original reports

Natural History of Human Epidermal Growth Factor Receptor 2–Amplified and Human Epidermal Growth Factor Receptor 2 Wild-Type Refractory Metastatic Colorectal Cancer in US Clinical Practice

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abstract

PURPOSE The molecular heterogeneity of metastatic colorectal cancer (mCRC) presents a therapeutic challenge, with few trials focused on patients with human epidermal growth factor receptor 2 amplification (HER2-Amp). Our limited understanding of real-world patterns and outcomes by HER2 status of treatment-refractory patients leaves treatment decisions with little contextual information. We conducted a retrospective cohort study to describe the natural disease history of patients with refractory mCRC using an electronic health record–derived database with oncogenomic information.

METHODS We included patients with stage IV or recurrent mCRC diagnosed from January 2011 through December 2019 from a deidentified clinicogenomic database. Patients with ≥ 2 documented clinic visits, ≥ 2 lines of therapy (LOT) after mCRC diagnosis, and comprehensive genomic profiling were eligible. Patient records defined by treatment-refractory LOT were allocated to the HER2-Amp or HER2 wild-type (WT) cohort on the basis of comprehensive genomic profiling. Index date was defined as the start of any treatment-refractory LOT (≥ 2 LOT; patients could contribute multiple records). Descriptive statistics included demographic and clinical characteristics, treatments, laboratory values, and biomarkers. Overall survival (OS) was calculated as time (in months) from the index date until death from any cause and analyzed using Kaplan-Meier methodology. Sensitivity analyses were conducted to test the robustness of the primary findings.

RESULTS A total of 576 patients were included (1,339 records); 63 (158 records) were HER2-Amp, and 513 (1,181 records) were HER2-WT. Demographics, clinical characteristics, biomarkers, and laboratory values were comparable between HER2 cohorts. OS was similar, with an unadjusted median OS of 11.2 months (95% CI, 8.6 to 15.1) and 9.9 months (95% CI, 8.3 to 10.9) across LOT for HER2-Amp and HER2-WT cohorts, respectively.

CONCLUSION This study showed considerable treatment heterogeneity and poor outcomes among patients with treatment-refractory mCRC, emphasizing a substantial unmet therapeutic need.

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ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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INTRODUCTION

Colorectal cancer is one of the most common cancer types and causes of cancer death worldwide,[1] and many patients are diagnosed at the metastatic stage.[2] Metastatic colorectal cancer (mCRC) presents a particular therapeutic challenge because of its molecular heterogeneity.[2] Resistance to anti–epidermal growth factor receptor (EGFR) treatment has been observed in tumors with *RAS*, *BRAF*, and *PIK3CA* alterations or with amplified human epidermal growth factor receptor 2 (HER2).[3-5] Historically, fewer clinical trials have focused on patients with HER2 amplification because of its relatively low prevalence in mCRC (approximately 1%-6%),[6,7] which has created a substantial unmet need for viable treatment options.

Emerging treatment strategies for patients with HER2-amplified (HER2-Amp) mCRC have focused on combination therapy, as the HERACLES and MyPathway clinical programs have shown promising results for pertuzumab-trastuzumab regimens in patients refractory to standard treatments.[8,9] The single-arm nature of these trials heightens the importance of contextual research, such as evaluation of external control arms[10] and real-world outcomes to elucidate

CONTEXT

Key Objective

What are the characteristics, treatment patterns, biomarker profiles, and survival outcomes of patients with human epidermal growth factor receptor 2 (HER2)–amplified or HER2 wild-type refractory metastatic colorectal cancer (mCRC) in real-world clinical practice? To answer these questions, we conducted an observational natural history study using a database combining deidentified patient-level electronic health record–derived information with genomic testing results.

Knowledge Generated

We found generally similar patient characteristics, treatment regimens, and overall survival for patients with HER2-amplified or HER2 wild-type treatment-refractory mCRC. There is a prominent unmet treatment need in this setting because of the relatively small proportion of patients with HER2-amplified tumors. This study further demonstrated the feasibility and relevance of deriving a biomarker-selected, real-world study population from a deidentified electronic health record–derived database.

Relevance

The use of real-world data to examine the course for HER2-amplified mCRC in clinical practice provides important contextual information related to the use of HER2-targeted therapies in this rare population.

the natural history of refractory patients with or without HER2-Amp tumors. Specifically, better understanding of the real-world characteristics, treatment experience, biomarker profiles, and survival of patients with HER2-Amp or HER2 wild-type (HER2-WT) refractory mCRC would inform interpretation of research and provide essential context for clinical and health policy decisions.

To better understand the characteristics and outcomes of HER2-Amp and HER2-WT patients, we conducted an observational natural history study using an electronic health record (EHR)–derived database with oncogenomic information from patients with refractory mCRC in US clinical practice.

METHODS

Data Source

This natural history study used the nationwide (US-based) Flatiron Health (FH)-Foundation Medicine (FMI) Clinico-Genomic Database (CGDB; Foundation Medicine, Cambridge, MA). The retrospective, longitudinal, EHR-derived clinical data comprised deidentified patient-level information from structured data (prescribed treatments and laboratory values) and unstructured data (biomarkers), curated via technology-enabled chart abstraction from physician notes and other documents, and were linked to genomic data derived from FMI comprehensive genomic profiling (CGP) tests in the FH-FMI CGDB by deidentified, deterministic matching.[11] The deidentified data were drawn from approximately 280 US cancer clinics (approximately 800 sites of care, primarily community-based cancer centers). Genomic alterations were identified via CGP of > 300 cancer-related genes on FMI's next-generation sequencing (NGS)–based FoundationOne panel.[12,13] To date, more than 400,000 samples have been sequenced from patients across the United States.

The CGDB includes patients from the FH database who underwent genomic profiling by FMI and provides deidentified, patient-level genomic data, including specimen features (tumor mutational burden [TMB] and pathologic purity), alteration-level details (genomic position, reference alleles, and alternate alleles), and targeted therapeutic options reported to the clinician at the time of testing.

Institutional review board approval of the protocol for FH research activities was obtained before study conduct for the CGDB data source, and a waiver of informed consent was obtained. All data were deidentified, and provisions were in place to prevent reidentification to protect patient confidentiality.

Population

Eligible patients had stage IV or recurrent, chart-confirmed mCRC diagnosed on or after January 1, 2011 (CRC diagnosis: ICD-9 153.x or 154.x, or ICD-10 C18x, C19x, C20x, or C21x). Patients were followed to the end of the study period (December 31, 2019), death, or loss to follow-up. Patients were required to have ≥ 2 documented clinical visits in the FH network, ≥ 2 lines of therapy (LOT) after mCRC diagnosis, and a known HER2 status (HER2-Amp or HER2-WT). Patient records also had to include CGP testing by FMI on a tumor sample with pathologist-confirmed histology and ≥ 1 FMI test with the FoundationOne or FoundationOne CDx assay reported within 30 days before or any time after mCRC diagnosis, with documentation of a passed quality control test.

Exclusions were as follows: a first FMI report date > 60 days after the last visit date in the FH network; a ≥ 90-day gap between mCRC diagnosis date and first recorded activity in the FH network after metastatic diagnosis date (to avoid misclassification of the LOT); history of treatment with a HER2-targeted therapy (pertuzumab, trastuzumab or

biosimilar, lapatinib, neratinib, or trastuzumab-emtansine during or before second-line therapy); or evidence of clinical study treatment during or before second-line therapy (trial participation was allowed after second-line therapy).

Patients were allocated to the HER2-Amp or HER2-WT cohort on the basis of their FMI test results. HER2-Amp status was defined as having an erythroblastic oncogene B (*ERBB2*) amplification (copy-number amplification) with a known functional status. HER2-WT status was defined as the absence of any HER2-Amp result in all FMI tests recorded in the CGDB for a given patient. HER2-Amp and HER2-WT patients were sampled separately. The cohort of HER2-Amp patients consisted of all available HER2-Amp patients in the database; the HER2-WT cohort comprised a random sample of available qualifying HER2-WT patients from the database. Any eligible genomic test indicating HER2-Amp status determined allocation to the HER2-Amp cohort. Patients were followed from their index date, defined as the start date of any treatment-refractory LOT (any line of treatment after first-line treatment, $\geq$ 2 LOTs; Appendix Fig A1). This study evaluated records of initiation of a treatment-refractory LOT as the primary unit of observation to minimize bias.[14] As such, a patient could contribute multiple records with corresponding index dates (thus, multiple index dates aligned with multiple LOTs). Where required, standard errors and confidence intervals were calculated using bootstrapping to account for correlations within subject observations.

Characteristics and Outcomes

Clinical and demographic characteristics were assessed from the mCRC diagnosis date to the index date, including age, sex, insurance type, type of metastatic diagnosis, metastases, Eastern Cooperative Oncology Group (ECOG) performance status, tumor staging at initial diagnosis, cardiovascular events, and left ventricular ejection fraction $<$ 50%. ECOG performance status was assessed from 30 days before 7 days after the index date. If characteristics were available from multiple dates within an assessment period, the information from the collection date closest to the index date was used. If patients contributed multiple index dates (from multiple LOT), characteristics were assessed for each of the index dates.

Treatment variables included LOT number ($\geq$ 2), time from initial mCRC diagnosis to start of first-line therapy and to index date, treatment in the premetastatic setting, and specific treatment regimens received overall and by biomarker status. The mCRC LOT was determined by the presence of systemic antineoplastic therapies on the basis of structured medication administrations, noncanceled medication orders, and abstracted records of oral or intravenous therapies. Three days of overlap between abstracted oral agents and any other drug was allowed. Megestrol, colony-stimulating factors, rituximab, and anastrozole were excluded. Laboratory measurements included albumin, alkaline phosphatase, creatinine, hemoglobin, lymphocytes, neutrophils, platelet count, total protein, and glucose, all categorized as normal, above the upper limit of normal, or below the lower limit of normal.

Biomarker evaluations from FMI test or abstracted from the EHR included alterations in *BRAF* V600E; known or likely functional short variants in *KRAS*, *NRAS*, *EGFR*, *PIK3CA*, *TP53*, *APC*, *SMAD4*, *CDKN2A*, or *PTEN*; deficient mismatch repair and microsatellite instability-high (dMMR/MSI-high) or microsatellite stable (MSS); and TMB. Biomarker status was based on any evidence of positive biomarker results occurring within 30 days before or any time after the mCRC diagnosis date. In the case of discordant results, any evidence of a positive result considered the patient to be positive for that biomarker.

Overall survival (OS) was defined as time in months from the index date until death from any cause or loss to follow-up. Date of death was a composite end point on the basis of mortality data curated from structured and unstructured information in the EHRs (eg, clinician notes), obituary records, or the Social Security Death Index.[15]

Statistical Analyses

Descriptive statistics summarized demographic and clinical characteristics, treatments, laboratory measurements, and biomarkers for the HER2-Amp and HER2-WT cohorts. OS was analyzed using Kaplan-Meier methodology. Risk set adjustment was used to ensure patients were only included into the risk set after the later of either their first FMI report date or their second visit in the FH network. Patients without a recorded death event were censored at the latest date of either their last recorded activity (clinical visit and laboratory value) or last specimen collection or reporting in FMI.

Three sensitivity analyses were conducted to test the robustness of the primary findings. First, the results were analyzed for patients with HER2-Amp status from both FMI and non-FMI assays (non-FMI immunohistochemistry and NGS) to evaluate the potential impact of excluding patients with HER2-Amp status detected via non-FMI tests. The second sensitivity analysis restricted the index date to the first treatment refractory LOT (each patient could only belong to one LOT subgroup) to examine the potential impact of including index dates that occurred before the qualifying FMI test. Finally, patients without a death event were censored at the study cutoff date (December 31, 2019) to evaluate the impact of different censoring criteria on OS estimates. Statistical analyses were performed using R version 4.0.0.[16]

RESULTS

A total of 589 patients with an mCRC diagnosis had an eligible HER2 test, but 13 (2%) were excluded because of ineligible timing of their first FMI test (after their last record of activity in the EHR database). A total of 576 patients with

treatment-refractory mCRC met all eligibility criteria and were included in the study, contributing 1,339 records on the basis of initiation of ≥ 1 treatment-refractory LOT (Fig 1). Sixty-three patients (11%) were allocated to the HER2-Amp cohort, contributing 158 records, and 513 (89%) were allocated to the HER2-WT cohort, contributing 1,181 records. Demographic and clinical characteristics were generally similar between the HER2-Amp and HER2-WT cohorts, with some differences in race, type of metastatic disease, insurance, and year of diagnosis (Table 1). Numerically greater proportions of patients in the HER2-Amp cohort were listed as Black or African American and as having commercial insurance compared with the HER2-WT cohort.

Concomitant Biomarkers and Laboratory Assessments

Biomarker and laboratory measures were generally similar between cohorts, with *TP53* and *APC* being the most common alterations (Table 2). Concomitant genomic alterations were generally similar between cohorts, with the exception of *KRAS* and *BRAF* V600 alterations being more common in the HER2-WT cohort (52% *v* 18%, and 6% *v* 1%, respectively) and *TP53* alterations being more common in the HER2-Amp cohort (91% *v* 76%, respectively; Table 2).

Treatment Regimens by HER2 Status

Any fluorouracil, leucovorin, and irinotecan (FOLFIRI) or infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX) regimen comprised the most prevalent treatment regimens in the refractory setting overall, accounting for 31% and 13% of all treatment regimens across cohorts, respectively (Table 3). The distribution of each was similar between cohorts, with FOLFIRI accounting for 27% and 32% of HER2-Amp and HER2-WT records, respectively, and FOLFOX accounting for 11% and 13% of HER2-Amp and HER2-WT records, respectively. The most common single regimen was FOLFIRI-bevacizumab (Table 3).

Among HER2-WT patients, 29% with *KRAS*-WT received cetuximab or panitumumab as monotherapy or as part of a combination regimen, compared with 3% of those with *KRAS* mutations. Specifically, a greater proportion of *KRAS*-WT patients received FOLFIRI or FOLFOX with cetuximab or panitumumab (17%) than did those with *KRAS* mutations (1%). Only one HER2-Amp patient and 36 HER2-WT patients were MSI-high; 31% and 11% of the MSI-high HER2-WT patients received pembrolizumab and nivolumab, respectively, compared with 1% each of the MSS HER2-WT patients. No substantive differences in treatment regimens were observed among HER2-Amp or HER2-WT patients on the basis of *PIK3CA* mutation status. Patients without evidence of TMB > 10 mutations/Mb, MSI-high status, or *KRAS*, *BRAF* V600, or *PIK3CA* mutations were treated similarly regardless of HER2 status (data not shown).

OS by HER2 Status

OS was similar between the HER2-Amp and HER2-WT cohorts, with an unadjusted median OS of 11.2 months (95% CI, 8.6 to 15.1) and 9.9 months (95% CI, 8.3 to 10.9), respectively (Fig 2). Although the HER2-Amp cohort showed a numerically longer OS, the analysis was unadjusted, and the difference was not statistically significant. Numerically longer median OS for the HER2-Amp cohort was consistent across LOT, with slightly shorter median OS in later LOT (Table 4).

Sensitivity Analyses

Sensitivity analysis results were generally consistent with the primary findings. The first sensitivity analysis using information from both non-FMI and FMI tests yielded three additional patients in the HER2-Amp cohort, with small, purely numerical differences in some patient characteristics, biomarkers, and laboratory values, which did not change the interpretation of results. OS findings were consistent with the primary analysis. The results from the second and third sensitivity analyses, using a more

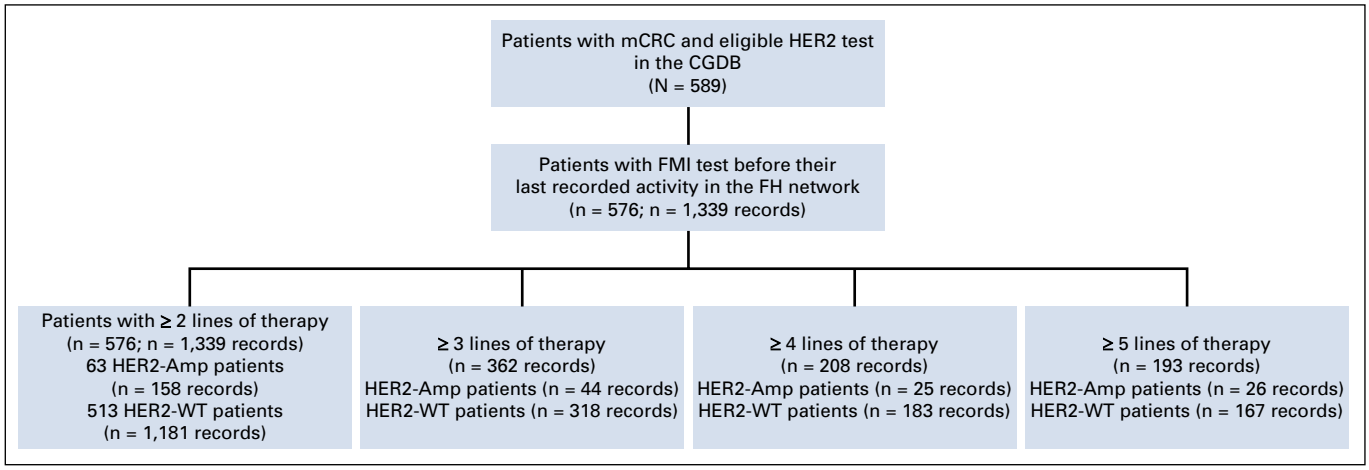

FIG 1. Patient attrition. Amp, amplified; CGDB, Clinico-Genomic Database; FH, Flatiron Health; FMI, Foundation Medicine; HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer; WT, wild-type.

TABLE 1. Demographic and Clinical Characteristics by HER2 Status (summary of records across all LOT index dates)

Records	HER2-Amp Cohort (n = 158 records)	HER2-WT Cohort (n = 1,181 records)
Male	88 (56)	648 (55)
Age, years, median (IQR)		
At mCRC diagnosis	56 (15.0)	58 (16.0)
At index date	60 (14.8)	60 (17.0)
Race		
White	91 (58)	825 (70)
Black or African American	18 (11)	70 (6)
Asian	11 (7)	37 (3)
Hispanic or Latino	9 (6)	64 (5)
Other	24 (15)	130 (11)
Unknown	5 (3)	55 (5)
Insurance type at index date		
Commercial	106 (67)	640 (54)
Medicare	10 (6)	193 (16)
Medicaid	< 4 records	23 (2)
Other government program	4 (3)	18 (2)
Other payer	23 (15)	170 (14)
Unknown	13 (8)	137 (12)
Stage at initial diagnosis		
I	< 4 records	32 (3)
II	5 (3)	80 (7)
III	35 (22)	237 (20)
IV	114 (72)	796 (67)
Unknown	< 4 records	36 (3)
ECOG performance status		
0	54 (34)	314 (27)
1	48 (30)	464 (39)
2+	15 (9)	110 (9)
Unknown	41 (26)	293 (25)
Sites of metastases[a]		
Liver	131 (83)	909 (77)
Lung	83 (53)	562 (48)
Brain	2 (1)	26 (2)
CNS (other than brain)	0 (0)	0 (0)
Bone	10 (6)	84 (7)
Lymph nodes	54 (34)	455 (39)
Cardiovascular events on or before the index date	33 (21)	270 (23)
Left ventricular ejection fraction < 50%	< 4 records	37 (3)
Total LOT		
2	63 (40)	513 (43)
3	44 (28)	318 (27)
4	25 (16)	183 (15)
≥ 5	26 (16)	167 (14)
Months from mCRC diagnosis to initiation of first-line therapy, median (IQR)	1.0 (1.1)	1.1 (1.2)
Months from mCRC diagnosis to index date, median (IQR)[b]	18.2 (18.9)	17.2 (19.8)
Year of index date (start of refractory LOT)		
2011	0	< 4 records
2012	0	4 (0.3)
2013	0	16 (1)
2014	< 4 records	50 (4)
2015	10 (6)	117 (10)
2016	14 (9)	165 (14)
2017	35 (22)	236 (20)
2018	34 (22)	298 (25)
2019	62 (39)	293 (25)
Premetastatic setting treatment history	43 (27)	301 (25)

NOTE. Values are listed as No. (%) unless otherwise specified. Cells with < 4 records have been masked.

Abbreviations: Amp, amplified; ECOG, Eastern Cooperative Oncology Group; HER2, human epidermal growth factor receptor 2; IQR, interquartile range; LOT, line of therapy; mCRC, metastatic colorectal cancer; WT, wild-type.

[a]Proportions do not sum to 100% because patients could have had > 1 metastatic site.

[b]Median number of months from mCRC diagnosis to index date calculated across all LOT index dates.

restrictive index date and adjusting the censoring criteria to the study cutoff date, respectively, were consistent with the primary analyses (data not shown). As such, the main analysis was robust, as changes to test sources and variable timing in the sensitivity analyses yielded similar results.

DISCUSSION

This natural history study illustrated the demographic and clinical characteristics, treatment utilization, and survival of patients with HER2-Amp or HER2-WT treatment-refractory mCRC in US clinical practice. Overall, patient characteristics, treatment regimens, and median OS were similar between HER2-Amp and HER2-WT patients, with only unremarkable differences observed. This study further demonstrated the feasibility and relevance of deriving a biomarker-selected, real-world study population from a deidentified EHR-derived database.

TABLE 2. Biomarker and Laboratory Evaluations by HER2 Status

Records	HER2-Amp Cohort (n = 158 records), No. (%)	HER2-WT Cohort (n = 1,181 records), No. (%)
Alterations		
BRAF V600	2 (1)	71 (6)
KRAS	28 (18)	609 (52)
NRAS	4 (3)	42 (4)
EGFR	2 (1)	19 (2)
PIK3CA	24 (15)	219 (19)
TP53	144 (91)	892 (76)
APC	134 (85)	1,017 (86)
SMAD4	14 (9)	157 (13)
CDKN2A	7 (4)	10 (1)
PTEN	12 (8)	58 (5)
dMMR/MSI-high	1 (1)	36 (3)
TMB, mutations/Mb		
≥ 10	12 (8)	110 (9)
≥ 16	0	37 (3)
Albumin		
Above ULN	1 (1)	0
Normal	106 (67)	794 (67)
Below LLN	25 (16)	237 (20)
Unknown	26 (16)	150 (13)
Alkaline phosphatase		
Above ULN	48 (30)	401 (34)
Normal	83 (53)	618 (52)
Below LLN	1 (1)	7 (1)
Unknown	26 (16)	155 (13)
Creatinine		
Above ULN	13 (8)	82 (7)
Normal	104 (66)	822 (70)
Below LLN	16 (10)	139 (12)
Unknown	25 (16)	138 (12)
Hemoglobin		
Above ULN	0	1 (< 1)
Normal	71 (45)	470 (40)
Below LLN	66 (42)	603 (51)
Unknown	21 (13)	107 (9)
Lymphocytes		
Above ULN	1 (1)	9 (1)
Normal	92 (58)	682 (58)
Below LLN	41 (26)	354 (30)
Unknown	24 (15)	136 (12)
Neutrophils		
Above ULN	15 (9)	116 (10)
Normal	88 (56)	680 (58)
Below LLN	1 (1)	29 (2)
Unknown	54 (34)	356 (30)
Platelet count		
Above ULN	8 (5)	33 (3)
Normal	105 (66)	794 (67)
Below LLN	21 (13)	235 (20)
Unknown	24 (15)	119 (10)
Total protein		
Above ULN	1 (1)	11 (1)
Normal	108 (68)	856 (72)
Below LLN	23 (15)	173 (15)
Unknown	26 (16)	141 (12)
Glucose		
Above ULN	66 (42)	504 (43)
Normal	62 (39)	455 (39)
Below LLN	1 (1)	11 (1)
Unknown	29 (18)	211 (18)

NOTE. Thresholds for ULN and LLN were determined by the individual laboratories and vary because of testing equipment, chemical reagents used, and analysis techniques.

Abbreviations: Amp, amplified; dMMR/MSI-high, deficient mismatch repair and microsatellite instability-high; HER2, human epidermal growth factor receptor 2; LLN, lower limit of normal; TMB, tumor mutational burden; ULN, upper limit of normal; WT, wild-type.

This study provides important insight into a rare cohort of patients with mCRC who, given the high prevalence of mCRC overall, are likely to comprise a substantial absolute number of patients with unmet treatment needs. Treatments received by patients in these cohorts were generally aligned with published recommendations.[17] Specifically, we observed more prevalent FOLFIRI or FOLFOX plus cetuximab or panitumumab regimens among *KRAS*-WT patients and more use of pembrolizumab or nivolumab among MSI-high than MSS HER2-WT patients, aligning with standards of care and the National Comprehensive Cancer Network guidelines. The genomic alterations observed in our study were generally consistent with those reported by the Cancer Genome Atlas Network (CGAN) for *APC* (85% HER2-Amp, 86% HER2-WT; and 81% in CGAN), *KRAS* (18% HER2-Amp, 52% HER2-WT; and 43% in CGAN), *PIK3CA* (15% HER2-Amp, 19% HER2-WT; and 18% in CGAN), and *SMAD4* (9% HER2-Amp, 13% HER2-WT; and 10% in CGAN).[18] We did observe higher proportions of *TP53* in our HER2-Amp (91%) and HER2-WT (76%) cohorts compared with 60% in the CGAN, possibly indicating more advanced disease in our cohorts.[18] The lower prevalence of *KRAS* or *BRAF* V600 alterations

TABLE 3. Records of Second-Line or Later Treatment Regimens Overall and by HER2 Status

Overall (N = 1,339 records), No. (%)		HER2-Amp (n = 158 records), No. (%)		HER2-WT (n = 1,181 records), No. (%)	
Most common consolidated second-line or later treatment, any FOLFIRI or FOLFOX regimen					
Any FOLFIRI regimen	420 (31)	Any FOLFIRI regimen	42 (27)	Any FOLFIRI regimen	378 (32)
Any FOLFOX regimen	172 (13)	Any FOLFOX regimen	17 (11)	Any FOLFOX regimen	155 (13)
Specific second-line or later treatment regimens					
FOLFIRI, bevacizumab	206 (15)	FOLFIRI, bevacizumab	18 (11)	FOLFIRI, bevacizumab	188 (16)
Trifluridine/tipiracil	127 (9)	Regorafenib	12 (8)	Trifluridine/tipiracil	119 (10)
Regorafenib	105 (8)	Clinical study drug[a]	9 (6)	FOLFOX, bevacizumab	95 (8)
FOLFOX, bevacizumab	103 (8)	FOLFIRI, cetuximab	8 (5)	Regorafenib	93 (8)
Clinical study drug[a]	66 (5)	FOLFOX, bevacizumab	8 (5)	Clinical study drug[a]	57 (5)
FOLFIRI	61 (5)	Trifluridine/tipiracil	8 (5)	FOLFIRI	56 (5)
FOLFIRI, panitumumab	56 (4)	FOLFIRI, panitumumab	7 (4)	FOLFIRI, panitumumab	49 (4)
FOLFOX	45 (3)	Irinotecan, cetuximab	7 (4)	FOLFOX	42 (4)
FOLFIRI, cetuximab	44 (3)	Panitumumab	6 (4)	FOLFIRI, cetuximab	36 (3)
Irinotecan, cetuximab	37 (3)	Fluorouracil, leucovorin, bevacizumab	5 (3)	Irinotecan, cetuximab	30 (3)
Other[b]	487 (36)	FOLFIRI	5 (3)	Other[b]	417 (35)
		Irinotecan, panitumumab	5 (3)		
		Capecitabine, irinotecan	4 (3)		
		Other[b]	56 (35)		

Abbreviations: Amp, amplified; FOLFIRI, fluorouracil, leucovorin, and irinotecan; FOLFOX, infusional fluorouracil, leucovorin, and oxaliplatin; HER2, human epidermal growth factor receptor 2; WT, wild-type.

[a]Clinical trial participation was allowable after second-line therapy.

[b]Other category includes lines of therapy used in ≤ 2% of records.

observed among our HER2-Amp cohort compared with the HER2-WT cohort was consistent with a recent study by Ross [6] and a meta-analysis exploring *KRAS* and *BRAF* as therapeutic targets in CRC.[19] The CGAN reported HER2 amplification and *KRAS*, *NRAS*, and *BRAF* mutations to be mutually exclusive.[18] It should be noted that our study population was enriched for HER2-Amp patients and is, therefore, not representative of all treatment-refractory mCRC patients (and HER2 prevalence at large).

We did not observe a statistically significant difference in OS between the HER2-Amp and HER2-WT cohorts. The numerically greater median OS observed in our HER2-Amp cohort was from an unadjusted analysis and might be affected by imbalanced patient characteristics such as the

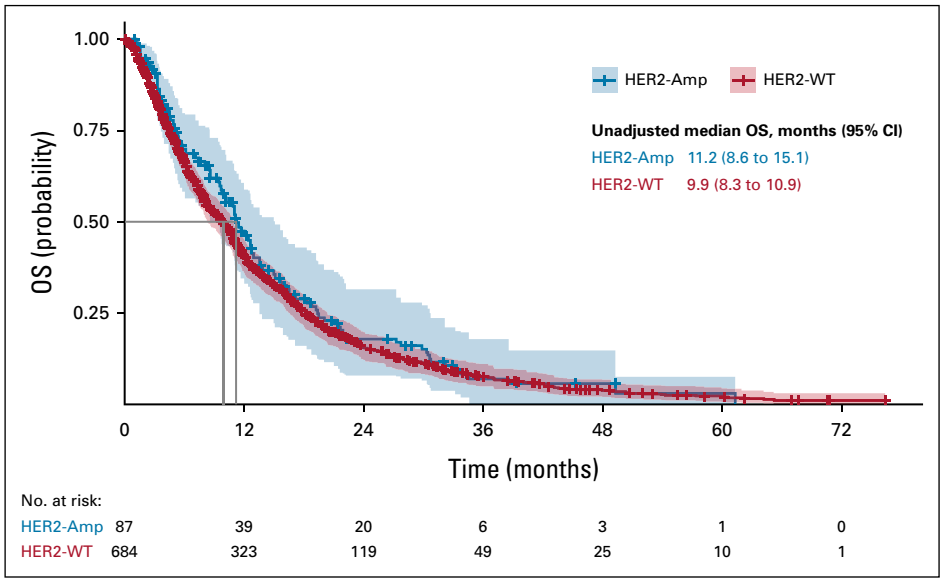

FIG 2. Unadjusted OS by HER2 status. The number of records at time 0 is less than the total number of records because of the risk set adjustment, in which only records after the date of the first FMI test were included (ie, when the patient's time at risk started). Amp, amplified; FMI, Foundation Medicine; HER2, human epidermal growth factor receptor 2; OS, overall survival; WT, wild-type.

TABLE 4. Unadjusted Median Overall Survival (95% CI) by HER2 Status and LOT, Months

LOT	HER2-Amp Cohort	HER2-WT Cohort
Overall	11.2 (8.6 to 15.1)	9.9 (8.3 to 10.9)
LOT 2	13.6 (11.0 to 21.5)	11.8 (10.8 to 13.9)
LOT 3	11.1 (4.9 to 19.4)	9.2 (7.1 to 10.8)
LOT 4	11.4 (5.3 to 16.2)	7.8 (6.6 to 10.2)

Abbreviations: Amp, amplified; HER2, human epidermal growth factor receptor 2; LOT, line of therapy; WT, wild-type.

lower prevalence of *KRAS* and *BRAF* V600 alterations. The similar observed OS is consistent with OS outcomes by HER2 status reported in the literature, where the impact of HER2 amplification on prognosis for patients with mCRC remains unclear.[19-21] Richman et al[19] reported no association of OS with HER2 overexpression from the QUASAR, FOCUS, and PICCOLO trials. Conradi et al[21] reported no difference in disease-free survival between HER2-Amp and HER2-WT patients with stage II/III CRC but a better 5-year cancer-specific survival among HER2-Amp patients (96% *v* 80%, respectively). Other studies have reported worse survival outcomes for patients with HER2-Amp status.[20,22] The challenging prognosis and subsequent therapeutic opportunities for patients with *KRAS* and/or *BRAF* alterations should also be noted,[23] which might have played a more nuanced role in our broader assessment of HER2-Amp or HER2-WT status. Furthermore, the authors note that MSI-high HER2-WT patients treated with immune checkpoint inhibitors may have longer OS; however, only 36 of the 1181 HER2-WT patients in this study were MSI-high and only 15 of those were treated with immune checkpoint inhibitors, which was not expected to affect the OS findings. Future research may further investigate if HER2 status affects OS or if other factors are responsible for the observed trend.

This study used a large, EHR-derived, real-world data set with biomarker and laboratory evaluations from patients treated in US clinical practice. The size of our cohorts and scope of available data were well suited to our objective of understanding the natural history of patients with treatment-refractory mCRC by HER2 status. The FMI assay used to identify HER2-Amp patients is a US Food and Drug Administration–approved companion diagnostic for HER2-targeted therapy in breast cancer and has been evaluated for clinical concordance with other assays (ie, Dako HER2 FISH PharmDx; FoundationOne CDx). Since FH encompasses US sites only, the data may or may not be generalizable to populations outside of the United States, given the epigenetic and other factors that may differentiate US and ex-US patients despite similar genomic characteristics. Our requirement to include patients with a record of genomic testing may have selected a younger population with treatment-refractory mCRC (related to insurance coverage for NGS in March 2018), where our observed median age at mCRC diagnosis of 56 to 58 years is lower than that of 67 years at diagnosis reported by the Surveillance, Epidemiology, and End Results Program; this may have introduced a selection bias that would limit the generalizability of results.[24] Inclusion in the CGDB requires patients to have lived long enough to receive an FMI test and to have ≥ 2 visits within the FH network. To account for this potential bias because of left truncation, we included patients in the risk set for the time-to-event calculations after the later of either their first FMI report date or their second visit in the FH network. The FH data are subject to the inherent limitations of observational data sources, such as the potential for missing, inaccurate, or incomplete data, or selective reporting of results. Data abstraction by specially trained human abstractors using predefined procedures as well as quality assurance and quality control measures aims to reduce such potential concerns. Finally, information about treatment received outside of the FH network sites may not have been captured unless it was documented in unstructured notes in the patient's EHR. This could have introduced a risk of missing health information across the cohort, which could have led to a misclassification of LOT. To reduce the risk of including patients who may have been referred into a practice within the FH network, patients with a gap of ≥ 90 days between mCRC diagnosis and treatment initiation were excluded.

This study has shown generally similar patient characteristics, treatment regimens, and OS for patients with HER2-Amp or HER2-WT treatment-refractory mCRC. There is a prominent unmet treatment need for HER2-Amp patients in this setting owing to the relatively small proportion of patients with mCRC and HER2-Amp tumors. Use of real-world data to examine the characteristics, treatment patterns, and clinical outcomes of patients with HER2-Amp mCRC provides important clinical contextualization for the use of HER2-targeted therapies in this rare population. This study may inform clinical trial design and research priorities as well as health policy decisions that may affect patients with refractory mCRC.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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APPENDIX

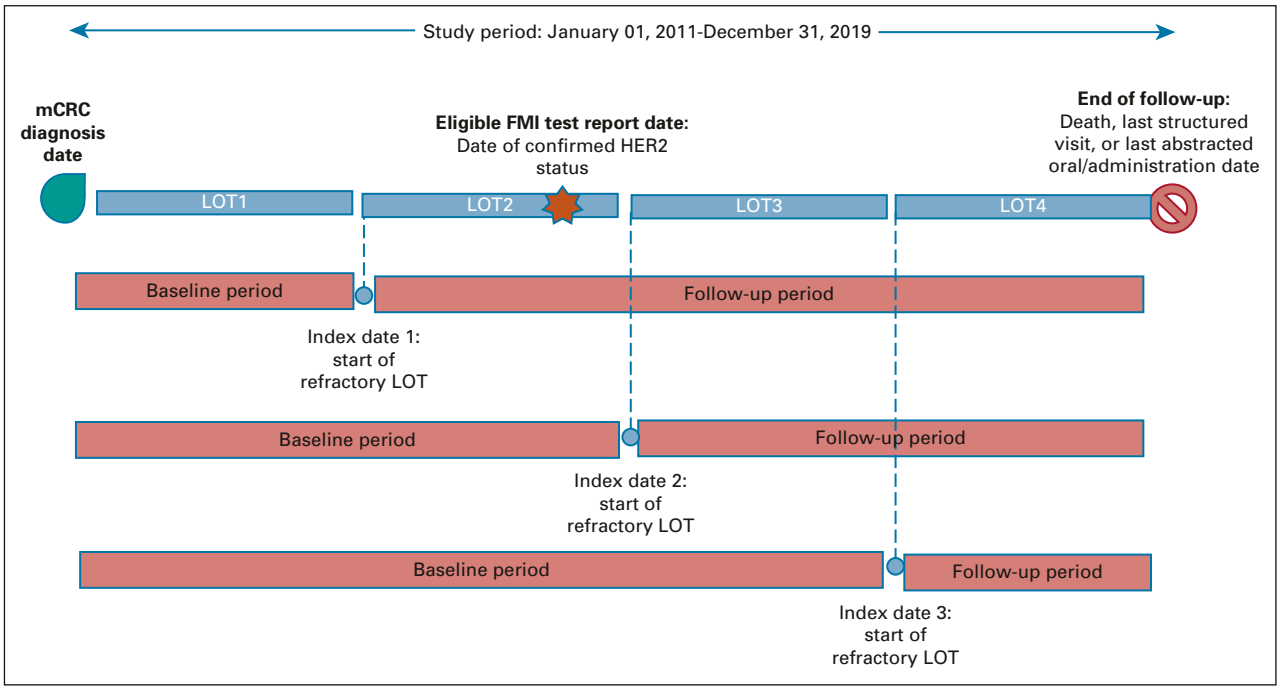

FIG A1. Study design. FMI, Foundation Medicine; HER2, human epidermal growth factor receptor 2; LOT, line of therapy; mCRC, metastatic colorectal cancer.