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FMB: Study design, data collection and interpretation, manuscript writing and revision
HH: Study design, data collection and interpretation, manuscript writing and revision
KPSR: Data collection and interpretation, manuscript writing and revision
RRM: Data collection and interpretation, manuscript writing and revision
MF: Data collection and interpretation, manuscript writing and revision
AV: Data collection and interpretation, manuscript writing and revision
CS: Study design, data collection and interpretation, manuscript writing and revision
RK: Study design, data collection and interpretation, manuscript writing and revision
HB: Study design, data collection and interpretation, manuscript writing and revision
CS: Study design, data collection and interpretation, manuscript writing and revision
RB: Study design, data collection and interpretation, manuscript writing and revision
DRS: Study design, data collection and interpretation, manuscript writing and revision
MSB: Study design, data collection and interpretation, manuscript writing and revision
SB: Statistical analysis, data collection and interpretation, manuscript writing and revision
AS: Study design, data collection, manuscript writing and revision
KS: Study design, data collection and interpretation, manuscript writing and revision
VC: Study design, data collection and interpretation, manuscript writing and revision
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DECLARATION OF INTERESTS

FMB has served as a consultant for Dialecta and Sumitomo Dainipon; served on advisory committees for Inflection Biosciences, Pieris, and DarwinHealth; and received research funding from Aileron Therapeutics, AstraZeneca, Bayer, Calithera Biosciences, CytomX Therapeutics, Debiopharm Group, Genentech, Novartis, PUMA Biotechnology, Zymeworks, Pfizer, Jounce, eFFECTOR, Curis, Abbvie, and Taiho Pharmaceutical.

HH is employed by and owns stock in Roche/Genentech. He has served as a consultant for Acceleron Pharma, Bristol-Myers Squibb, Roche/Genentech, GlaxoSmithKline, Incyte, Lilly, Novartis, OncoMed, and TRACON Pharma; received honoraria from Roche/Genentech and Lilly/ImClone; and received travel, accommodation, and expense reimbursement from Roche/Genentech and TRACON Pharmaceuticals. His former institution (Duke University Medical Center) received research funding from Bristol-Myers Squibb, Roche/Genentech, GlaxoSmithKline, Lilly, Macrogenics, NCI, Novartis, Regeneron, and TRACON Pharma.

RRM has served on the advisory boards of Ipsen and Bristol-Myers Squibb.

MF has served on advisory boards for Amgen, Array, Genentech, Merck, Taiho, Seattle Genetics, and Sirtex; has received speaker fees from Amgen, Genentech, Sirtex, and Taiho; and has received research support (paid to his institution) from Amgen, AstraZeneca, and Novartis.

AV has received personal fees from AstraZeneca, Bristol-Myers Squibb, Roche/Genentech; has received grant funding from Amgen; and has received non-financial support from Caris Life Sciences.

C. Swanton has received honoraria or consultant fees from Roche/Genentech, Ventana, Celgene, Pfizer, Novartis, and Bristol-Myers Squibb; owns stock in GRAIL, Epic Biosciences, Apogen Biotech, and Achilles Therapeutics (co-founder); and has received grants from Pfizer and AstraZeneca.

RK has received grants from Incyte, Roche/Genentech, Merck Serono, Pfizer, Sequenom, Foundation Medicine, Guardant Health, and Konica Minolta; consulting fees from LOXO, X-Biotech, Actuate Therapeutics, Roche/Genentech, and NeoMed; and has an ownership interest in CureMatch.

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C. Sweeney has served as a consultant for Astellas Pharma, AstraZeneca, Bayer, Tolmar, Genentech/Roche, Janssen Biotech, and Sanofi; owns stock in Leuchemix; and has patents with Leuchemix and Exelixis. His institution has received research funding from Astellas Pharma, Exelixis, and Janssen Biotech.

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DRS has served as a consultant for and received travel, accommodations, and expense reimbursement from AstraZeneca, Biodesix, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Clovis Oncology, Roche/Genentech, Lilly, Novartis, and Pfizer; served on speakers' bureaus for Novartis; and owned stock in Foundation Medicine and Illumina. His institution has received research funding from Amgen, Astex Pharmaceuticals, AstraZeneca, BIND Biosciences, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Clovis Oncology, CytRx Corporation, Daiichi Sankyo, EMD Serono, Genentech/Roche, ImClone Systems, Immunogen, Lilly, Novartis,

Pertuzumab and trastuzumab for HER2-amplified metastatic colorectal cancer: an updated report from MyPathway, a multicentre, open-label, phase 2a multiple basket study

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Abstract

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American Society of Clinical Oncology - Gastrointestinal Cancers Symposium 2016, San Francisco, CA, USA, January 21–23, 2016. Hurwitz H, Hainsworth J, Swanton C, et al. Targeted therapy for gastrointestinal (GI) tumors based on molecular profiles: early results from MyPathway, an open-label phase IIa basket study in patients with advanced solid tumors. Abstract 653.

American Society of Clinical Oncology 52nd Annual Meeting, Chicago, IL, USA, June 3–7, 2016. Hainsworth J, Meric-Bernstam F, Swanton C, et al. Targeted therapy for advanced solid tumors based on molecular profiles: early results from MyPathway, an open-label, phase IIa multiple basket study. Abstract LBA11511.

American Society of Clinical Oncology - Gastrointestinal Cancers Symposium 2017, San Francisco, CA, USA, January 19–21, 2017. Hurwitz H, Pratap Singh Raghav K, Burris H, et al. Pertuzumab + trastuzumab for HER2-amplified/overexpressed metastatic colorectal cancer (mCRC): interim data from MyPathway. Abstract 676.

Background—Therapies targeting HER2 have improved clinical outcomes in HER2-positive breast/gastric cancers, and are emerging as potential treatments for HER2-positive metastatic colorectal cancer (mCRC). MyPathway evaluates the efficacy of targeted therapies in non-indicated tumour types with potentially predictive molecular alterations. We present results for a HER2-targeted treatment regimen, pertuzumab + trastuzumab, in patients with HER2-amplified mCRC.

Methods—MyPathway is an ongoing, phase 2a multiple basket study. Patients in this subset analysis were ≥18 years and had treatment-refractory HER2-amplified mCRC with measurable or evaluable disease and an Eastern Cooperative Oncology Group performance status score ≤2. Patients received pertuzumab (840-mg IV loading dose, then 420 mg every 3 weeks [q3w]) and trastuzumab (8-mg/kg IV loading dose, then 6 mg/kg q3w). The primary endpoint was objective response rate (ORR) based on investigator-reported tumour responses in the efficacy analysis population (patients treated and evaluated for efficacy, or who discontinue treatment for any reason prior to the first post-baseline tumour assessment). This ongoing trial is registered with Clinicaltrials.gov, number .

Findings—Among 57 evaluable patients as of August 1, 2017, one patient had a complete objective response and 17 had partial responses, for an ORR of 32% (95% CI 20–45). Grade ≥3 treatment-emergent adverse events were observed in 37% (21/57) of patients, most commonly hypokalaemia and abdominal pain (each n=3). Serious treatment-emergent adverse events were reported in 18% (10/57) of patients. There were no treatment-related deaths.

Interpretation—Dual HER2-targeted therapy with pertuzumab + trastuzumab is well-tolerated and may represent a therapeutic opportunity for patients with heavily pretreated, HER2-amplified mCRC.

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INTRODUCTION

Colorectal tumours are highly heterogeneous and frequently harbour mutations that render them refractory to common treatments.[1] Most prominently, agents targeting epidermal growth factor receptor (EGFR), such as cetuximab and panitumumab, are clinically ineffective in *RAS*-mutated tumours, which comprise 50% of metastatic colorectal cancer (mCRC) cases.[1] A number of additional molecular alterations have recently been implicated in resistance to anti-EGFR therapies, including activating mutations in *BRAF* and *PIK3CA*, and amplification of human epidermal growth factor receptor 2 (HER2).[1,2]

HER2 amplification and/or overexpression is found in 2–6% of patients with stage 3/4 CRC.[3–5] The low prevalence of HER2 alterations has limited research into effective treatment options, resulting in a significant unmet medical need in this patient population. HER2 itself is a well-studied oncogenic target in other cancer types, and recent studies have implicated it as a potential target of interest for HER2-positive CRC.[6–9] In the preclinical setting, HER2-targeted monotherapy with the anti-HER2 antibodies trastuzumab or pertuzumab, or the small molecule lapatinib, had limited activity against HER2-amplified CRC tumour grafts or xenografts.[6,8] However, efficacy increased notably with combination HER2-targeted regimens, including pertuzumab + lapatinib and trastuzumab + lapatinib.[6,8] On the basis of

this work, the phase 2 HERACLES trial assessed trastuzumab + lapatinib treatment in patients with HER2-positive, *KRAS* exon 2 wild-type mCRC, with a promising 30% (8/27, 95% confidence interval [CI] 14–50) response rate.[9]

Trastuzumab-based treatment regimens are approved for breast, gastric, and gastroesophageal junction adenocarcinoma[10], with promising activity observed in additional cancer types.[11–13] In particular, the dual HER2-targeted combination of pertuzumab + trastuzumab with chemotherapy comprises a first-line standard of care for patients with HER2-positive metastatic breast cancer.[14] Pertuzumab and trastuzumab interact with distinct HER2 domains and, in combination, produce additive inhibition of breast tumours.[15,16] However, no studies thus far have assessed the efficacy of pertuzumab + trastuzumab in the treatment of HER2-positive mCRC, nor the impact of co-occurring alterations, such as *KRAS* mutations, on HER2-targeted treatment in mCRC.

MyPathway () is an ongoing, phase 2a, multiple basket study designed to evaluate the activity of established targeted therapies for non-approved indications based on tumour molecular profile. Patients have advanced solid tumours harbouring genetic or molecular alterations potentially predictive of a response from treatment with pertuzumab + trastuzumab, vemurafenib ± cobimetinib, vismodegib, erlotinib, alectinib, or atezolizumab. Here, we present the results for efficacy and biomarker analyses in patients with HER2-amplified mCRC treated with pertuzumab + trastuzumab.

METHODS

Study design and participants

MyPathway is a multicentre, non-randomized, open-label, multiple basket, phase 2a trial of patients with advanced solid tumours harbouring potentially predictive molecular alterations (appendix p 5). Patients in this analysis were enrolled from 25 sites (appendix p 1) and had treatment-refractory mCRC with HER2 amplification, as assessed by a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory test and reviewed by a study medical monitor for eligibility; measurable or evaluable lesions[17]; an Eastern Cooperative Oncology Group (ECOG) performance status score ≤2; adequate organ function based on laboratory assessment of absolute neutrophil count, platelet count, haemoglobin, serum creatinine, aspartate aminotransferase (AST) and alanine aminotransferase (ALT), total bilirubin, and alkaline phosphatase; a life expectancy ≥12 weeks; and were age ≥18 years. Patients were required to have previously received standard first-line therapy for mCRC, and, in the judgement of the treating physician, had no further therapies suitable to convey clinical benefit. Patients with previous HER2-targeted treatment or contraindications to study therapy, hematologic malignancies or uncontrolled concurrent malignancy, concurrent administration of any other anti-cancer therapy, active or untreated brain metastases, history of carcinomatous meningitis, select cardiovascular events within 6 months prior to study entry, pulmonary embolism within 30 days prior to study entry, history or presence of clinically significant ventricular or atrial dysrhythmia >grade 2, or any other severe acute or chronic medical or psychiatric condition or laboratory abnormality were excluded. Additional inclusion and exclusion criteria are available in the online protocol.

MyPathway is being conducted in accordance with International Conference on Harmonisation Good Clinical Practice guidelines and the Declaration of Helsinki. The protocol was approved by the institutional review board/ethics committee at each trial centre. All patients provided written informed consent prior to screening.

Procedures

Pertuzumab (840-mg intravenous [IV] loading dose, followed by 420 mg given by IV every 3 weeks) and trastuzumab (8-mg/kg IV loading dose, followed by 6 mg/kg given by IV every 3 weeks) were administered in accordance with the United States Package Inserts[10,18] until disease progression, unacceptable toxicity, or other discontinuation criteria were met. Toxicities were evaluated based on the Common Terminology Criteria for Adverse Events (CTCAE) version 4. In the event of a grade 3–4 adverse event (AE) associated with pertuzumab or trastuzumab, further dosing was held until the AE resolved to grade ≤1. Upon resolution, dosing resumed at the full dose. If the grade 3–4 AE recurred, the associated treatment was discontinued. Should an AE require discontinuation of pertuzumab or trastuzumab, patients benefiting from therapy were permitted to continue treatment with trastuzumab or pertuzumab, respectively, at the discretion of their treating physician.

Tumour burden was evaluated by the investigator per RECIST v1·1[17] at baseline and every 6 weeks (every two treatment cycles) for the first 24 weeks, and then every 12 weeks (every four treatment cycles) thereafter, using computerized tomography scans. As MyPathway was designed as a signal-seeking study, per the study protocol, 4 week confirmatory tumour assessments were not required.

Safety was evaluated on day 1 of each treatment cycle and at the end of treatment, with significant AEs (defined as serious AEs, AEs leading to treatment modification [e.g., dose reduction, dose delay, treatment discontinuation], or protocol-defined AEs of special interest), per the CTCAE version 4.0, were captured in the electronic Case Report Form. Additionally, patients were tested for left ventricular ejection fraction (baseline, cycle 5 day 1, and cycle 9 day 1) and received laboratory tests for complete blood count (baseline; day 1 of cycles 1, 2, 3, 7, and every 3 cycles thereafter; and end of treatment), plasma biomarkers (day 1 cycle 1, day 1 cycle 3, and end of treatment), comprehensive metabolic profile (baseline; day 1 of cycles 1, 2, 3, 7, and every 3 cycles thereafter; and end of treatment), and pregnancy (baseline, day 1 cycle 4, and every 3 cycles thereafter). Additional details are presented in the online protocol.

Prior to study enrolment, archival or fresh tissue samples were tested locally for HER2-positivity by fluorescence/chromogenic in situ hybridization (FISH/CISH; HER2 amplification based on HER2/CEP17 ratio >2·0 or HER2 copy number >6·0), next-generation sequencing (NGS; HER2 amplification based on copy number gain), and/or immunohistochemistry (IHC; HER2 overexpression based on IHC 3+ staining). Patients could receive any combination of tests and any relevant NGS panel, as determined by the investigator, using routine procedures in CLIA-validated laboratories. FoundationOne NGS (Foundation Medicine, Cambridge, Massachusetts, USA)[19] was performed in patients with available archival tissue without prior FoundationOne results. A bright-field, single slide–

based HER2 gene-protein assay (GPA) for CISH/IHC (Ventana Medical Systems, Tucson, Arizona, USA)[20] was conducted in patients with archival tissue, if available.

HER2 status, co-occurring molecular alterations (eg, *KRAS* mutations), and microsatellite instability (MSI) status were captured from local genomic testing, as reported at enrolment. If archival tissue was available, local testing data were supplemented with centrally-derived FoundationOne NGS and Ventana GPA results, as described above. Patients with *KRAS* wild-type mCRC were defined as those with no mutation identified after *KRAS* screening.

Local HER2 testing platforms, NGS panels, and additional molecular assays (eg, *KRAS* testing) were extracted from patient records and captured in the study database.

Outcomes

The primary endpoint was objective response rate (ORR) based on investigator-reported tumour responses, and was determined based on the best overall response up to the data cutoff date for each patient. ORR was defined as the percentage of patients with a complete response (CR) or partial response (PR) at any time. Secondary endpoints included clinical benefit rate (CBR; defined as the percentage of patients with an objective response or stable disease [SD] for >4 months), duration of response (DOR; time from first response to progression/death or last tumour assessment in patients with complete or partial response [CR or PR]), progression-free survival (PFS; time from first treatment to progressive disease/death or last tumour assessment), overall survival (OS; time from first treatment to death or date last known to be alive), and safety. Exploratory analyses included correlation of tumour biomarkers with response.

Statistical analysis

ORR was evaluated in the efficacy analysis population, defined as patients treated and evaluated for efficacy, or who discontinued treatment for any reason prior to the first post-baseline tumour assessment. The Clopper-Pearson estimation method was used to calculate 95% CI for ORR. Median PFS, OS, and DOR and their 95% CIs were estimated via Kaplan–Meier analysis in the efficacy analysis population. ORR, DOR, PFS, and OS were also determined in the biomarker-evaluable population, defined as treated patients with valid biomarker data of interest. Statistical analyses were completed using SAS version 9.4 (SAS Institute, Cary, North Carolina, USA) or R version 3.4.4 (R Foundation, Vienna, Austria).

Simon’s optimal two-stage design was used to evaluate the futility or efficacy of treatment. At least 2/13 tumour responses in stage one were required to proceed to stage two, where at least 6/34 responses were required to demonstrate efficacy. The design had approximately 80% power to detect a null hypothesis of 10% ORR versus an alternative hypothesis of 25% ORR with a 10% one-sided type I error rate. Upon adequate demonstration of efficacy, accrual of up to 75 patients was permitted.

This study is registered with ClinicalTrials.gov, .

Role of funding source

MyPathway was designed by the Sarah Cannon Research Institute and F. Hoffmann-La Roche/Genentech in collaboration with the study Steering Committee. F. Hoffmann-La Roche/Genentech funded the study and was involved in the study design; data collection, analysis, and interpretation; and writing of this report. The first authors prepared the initial manuscript draft, with support from a sponsor-funded medical writer. Decisions regarding authorship and author order were made by the Steering Committee. All authors had full access to all study data, were involved in data analysis/interpretation, contributed to subsequent manuscript drafts, made the decision to submit this manuscript for publication, and vouch for the accuracy and completeness of the report. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

RESULTS

An interim analysis of patients with HER2-amplified mCRC in MyPathway indicated PRs in 3/13 patients, passing Simon stage one criteria for cohort expansion.[21] The current analysis included 57 patients with HER2-amplified mCRC who initiated treatment with pertuzumab + trastuzumab between October 20, 2014 and June 22, 2017 (figure 1). All patients enrolled in this cohort were deemed eligible and evaluable for efficacy.

At the August 1, 2017 data cutoff, 12% of patients (7/57) remained on treatment; 32% (18/57) had discontinued treatment, but remained in follow-up; and 56% (32/57) had discontinued the study (figure 1). The most common reason for treatment discontinuation was disease progression (96% [48/50]). Median follow-up from treatment initiation was 7·3 (interquartile range [IQR], 3·9–11·4) months.

Most patients were heavily pretreated, with a median of four (IQR, 2–5) prior treatment regimens, and most had *KRAS* wild-type disease (table 1). Patients with rectal cancer comprised 35% (20/57) of the study population. Of patients with colon cancer (65% [37/57]), 62% (23/37) had left-sided colon primary tumours, 32% (12/37) had right-sided tumours, 3% (1/37) had a transverse tumour, and 3% (1/37) had a colon tumour with unknown location.

All patients in these analyses were determined to have HER2-amplified mCRC by local NGS or FISH/CISH testing (appendix p 6). In patients with HER2 amplification data by both NGS and FISH/CISH, concordance for amplification was 81% (26/32) (appendix p 2). Among 35 patients tested by IHC, HER2 overexpression was observed in 27 patients (77%) and was not observed in eight patients (23%) (table 1). Three patients had HER2 mutations (S310F, G776C, and T862A plus A2584G) out of 47 patients tested (appendix p 3).

The HER2-amplified mCRC cohort met its primary efficacy endpoint when 13/34 patients in the efficacy analysis population experienced PR, passing Simon stage two criteria.[22] Median treatment duration was 2·1 (IQR, 0·7–7·2) months for the 57 patients included in the current, updated analysis. In these 57 patients, pertuzumab + trastuzumab conferred an objective response in 18 patients, including one CR, for an ORR of 32% (95% CI 20–45) and CBR of 44% (n=25, 95% CI 31–58). In 17 of the 18 responders, the initial response assessment was

confirmed in the subsequent reevaluation. The 18th responder did not receive a reassessment for response confirmation prior to the database cut-off date. The best percent change in target lesion size by patient is shown in figure 2A. Median DOR was 5·9 (95% CI 2·8–11.1) months in patients with an objective response; four patients had a response lasting >12 months (figure 2B). By data cutoff, 50 of 57 patients (88%) had progressed and 25 (44%) had died. Estimated median PFS was 2·9 (95% CI 1·4–5·3) months and estimated median OS was 11·5 (95% CI 7·7–not estimable [NE]) months (figure 3). Of three patients with HER2-mutated tumours, one experienced a partial response and one had SD. None of eight patients with HER2 amplification without overexpression experienced a response (SD, n=3; PD, n=5).

To determine common oncogenic mutations co-occurring with HER2-amplification, data were obtained from local genetic testing as reported at enrolment (n=55, including n=53 NGS, n=1 real-time polymerase chain reaction [RT-PCR], and n=1 NGS plus RT-PCR), or from central NGS testing if locally-derived data for a specific gene were not available (n=9). Mutations occurring in ≥10% of patients tested for each gene included *TP53*, *APC*, *KRAS* (most commonly G12D or G12V on exon 2), *PIK3CA* (most commonly E545K), and *SMAD4* (appendix pp. 3 and 7). One patient had a *BRAF* mutation (V600E). No mutations were observed in *AKT1*, *ALK*, *BRCA1*, *FGFR1*, *MET*, *NRAS*, *PTCH1*, or *SMO*. Additionally, of nine patients with *HRAS* testing data, none had *HRAS* mutations. All patients with known MSI status (n=28) had low/stable MSI.

Mutations in several genes have been associated with resistance to EGFR-targeted therapy, including *KRAS*, *BRAF*, and *PIK3CA*.[1] Therefore, we conducted an exploratory analysis to determine the association of genomic co-alterations with ORR, PFS and OS. In patients with *KRAS* wild-type mCRC (43/56 tested patients, with 23 patients tested prior to and seven tested following anti-EGFR treatment), ORR was 40% (17/43, 95% CI 25–56), CBR was 56% (24/43, 95% CI 40–71), median DOR was 6·1 (95% CI 2·9–11·1) months, median PFS was 5·3 (95% CI 2·7–6·1) months, and median OS was 14·0 (95% CI 8·0–NE) months (figure 2, table 2). In comparison, ORR in the *KRAS*-mutated group was 8% (1/13, 95% CI 0·2–36), with no additional patients with clinical benefit. DOR in the patient with a response was 2·7 months. In this exploratory analysis, median PFS (1·4 [95% CI 1·2–2·8] months) and OS (8·5 [95% CI 3·9–NE] months) were notably shorter in patients with *KRAS*-mutated tumours versus those with *KRAS* wild-type disease (figure 4, appendix p8).

Clinical outcomes (ORR, CBR, median PFS and median OS) by subgroups based on *KRAS* status in patients with and without anti-EGFR therapy, *PIK3CA* status, MSI status, tumour location, and number of prior regimens are shown in table 2. Among patients with *KRAS* wild type mCRC, those with prior anti-EGFR therapy had numerically lower ORR, CBR, median PFS, and median OS compared with patients without prior EGFR therapy. In patients with *KRAS* wild-type status determined prior to anti-EGFR treatment, ORR from pertuzumab + trastuzumab treatment was 30% (7/23), versus 57% (4/7) in the small subgroup of patients with *KRAS* wild-type status determined following anti-EGFR therapy. Of note, clinical outcomes for patients with *PIK3CA*-mutated tumours are based on an exploratory analysis given the small size of this subgroup (n=8). In patients with no *KRAS,*

PIK3CA, or *BRAF* mutations (33/48 tested patients), ORR was 48% (16/33) and CBR was 67% (22/33). The single patient with a *BRAF* mutation had PD as the best response.

Patients with right-sided colon tumours experienced poorer ORR and CBR and had shorter median PFS and OS than patients with left-sided or rectal tumours (table 2). Of note, *KRAS* mutations were more common in right-sided (50% [6/12]) than left-sided tumours (4% [1/23]).

To determine the association of HER2 gene copy number with response, efficacy was assessed by NGS-derived copy number and *KRAS* status. In patients with wild-type *KRAS*, median HER2 copy number was 84 (IQR, 16–133). Those with lower-than-median copy number had a numerically lower ORR and CBR compared with those with higher-than-or-equal-to-median copy number (appendix pp 4 and 9). Amongst patients with *KRAS* mutations, median copy number was 67 (IQR, 21–90); the single responder in this group had 77 copies of HER2.

As HER2 testing methodologies used for enrolment were not standardized in this study, efficacy was also assessed in a patient subgroup with HER2 positivity determined via a single testing method. We observed an ORR and CBR of 43% (both 13/30) in patients with *KRAS* wild-type disease and HER2 amplification determined by FoundationOne NGS, the most common methodology used locally or centrally in this analysis, versus an ORR of 40% (17/43) and CBR of 56% (24/43) in the *KRAS* wild-type population unselected for HER2 testing methodology.

Treatment-emergent adverse events (TEAEs), serious TEAEs, and grade 3–4 TEAEs were reported in 93% (53/57), 18% (10/57), and 37% (21/57) of patients, respectively. Three of 57 patients (5%) had a dose reduction due to adverse events and one patient (2%) withdrew from treatment due to an adverse event (increase in bilirubin level). The most common all-grade TEAEs were diarrhoea (33% [19/57]), fatigue (32% [18/57]), and nausea (30% [17/57]) (table 3). The most common grade 3–4 TEAEs were hypokalaemia and abdominal pain (each 5% [3/57]). Two patients experienced serious drug-related TEAEs, one with an infusion related reaction and one with chills. No patients had a fatal TEAE. Twenty five patients died during the study; death was due to disease progression in 22 patients and the cause was unknown in 3 patients.

DISCUSSION

To our knowledge, MyPathway is the first reported clinical trial to investigate the activity of pertuzumab + trastuzumab, a regimen free of systemic chemotherapy, in patients with HER2-amplified mCRC irrespective of *KRAS* status. In our analysis, objective responses were observed in 32% of patients, with responses lasting a median of 5·9 months; four patients had response durations longer than 12 months. Clinical benefit was observed in 44% of patients and median PFS was 2·9 months. Median OS was 11·5 months, a duration that compares favourably with OS observed in trials of other treatments for refractory mCRC.[24] Patients with *KRAS* wild-type mCRC had particularly promising outcomes, with an ORR of 40%, CBR of 56%, median DOR of 6·1 months, median PFS of 5·3 months, and median OS

of 14·0 months. Our data suggest promising efficacy and durable responses in heavily pretreated patients (median of four prior lines of therapy) with HER2-amplified mCRC. Outcomes observed with pertuzumab + trastuzumab are particularly striking when compared with the low response rates (<5%) from treatments currently indicated for mCRC past the second line.[23]

Mutations in *KRAS, NRAS, PIK3CA*, and other genes are associated with resistance to EGFR inhibitors and can co-occur with HER2 alterations,[1,25] but their impact on the efficacy of HER2-targeted treatments in patients with HER2-positive mCRC has been unclear. Patients with *KRAS* exon 2 mutations were excluded from the recent phase 2 HERACLES trial, the largest study of HER2-targeted therapy in this population prior to MyPathway. An ORR of 30% was observed among the 27 patients with HER2-positive, *KRAS* wild-type mCRC treated with trastuzumab + lapatinib in HERACLES.[9] In MyPathway, 23% of patients with HER2-amplified mCRC had *KRAS* mutations. ORR for this subgroup was only 8%, versus 40% in patients with wild-type *KRAS*, suggesting that patients with HER2-amplified, *KRAS* wild-type mCRC derive greater benefit from pertuzumab + trastuzumab than those with *KRAS*-mutated mCRC. Similarly, we observed that mutations in *PIK3CA* were associated with lower ORR (13%) versus wild-type *PIK3CA* (43%).

Given the small size of the *PIK3CA*-mutated subgroup and the limited number of patients with other *RAS/RAF* mutations, additional investigation will be required to verify the impact of mutations in these genes on HER2-targeted therapy. However, in a recent analysis of circulating tumour DNA profiles to identify biomarkers of resistance to lapatinib and trastuzumab in the HERACLES trial, alterations in *RAS*/*RAF* were seen in six (86%) of seven patients who were refractory to treatment, but were observed in only three (14%) of 22 patients with clinical benefit.[26] Furthermore, in patients with clinical benefit followed by progression, emerging *KRAS* mutant clones were identified in two patients, and *BRAF* amplification was identified in one patient. These data suggest that liquid biopsies may have a role in assessing markers of intrinsic and acquired resistance.

Previous studies have reported a poorer prognosis for patients with right- versus left-sided CRC tumours.[27] In the current analysis, we observed a lower prevalence of HER2-amplified right-sided tumours versus left-sided or rectal tumours. Patients with right-sided colon tumours experienced lower ORR (8%) than those with left-sided (35%) or rectal tumours (40%), as well as numerically shorter median PFS (1·4 *vs* 4·1 and 2·8 months, respectively) and OS (5·7 *vs* 22·1 and 10·3 months). However, right-sided tumours in this analysis were also associated with a higher prevalence of *KRAS* mutations versus left-sided or rectal tumours (50% *vs* 4% and 30%, respectively). As such, it remains to be seen whether pertuzumab + trastuzumab efficacy differs by tumour sidedness, independent of *KRAS* status. The determination of HER2 status using FISH/CISH and/or IHC is well established in breast cancer[28] as well as gastric cancer[29] and has also been determined for CRC.[30] In the current analysis, 70% of patients had HER2 amplification assessed by local NGS prior to enrolment, with elevated copy number observed in all but one patient. In a post-hoc analysis evaluating the validity of NGS-determined HER2 positivity and its utility as a predictor of response, we found that in patients with both FISH/CISH and NGS (local or central) testing,

concordance for HER2 amplification status was 81%. ORR in patients with *KRAS* wild-type mCRC and FoundationOne NGS-determined HER2 amplification was 43%, versus 40% in the overall *KRAS* wild-type population. These preliminary results suggest that NGS may be a viable approach to determine HER2 amplification in patients with mCRC. HER2-amplified patients were included in this report irrespective of HER2 overexpression, which was defined as >10% of cells with intense circumferential, basolateral, or lateral staining. Of note, HERACLES diagnostic criteria for HER2 positivity in CRC required HER2 overexpression in ≥50% of cells or >10% but <50% of cells, if combined with HER2 amplification.[30]

An analysis of efficacy by NGS-derived HER2 copy number suggested that patients with higher-than-median copy number had higher response rates than those with lower copy number, consistent with results from HERACLES.[9] Among 16 responders with known HER2 copy number in MyPathway, 12 had higher-than-median (≥74) copies. These and other data may position HER2 copy number variation as an additional biomarker for treatment selection in patients with HER2-amplified mCRC.

Taken together, these data support HER2 as a clinically relevant and actionable target in HER2-amplified, *KRAS* wild-type mCRC. However, it is of note that of eight patients with HER2 amplification without overexpression, none experienced a response. Additional research is warranted to explore HER2 gene amplification, gene expression, and protein expression levels and their clinical significance in mCRC. The optimal HER2-targeted approach and sequencing of therapy for HER2-positive mCRC is yet to be established. While preclinical studies reported limited activity for HER2-targeted monotherapy against CRC tumours, dual HER2-targeted combination regimens were associated with significant reductions in tumour size.[6,8] A recent study in gastric cancer indicated that pertuzumab added to the current standard of care, trastuzumab + chemotherapy,[31] did not confer a survival benefit (HR 0·84, 95% CI 0·71–1·00).[32] However, the combination of pertuzumab + trastuzumab has shown additive activity against breast tumours[15,16] and, with a taxane, is considered a first-line standard of care in metastatic breast cancer. Efficacy data for other HER2-targeted regimens are also anticipated from two new single-arm phase 2 trials: trastuzumab emtansine (T-DM1) from HERACLES-RESCUE, and pertuzumab + T-DM1 from HERACLES-B. Pertuzumab + trastuzumab is also being investigated in the TRIUMPH trial, a multicentre Phase II trial in Japan, accruing patients with HER2-positive mCRC based on tissue analysis or circulating tumour DNA analysis.[33] The MyPathway strategy is also being investigated in a randomised trial, NCISWOG S1613, assessing pertuzumab + trastuzumab versus cetuximab + irinotecan in *RAS/BRAF* wild-type mCRC. Finally, further study is needed to assess the role of continued HER2 blockade following progression on HER2-targeted therapy, a strategy that was observed to have anecdotal success in a case report of a patient with HER2-amplified CRC.[34]

Diarrhoea, fatigue, and nausea were the most frequently reported TEAEs in this analysis and were generally low grade, consistent with known safety profiles for pertuzumab and trastuzumab in breast cancer. Pertuzumab binds to an EGFR heterodimerization site on HER2 and as such, is associated with anti-EGFR–related adverse events, such as diarrhoea,

while fatigue and nausea are commonly attributed to trastuzumab treatment.[10,18] No grade 3/4 TEAEs were observed in >6% of the analysis population.

Limitations of the current analysis include lack of randomization or a control group; non-blinded investigator assessments; small patient cohorts in the subgroup analyses; local HER2 testing, with variability in permitted testing methodologies; optional co-mutation/MSI testing conducted with site-determined methodology; and limited archival samples available for central genomic, FISH/CISH, or IHC re-testing. Despite variability in testing methodologies, pertuzumab + trastuzumab conferred a promising response rate overall, suggesting diverse methods can identify patients who may benefit from HER2-targeted treatment. Additionally, data for *KRAS* and HER2 status were captured from assays on archival tissue obtained up to 37 months prior to enrolment in MyPathway. The potential subsequent development of *KRAS* mutations in tumours previously identified as *KRAS* wild-type could result in the underestimation of ORR for patients with wild-type *KRAS*, as suggested by a small subgroup analysis showing higher ORR in patients with *KRAS* wild-type status determined after (*vs* prior to) anti-EGFR therapy. Finally, of seven patients still on study treatment at data cutoff, two patients had ongoing SD, which may also underestimate our assessment of ORR. MyPathway is an ongoing trial; we expect to perform a final analysis of patients enrolled on the HER2 positive basket cohort, which will include patients with HER2-positive CRC.

Results from MyPathway and HERACLES demonstrate the potential for dual HER2-targeted treatment in patients with HER2-positive mCRC, and highlight the importance of molecular testing in colorectal cancer. Although the overall incidence of HER2 amplification or overexpression is low in this population, the prevalence of mCRC and the promising response rates from our study suggest a sizeable population of patients who could potentially benefit from dual HER2-targeted therapy. Meaningful activity was not demonstrated in patients with HER2-amplified, *KRAS* mutant tumours, suggesting that HER2 status in conjunction with *KRAS* status should be considered in patient selection. Pertuzumab + trastuzumab is active in HER2-amplified, *KRAS* wild-type mCRC, representing a therapeutic opportunity for this population, particularly in patients refractory to or unable to tolerate chemotherapy. The efficacy from this study suggests that early assessment of HER2 status, and earlier line use of this therapy, may be considered.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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PANEL: RESEARCH IN CONTEXT

Evidence before this study

We searched for clinical trials assessing HER2-targeted therapies in patients with HER2-positive colorectal cancer (CRC) published between September 25, 1998 (the initial FDA approval date of trastuzumab for metastatic breast cancer) and August 1, 2017 (the data cutoff for the current analysis) from PubMed. Search terms included “colorectal cancer” plus [“HER2” or “HER-2”] plus [“pertuzumab,” “trastuzumab,” “lapatinib,” or “trastuzumab emtansine”]. Trials of patients not screened for HER2 positivity were omitted.

Out of the 62 entries returned from PubMed and references from several review articles, we identified three clinical trials with efficacy results from HER2-targeted treatment in patients with HER2-positive CRC. All three trials were conducted in patients with HER2-positive advanced/metastatic CRC (mCRC), and all reported objective responses with HER2-targeted treatment. However, two of these trials closed early due to low accrual, one of which reported objective responses in 5/21 patients refractory to initial therapy and treated with trastuzumab + 5-fluororuacil, leucovorin, and oxaliplatin (Clark, abstract in Proc Am Soc Clin Oncol 2003), and the other of which reported responses in 5/7 patients treated with trastuzumab + irinotecan in the second line (Ramanathan, Cancer Invest 2004). Of note, both of these trials screened patients for HER2-positivity based on immunohistochemistry (IHC) 2+ criteria, and were carried out before the widespread availability of next-generation sequencing (NGS) eased the identification of HER-amplified tumours. The third and most recent trial, HERACLES (Sartore-Bianchi, Lancet Oncol 2016), studied patients with a median of five prior lines of therapy screened for HER2 positivity based on fluorescence in situ hybridization (FISH) and IHC. HERACLES reported responses in 8/27 patients with *KRAS* exon two wild-type disease treated with weekly trastuzumab + daily lapatinib. Results from these previous studies suggest that HER2-targeted treatment has activity in patients with HER2-positive mCRC. Benefiting from the growing availability of tumour molecular profiling, the ongoing MyPathway phase 2a trial evaluates the efficacy of targeted regimens in non-indicated advanced solid tumours with relevant genetic or molecular alternations, irrespective of tumour location. In this current subset analysis of data from MyPathway, we assess the efficacy of HER2-amplified mCRC treatment with pertuzumab + trastuzumab, free of systemic chemotherapy. This dual HER2-targeted regimen, in combination with a taxane, comprises a first-line standard of care in patients with HER2-positive metastatic breast cancer.

Added value of this study

To our knowledge, this analysis of patients in the MyPathway basket study is the first to assess pertuzumab + trastuzumab in the treatment of HER2-amplified CRC. We observed encouraging activity with durable responses and prolonged overall survival in a heavily pretreated population. Biomarker analyses undertaken to identify tumour characteristics associated with response to therapy indicated that efficacy was notably higher in patients

with wild-type *KRAS* compared with *KRAS*-mutated disease. These data suggested that *KRAS* mutations may be associated with lower response to anti-HER2 targeted therapies in mCRC.

Implications of all the available evidence

Results from MyPathway (reported herein) and HERACLES (Sartore-Bianchi, Lancet Oncol 2016) support the use of dual HER2-targeted therapy, trastuzumab + pertuzumab or lapatinib, in patients with HER2-positive, *KRAS* wild-type mCRC. Data from this analysis suggest that pertuzumab + trastuzumab produces an encouraging response rate in heavily pre-treated patients. Taken together, these studies validate HER2 as a therapeutic target in mCRC and highlight dual HER2-targeted treatment as a viable option for selected patients with HER2-amplified/overexpressing disease.

DATA SHARING

Qualified researchers may request access to de-identified patient level data through the Clinical Study Data Request platform (www.clinicalstudydatarequest.com) and will be provided with accompanying clinical study documentation (protocol and any associated amendments, annotated case report form, reporting and analysis plan, dataset specifications, clinical study report).

Researchers requesting access to clinical study documentation only can do so via the following link: http://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing/clinical_study_documents_request_form.htm

Documents are made available on application, per scope and timing criteria as published on the Clinical Study Data Request platform.

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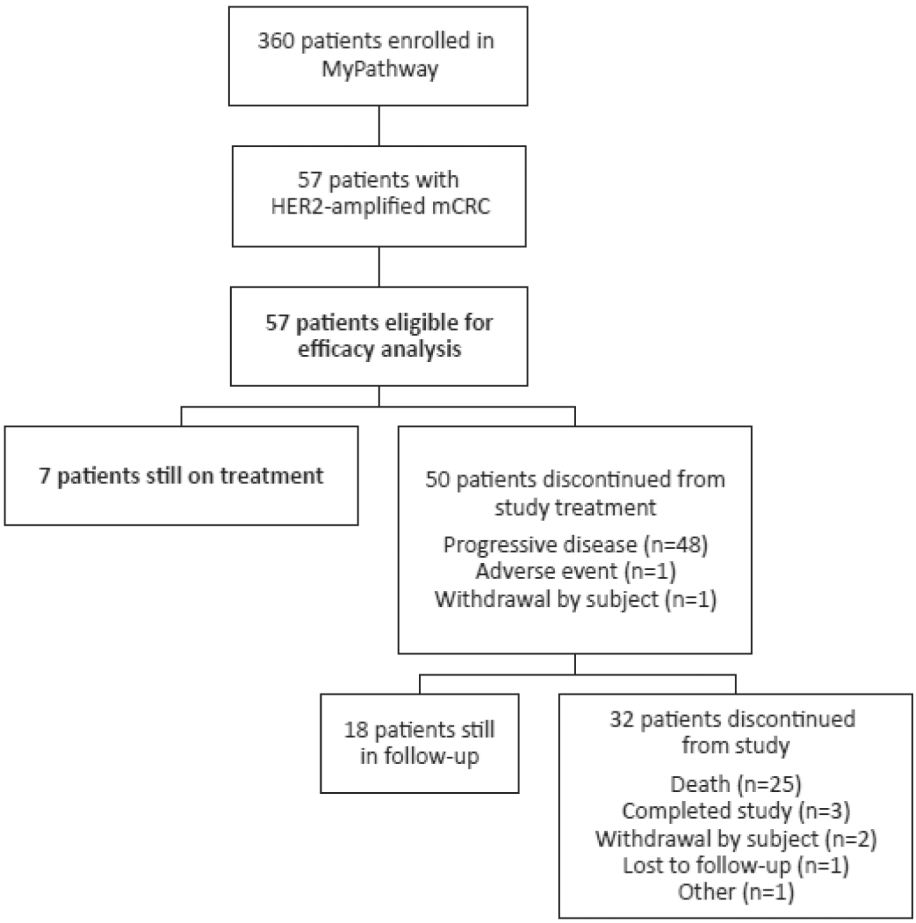

Figure 1. Trial Profile

HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer.

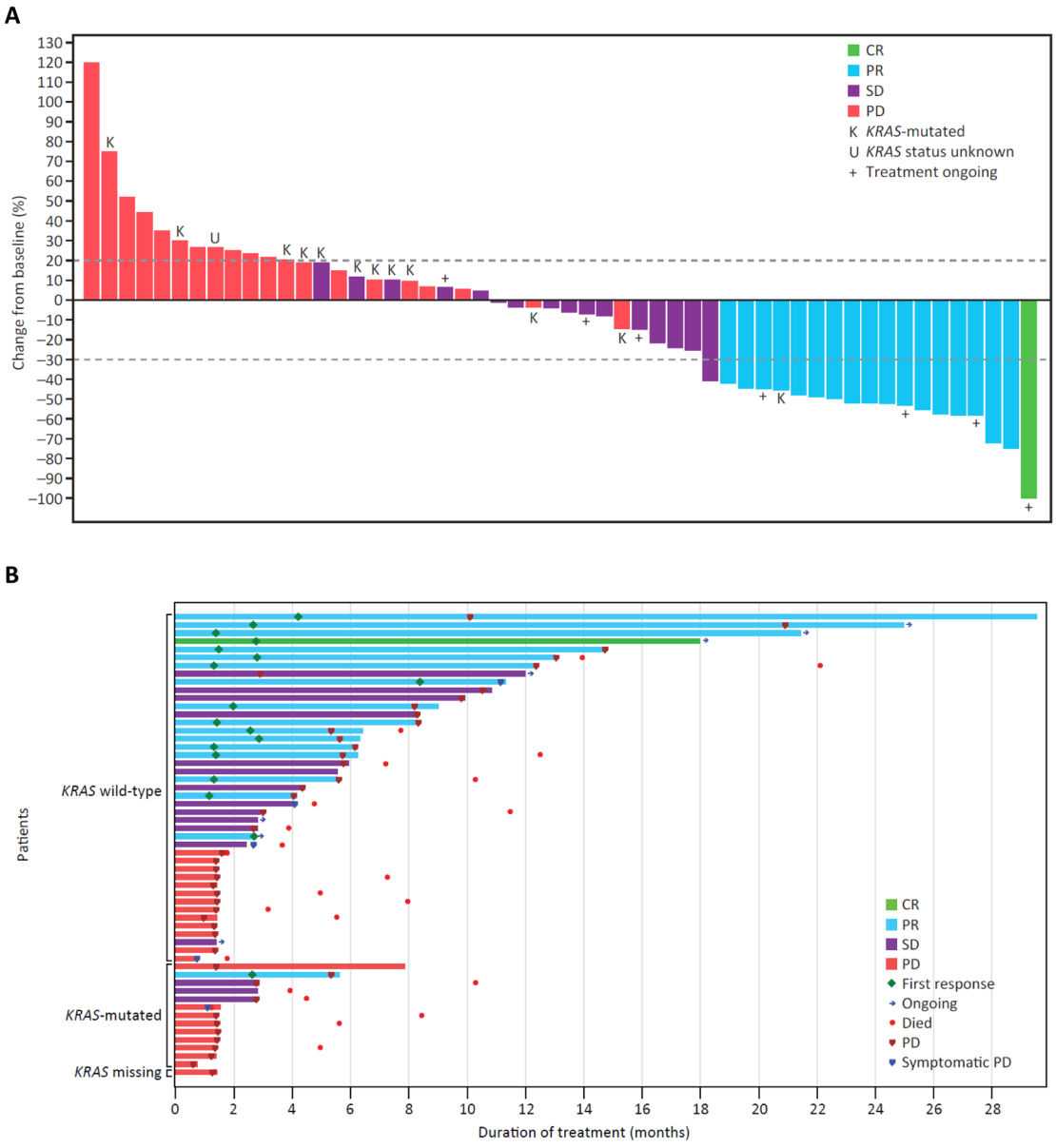

Figure 2: (A) Best change in target lesion size by patient (n=54)[a,b], and (B) time on treatment by patient (n=57)[c] for HER2-amplified mCRC treated with pertuzumab + trastuzumab

[a]Three patients are excluded from this plot: two patients (including one with a *KRAS* mutation) who discontinued treatment due to clinical progression without a post-baseline tumour assessment, and one patient with a discrepancy in the number of target lesions between screening and the post-baseline assessment.

[b]One patient with SD had a 41% reduction in target lesion size at his final assessment on study, but treatment was discontinued due to symptomatic deterioration. As such, the patient's status was classified as a PD rather than a PR at the final assessment, with an overall best response of SD.

[c]Treatment bars extend to three weeks (ie, one cycle) past the date of last drug administration in order to capture actual treatment duration.

CR, complete response; HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer; PD, progressive disease; PR, partial response; SD, stable disease.

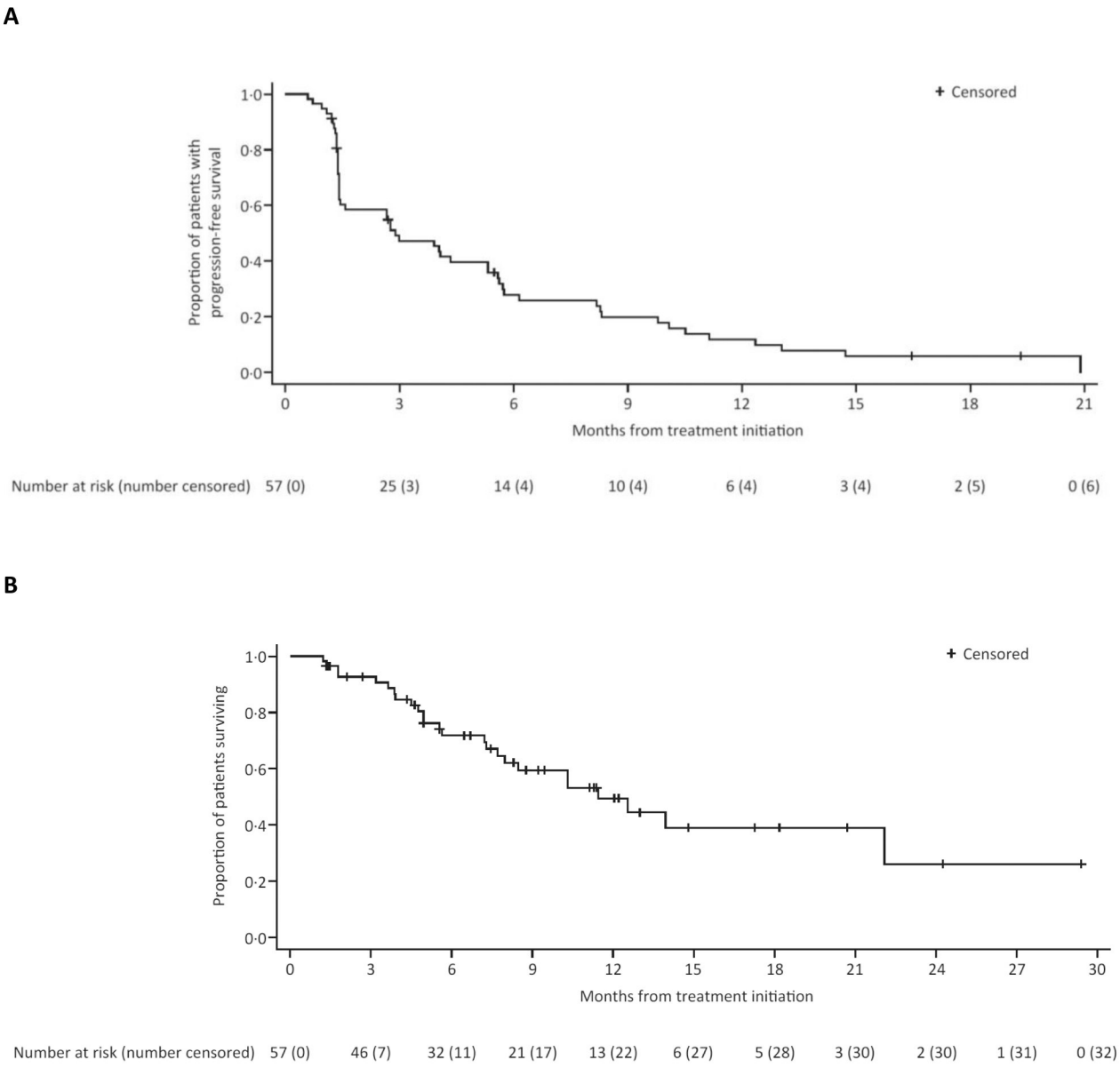

Figure 3: (A) Progression-free survival, and (B) overall survival in patients with HER2-amplified mCRC treated with pertuzumab + trastuzumab (n=57)

HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer.

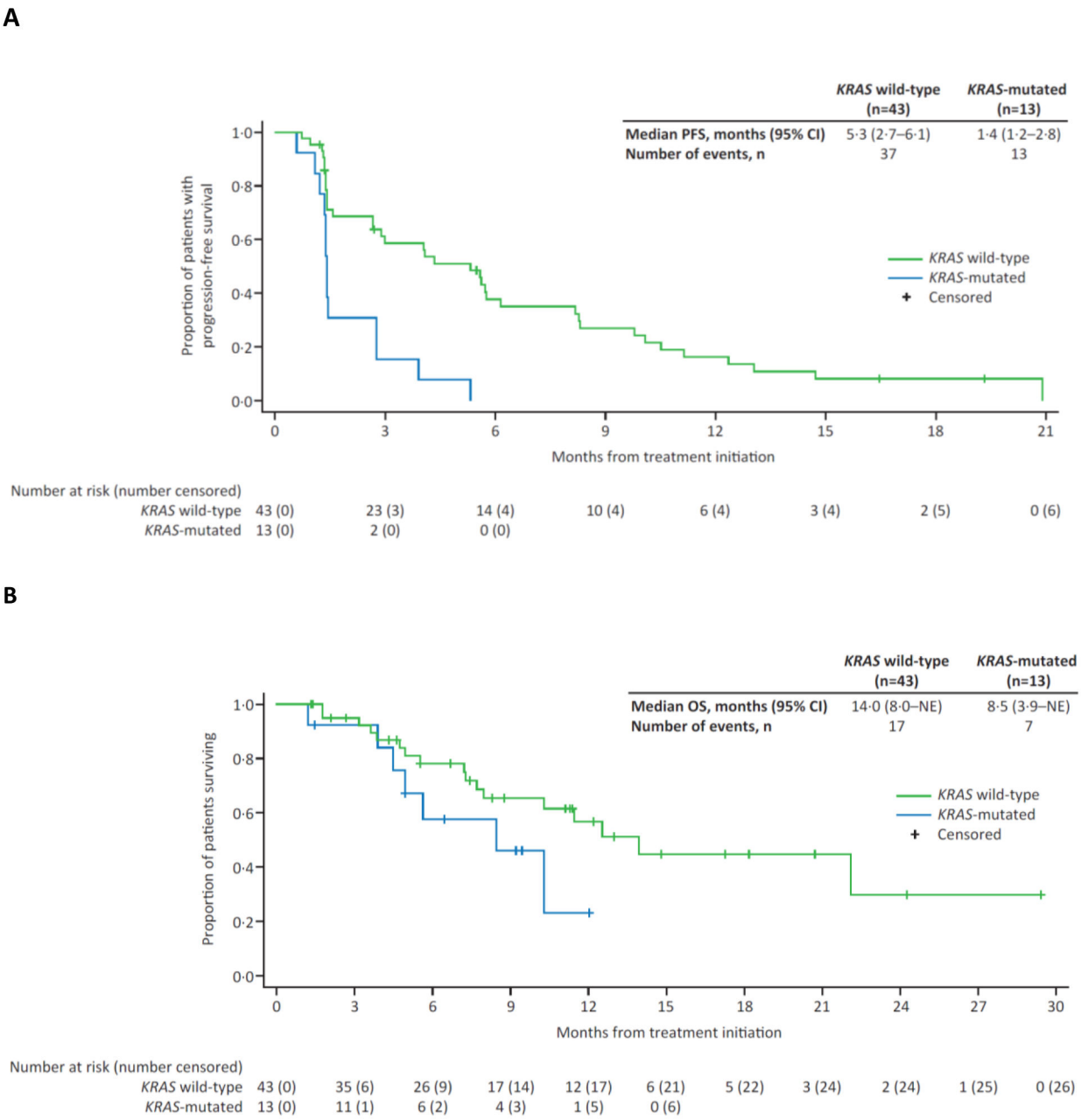

Figure 4: Exploratory analysis of (A) progression-free survival and (B) overall survival by *KRAS* status (n=56) in patients with HER2-positive mCRC

[a]Two patients had missing tumour response data.

[b]One patient had missing tumour response data.

CI, confidence interval; HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer; NE, not estimable; OS, overall survival; PFS, progression-free survival.

Table 1:

Baseline demographics and clinical characteristics

Characteristic	Patients (n=57)[a]
Median age, years (IQR)	55 (45–67)
Sex, n (%)	
Male	29 (51)
Female	28 (49)
Race, n (%)	
White	45 (79)
Black or African American	4 (7)
Asian	2 (4)
American Indian or Alaska Native	1 (2)
Other	5 (9)
ECOG performance score, n (%)	
0	21 (37)
1	35 (61)
2	1 (2)
Median time from initial diagnosis of metastatic disease to first treatment, months (IQR)[b]	27.0 (15.9–38.7)
Tumour site, n (%)	
Colon	37 (65)
Right side	12 (21)
Left side	23 (40)
Transverse	1 (2)
Unknown	1 (2)
Rectum	20 (35)
HER2 status, n (%)[c]	
Amplification, no overexpression	8 (14)
Amplification, overexpression status unknown	22 (39)
Amplification and overexpression	27 (47)
Median number of prior regimens (IQR)	4 (2–5)
Number of prior regimens, n (%)	
1	4 (7)
2	13 (23)
3	8 (14)
4	13 (23)
5	12 (21)
6	4 (7)
7	1 (2)
8	1 (2)
9	1 (2)
KRAS status, n (%)[d]	

Characteristic	Patients (n=57)[a]
Wild-type	43 (75)
Mutated	13 (23)
Unknown	1 (2)
NRAS status, n (%)	
Wild-type	55 (96)
Mutated	0
Unknown	2 (4)
EGFR inhibitor in prior therapy, n (%)	
Prior anti-EGFR exposure[e]	32 (56)
Cetuximab only	17 (30)
Panitumumab only	10 (18)
Cetuximab and panitumumab[f,g]	5 (9)
No prior anti-EGFR exposure	25 (44)

[a] Percentages may not add to 100% due to rounding.

[b] In n=56 patients.

[c] HER2 amplification and overexpression statuses are based on local testing results and supplemented by central data, if local data were not available (appendix p 6).

[d] Specific KRAS mutations are shown in appendix p. 3.

[e] Of the 32 patients with prior anti-EGFR exposure, 31 had *KRAS* wild-type mCRC, and one patient had unknown *KRAS* status.

[f] Patients may have received cetuximab and panitumumab in different lines of therapy.

[g] One patient also received irinotecan.

CISH, chromogenic in situ hybridization; CLIA, Clinical Laboratory Improvement Amendments; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; IQR, interquartile range; mCRC, metastatic colorectal cancer; NGS, next-generation sequencing.

Table 2:

Clinical outcomes by subgroup[a]

Subgroup	ORR n (% [95% CI])	CBR[b] n (% [95% CI])	Median DOR[c] Months (95% CI)	Median PFS[d] Months (95% CI)	Median OS[d] Months (95% CI)
All patients (n=57)	18 (32 [20–45])	25 (44 [31–58])	5·9 (2·8–11.1)	2·9 (1·4–5·3)	11·5 (7·7–NE)
KRAS status[e] (n=56 tested)					
Wild-type (n=43)	17 (40 [25–56])	24 (56 [40–71])	6·1 (2·9–11·1)	5·3 (2·7–6·1)	14·0 (8·0–NE)
Mutated (n=13)	1 (8 [0·2–36])	1 (8 [0·2–36])	2·7	1·4 (1·2–2·8)	8·5 (3·9–NE)
PIK3CA status (n=48 tested)					
Wild-type (n=40)	17 (43 [27–59])	23 (58 [41–73])	6·1 (2·8–11·1)	5·3 (2·8–6·1)	14·0 (8·5–NE)
Mutated[f] (n=8)	1 (13 [0·3–53])	2 (25 [3–65])	4·4	1·4 (1·1–5·7)	7·3 (1·2–12·6)
MSI status (n=28 tested)					
Low/stable (n=28)	7 (25 [11–45])	10 (36 [19–56])	3·9 (2·8–NE)	2·7 (1·4–4·3)	7·7 (4·5–NE)
High (n=0)	NA	NA	NA	NA	NA
Prior anti-EGFR therapy in patients without *KRAS* mutations (n=43)					
Any (n=31)	11 (36 [19–55])	16 (52 [33–70])	5·9 (2·8–11·1)	4·1 (1·6–8·2)	11·5 (7·2–22·1)
None (n=12)	6 (50 [21–79])	8 (67 [35–90])	6·9 (2·8–NE)	5·6 (1·3–14·7)	NE (3·2–NE)
Tumour location (n=56)					
Colon, left side (n=23)[g]	8 (35 [16–57])	12 (52 [31–73])	9·0 (2·9–NE)	4·1 (1·4–9·8)	22·1 (11·5–22·1)
Colon, right side (n=12)[h]	1 (8 [0·2–39])	2 (17 [2–48])	10·3	1·4 (1·2–3·9)	5·7 (1·3–14·0)
Colon, transverse (n=1)[i]	1 (100)	1 (100)	2·8	5·3	7·7
Rectum (n=20)[j]	8 (40 [19–64])	10 (50 [27–73])	4·3 (2·7–5·9)	2·8 (1·4–5·6)	10·3 (5·6–NE)
Number of prior regimens (n=57)					
<4 (n=25)	8 (32 [15–54])	10 (40 [21–61])	5·9 (2·7–NE)	2·8 (1·4–5·6)	NE (5·7–NE)
≥4 (n=32)	10 (31 [16–50])	15 (47 [29–65])	5·9 (2·8–11·1)	3·0 (1·4–5·7)	10·3 (7·2–14·0)

[a] Subgroup ns are based on available data.

[b] CBR is defined as the percentage of patients with CR, PR, or SD for >4 months.

[c] Medians are based on patients with CR or PR.

[d] Time to event is estimated by the Kaplan-Meier method.

[e] Specific mutations for *KRAS* and *PIK3CA* are shown in appendix p 3.

[f] Two patients with mutated *PIK3CA* also had mutated *KRAS*; patients had a PD as the best response.

[g] 4% (1/23) patients with left-sided colon cancer had *KRAS*-mutated disease.

[h] 50% (6/12) of patients with right-sided colon cancer had *KRAS*-mutated disease, and one had unknown *KRAS* status. Of the five patients with right-sided colon cancer and *KRAS* wild-type mCRC, one patient responded to treatment.

[i] Patient with transverse colon cancer had KRAS wild-type disease.

[j] 30% (6/20) of patients with rectal cancer had *KRAS*-mutated disease.

CBR, clinical benefit rate; CI, confidence interval; CR, complete response; DOR, duration of response; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; MSI, microsatellite instability; NA, not applicable; NE, not estimable; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.

Table 3:

TEAEs in HER2-amplified mCRC treated with pertuzumab + trastuzumab (n=57) including all grade 1–2 TEAEs observed in ≥10% of patients and all grade ≥3 TEAEs[a]

TEAE, n (%)	Grade 1–2	Grade 3	Grade 4
Diarrhoea	17 (30)	2 (4)	0
Fatigue	18 (32)	0	0
Nausea	16 (28)	1 (2)	0
Anaemia	12 (21)	2 (4)	0
Abdominal pain	10 (18)	3 (5)	0
Chills	13 (23)	0	0
Dyspnoea	11 (19)	1 (2)	0
Vomiting	10 (18)	1 (2)	0
Infusion related reaction	9 (16)	1 (2)	0
Blood alkaline phosphatase increased	7 (12)	2 (4)	0
Decreased appetite	8 (14)	1 (2)	0
Blood bilirubin increased	6 (11)	2 (4)	0
Cough	7 (12)	0	0
Insomnia	7 (12)	0	0
Dry skin	6 (11)	0	0
Oedema peripheral	6 (11)	0	0
Pyrexia	6 (11)	0	0
Rash	6 (11)	0	0
Aspartate aminotransferase increased	4 (7)	2 (4)	0
Hypokalaemia	4 (7)	2 (4)	1 (2)
Hyponatraemia	4 (7)	2 (4)	0
Urinary tract infection	5 (9)	1 (2)	1 (2)
Acute kidney injury	0	1 (2)	0
Alanine aminotransferase increased	4 (7)	1 (2)	0
Cellulitis	1 (2)	1 (2)	0
Chronic obstructive pulmonary disease	0	1 (2)	0
Clostridium difficile colitis	0	1 (2)	0
Device related infection	0	1 (2)	0
Facial pain	0	1 (2)	0
Infection	0	1 (2)	0
Lymphocyte count decreased	3 (5)	1 (2)	0
Lymphopaenia	0	1 (2)	0
Non-cardiac chest pain	0	1 (2)	0
Ophthalmic herpes zoster	0	1 (2)	0
Pleural effusion	0	1 (2)	0

TEAE, n (%)	Grade 1–2	Grade 3	Grade 4
Small intestinal obstruction	0	1 (2)	0
Spinal cord compression	0	1 (2)	0
Superior mesenteric artery syndrome	0	1 (2)	0
Syncope	0	1 (2)	0
Left ventricular dysfunction	0	0	1 (2)

[a]There were no grade 5 TEAEs.HER2, human epidermal growth factor receptor 2; mCRC, metastatic colorectal cancer, TEAE, treatment-emergent adverse event.