldron RP, Bennani F, *et al*. Is overexpression of HER-2 a predictor of prognosis in colorectal cancer? BMC Cancer 2009;9:1.
16. Richman SD, Southward K, Chambers P, Cross D, Barrett J, Hemmings G, *et al*. HER2 overexpression and amplification as a potential therapeutic target in colorectal cancer: Analysis of 3256 patients enrolled in the QUASAR, FOCUS and PICCOLO colorectal cancer trials. J Pathol 2016;238:562-70.
17. Kavuri SM, Jain N, Galimi F, Cottino F, Leto SM, Migliardi G, *et al*. HER2 activating mutations are targets for colorectal cancer treatment. Cancer Discov 2015;5:832-41.
18. Yonesaka K, Zejnullahu K, Okamoto I, Satoh T, Cappuzzo F, Souglakos J, *et al*. Activation of ERBB2 signaling causes resistance to the EGFR-directed therapeutic antibody cetuximab. Sci Transl Med 2011;3:99ra86.
19. Raghav KP, Overman MJ, Yu R, Meric-Bernstam F, Menter D, Kee BK, *et al*. HER2 amplification as a negative predictive biomarker for anti-epidermal growth factor receptor antibody therapy in metastatic colorectal cancer. J Clin Oncol 2016;34(15_suppl):3517.
20. Clark JW, Niedzwiecki D, Hollis D, Mayer R. Phase-II trial of 5-fluororuacil (5-FU), leucovorin (LV), oxaliplatin (Ox), and trastuzamab (T) for patients with metastatic colorectal cancer (CRC) refractory to initial therapy. Onkologie 2003;26(Suppl 3):13-46.
21. Ramanathan RK, Hwang JJ, Zamboni WC, Sinicrope FA, Safran H, Wong MK, *et al*. Low overexpression of HER-2/neu in advanced colorectal cancer limits the usefulness of trastuzumab (Herceptin) and irinotecan as therapy. A phase II trial. Cancer Invest 2004;22:858-65.
22. Bertotti A, Migliardi G, Galimi F, Sassi F, Torti D, Isella C, *et al*. A molecularly annotated platform of patient-derived xenografts ("xenopatients") identifies HER2 as an effective therapeutic target in cetuximab-resistant colorectal cancer. Cancer Discov 2011;1:508-23.
23. Tosi F, Sartore-Bianchi A, Lonardi S, Amatu A, Leone F, Ghezzi S, *et al*. Long-term clinical outcome of trastuzumab and lapatinib for HER2-positive metastatic colorectal cancer. Clin Colorectal Cancer 2020;19:256-62.e2.
24. Sartore-Bianchi A, Lonardi S, Martino C, Fenocchio E, Tosi F, Ghezzi S, *et al*. Pertuzumab and trastuzumab emtansine in patients with HER2-amplified metastatic colorectal cancer: The phase II HERACLES-B trial. ESMO Open 2020;5:e000911.
25. Ross JS, Fakih M, Ali SM, Elvin JA, Schrock AB, Suh J, *et al*. Targeting HER2 in colorectal cancer: The landscape of amplification and short variant mutations in ERBB2 and ERBB3. Cancer 2018;124:1358-73.
26. Grothey A, Van Cutsem E, Sobrero A, Siena S, Falcone A, Ychou M, *et al*. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): An international, multicentre, randomised, placebo-controlled, phase 3 trial. Lancet 2013;381:303-12.
27. Mayer RJ, Van Cutsem E, Falcone A, Yoshino T, Garcia-Carbonero R, Mizunuma N, *et al*. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. N Engl J Med 2015;372:1909-19.
28. Gupta R, Garrett-Mayer E, Halabi S, Rothe M, Garrett-Mayer E, Mangat PK, *et al*. Pertuzumab plus trastuzumab (P+T) in patients (Pts) with colorectal cancer (CRC) with ERBB2 amplification or overexpression: Results from the TAPUR study. JCO Precis Oncol 2022;6:e2200306.
29. Yoshino T, Yamanaka T, Shiozawa M, Nakamura Y, Okamoto W, Kato T, *et al*. TRIUMPH: Primary efficacy of a phase II trial of trastuzumab (T) and pertuzumab (P) in patients (pts) with metastatic colorectal cancer (mCRC) with HER2 (ERBB2) amplification (amp) in tumour tissue or circulating tumour DNA (ctDNA): A GOZILA sub-study. Ann Oncol 2019;30:v199-200.
30. Yoshino T, Bartolomeo M Di, Raghav KPS, Masuishi T, Loupakis F, Kawakami H, *et al*. Trastuzumab deruxtecan (T-DXd; DS-8201) in patients (pts) with HER2-expressing metastatic colorectal cancer (mCRC): Final results from a phase 2, multicenter, open-label study (DESTINY-CRC01). J Clin Oncol 2021;39(15Suppl):3505.
31. Strickler JH, Ng K, Cercek A, Fountzilas C, Sanchez FA, Hubbard JM, *et al*. MOUNTAINEER: Open-label, phase II study of tucatinib combined with trastuzumab for HER2-positive metastatic colorectal cancer (SGNTUC-017, trial in progress). J Clin Oncol 2021;39 Suppl 3:TPS153.
32. Li W, Chang J, Xu M, Zhu X. Anti-HER2 therapy with pyrotinib and trastuzumab in refractory HER2-positive metastatic colorectal cancer: A preliminary report from HER2-FUSCC-G study. J Clin Oncol 2022;40 Suppl 44:97.
33. NCT03929666. 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. Available from: https://clinicaltrials.gov/ct2/show/NCT03929666
34. Jiang S, Good D, Wei MQ. Vaccinations for colorectal cancer: Progress, strategies, and novel adjuvants. Int J Mol Sci 2019;20:3403.
35. NCT03740256. Binary Oncolytic Adenovirus in Combination with HER2-Specific Autologous CAR VST, Advanced HER2 Positive Solid Tumors (VISTA). Available from: https://clinicaltrials.gov/ct2/show/NCT03740256
36. NCT01935843. Treatment of Chemotherapy Refractory Human Epidermal Growth Factor Receptor-2 (HER-2) Positive Advanced Solid Tumors (CART-HER-2). Avaliable from: https://clinicaltrials.gov/ct2/show/NCT01935843
37. Siena S, Bardelli A, Sartore-Bianchi A, Martino C, Siravegna G, Magri A, *et al*. HER2 amplification as a 'molecular bait' for trastuzumab-emtansine (T-DM1) precision chemotherapy to overcome anti-HER2 resistance in HER2 positive metastatic colorectal cancer: The HERACLES-RESCUE trial. J Clin Oncol 2016;34 Suppl 4:TPS774.
38. Vernieri C, Milano M, Brambilla M, Mennitto A, Maggi C, Cona MS, *et al*. Resistance mechanisms to anti-HER2 therapies in HER2-positive breast cancer: Current knowledge, new research directions and therapeutic perspectives. Crit Rev Oncol Hematol 2019;139:53-66.

How to cite this article: Gohel S, Lavingia V. HER2: A new promising target in metastatic colorectal cancer. Int J Mol Immuno Oncol 2023;8:3-8.