DRUG THERAPY

original reports abstract

Pertuzumab Plus Trastuzumab for Treatment-Refractory *HER2*-Amplified Metastatic Colorectal Cancer: Comparison of the MyPathway Trial With a Real-World External Control Arm

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PURPOSE We compared overall survival (OS) in patients with human epidermal growth factor receptor 2 (*HER2*)–amplified, treatment-refractory metastatic colorectal cancer (mCRC) receiving pertuzumab plus trastuzumab (PER-HER) in the phase IIa MyPathway multibasket study (ClinicalTrials.gov identifier: NCT02091141) with OS in those receiving routine clinical care in an electronic health record–derived external control arm.

METHODS A noninterventional study was conducted using patient-level data from MyPathway participants receiving PER-HER and real-world patients with *HER2*-amplified treatment-refractory mCRC receiving routine clinical care. This study used a deidentified US-based clinico-genomic database (CGDB). For patients in the CGDB who met study eligibility criteria at multiple index dates (treatment initiation dates in the treatment-refractory setting), all eligible index dates were used for the analysis. Standardized mortality ratio weighting on the basis of propensity score derived a pseudopopulation (postweighting population) balancing key prognostic variables between arms. Multivariate Cox proportional hazards models were used for estimation of the hazard ratio (HR) in the primary OS analysis. A series of sensitivity analyses were conducted to investigate the robustness and consistency of the primary analysis.

RESULTS The PER-HER arm comprised 57 patients enrolled in the MyPathway study by August 1, 2017 (data cutoff); the external control arm comprised 18 patients (27 index dates) with *HER2*-amplified mCRC who met the major MyPathway eligibility criteria in CGDB collected between 2011 and 2019. The estimated HR for OS from the multivariate Cox proportional hazards model in the postweighting population was 0.729 (95% CI, 0.184 to 3.900). The results of sensitivity analyses were consistent with the primary analysis in terms of the point estimate of HR.

CONCLUSION Despite a small sample size, these findings suggest that PER-HER could have a potential OS benefit for this population.

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INTRODUCTION

Colorectal cancer (CRC) is the third most prevalent type of cancer and second leading cause of cancer-related deaths worldwide.[1] Standard-of-care chemotherapy regimens may provide overall survival (OS) benefits up to approximately 24 months,[2,3] with further benefit up to a total of 30 months with the addition of biologic therapy in appropriate patients.[4-6] However, patients are likely to experience disease progression, and later-line therapies have offered only incremental survival benefits with notable toxicity.[7] Treatment options and outcomes are particularly limited for patients with treatment-refractory metastatic CRC (mCRC) and human epidermal growth factor receptor 2 (*HER2*) gene amplification (*HER2*-Amp), which is prevalent in approximately 3%-6% of patients with CRC[8,9] and in 4%-14% of those with *RAS/BRAF* wild-type CRC.[10-12]

Combination therapy of pertuzumab plus trastuzumab (PER-HER) showed promising results for patients with treatment-refractory *HER2*-Amp mCRC in the single-arm, phase IIa MyPathway multibasket study and is listed in the National Comprehensive Cancer Network guidelines for *HER2*-Amp mCRC along with trastuzumab plus lapatinib or fam-trastuzumab deruxtecan-nxki as a category 2A recommendation.[13] PER-HER demonstrated an objective response rate of 32% with a median OS of 11.5 months and a median progression-free survival of 2.9 months in MyPathway.[14] Similar efficacy was observed with PER-HER in the multicenter phase II TRIUMPH study.[15]

Interpretation of findings from single-arm trials for clinical and health policy decision making can be supported by contextual information from an external control (EC) arm derived from real-world data

ASSOCIATED CONTENT

Data Supplement

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

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CONTEXT

Key Objective

Does the combination of pertuzumab and trastuzumab confer an overall survival (OS) benefit in patients with treatment-refractory human epidermal growth factor receptor 2 (*HER2*)–amplified metastatic colorectal cancer? To answer this question, we conducted a noninterventional study using patient-level data from participants receiving pertuzumab and trastuzumab in the MyPathway study and from real-world patients in a deidentified clinico-genomic database receiving routine clinical care.

Knowledge Generated

We constructed an external control of patients who met major eligibility criteria of the MyPathway study and adjusted for potential confounding using propensity score–based weighting. The estimated hazard ratio (HR) for an OS of 0.729 (95% CI, 0.184 to 3.900) from multivariate Cox proportional hazards models showed a favorable trend for pertuzumab and trastuzumab compared with external controls. A series of sensitivity analyses were consistent in terms of the HR.

Relevance

Although several limitations exist, the combination of pertuzumab and trastuzumab appeared to have an OS benefit for patients with treatment-refractory *HER2*–amplified metastatic colorectal cancer.

sources.[16] To support informed, evidence-based treatment decisions, we constructed an EC arm of patients with *HER2*-Amp mCRC receiving routine clinical care. The primary objective was to compare OS in patients with treatment-refractory *HER2*-Amp mCRC receiving PER-HER in the MyPathway study or routine clinical care in the electronic health record (EHR)–derived real-world data EC arm.

METHODS

Study Design and Data Sources

We conducted a noninterventional study with secondary use of observational and clinical trial data using patient-level data from participants receiving PER-HER in the phase IIa MyPathway multibasket study (PER-HER arm; ClinicalTrials.gov identifier: NCT02091141) and from patients with mCRC in the deidentified US-based Flatiron Health (FH)/Foundation Medicine Inc (FMI) Clinico-Genomic Database (CGDB) who received therapy in the treatment-refractory setting as part of routine clinical care (EC arm; Fig 1).

The design and primary findings from patients with mCRC in the MyPathway study have been reported previously.[14] Briefly, MyPathway is an ongoing nonrandomized, multicenter, open-label multibasket phase IIa trial in the United States for patients with advanced solid tumors, including CRC. Eligible adults (age ≥ 18 years) with treatment-refractory *HER2*-Amp mCRC received intravenous pertuzumab (840 mg loading dose followed by 420 mg once every 3 weeks) and intravenous trastuzumab (8 mg/kg loading dose followed by 6 mg/kg once every 3 weeks) until disease progression, unacceptable toxicity, or study discontinuation. The primary end point was objective response rate, defined as the proportion of patients with partial or complete response according to investigator-reported best overall tumor response up to the data cut-off for each patient.

Retrospective longitudinal clinical data were derived from EHR data in the FH database (Flatiron Health, New York, NY) compromising patient-level information from structured (eg, laboratory values and prescribed treatments) and unstructured data (eg, biomarker reports) collected via technology-enabled chart abstraction from physicians' notes and other clinical documents. The FH database contains oncologist-defined, rule-based lines of therapy using structured data for drug orders and administrations.

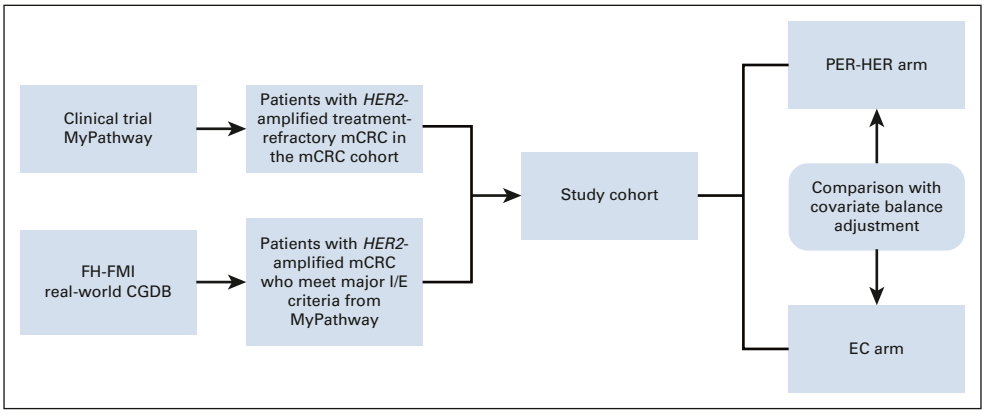

FIG 1. Study design. CGDB, clinico-genomic database; EC, external control; FH, Flatiron Health; FMI, Foundation Medicine Inc; HER2, human epidermal growth factor receptor 2; I/E, inclusion/exclusion; mCRC, metastatic colorectal cancer; PER-HER, pertuzumab plus trastuzumab.

Data were deidentified and subject to obligations to prevent reidentification and protect patient confidentiality. The deidentified data originated from approximately 280 US cancer clinics (≈800 sites of care, primarily community-based cancer centers). The CGDB includes patients from the FH database who underwent comprehensive genomic profiling (CGP) by FMI (Foundation Medicine, Cambridge, MA) and provides deidentified patient-level genomic data linked by deterministic matching, including specimen features (eg, tumor mutation burden and tumor purity), alteration-level details (eg, genomic position and reference and alternate alleles), and targeted therapeutic options reported to the clinician at the time of testing.[17] We used data collected between January 1, 2011, and December 31, 2019.

Institutional review board approval of the parent study protocol for data collection was obtained before study conduct (Registration No. IRB00000533) and included a waiver of informed consent. The conduct of this study was approved by the ethics committee in Japan (Registration No. 11001059) before initiation.

Patient Population

The PER-HER arm included patients with treatment-refractory *HER2*-Amp mCRC enrolled in the MyPathway study by the data cutoff of August 1, 2017. For the EC arm, patients with *HER2*-Amp mCRC were selected from the CGDB. Detailed inclusion and exclusion criteria for selecting patients with *HER2*-Amp mCRC in the CGDB are provided in the Data Supplement.

The EC arm comprised patients with *HER2*-Amp mCRC who met the major eligibility criteria of the MyPathway study at the initiation of therapy in the treatment-refractory setting. In brief, eligible patients in the EC arm were age 18 years or older, had mCRC with *HER2*-Amp status as assessed with CGP by FMI, were treatment-refractory (had received ≥ 2 lines of treatment [LOTs]), received standard first-line therapy including fluoropyrimidines and either irinotecan or oxaliplatin, and received prior treatment other than study drugs or HER2-targeted therapies. Other eligibility criteria of the MyPathway study were also applied depending on the availability of data (Data Supplement).

The index date for the PER-HER arm was defined as the date of initiation of PER-HER. The EC arm index date was defined as the date of initiation of treatment after the first FMI test providing confirmation of *HER2*-Amp status. Multiple index dates for patients who received multiple treatments in the refractory setting were included in the analysis if the index dates were eligible according to the prespecified criteria (Data Supplement).[18,19]

Variables

Baseline patient demographics and clinical characteristics were used as recorded before and closest to the index date. Variables included age, sex, race, Eastern Cooperative Oncology Group performance status (ECOG PS; within 30 days before and closest to the index date), year of index date, time from initial metastatic diagnosis to index date, tumor site, *HER2* status, number of previous metastatic treatment regimens, mutational status (*KRAS*, *NRAS*, *RAS/RAF*, and *PIK3CA*), microsatellite instability status, liver metastases, lung metastases, and previous exposure to antiepidermal growth factor receptor (anti-EGFR) therapy and antivascular endothelial growth factor therapy, irinotecan or oxaliplatin. The primary end point of interest was OS, defined as the time from index treatment initiation to death. The rationale for selection of the primary end point is included in the Data Supplement.

Statistical Analysis

Descriptive statistics summarized demographic and clinical characteristics, including medical and treatment history, for each index date. For the primary OS analysis, patients without recorded death events were censored at the last contact date for the PER-HER arm. For the EC arm, patients without a death record were censored at the last known confirmed activity date documented in the EHR or the latest specimen reported date, whichever was later.

Standardized mortality ratio weighting on the basis of propensity score was used to derive a pseudopopulation (postweighting population) in which key prognostic variables were expected to be balanced between arms. Stabilized weights were applied for each arm. Propensity score was estimated using logistic regression with treatment assignment as the dependent variable. Four models for estimating propensity score were prespecified in the protocol: (1) a full model using all key potential prognostic variables, (2) a full model excluding ECOG PS, (3) an intermediate model, and (4) a minimum model (Data Supplement). The propensity score with each model was estimated and assessed in terms of model stability in this order without accessing outcome data. The first model considered to be stable was used for the primary analysis. Further details regarding the rationale for selection of potential prognostic factors are included in the Data Supplement. Distribution of the propensity score was graphically depicted for pre- and postweighting populations. Truncation of weights at the 99th percentile over the first percentile was performed (weights of patients were capped at the 99th percentile over the first percentile). Standardized mean differences (SMDs) were computed to assess the balance of weighted covariates.

In the postweighting population, multivariate Cox proportional hazards (PH) models, which included the covariates defined for the minimum model for estimating propensity score, were used for estimation of the hazard ratio (HR) in the primary analysis. The Kaplan-Meier method was used to estimate OS distribution. Analysis with univariate Cox PH models, with only the treatment arm as a covariate, was also conducted. Bootstrapping was used for estimation of

95% CIs. The Kaplan-Meier method was also applied in the crude population (preweighting population) as a descriptive analysis. A series of prespecified subgroup and sensitivity analyses were conducted, including a risk set adjustment approach in which index dates before the first FMI test providing confirmation of *HER2*-Amp status were considered eligible for analysis on the condition that these index dates were included in the risk set only after the first FMI test.

Amendments to the statistical analysis plan were made before and after data availability; this report reflects the final implementation of all amendments as detailed in the Data Supplement. All analyses were performed using the R statistical package.

RESULTS

Analytic Cohort and Final Model Selection

A total of 57 patients from the MyPathway study were included in the PER-HER arm. One patient had a missing metastasis diagnosis date and could not be included in the primary analysis (time from initial metastatic diagnosis to index date was used as a covariate for the estimation of propensity score in all prespecified models). Sixty-four patients with *HER2*-Amp mCRC were selected from the CGDB. Attrition of patients with *HER2*-Amp mCRC in the CGDB is provided in the Data Supplement. Of a total of 64 patients with *HER2*-Amp mCRC in the CGDB, 18 patients (28%) met the corresponding MyPathway eligibility criteria, with a total of 27 treatment initiation index dates (Fig 2).

The primary propensity score model was determined to be the intermediate model with covariates for age, tumor site, number of previous metastatic treatment regimens, time from initial metastatic diagnosis to index date, *KRAS* status, and previous exposure to anti-EGFR therapy. Propensity score distributions of the pre- and postweighting populations with an intermediate model are provided in the Data Supplement.

Patients

The pre- and postweighting baseline characteristics of the PER-HER and EC arms are presented in Table 1. Most postweighting characteristics were balanced better than those in the preweighting population. Age, tumor site, and previous exposure to anti-EGFR therapy included in the primary propensity score model had smaller postweighting SMDs. However, SMDs for some variables, such as time from initial metastatic diagnosis to index date and number of previous metastatic treatment regimens, had larger postweighting SMDs.

In the preweighting population, the most common previous metastatic treatment regimen as first-line therapy was bevacizumab with fluorouracil, folinic acid, and oxaliplatin in both the PER-HER (29%) and EC (48%) arms (Data Supplement). Index treatment regimens and subsequent postindex treatments in the preweighting population are presented in the Data Supplement. The duration of follow-up was similar between arms, with a median follow-up of 7.3 months for the PER-HER arm and 6.1 months for the EC arm.

Overall Survival

A total of 25 deaths (45%) in the PER-HER arm and 13 deaths (48%) in the EC arm occurred during the study period. In the postweighting population, the median OS was 11.47 months (95% CI, 7.72 to 22.11) in the PER-HER arm and 9.72 (7.43 to 22.21) in the EC arm (Data Supplement). In the primary analysis, the estimated HR for OS from the multivariate Cox PH model in the postweighting population was 0.729 (95% CI, 0.184 to 3.900; Table 2). The estimated HR for OS from the univariate analysis (without accounting for covariates) was 1.04 (0.43 to 3.94) in the postweighting population. The prespecified subgroup analyses in the postweighting population generally yielded consistent findings as those observed in the primary analysis although most subgroup analyses were with small sample sizes (Data Supplement).

Sensitivity Analyses

Sensitivity analyses estimating HRs for OS from multivariate models in the postweighting populations yielded consistent results with the primary findings (Table 3). Results from the pre- and postweighting univariate models are provided in the Data Supplement. Estimated HRs were consistently < 1.0 in all sensitivity analyses using multivariate models in the postweighting population. The OS analysis using a risk set adjustment approach also yielded consistent results with the primary findings (Data Supplement).

DISCUSSION

This study was designed to provide comparative evidence to support the interpretation of findings from the MyPathway study. To generate comparative evidence for a rare biomarker-defined treatment-refractory mCRC, this study used patient-level data from the *HER2*-Amp mCRC cohort of the MyPathway study and a real-world EC arm derived from the FH/FMI CGDB. The study sample sizes were small, and hypothesis testing for superiority in OS between arms was not planned. Although the CI was wide, the HR point estimate for OS from the multivariate Cox PH model was favorable for the PER-HER arm in the postweighting population. The subgroup and sensitivity analyses supported the robustness of the primary findings.

To maximize the comparability of each arm, the eligibility criteria for the MyPathway trial were applied as closely as possible to the real-world data set as a first step and propensity score–based weighting was used to derive the pseudopopulation in which the distribution of key prognostic factors was expected to be balanced between arms. However, the results in the postweighting population indicated that there was still imbalance in some of the key

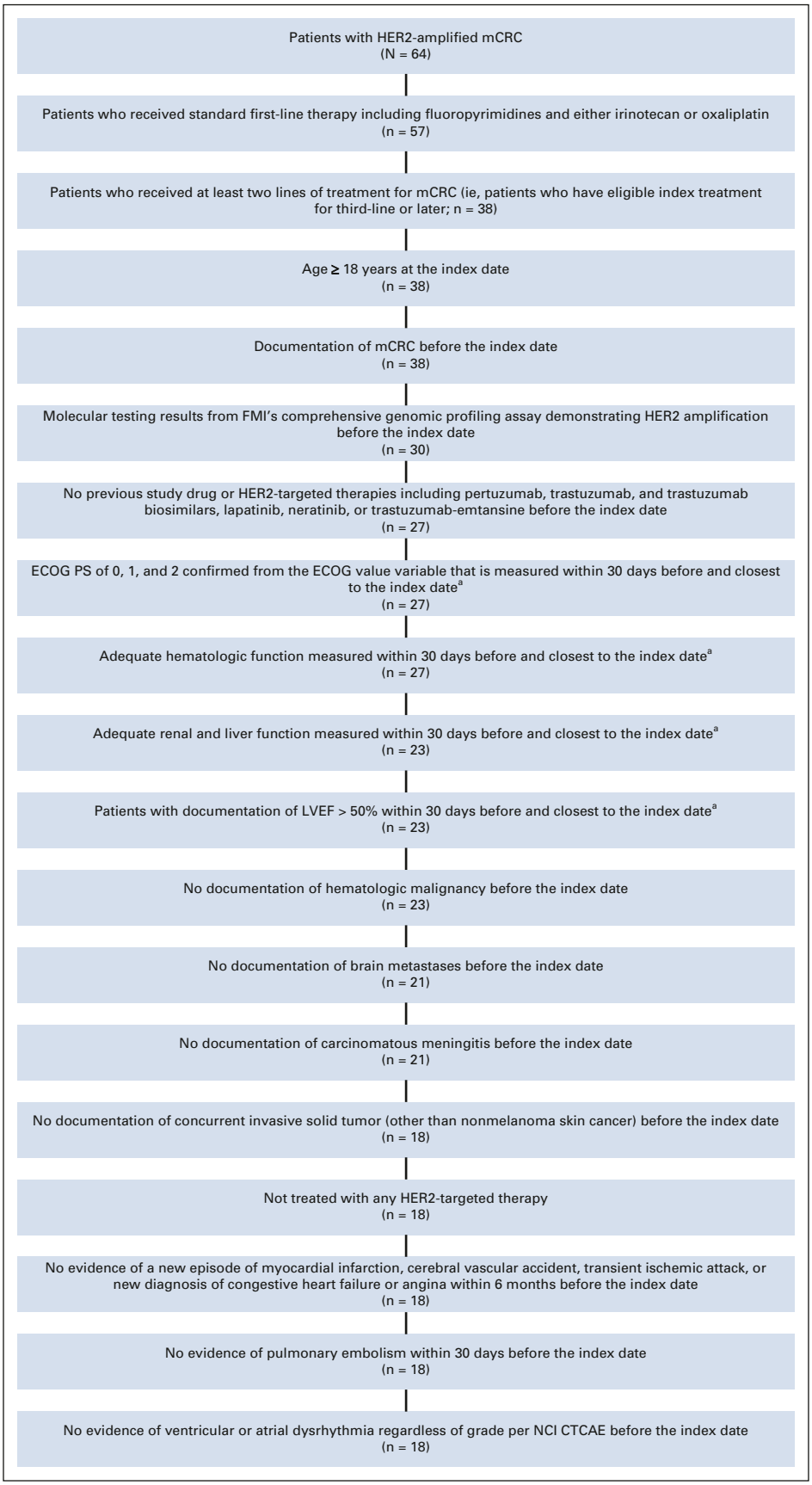

FIG 2. EC arm patient attrition. CTCAE, Common Terminology Criteria for Adverse Events; EC, external control; ECOG PS, Eastern Cooperative Oncology Group performance status; FMI, Foundation Medicine Inc; HER2, human epidermal growth factor receptor 2; LVEF, left ventricular ejection fraction; mCRC, metastatic colorectal cancer; NCI, National Cancer Institute.
[a]Patients with missing value are allowed to be included.

TABLE 1. Baseline Demographic and Clinical Characteristics of the Pre- and Postweighting Populations

Characteristic	Preweighting Population			Postweighting Population		
	EC arm (n = 27)[a] No. (%)	PER-HER arm (n = 56) No. (%)	SMD	EC arm (n = 22.85)[a] No. (%)	PER-HER arm (n = 56.00) No. (%)	SMD
Age, mean (SD), years	57.3 (10.0)	56.1 (13.0)	0.104	55.99 (11.10)	56.12 (12.96)	0.011
Sex						
Male	13.0 (48.1)	28.0 (50.0)	0.037	12.5 (54.7)	28.0 (50.0)	0.095
Female	14.0 (51.9)	28.0 (50.0)		10.3 (45.3)	28.0 (50.0)	
Race[b]						
White	13.0 (50.0)	45.0 (80.4)	0.689	9.1 (42.6)	45.0 (80.4)	0.870
Black or African American	≤ 5.0 (≤ 19.2)	3.0 (5.4)		2.8 (13.3)	3.0 (5.4)	
Asian	≤ 5.0 (≤ 19.2)	2.0 (3.6)		4.4 (20.9)	2.0 (3.6)	
Others	6.0 (23.1)	6.0 (10.7)		4.9 (23.2)	6.0 (10.7)	
ECOG PS						
0	8.0 (29.6)	20.0 (35.7)	1.244	4.8 (20.9)	20.0 (35.7)	1.258
1	7.0 (25.9)	35.0 (62.5)		7.3 (31.9)	35.0 (62.5)	
2	3.0 (11.1)	1.0 (1.8)		2.5 (11.0)	1.0 (1.8)	
Missing	9.0 (33.3)	0		8.3 (36.3)	0	
Year of index date						
2014	0	3.0 (5.4)	2.725	0	3.0 (5.4)	2.906
2015	2.0 (7.4)	19.0 (33.9)		1.2 (5.3)	19.0 (33.9)	
2016	2.0 (7.4)	25.0 (44.6)		2.3 (10.2)	25.0 (44.6)	
2017	2.0 (7.4)	9.0 (16.1)		0.9 (4.0)	9.0 (16.1)	
2018	5.0 (18.5)	0		3.7 (16.1)	0	
2019	16.0 (59.3)	0		14.7 (64.4)	0	
Time from initial metastatic diagnosis to index date, mean (SD), months	27.8 (11.5)	31.1 (23.5)	0.180	24.85 (11.62)	31.10 (23.49)	0.337
Tumor site						
Colon, right side	3.0 (11.1)	12.0 (21.4)	0.411	3.9 (17.3)	12.0 (21.4)	0.354
Colon, left side	12.0 (44.4)	22.0 (39.3)		8.0 (34.8)	22.0 (39.3)	
Colon, transverse	0	1.0 (1.8)		0	1.0 (1.8)	
Colon, unknown	0	1.0 (1.8)		0	1.0 (1.8)	
Rectum	12.0 (44.4)	20.0 (35.7)		10.9 (47.9)	20.0 (35.7)	
HER2 status (IHC)						
No overexpression	0	7.0 (12.5)	1.543	0	7.0 (12.5)	1.644
Overexpression	1.0 (3.7)	27.0 (48.2)		0.4 (1.9)	27.0 (48.2)	
Overexpression status unknown	26.0 (96.3)	22.0 (39.3)		22.4 (98.1)	22.0 (39.3)	
HER2 status (FISH CISH)						
Amplification	2.0 (7.4)	40.0 (71.4)	1.768	0.9 (4.0)	40.0 (71.4)	1.986
No amplification	2.0 (7.4)	3.0 (5.4)		1.5 (6.4)	3.0 (5.4)	
NA	23.0 (85.2)	13.0 (23.2)		20.5 (89.6)	13.0 (23.2)	
HER2 status (NGS)						
Amplification	27.0 (100.0)	41.0 (73.2)	0.855	22.9 (100.0)	41.0 (73.2)	0.855
No amplification	0	3.0 (5.4)		0	3.0 (5.4)	
NA	0	12.0 (21.4)		0	12.0 (21.4)	

(Continued on following page)

TABLE 1. Baseline Demographic and Clinical Characteristics of the Pre- and Postweighting Populations (Continued)

Characteristic	Preweighting Population			Postweighting Population		
	EC arm (n = 27)[a] No. (%)	PER-HER arm (n = 56) No. (%)	SMD	EC arm (n = 22.85)[a] No. (%)	PER-HER arm (n = 56.00) No. (%)	SMD
No. of previous metastatic treatment regimens						
< 4	19.0 (70.4)	32.0 (57.1)	0.278	17.2 (75.2)	32.0 (57.1)	0.389
≥ 4	8.0 (29.6)	24.0 (42.9)		5.7 (24.8)	24.0 (42.9)	
KRAS status						
Mutation	5.0 (18.5)	13.0 (23.2)	0.116	3.9 (17.2)	13.0 (23.2)	0.150
No clear evidence of mutation	22.0 (81.5)	43.0 (76.8)		18.9 (82.8)	43.0 (76.8)	
NRAS status						
Mutation	0	0	< 0.001	0	0	< 0.001
No clear evidence of mutation	27.0 (100.0)	56.0 (100.0)		22.9 (100.0)	56.0 (100.0)	
RAS RAF status						
Mutation	5.0 (18.5)	14.0 (25.0)	0.158	3.9 (17.2)	14.0 (25.0)	0.192
No clear evidence of mutation	22.0 (81.5)	42.0 (75.0)		18.9 (82.8)	42.0 (75.0)	
PIK3CA status						
Mutation	3.0 (11.1)	8.0 (14.3)	0.095	5.2 (22.8)	8.0 (14.3)	0.221
No clear evidence of mutation	24.0 (88.9)	48.0 (85.7)		17.6 (77.2)	48.0 (85.7)	
MSI status						
Stable	19.0 (70.4)	27.0 (48.2)	0.486	17.2 (75.1)	27.0 (48.2)	0.590
Low	0	1.0 (1.8)		0	1.0 (1.8)	
Unknown	8.0 (29.6)	28.0 (50.0)		5.7 (24.9)	28.0 (50.0)	
Previous exposure to anti-EGFR therapy						
None	6.0 (22.2)	24.0 (42.9)	0.492	10.3 (45.1)	24.0 (42.9)	0.149
Cetuximab only	11.0 (40.7)	17.0 (30.4)		7.7 (33.6)	17.0 (30.4)	
Panitumumab only	5.0 (18.5)	10.0 (17.9)		2.9 (12.7)	10.0 (17.9)	
Cetuximab and panitumumab	5.0 (18.5)	5.0 (8.9)		2.0 (8.6)	5.0 (8.9)	
Previous exposure to irinotecan	25.0 (92.6)	50.0 (89.3)	0.115	21.2 (92.6)	50.0 (89.3)	0.114
Previous exposure to oxaliplatin	20.0 (74.1)	45.0 (80.4)	0.150	16.8 (73.4)	45.0 (80.4)	0.166
Previous exposure to anti-VEGF therapy[c]	27.0 (100.0)	41.0 (73.2)	0.855	22.9 (100.0)	41.0 (73.2)	0.855
Liver metastases	24.0 (88.9)	42.0 (75.0)	0.367	20.2 (88.5)	42.0 (75.0)	0.356
Lung metastases	19.0 (70.4)	42.0 (75.0)	0.104	13.9 (61.0)	42.0 (75.0)	0.303

Abbreviations: CISH, chromogenic in situ hybridization; EC, external control; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; MSI, microsatellite instability; NA, not available; NGS, next-generation sequencing; PER-HER, pertuzumab plus trastuzumab; SD, standard deviation; SMD, standardized mean difference; VEGF, vascular endothelial growth factor.

[a]No. of eligible index dates from 18 patients.

[b]There was one patient (one index date) with missing value in the EC arm.

[c]Anti-VEGF therapy includes bevacizumab, aflibercept, ramucirumab, and regorafenib. There was no previous exposure to other anti-VEGF therapies such as pazopanib, sorafenib, and sunitinib in both arms.

prognostic factors. This was considered because of a small sample inference and suggested a need for further adjustment of these variables at the analysis stage. In the primary analysis, the predetermined multivariate Cox PH model that includes these key prognostic factors was used to adjust the imbalance in the estimation of HR.

The use of the FH/FMI CGDB to derive EC arms in our study was supported by a recent publication that demonstrated the feasibility of deriving an EC arm in patients with refractory mCRC using the FH/FMI CGDB.[20] Median OS estimates were similar between the EC arm and the randomized control arm from the IMblaze370

TABLE 2. Estimated HRs for Overall Survival in the Pre- and Postweighting Populations

HR (95% CI)[a]	Preweighting Population	Postweighting Population
Univariate model	0.897 (0.456 to 1.765)	1.041 (0.425 to 3.943)
Multivariate model (primary analysis)	—	0.729 (0.184 to 3.900)

NOTE. Tumor site, number of previous metastatic treatment regimens, time from initial metastatic diagnosis to index date, *KRAS* status, and previous exposure to antiepidermal growth factor receptor therapy were used for covariate adjustments.

Abbreviation: HR, hazard ratio.

[a]Bootstrapping was used for estimation of 95% CI in the postweighting population.

trial of atezolizumab with or without cobimetinib versus regorafenib as later-line treatment for adults with unresectable locally advanced or mCRC (ClinicalTrials.gov identifier: NCT02788279). That study was one of the first proof-of-concept applications of an EC arm in mCRC, as is our study, following work with EHR-derived data sets for non–small-cell lung cancer.[21]

Our study should be interpreted with certain contextual factors and limitations. Although ECOG PS is one of the key prognostic factors, it is often not available in real-world data sets as it is not routinely collected in clinical practice. Therefore, this study allowed the inclusion of the patients with missing ECOG PS, which accounted for 33% of patients in the EC arm. In this sense, the potential imbalance in ECOG PS distribution might have affected the OS comparison. There were differences in the selection of *HER2*-positive patients between the PER-HER and EC arms.[14] The sensitivity analysis using patients confirmed to have *HER2*-Amp by the next-generation sequencing test in the PER-HER arm (42 of 57 patients) was consistent with the primary analysis, suggesting that biomarker testing methods might not have had a major impact on the interpretation of our findings. There was a difference in the distribution of the year of index date between the two arms. Because the EC arm was from a later calendar time, these patients would have been more likely to have taken advantage of available treatment advances for CRC. In fact, the postindex subsequent treatments in the EC arm differed from those in the PER-HER arm in that common subsequent therapy included not only chemotherapies but also trastuzumab and pembrolizumab, which might have provided some OS benefits in the EC arm.

The definition of LOTs in each arm might have not been fully aligned. In MyPathway, LOTs were not systematically defined and were left up to the investigator's discretion. Thus, LOTs in the PER-HER arm were redefined to exclude neoadjuvant and adjuvant therapies using metastatic diagnosis date for each patient and to make it more comparable with the EC arm. However, there was no guarantee that the LOTs defined in MyPathway would be the same as those from FH. In MyPathway, patients who received standard first-line therapy for mCRC and in whom a trial of targeted therapy is considered as the best available treatment option are enrolled. Because the determination of whether the study drug is the best available option was left up to the investigator and was impossible to define in this study, eligibility criteria for the EC arm were decided on the basis of the treatment algorithm for mCRC to only include patients who had received ≥ 2 previous metastatic LOTs. As a result of our analysis, 50 of 56 patients in the

TABLE 3. Sensitivity Analysis Results: Multivariable Models in the Postweighting Population

Sensitivity Analysis	Details[a]	Multivariable Model HR (bootstrap 95% CI)
Analysis without any truncation	No truncation was implemented to investigate the impact of truncation and/or patients with a relatively extreme propensity score. The intermediate propensity score model was used	0.729 (0.184 to 3.912)
Analysis of patients with *HER2*-Amp status confirmed by the NGS test in the PER-HER arm	Restricted analysis to the patients with the NGS test, which provides *HER2*-Amp in the PER-HER arm (42 of 57 patients in MyPathway). The intermediate propensity score model was used	0.623 (0.083 to 4.152)
Use the earliest treatment date as the index date	The index date for each patient was defined as the first eligible treatment for treatment-refractory mCRC after the first FMI test that provided confirmation of *HER2*-Amp status. The intermediate propensity score model was used	0.817 (0.143 to 6.689)
Use the latest treatment date as the index date	The index date for each patient was defined as the latest eligible treatment for treatment-refractory mCRC after the first FMI test that provided confirmation of *HER2*-Amp status. The intermediate propensity score model was used	0.456 (0.092 to 3.145)
Analysis excluding *KRAS* status from the propensity score model[b]	The intermediate propensity score model excluding *KRAS* status was used	0.607 (0.206 to 2.835)

Abbreviations: Amp, amplification; FMI, Foundation Medicine Inc; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; mCRC, metastatic colorectal cancer; NGS, next-generation sequencing; PER-HER, pertuzumab plus trastuzumab; PH, proportional hazards.

[a]For the multivariate PH model, covariates defined for the minimum propensity score model were used for adjustment.

[b]For the multivariate PH model, covariates defined for the minimum propensity score model excluding *KRAS* status were used.

PER-HER arm received two metastatic LOTs or more before enrolling in MyPathway and a greater number of patients received ≥ 4 prior LOTs in the PER-HER arm compared with the EC arm. However, as the PER-HER arm included few patients treated with second-line therapy, there is still a possibility that the study was potentially biased toward overestimation of the treatment effect of pertuzumab and trastuzumab.

Potential prognostic factors, including unmeasured factors that were not included in the propensity score model or outcome model as covariates, might not have been well balanced between the arms. Limitations applicable to all observational studies are applicable to this study as well.

The requirement of FMI's CGP assay might have introduced a selection bias for patients with access to and/or under the care of physicians with distinct practice patterns, which may not be representative of all patients with mCRC in the United States. Although the data from FH/FMI CGDB were obtained under strict quality control methods, inherent limitations of such data exist, such as the potential for missing information because of documentation practices or partial receipt of care outside of the FH network.

In summary, although the sample size of this study was limited, the findings of this study suggest that the combination of pertuzumab and trastuzumab could have a potential benefit in OS for patients with treatment-refractory *HER2*-Amp mCRC. Additional research is needed to refine and advance these findings and to provide patients with treatment-refractory *HER2*-Amp mCRC with more effective therapeutic options.

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DATA SHARING STATEMENT

The data that support the findings of this study have been originated by Flatiron Health Inc and Foundation Medicine Inc. These deidentified data may be made available upon request and are subject to a license agreement with Flatiron Health and Foundation Medicine; interested researchers should contact cgdb-fmi@flatiron.com and dataaccess@flatiron.com to determine licensing terms.

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