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Clinical Studies

Survival outcomes of *ERBB2*-amplified metastatic colorectal cancer treated with first-line chemotherapy

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BACKGROUND: HER2-positive or *ERBB2* amplified (*ERBB2* amp+) metastatic colorectal cancer (mCRC) is an important subgroup due to emerging HER2-targeted therapies. Although *ERBB2* amplification is associated with anti-EGFR antibody resistance, optimal first-line treatment remains unclear.

METHODS: We analysed data from the Flatiron Health-Foundation Medicine CRC clinico-genomic database, including patients with stage IV or recurrent mCRC diagnosed between January 2012 and March 2022 who underwent tissue-based comprehensive genomic profiling. *ERBB2* amp+ was defined as an *ERBB2* copy number ≥ 3 of the tumour base ploidy.

RESULTS: Among 5545 patients, 144 (3.1%) had *ERBB2* amp+ mCRC. These patients showed significantly worse real-world progression-free survival (rwPFS) than *ERBB2* amp− patients (median 7.6 vs. 8.7 months; hazard ratio [HR]: 1.20, 95% confidence interval [CI]: 1.01–1.43, $p = 0.04$). This trend persisted in patients with left-sided *RAS/BRAF* V600E wild-type and non-MSI-H mCRC treated with chemotherapy plus anti-EGFR antibody (median 8.7 vs. 12.5 months; HR: 2.18, $p = 0.02$; adjusted HR: 2.33, $p = 0.046$) or chemotherapy plus bevacizumab (median 8.9 vs. 10.5 months; HR: 1.65, $p = 0.04$; adjusted HR: 1.75, $p = 0.04$). Real-world overall survival did not differ significantly.

CONCLUSION: *ERBB2* amp+ mCRC is a small but clinically relevant subgroup with inferior rwPFS across current first-line treatments, highlighting the need for better strategies.

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INTRODUCTION

Patients with human epidermal growth factor receptor 2 (HER2)-positive metastatic colorectal cancer (mCRC) are a small but increasingly important subgroup due to emerging HER2-targeted therapies [1–4]. The frequency of HER2-positive mCRC, also known as *ERBB2* amplification positive (*ERBB2* amp+) mCRC, is 2–4%, and there is mixed evidence on the relationship between *ERBB2* amp+ and prognosis in patients with CRC [5–9]. Heppner et al. retrospectively analysed 1645 patients and reported that those with *ERBB2* amp+ CRC had a poorer prognosis than those with *ERBB2* amplification negative (*ERBB2* amp−) CRC. In contrast, an analysis of samples from the FOCUS/PICCORO trial by Richman et al. showed no difference in prognosis between those with *ERBB2* amp+ and *ERBB2* amp− CRC [6, 10]. A consensus is yet to be reached on the impact of *ERBB2* amp+ on the prognosis of patients with mCRC.

HER2 is a member of the epidermal growth factor receptor (EGFR) family. Anti-EGFR antibody therapies, such as cetuximab and panitumumab, block EGFR signalling, which is crucial for cell growth

and survival in many cancers. They are commonly used in mCRC, particularly in patients with *KRAS* wild-type tumours. The randomised Phase III PARADIGM study showed that using FOLFOX plus panitumumab as a first-line treatment for patients with left-sided *RAS* wild-type mCRC prolonged overall survival compared with FOLFOX plus the vascular endothelial growth factor inhibitor, bevacizumab [11]. Therefore, anti-EGFR antibody therapies are recommended as molecularly targeted drugs for first-line treatment of patients with left-sided *RAS* wild-type mCRC. However, *ERBB2* transmits a signal similar to EGFR, and the signalling pathway suggests that *ERBB2* amp+ is a negative predictor of the therapeutic efficacy of anti-EGFR antibody drugs [12]. Numerous retrospective studies have examined the effectiveness of anti-EGFR antibodies in later lines of therapy for mCRC and consistently reported diminished efficacy [8, 13–16]. Nevertheless, evidence regarding the association between *ERBB2* amp+ status and the efficacy of first-line anti-EGFR antibodies is limited. Therefore, whether an anti-EGFR antibody or bevacizumab is preferable as a first-line molecularly targeted drug for HER2-positive mCRC remains unclear.

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We conducted a retrospective study using a US-based real-world clinico-genomic database to assess the frequency and prognostic impact of *ERBB2* amplification in mCRC. We aimed to evaluate real-world overall survival (rwOS) and real-world progression-free survival (rwPFS) in patients with *ERBB2* amp+ versus amp- mCRC receiving first-line doublet chemotherapy with either an anti-EGFR antibody or bevacizumab.

MATERIAL AND METHODS

Data source and patients

In this retrospective study, we used data from the US-based, deidentified Flatiron Health-Foundation Medicine CRC clinico-genomic database (CGDB). In CGDB, clinical data from the Flatiron Health Research Database are linked to genomic data derived from Foundation Medicine Inc.'s comprehensive genomic profiling (CGP) tests (FoundationOne®CDx, FoundationOne®, FoundationOne Liquid®CDx, FoundationOne Liquid® and/or FoundationOne®Heme) by deterministic matching, providing a deidentified dataset [17, 18]. The inclusion criteria were as follows: (1) mCRC diagnosis between January 1, 2012, and March 31, 2022, (2) age ≥ 18 years at metastatic diagnosis, (3) at least two documented clinical visits in the Flatiron network, on different days, occurring on or after January 1, 2011, (4) underwent tissue-based CGP testing (FoundationOne® or FoundationOne®CDx) on a tumour sample with pathologist-confirmed histology that is consistent with colorectal cancer within 90 days of metastatic diagnosis, and (5) collected specimen passed quality control [19, 20]. Patients who underwent only liquid-based CGP or had 'Qualified' specimens were excluded due to reduced alteration detection sensitivity. Patients were eligible for survival analyses if they had at least one line of therapy (LOT) for metastatic disease as defined per Flatiron Health's LOT business rules. The data cut-off date was March 31, 2024. Clinical variables included age, sex, race/ethnicity, initial stage and primary tumour location (left, right, or unknown, based on the International Classification of Disease codes) [21].

Analysis of gene alterations

HER2-positive (*ERBB2* amp+) was defined as an *ERBB2* copy number of ≥ 3 of the tumour base ploidy according to the global consensus on the pathological diagnosis of HER2-positive mCRC [22]. Tumours that did not meet this criterion were defined as HER2-negative (*ERBB2* amp-). We examined the frequency of patients with *ERBB2* amp+ mCRC and evaluated the frequency of overlapping gene alterations/signatures of clinical significance in mCRC with *ERBB2* amplification (*RAS* mutation [mt], *BRAF* V600E mutation, and microsatellite instability-high [MSI-H]).

Treatments of interest

We focused on the first-line treatment and examined differences in survival time between both treatment groups. After assessing survival time in all patients with mCRC who received any first-line treatment and first-line doublet treatments, we focused on patients with left-sided mCRC without *RAS/BRAF* V600E mt or MSI-H treated with doublet plus anti-EGFR antibody or bevacizumab. Doublet therapy was defined as the combined chemotherapy treatment with fluoropyrimidine plus oxaliplatin or irinotecan. Anti-EGFR therapy comprised panitumumab or cetuximab.

Statistical analysis

rwOS and rwPFS were examined using the Kaplan-Meier method. rwOS and rwPFS were defined from the initiation of the first-line treatment to the date of death due to any cause and to the date of disease progression or death, whichever occurred first. Patients were censored at their last visit date. Survival differences were assessed using log-rank tests, and hazard ratios (HRs) were calculated using Cox proportional hazards models. HRs were adjusted for patient characteristics (excluding unknown status), such as age, sex, initial stage, race/ethnicity and primary location, and 95% confidence intervals (CIs) were estimated using 1000 bootstrap replicates. Continuous variables were compared using the Mann-Whitney U or Kruskal-Wallis tests, whereas categorical variables were compared using Fisher's exact test or the Chi-squared test. All statistical analyses were performed using R version 4.3.2. Two-sided tests were used with a significance level of $\alpha = 0.05$. The R scripts contain analysis of proprietary data (Flatiron Health, Foundation Medicine) and therefore cannot be publicly deposited. Code availability is restricted by data use agreements.

RESULTS

Patients and *ERBB2* amplification

Of the 15026 patients in the CGDB, 10959 (72.9%) had metastatic disease. We excluded patients who received only liquid-based CGP, leaving 9817 patients who underwent tissue-based CGP. Furthermore, we excluded 813 patients with insufficient specimen quality, eight with unknown specimen collection dates, and 3451 whose CGP was conducted more than 90 days after metastatic diagnosis (Fig. 1). The remaining 5545 patients were eligible for the analysis evaluating the frequency of patients with *ERBB2* amp+ mCRC. *ERBB2* amp+ was detected in 3.1% (171/5545) of the eligible patients with mCRC. The median copy number of *ERBB2* in qualifying specimens was 24 (range: 5–390; Supplementary Fig. 1). Of the patients with *ERBB2* amp+ mCRC, 15% had *RAS* mutation and 82% were *RAS* wild-type, *BRAF* V600E wild-type and MSI-H undetected.

Of the 4748 patients treated with systemic chemotherapy, 144 and 4604 were divided into the *ERBB2* amp+ and *ERBB2* amp- groups, respectively. The *ERBB2* amp+ group contained more young patients and fewer right-sided tumours (Table 1). In both groups, patients with stage IV disease at initial diagnosis accounted for 72% of each group. In addition, race and ethnicity had similar distributions in both groups.

First-line treatment

Of the 5545 patients in the overall cohort, 4748 received systemic chemotherapy in the metastatic setting (first-line treatment) and were eligible for survival analysis. Of these 4748 patients, 250 received doublet + anti-EGFR antibody and 2202 received doublet + bevacizumab as first-line treatment (Supplementary Fig. 2). The other 2296 patients received other treatment regimens: FOLFOX (30%), Capecitabine (14%), clinical study drug (7%), FOLFIRI (6%), CAPOX (5%) and others (38%). FOLFOX + panitumumab and FOLFOX + bevacizumab were the most frequently selected doublet + anti-EGFR antibody and doublet + bevacizumab treatments, respectively. In both *ERBB2* amp+ and *ERBB2* amp- groups, FOLFOX + bevacizumab was the most common selected first-line treatment. The second and third most frequent treatments were FOLFOX + anti-EGFR antibody in the *ERBB2* amp+ group, compared to FOLFOX and FOLFIRI + bevacizumab in the *ERBB2* amp- group (Supplementary Table 1).

Survival outcomes of all patients with *ERBB2* amp+ mCRC

The median follow-up period for patients who received any first-line chemotherapy was 21.7 and 21.5 months in the *ERBB2* amp+ and *ERBB2* amp- groups, respectively. The *ERBB2* amp+ group had a shorter rwPFS than the *ERBB2* amp- group (median PFS: 7.6 vs. 8.7 months; HR: 1.20, 95% CI: 1.01–1.43, $p = 0.04$) (Fig. 2). This trend persisted after adjusting for covariates (adjusted HR: 1.19, 95% CI: 0.93–1.56, $p = 0.19$). In contrast, no significant difference in rwOS was observed between the *ERBB2* amp+ and *ERBB2* amp- groups (median OS: 26.1 vs. 24.5 months; HR: 0.94, 95% CI: 0.77–1.14, $p = 0.52$; adjusted HR: 1.00, 95% CI: 0.76–1.31, $p = 0.99$). In the *ERBB2* amp+ group, 4% of the patients received anti-HER2 therapy as first-line, while 27% received similar therapy and subsequent treatment.

In addition, we compared rwPFS and rwOS between the patients with higher and lower *ERBB2* copy numbers in the *ERBB2* amp+ group. However, a cut-off for the *ERBB2* copy number that resulted in significantly different rwPFS or rwOS could not be determined (Supplementary Table 2).

Survival differences in the subgroup population

Of the patients with left-sided mCRC without *RAS/BRAF* V600E mt or MSI-high who were typically recommended for first-line doublet plus anti-EGFR antibody, those with *ERBB2* amp+ group had significantly shorter rwPFS (median rwPFS: 8.6 vs. 10.3 months; HR: 1.47, 95% CI: 1.11–1.95, $p < 0.01$; adjusted HR: 1.43, 95% CI: 1.04–2.00, $p = 0.03$) (Fig. 3). No significant difference was observed in rwOS between the *ERBB2* amp+ and *ERBB2* amp-

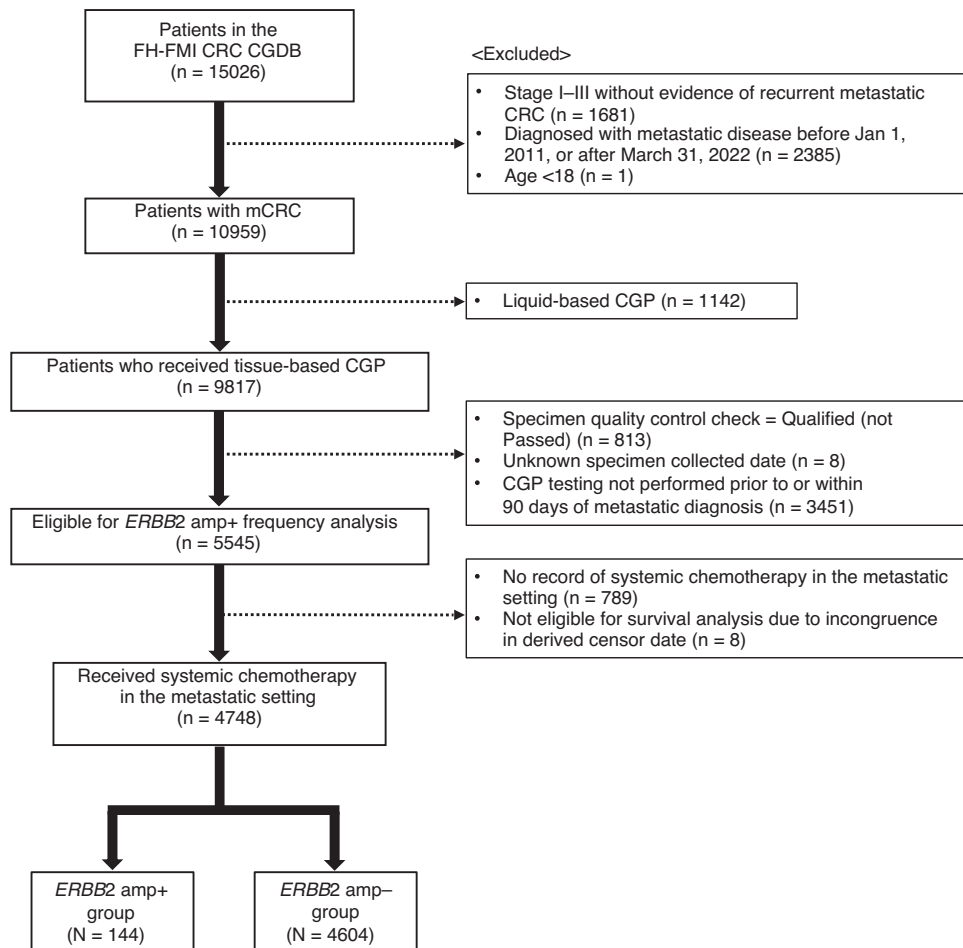


Fig. 1 Study flowchart. Patient flow diagram showing the selection process of patients for the analysis of *ERBB2* amplification in metastatic colorectal cancer. mCRC metastatic colorectal cancer, CGDB clinico-genomic database, CGP comprehensive genomic profiling.

Table 1. Characteristics of patients who received systemic chemotherapy.

Factor	Category	<i>ERBB2</i> amp+ n = 144	<i>ERBB2</i> amp- n = 4604	p-value
Age	Median (range)	58 (28-83)	61 (20-85)	<0.01
Sex	Male	87 (60%)	2484 (54%)	0.13
	Female	57 (40%)	2120 (46%)	
Initial Stage	I-III	35 (25%)	1215 (26%)	0.58
	IV	105 (72%)	3300 (72%)	
	Unknown	5 (3%)	85 (2%)	
Race/Ethnicity	Hispanic or Latino	11 (8%)	234 (5%)	0.50
	Not Hispanic or Latino, White	81 (56%)	2656 (58%)	
	Not Hispanic or Latino, Black or African American	13 (9%)	383 (8%)	
	Not Hispanic or Latino, Asian/Other Race/Unknown Race	18 (13%)	527 (11%)	
	Unknown	21 (14%)	804 (18%)	
Primary location	Left-sided	64 (45%)	1965 (42%)	<0.01
	Right-sided	15 (10%)	1039 (22%)	
	Unknown	65 (45%)	1600 (35%)	

Age denotes age at metastatic diagnosis. The race/ethnicity variable categorises 'Hispanic or Latino' as all Hispanic/Latino individuals regardless of race, while White, Black and Asian are limited to non-Hispanic individuals. 'Asian/Other Race/Unknown Race' includes patients with race categories masked due to small counts. Primary location (tumour sidedness) was determined using the International Classification of Diseases codes 9 and 10. Initial stage values are rounded to the nearest 5 to mask small counts.

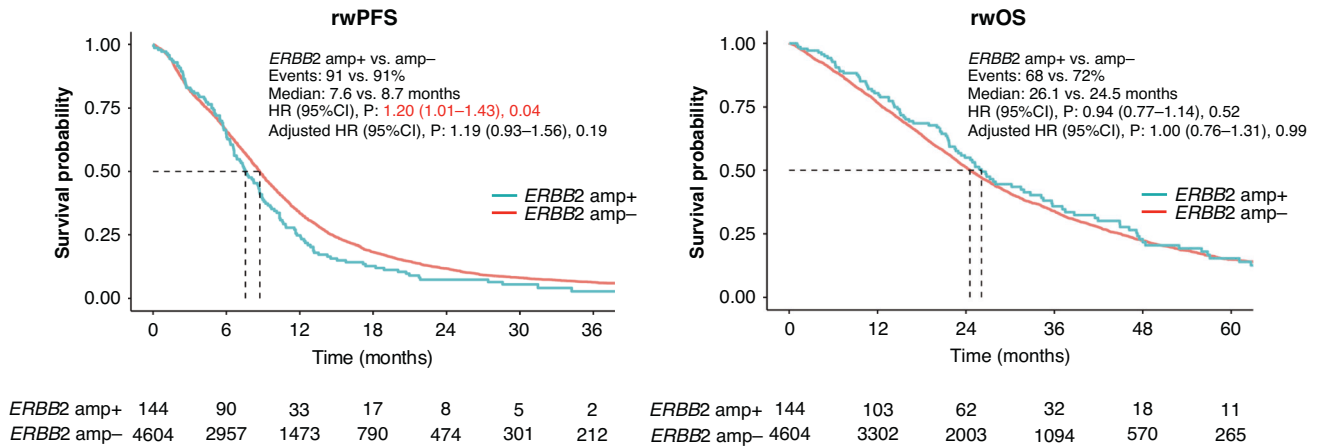


Fig. 2 Real-world progression-free survival and overall survival in all patients by *ERBB2* amplification status. Kaplan–Meier survival curves comparing rwPFS and rwOS in all patients by *ERBB2* amplification. rwPFS real-world progression-free survival, rwOS real-world overall survival, HR hazard ratio, CI confidence interval.

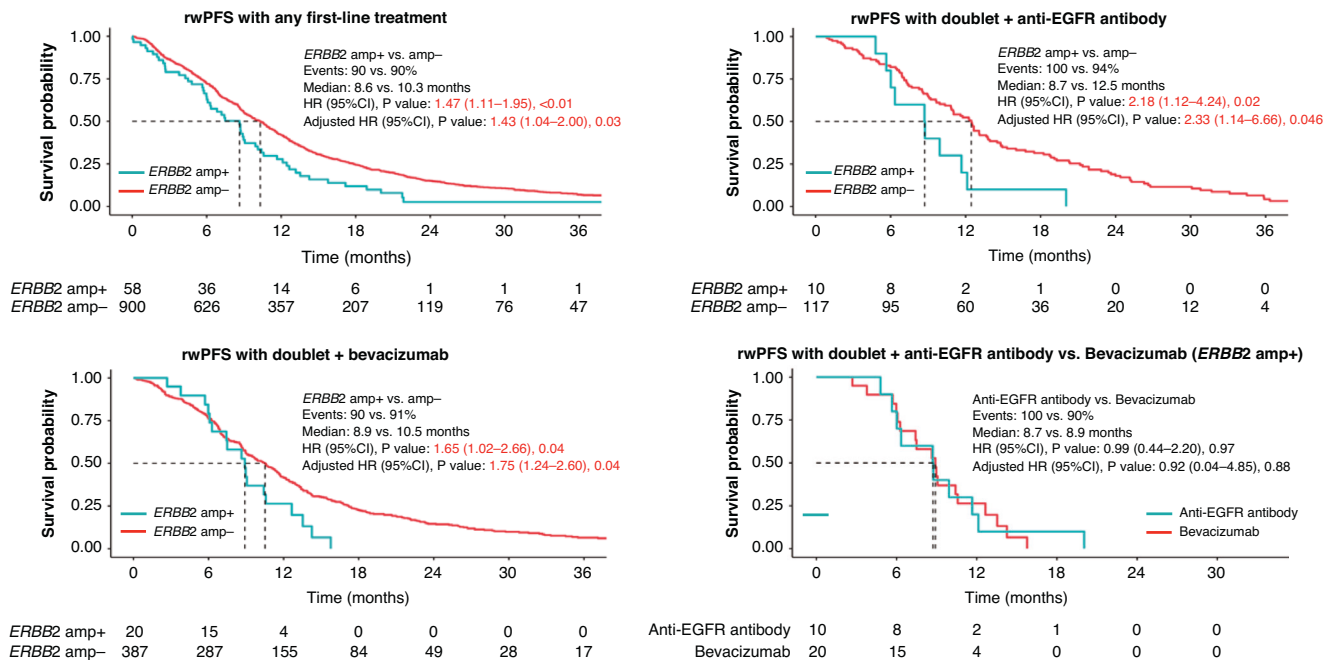


Fig. 3 Real-world progression-free survival in patients with left-sided, *RAS/BRAF* wild-type and MSI-H not detected mCRC by *ERBB2* amplification status. Kaplan–Meier survival curves comparing rwPFS in all patients by *ERBB2* amplification, and among patients with *ERBB2* amp+, and in patients treated with doublet + anti-EGFR antibody vs doublet + bevacizumab. rwPFS real-world progression-free survival, HR hazard ratio, CI confidence interval, MSI-H microsatellite instability-high.

groups (median rwOS: 30.2 vs. 32.2 months; HR: 1.11, 95% CI: 0.81–1.54, $p = 0.51$; adjusted HR: 1.10, 95% CI: 0.75–1.66, $p = 0.62$) (Supplementary Fig. 3). Patients were stratified into two treatment cohorts according to the first-line treatment: the anti-EGFR antibody cohort (patients treated with doublet chemotherapy plus anti-EGFR antibody) and the bevacizumab cohort (patients who received doublet chemotherapy plus bevacizumab).

In both cohorts, *ERBB2* amplification was associated with significantly shorter rwPFS. For the anti-EGFR antibody cohort, the median rwPFS was 8.7 and 12.5 months in the *ERBB2* amp+ ($n = 10$) and *ERBB2* amp- ($n = 117$) groups, respectively (HR: 2.18, 95% CI: 1.12–4.24, $p = 0.02$; adjusted HR: 2.33, 95% CI: 1.14–6.66, $p = 0.046$). In the bevacizumab cohort, the median rwPFS was 8.9 and 10.5 months in the *ERBB2* amp+ ($n = 20$) and *ERBB2* amp- ($n = 387$) groups, respectively (HR: 1.65, 95% CI: 1.02–2.66, $p = 0.04$; adjusted HR: 1.75, 95% CI: 1.24–2.60, $p = 0.04$). Direct

comparison between the anti-EGFR antibody cohort and the bevacizumab cohort showed no significant difference in rwPFS (HR: 0.99, 95% CI: 0.44–2.20, $p = 0.97$; adjusted HR: 0.92, 95% CI: 0.04–4.85, $p = 0.88$). Regarding rwOS, no significant difference was observed between *ERBB2* amp+ and *ERBB2* amp- groups in either treatment cohort or between treatment strategies in the *ERBB2* amp+ group (Supplementary Fig. 3).

DISCUSSION

In this study, we evaluated the frequency of *ERBB2* amplification in mCRC using a real-world dataset. Our results indicate that *ERBB2* amplification in patients with left-sided *RAS/BRAF* wild-type and non-MSI-H mCRC was associated with worse rwPFS following first-line treatment, regardless of doublet + anti-EGFR antibody or bevacizumab. In addition, no survival difference was observed

between patients with *ERBB2* amp+ and *ERBB2* amp− in the first-line doublet + anti-EGFR antibody and doublet + bevacizumab. To our knowledge, this is the first study to assess the prognostic impact of *ERBB2* amplification in the first-line treatment of mCRC using a real-world clinico-genomic database aligned with the global pathological consensus for diagnosing HER2-positive mCRC.

Consistent with previous reports, we observed *ERBB2* amplification in 3.1% of the mCRC, confirming that HER2-positive mCRC is a rare molecular subset of the disease [5–9]. In our study, *ERBB2* amp+ was not defined as per the immunohistochemistry-based HER2 scoring system. However, the frequency observed in our study reflects the real-world frequency of HER2 positivity defined by the immunohistochemistry-based criteria, given the high concordance between the immunohistochemistry-based HER2 scoring system and *ERBB2* copy number in CGP [22].

The *ERBB2* amp+ group showed worse rwPFS than the *ERBB2* amp− group for all first-line treatments investigated. The difference in rwPFS became smaller after adjusting for HR using patient characteristics. Notably, unknown status accounted for 35–40% of the data on race/ethnicity or primary tumour location, which may have limited the robustness of the adjustment. A significant difference in rwPFS already observed before adjustments indicates that *ERBB2* amplification likely has a certain impact on rwPFS in mCRC. In contrast, no significant difference was observed in rWOS between the *ERBB2* amp+ and amp− groups. Given that HER2-targeted therapies have recently become standard treatment for HER2-positive CRC, future analyses may suggest that, similar to breast cancer, HER2-positive CRC could evolve into a subtype with a favourable prognosis once patients receive the appropriate standard therapy [23].

In patients with CRC characterised as left-sided, *RAS*/*BRCA* wild-type and MSI undetected, the *ERBB2* amp+ group showed worse rwPFS in doublet + anti-EGFR antibody and doublet + bevacizumab subgroups. When compared directly, no difference in survival was observed between doublet + anti-EGFR antibody and doublet + bevacizumab subgroups in the *ERBB2* amp+ group. In addition, a biomarker analysis of the randomised Phase III PARADIGM trial showed that ctDNA-based *ERBB2* amplification was not associated with the difference in OS between FOLFOX plus panitumumab (*n* = 19) and FOLFOX plus bevacizumab (*n* = 13), supporting our result derived from the tissue-based data [24]. In addition, Sartore-Bianchi et al. suggested that the negative impact of *ERBB2* amplification on the clinical outcome of anti-EGFR antibodies is more substantial in more advanced lines in which the confounding impact of chemotherapy decreases [14]. As previously reported, the impact of *ERBB2* amplification on the anti-tumour effect of anti-EGFR antibody may be smaller in first-line treatment than in later-line treatment [25]. However, our findings demonstrated that *ERBB2* amplification was associated with poorer prognosis in mCRC, irrespective of whether patients received doublet plus anti-EGFR antibody or doublet plus bevacizumab as first-line treatment. These findings suggest that the currently available treatment options may be insufficient to overcome the poor prognosis associated with HER2 positivity, highlighting the need for HER2-targeted first-line treatment in this population. The MOUNTAINEER-03 Phase III trial (NCT05253651) was designed to investigate the efficacy and safety of first-line tucatinib in combination with trastuzumab and modified FOLFOX6 versus standard of care in patients with untreated HER2-positive *RAS* wild-type mCRC with the potential to address this unmet need. In addition, it may provide a more effective first-line treatment option for this specific population [26].

This study has some limitations. First, as an observational analysis of real-world data, it is subject to potential residual confounding; although adjusted HRs were estimated, unmeasured

variables may have influenced the observed associations. The impact of potential confounders should be examined in further analyses. Second, objective tumour response could not be evaluated due to the absence of imaging data or tumour measurements. Consequently, the study relied on PFS as a proxy outcome, which may not fully reflect clinically meaningful benefits such as tumour shrinkage or symptom improvement. Finally, 31% of the patients in the *ERBB2* amp+ group received anti-HER2 therapy, limiting the ability to interpret rWOS under the assumption of untreated *ERBB2* amplification and complicating efforts to isolate its prognostic effect.

CONCLUSIONS

In this large real-world cohort study, *ERBB2* amp+ mCRC accounted for a small but clinically distinct subgroup with worse rwPFS for the available first-line therapies. These findings highlight the limited efficacy of current treatment options and emphasise the urgent need for more effective treatments for *ERBB2* amp+ mCRC.

DATA AVAILABILITY

Data supporting this study's findings originated from and are the property of Flatiron Health, Inc. and Foundation Medicine, Inc. Requests for data sharing by license or by permission for the specific purpose of replicating results in this manuscript can be submitted to PublicationsDataAccess@flatiron.com and cgdb-fmi@flatiron.com.

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AUTHOR CONTRIBUTIONS

YM: designed the study, carried out statistical analyses, analysed and interpreted the results, and wrote the manuscript; HB: designed the study, developed its conceptualisation and wrote the manuscript; DN, ET and HP: conceived the research concept, managed patient recruitment, performed data curation and revised the manuscript; YN and TM: provided supervision and revised the manuscript; AO and TY: provided supervision, oversaw the project and revised the manuscript. All authors approved the final manuscript.

COMPETING INTERESTS

YM reports honoraria from MSD and Chugai Pharmaceutical. HB reports grants from Ono Pharmaceutical and GlaxoSmithKline; consulting fees from GxD and Guardant Health Japan; honoraria from Taiho Pharmaceutical, Ono Pharmaceutical and Guardant Health Japan. YN reports consulting fees from Guardant Health Pte Ltd., Natera Inc., Roche Ltd., Seagen Inc., Premo Partners Inc., Daiichi Sankyo Co. Ltd., Takeda Pharmaceutical Co. Ltd., Exact Sciences Corporation and Gilead Sciences Inc.; honoraria from Guardant Health Pte Ltd., MSD K.K., Eisai Co. Ltd., Zeria Pharmaceutical Co. Ltd., Miyarisan Pharmaceutical Co. Ltd., Merck Biopharma Co. Ltd., CareNet Inc., Hisamitsu Pharmaceutical Co. Inc., Taiho Pharmaceutical Co. Ltd., Daiichi Sankyo Co. Ltd., Chugai Pharmaceutical Co. Ltd., Becton Dickinson and Company, and Guardant Health Japan Corp. TM reports consulting fees from Takeda Pharmaceutical Co. Ltd., and honoraria from Miyarisan, Boston Medical Sciences, and Anaut Inc. DN, HP and ET report employment at Flatiron Health Inc., an independent member of the Roche Group, and stock ownership in Roche. ET also reports being a board member of Flatiron Health K.K. AO reports honoraria from Chugai Pharmaceutical Co. Ltd. and Ono Pharmaceutical Co. Ltd. TY reports grants from Bristol-Myers Squibb K.K., Caris MPI Inc., Chugai Pharmaceutical Co. Ltd., Daiichi Sankyo Co. Ltd., Eisai Co. Ltd., Exact Sciences Corporation, FALCO biosystems Ltd., Medical & Biological Laboratories Co. Ltd., Merus N.V., Miyarisan Pharmaceutical Co. Ltd., MSD K.K., Natera Inc., Nippon Boehringer Ingelheim Co. Ltd., Ono Pharmaceutical Co. Ltd., Pfizer Japan Inc., Sysmex Corp., Taiho Pharmaceutical Co. Ltd. and Takeda Pharmaceutical Co. Ltd.; consulting fees from Sumitomo Corp.; honoraria from Chugai Pharmaceutical Co. Ltd., Takeda Pharmaceutical Co. Ltd., Merck Biopharma Co. Ltd. and Ono Pharmaceutical Co. Ltd.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

The Institutional Review Board of the National Cancer Center Hospital East (2024-031) approved this study and waived the requirement for informed consent due to the observational retrospective study design, with an opportunity to opt out provided on the institution's website. All procedures were performed in accordance with the principles of the Declaration of Helsinki.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at <https://doi.org/10.1038/s41416-025-03270-4>.

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