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

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Summary

Background Therapies targeting HER2 have improved clinical outcomes in HER2-positive breast and gastric cancers, and are emerging as potential treatments for HER2-positive metastatic colorectal cancer. MyPathway evaluates the activity of targeted therapies in non-indicated tumour types with potentially predictive molecular alterations. We aimed to assess the activity of pertuzumab and trastuzumab in patients with *HER2*-amplified metastatic colorectal cancer.

Methods MyPathway is an ongoing, phase 2a, multiple basket study. Patients in this subset analysis were aged 18 years or older and had treatment-refractory, histologically confirmed *HER2*-amplified metastatic colorectal cancer with measurable or evaluable disease and an Eastern Cooperative Oncology Group performance status score of 2 or less, enrolled from 25 hospitals or clinics in 16 states of the USA. Patients received pertuzumab (840 mg loading dose, then 420 mg every 3 weeks, intravenously) and trastuzumab (8 mg/kg loading dose, then 6 mg/kg every 3 weeks, intravenously). The primary endpoint was the proportion of patients who achieved an objective response based on investigator-reported tumour responses. Analyses were done per protocol. This ongoing trial is registered with ClinicalTrials.gov, number NCT02091141.

Findings Between Oct 20, 2014, and June 22, 2017, 57 patients with *HER2*-amplified metastatic colorectal cancer were enrolled in the MyPathway study and deemed eligible for inclusionin this cohort analysis. Among these 57 evaluable patients, as of Aug 1, 2017, one (2%) patient had a complete response and 17 (30%) had partial responses; thus overall 18 of 57 patients achieved an objective response (32%, 95% CI 20–45). The most common treatment-emergent adverse events were diarrhoea (19 [33%] of 57 patients), fatigue (18 [32%] patients), and nausea (17 [30%] patients). Grade 3–4 treatment-emergent adverse events were recorded in 21 (37%) of 57 patients, most commonly hypokalaemia and abdominal pain (each three [5%] patients). Serious treatment-emergent adverse events were reported in ten (18%) patients and two (4%) of these adverse events (ie, chills and infusion-related reaction) were considered treatment related. There were no treatment-related deaths.

Interpretation Dual HER2-targeted therapy with pertuzumab plus trastuzumab is well tolerated and could represent a therapeutic opportunity for patients with heavily pretreated, *HER2*-amplified metastatic colorectal cancer.

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Introduction

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

HER2 amplification or overexpression is found in 2–6% of patients with advanced or metastatic colorectal cancer.[3–5] The low prevalence of HER2 alterations has constrained research into effective treatment options, resulting in a substantial unmet medical need in this patient population. HER2 itself is a well studied oncogenic target in other cancer types, and several studies[6–9] in the past decade have identified it as a potential target for the treatment of HER2-positive colorectal cancer. In the preclinical setting, HER2-targeted monotherapy with the anti-HER2 antibodies trastuzumab or pertuzumab, or the small molecule lapatinib, had little activity against *HER2*-amplified colorectal tumour grafts or xenografts.[6,8] However, anti-tumour activity increased notably with combination

Research in context

Evidence before this study

We searched PubMed for clinical trials assessing HER2-targeted therapies in patients with HER2-positive colorectal cancer published between Sept 25, 1998 (the initial US Food and Drug Administration approval date of trastuzumab for metastatic breast cancer), and Aug 1, 2017 (the data cutoff for the current analysis). Search terms were "colorectal cancer" plus ["HER2" or "HER-2"] plus ["pertuzumab", "trastuzumab", "lapatinib", or "trastuzumab emtansine"]. Trials of patients not screened for HER2 positivity were omitted. 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 colorectal cancer. All three trials were done in patients with HER2-positive advanced or metastatic colorectal cancer, and all reported objective responses with HER2-targeted treatment. However, two of these trials closed early due to low accrual; one reported objective responses in five of 21 patients refractory to initial therapy and treated with trastuzumab plus 5-fluororuacil, leucovorin, and oxaliplatin, and the other reported responses in five of seven patients treated with trastuzumab plus irinotecan in the second line. Notably, both these trials screened patients for HER2 positivity based on immunohistochemistry 2+ criteria, and were done before the widespread availability of next-generation sequencing eased the identification of *HER*-amplified tumours. The third and most recent trial, HERACLES, studied patients with a median of five prior lines of therapy screened for HER2 positivity based on fluorescence in situ hybridisation and immunohistochemistry. HERACLES reported responses in eight (30%) of 27 patients with *KRAS* exon two wild-type disease treated with weekly trastuzumab plus daily lapatinib. Results from these previous studies suggest that HER2-targeted treatment has activity in patients with HER2-positive metastatic colorectal cancer. Benefiting from the growing availability of tumour molecular profiling, the ongoing MyPathway phase 2a trial evaluates the activity 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 activity of *HER2*-amplified metastatic colorectal cancer treatment with pertuzumab plus 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 the best of our knowledge, this analysis of patients in the MyPathway basket study is the first to assess pertuzumab plus trastuzumab in the treatment of *HER2*-amplified colorectal cancer. We observed encouraging activity with durable responses and improved overall survival in a heavily pretreated population. Biomarker analyses undertaken to identify tumour characteristics associated with response to therapy indicated that activity was notably higher in patients with wild-type *KRAS* than in those with *KRAS*-mutated disease. These data suggest that *KRAS* mutations could be associated with lower response to anti-HER2 targeted therapies in metastatic colorectal cancer.

Implications of all the available evidence

Results from the MyPathway trial (reported herein) and the HERACLES trial support the use of dual HER2-targeted therapy, trastuzumab plus pertuzumab or lapatinib, in patients with HER2-positive, *KRAS* wild-type metastatic colorectal cancer. Data from this analysis suggest that pertuzumab plus trastuzumab produces encouraging responses in heavily pretreated patients. Taken together, these studies validate HER2 as a therapeutic target in metastatic colorectal cancer and highlight dual HER2-targeted treatment as a viable option for selected patients with *HER2*-amplified and overexpressing disease.

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HER2-targeted regimens, including pertuzumab plus lapatinib and trastuzumab plus lapatinib.[6,8] On the basis of this work, the phase 2 HERACLES trial[9] assessed trastuzumab plus lapatinib treatment in patients with HER2-positive, *KRAS* exon 2 wild-type metastatic colorectal cancer, with promising results: eight of 27 patients (30%, 95% CI 14–50) achieved an objective response.

Trastuzumab-based treatment regimens are approved for breast, gastric, and gastroesophageal junction adenocarcinoma,[10] with promising activity observed in other cancer types such as salivary-gland and bladder cancer.[11–13] In particular, the dual HER2-targeted combination of pertuzumab plus 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 have yet assessed the efficacy of pertuzumab plus trastuzumab in the treatment of HER2-positive metastatic colorectal cancer, and none have assessed the effect of co-occurring alterations, such as *KRAS* mutations, on HER2-targeted treatment in this setting.

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 in the study have advanced solid tumours harbouring genetic or molecular alterations potentially predictive of a response from treatment with pertuzumab plus trastuzumab, vemurafenib alone or plus cobimetinib, vismodegib, erlotinib, alectinib, or atezolizumab. In this Article, we present the activity results and biomarker analyses in patients with HER2-amplified metastatic colorectal cancer treated with pertuzumab plus trastuzumab.

Methods

Study design and participants

See Online for appendix

MyPathway is a multicentre, non-randomised, 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 hospitals or clinics in 16 states of the USA (appendix p 1). Participants were aged 18 years or older and had treatment-refractory metastatic colorectal cancer with *HER2* amplification, as assessed with a laboratory test certified by the Clinical Laboratory Improvement Amendments and reviewed by a study medical monitor for eligibility; measurable or evaluable lesions;[17] an Eastern Cooperative Oncology Group performance status score of 0–2; adequate organ function based on laboratory assessment of absolute neutrophil count, platelet count, haemoglobin, serum creatinine, aspartate aminotransferase and alanine aminotransferase, total bilirubin, and alkaline phosphatase; and a life expectancy of at least 12 weeks. Patients were required to have previously received standard first-line therapy for metastatic colorectal cancer, and to have no additional therapies available or suitable to convey clinical benefit, according to the judgment of the treating physician. Exclusion criteria were: previous HER2-targeted treatment or contraindications to study therapy, haematological 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 before study entry, pulmonary embolism within 30 days before study entry, history or presence of clinically significant ventricular or atrial arrhythmia worse than grade 2, or any other severe acute or chronic medical or psychiatric condition or laboratory abnormality. Additional inclusion and exclusion criteria are available in the online protocol (appendix pp 10–272).

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

Procedures

Pertuzumab (840 mg intravenous loading dose, followed by 420 mg given intravenously every 3 weeks) and trastuzumab (8 mg/kg intravenous loading dose, followed by 6 mg/kg given intravenously every 3 weeks) were administered to all participants in accordance with the US Package Inserts[10,18] until disease progression, unacceptable toxicity, or other discontinuation criteria (pregnancy, patient request to discontinue treatment, conditions requiring therapeutic interventions not permitted by protocol, or intercurrent illness [per investigator's discretion]) were met. Toxicities were evaluated on the basis of the Common Terminology Criteria for Adverse Events version 4.0. In the event of a grade 3–4 adverse event associated with pertuzumab or trastuzumab, further dosing was held until the adverse event resolved to grade 1 or less. Upon resolution, dosing resumed at the full dose. If the grade 3–4 adverse event recurred, the associated treatment was discontinued. Patients benefiting from therapy were permitted to continue treatment with trastuzumab if an adverse event required discontinuation of pertuzumab, or with pertuzumab if an adverse event required discontinuation of trastuzumab, at the discretion of their treating physician.

Tumour burden was evaluated by the investigator per the Response Evaluation Criteria in Solid Tumors version 1.1[17] at baseline and every 6 weeks (ie, every two treatment cycles) for the first 24 weeks, and then every 12 weeks (ie, every four treatment cycles) thereafter, using CT scans. Since 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 clinically significant adverse events (defined as serious adverse events, adverse events leading to treatment modification [eg, dose reduction, dose delay, or treatment discontinuation], or protocol-defined adverse events of special interest [ie, cases of potential drug-induced liver injury (jaundice), suspected transmission of an infectious agent by the study treatment, or asymptomatic decline in left ventricular ejection fraction requiring treatment or leading to discontinuation of trastuzumab and pertuzumab]), per the Common Terminology Criteria for Adverse Events version 4.0, captured in the electronic Case Report Form. Additionally, patients were tested for left ventricular ejection fraction (at baseline, and on day 1 of cycles five and nine) and underwent laboratory tests for complete blood count (at baseline; on day 1 of cycles one, two, three, and seven, and every three cycles thereafter; and at the end of treatment), plasma biomarkers (on day 1 of cycles one and three and at the end of treatment), comprehensive metabolic profile (at baseline; on day 1 of cycles one, two, three, and seven, and every three cycles thereafter; and at the end of treatment), and pregnancy (at baseline, on day 1 of cycle four, and every three cycles thereafter). Additional details are presented in the online protocol.

Before study enrolment, archival or fresh tissue samples were tested locally for HER2 positivity by fluorescence or chromogenic in situ hybridisation (FISH or CISH; *HER2* amplification based on *HER2* to chromosome 17 ratio >2·0 or *HER2* copy number >6·0), next-generation sequencing (NGS; *HER2* amplification based on copy number gain), or immunohistochemistry (HER2 overexpression based on immunohistochemistry 3+ staining). Patients could receive any combination of tests and any relevant NGS panel, as determined by the investigator, using routine

procedures in Clinical Laboratory Improvement Amendments-validated laboratories. FoundationOne NGS (Foundation Medicine, Cambridge, MA, USA)[19] was done in patients with available archival tissue without previous FoundationOne results. A bright-field, single slide-based HER2 gene–protein assay for CISH or immunohistochemistry (Ventana Medical Systems, Tucson, AZ, USA)[20] was conducted in patients with archival tissue, if available.

HER2 status, co-occurring molecular alterations (eg, *KRAS* mutations), and microsatellite-instability 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 gene–protein assay results. Patients with *KRAS* wild-type metastatic colorectal cancer 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.

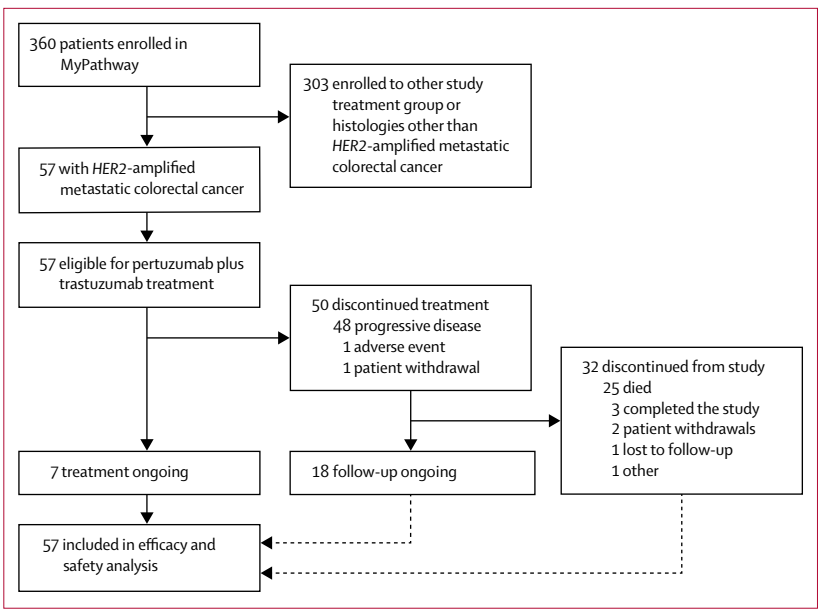

Figure 1: **Trial profile**

Outcomes

The primary endpoint was the proportion of patients who achieved an objective response on the basis of investigator assessed and reported tumour responses, and it was determined on the basis of the best overall response up to the data cutoff date for each patient. The patients were judged to have achieved an objective response if they had a complete or partial response (according to RECIST version 1.1) at any time. Secondary endpoints included the proportion of patients who achieved disease control (defined as patients with an objective response or stable disease for >4 months), duration of response (time from first response to progression or death or to last tumour assessment in patients with complete or partial response), progression-free survival (time from first treatment to progressive disease or death or to last tumour assessment), overall survival (time from first treatment to death or date last known to be alive), and safety. An additional secondary endpoint were overall responses as determined by an independent review committee in patients with HER2-amplified colorectal cancer who achieved a complete or partial response as per investigator assessment; this has not been completed and is not reported in this Article.

Statistical analysis

Simon's optimal two-stage design was used to evaluate the futility or activity of treatment. At least two responses out of 13 treated patients in stage one were required to proceed to stage two, where at least six responses in 34 patients were required to demonstrate activity. The design had around 80% power to detect the difference between the null hypothesis of 10% of the patients achieving an objective response and the alternative hypothesis of 25% of the patients achieving an objective response with a 10% one-sided type I error. Upon adequate demonstration of activity, accrual of up to 75 patients was permitted.

The proportion of patients with an objective response and disease control was evaluated in the efficacy analysis population, defined as patients who received at least one dose of study treatment and had a baseline tumour assessment. The Clopper-Pearson estimation method was used to calculate 95% CIs for the proportion of patients with objective response and the proportion of patients who achieved disease control. Median progression-free survival, overall survival, and duration of response and their 95% CIs were estimated via Kaplan–Meier analysis in the efficacy analysis population. The proportion of patients who achieved an objective response and who achieved disease control, duration of response, progression-free survival, and overall survival were also determined in the biomarker-evaluable population, defined as treated patients with valid biomarker data of interest. Safety was assessed in the group of all treated patients.

Post-hoc exploratory analyses included correlation of tumour biomarkers with response. We did a post-hoc subgroup analysis to assess clinical outcomes (proportion of patients with objective response and with disease control, median progression-free survival, and median overall survival) in patients categorised on the basis of the status of tumour biomarkers identified in the exploratory analyses; in patients with and without previous anti-EGFR therapy; and in patients categorised by tumour location and number of previous treatment regimens.

Statistical analyses were completed using SAS version 9.4 or R version 3.4.4.

	Patients (n=57)*
Age, years	55 (45–67)
Sex	
Male	29 (51%)
Female	28 (49%)
Race	
White	45 (79%)
Black or African-American	4 (7%)
Asian	2 (4%)
American Indian or Alaska Native	1 (2%)
Other	5 (9%)
ECOG performance status score	
0	21 (37%)
1	35 (61%)
2	1 (2%)
Time from initial diagnosis of metastatic disease to first treatment, months†	27·0 (15·9–38·7)
Tumour site	
Colon, right side	12 (21%)
Colon, left side	23 (40%)
Colon, transverse	1 (2%)
Colon, unknown	1 (2%)
Rectum	20 (35%)
HER2 status‡	
Amplification, no overexpression	8 (14%)
Amplification, overexpression status unknown	22 (39%)
Amplification and overexpression	27 (47%)
Number of previous treatment regimens	4 (2–5)
Number of previous treatment regimens	
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§	
Wild type	43 (75%)
Mutated	13 (23%)
Unknown	1 (2%)
NRAS status	
Wild type	55 (96%)
Mutated	0 (0%)
Unknown	2 (4%)
Previous anti-EGFR exposure¶	32 (56%)
Cetuximab only	17 (30%)
Panitumumab only	10 (18%)
Cetuximab and panitumumab||**	5 (9%)

Data are median (IQR) or n (%). ECOG= Eastern Cooperative Oncology Group. *Percentages might not add up to 100% due to rounding. †n=56 patients. ‡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). §Specific *KRAS* mutations are shown in the appendix (p 3). ¶Of the 32 patients with prior anti-EGFR exposure, 31 had *KRAS* wild-type metastatic colorectal cancer, and one patient had unknown *KRAS* status. ||Patients might have received cetuximab and panitumumab in different lines of therapy. **One patient also received irinotecan.

Table 1: **Baseline characteristics**

This study is registered with ClinicalTrials.gov, number NCT02091141.

Role of funding source

The funder of the study was involved in the study design, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all study data and the corresponding author had final responsibility for the decision to submit for publication.

Results

360 patients with different tumor types bearing pre-specified biomarkers were enrolled in the MyPathway trial. Here we report the interim analysis of patients with *HER2*-amplified metastatic colorectal cancer patients enrolled between Oct 20, 2014 and June 22, 2017 (figure 1). This interim analysis indicated partial response in three (23%) of 13 patients, passing the Simon stage one criteria for cohort expansion.[21] This Article reports on 57 patients with *HER2*-amplified metastatic colorectal cancer who initiated treatment with pertuzumab plus trastuzumab between Oct 20, 2014, and June 22, 2017 (figure 1). All patients enrolled in this cohort were eligible and evaluable for activity and safety.

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

Most patients were heavily pretreated, with a median of four previous treatment regimens (IQR 2–5), and most (43 [75%] of 57 patients) had *KRAS* wild-type disease (table 1). 20 (35%) of 57 patients had rectal cancer and 37 (65%) had colon cancer. Of the 37 patients with colon cancer, 23 (62%) had left-sided colon primary tumours, 12 (32%) had right-sided tumours, one (3%) had a transverse tumour, and one (3%) had a colon tumour with unknown location.

All 57 patients were determined to have *HER2*-amplified metastatic colorectal cancer by local NGS or by FISH or CISH testing (appendix p 6). Concordance for amplification was found in 26 (81%) of 32 patients with *HER2* amplification data by both NGS and FISH

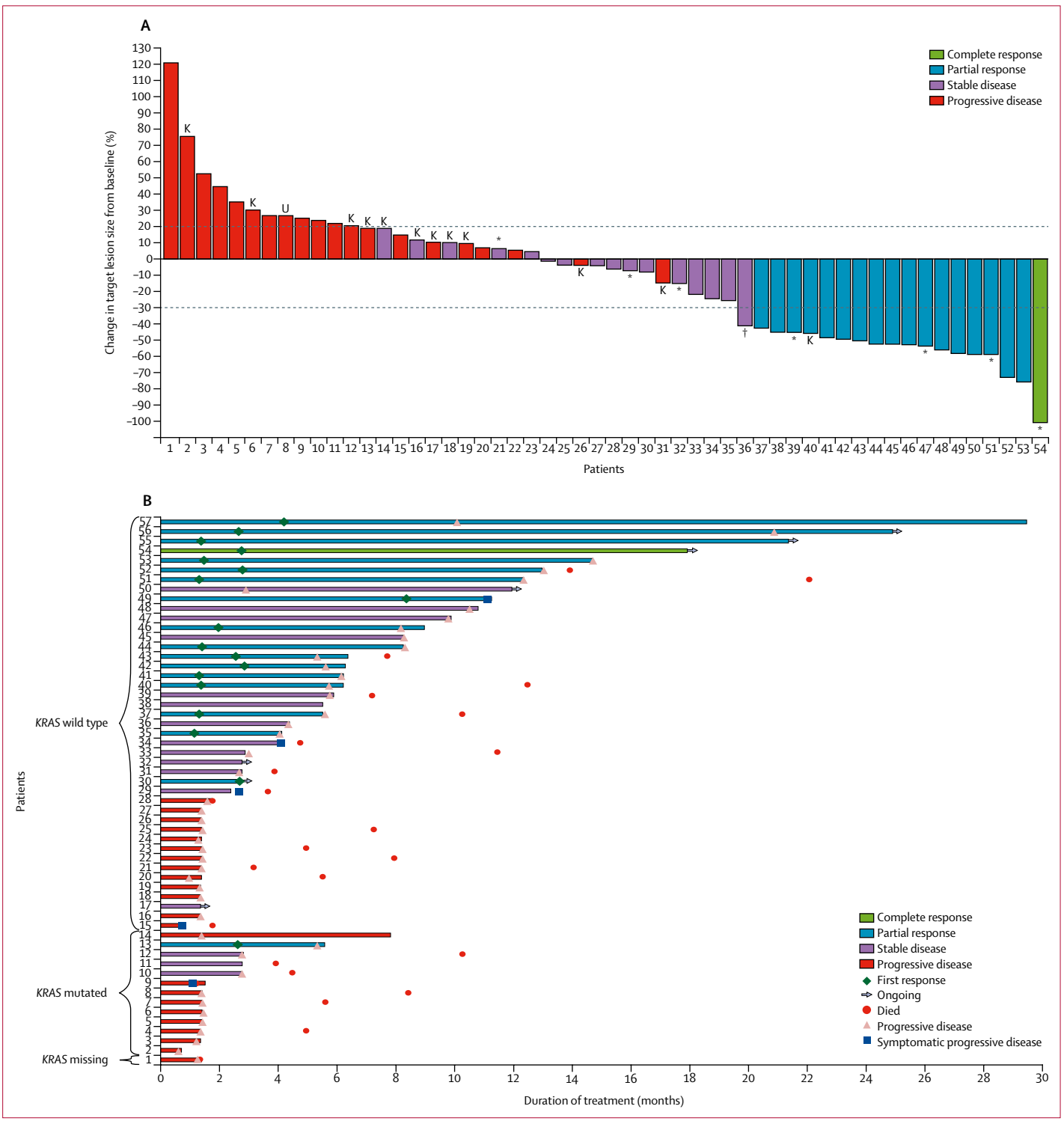

Figure 2: **Best change in target lesion size by patient (A) and duration of treatment by patient (B)**
(A) n=54. Three patients are excluded: two patients (including one with a *KRAS* mutation) who discontinued treatment due to clinical progression without a post-baseline tumour assessment, and one patient with a discrepancy in the number of target lesions between screening and the post-baseline assessment. Dashed lines represent 20% progression (progressive disease) and 30% tumor regression (partial response). (B) n=57. Treatment bars extend to 3 weeks (ie, one cycle) past the date of last drug administration to capture actual treatment duration. Patient numbering is independent for each panel; numbers in panel (A) do not correspond with the numbers in panel (B). K=KRAS-mutated. U=KRAS status unknown. *Treatment ongoing. †Patient with stable disease who had a 41% reduction in target lesion size at their final assessment on study, but whose treatment was discontinued because of symptomatic deterioration; as such, the patient's status was classified as a progressive disease rather than a partial response at the final assessment, with an overall best response of stable disease.

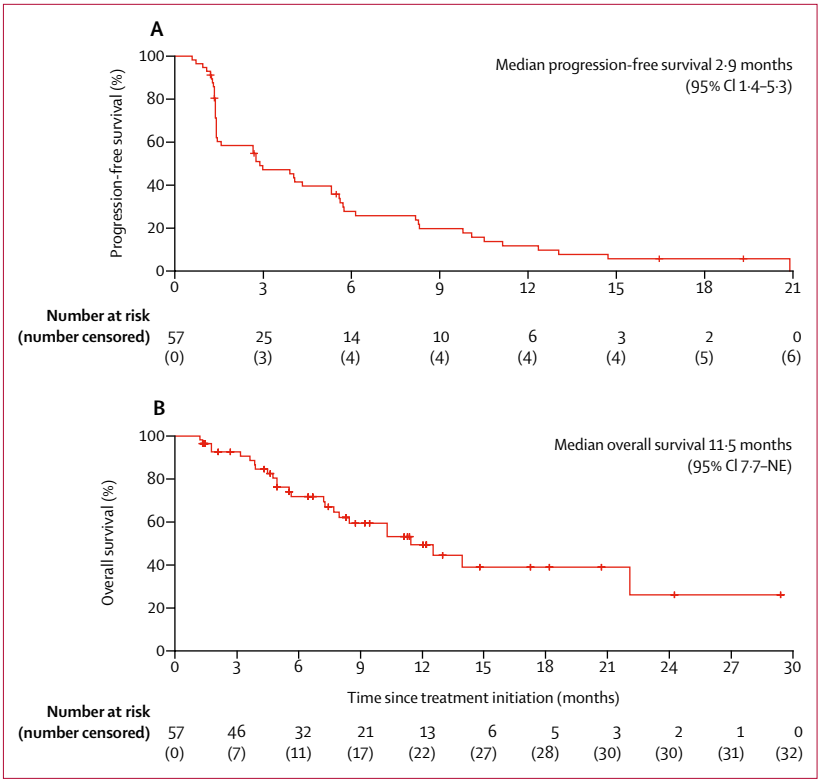

Figure 3: **Progression-free survival (A) and overall survival (B)**
NE=not estimable.

or CISH (appendix p 2). In 35 patients tested by immunohistochemistry, HER2 overexpression was observed in 27 (77%) patients and was not observed in eight patients (23%; table 1). Three (6%) of 47 patients tested had *HER2* mutations (Ser310Phe, Gly776Cys, and Thr862Ala plus Ala2584Glyl; appendix p 3).

The *HER2*-amplified metastatic colorectal cancer cohort met its primary activity endpoint when a partial response was recorded in 13 (38%) of 34 patients in the efficacy analysis population, passing Simon stage two criteria.[22] Median treatment duration was 2·1 months (IQR 0·7–7·2) for the 57 patients included in this analysis. 18 (32%, 95% CI 20–45) of these 57 patients achieved an objective response to pertuzumab plus trastuzumab treatment, including one (2%) patient with a complete response and 17 (29%) patients with a partial response. 25 (44%, 95% CI 31–58) patients achieved disease control. In 17 (94%) of the 18 patients with an objective response, the initial response assessment was confirmed in the subsequent re-evaluation, whereas one (5%) of these patients did not receive a reassessment for response confirmation before the database cutoff date. The best percent change in target lesion size by patient is shown in figure 2A. Median duration of response was 5·9 months (95% CI 2·8–11·1) in patients with an objective response; four (22%) patients had a response lasting longer than 12 months (figure 2B).

By the data cutoff date (Aug 1, 2017), 50 (88%) of 57 patients had progressed and 25 (44%) had died. Estimated median progression-free survival was 2·9 months (95% CI 1·4–5·3) and estimated median overall survival was 11·5 months (95% CI 7·7–not estimable; figure 3). Of the three patients with *HER2*-mutated tumours, one achieved a partial response, one had stable disease, and one had progressive disease. None of the eight patients with *HER2* amplification without overexpression achieved a response (three had stable disease and five had progressive disease).

To determine common oncogenic mutations co-occurring with *HER2* amplification, data were obtained from local genetic testing as reported at enrolment for 55 patients (53 samples were tested with NGS, one with real-time PCR [rtPCR], and one with NGS plus rtPCR), or from central NGS testing if locally derived data for a specific gene were not available (nine patients). Mutations occurring in 10% or more of the patients tested for each gene included *TP53*, *APC*, *KRAS* (most commonly Gly12Asp or Gly12Val on exon 2), *PIK3CA* (most commonly Glu545Lys), and *SMAD4* (appendix pp 3, 7). One patient had a *BRAF* mutation (Val600Glu). No mutations were observed in *AKT1*, *ALK*, *BRCA1*, *FGFR1*, *MET*, *NRAS*, *PTCH1*, or *SMO* (appendix p 7). Additionally, of nine patients with *HRAS* testing data, none had *HRAS* mutations. All patients with known microsatellite instability status (28 [49%] of 57 patients) had low or stable microsatellite instability.

Mutations in several genes have been associated with resistance to EGFR-targeted therapy, including *KRAS*, *BRAF*, and *PIK3CA*.[1] Therefore, we did a post-hoc exploratory analysis to evaluate the association of genomic co-alterations with the proportion of patients who achieved an objective response or disease control, progressive-free survival, and overall survival. 43 (77%) of 56 tested patients had *KRAS* wild-type metastatic colorectal cancer (23 [41%] of 56 patients were tested before and seven [13%] after anti-EGFR treatment; the remaining 25 patients did not have anti-EGFR therapy). Clinical outcomes by *KRAS* mutation status are shown in table 2. In a post-hoc exploratory analysis of survival outcomes in patients by *KRAS* mutation status, median progression-free survival and overall survival were notably shorter in patients with *KRAS*-mutated tumours than in those with *KRAS* wild-type disease (figure 4; appendix p 8).

In addition to our subgroup analysis by *KRAS* status, we also did subgroup analyses to assess clinical outcomes in patients with and without anti-EGFR therapy within the *KRAS* wild-type subgroup, and in patients categorised by *PIK3CA* status, by microsatellite instability status, by tumour location, and by number of prior regimens. In patients with *KRAS* wild-type metastatic colorectal cancer, those with previous anti-EGFR therapy had numerically worse clinical outcomes than patients without previous anti-EGFR therapy. In the 23 patients with *KRAS* wild-type status determined

	Patients with objective response, n (%, 95% CI)	Patients with disease control*, n (%, 95% CI)	Median DOR†, months (95% CI)	Median PFS‡, months (95% CI)	Median OS‡, months (95% CI)s
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§ (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¶ (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 or 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
Previous 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)‖	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)**	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)††	1 (100%)	1 (100%)	2·8	5·3	7·7
Rectum (n=20)‡‡	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 previous treatment 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)

The numbers of participants in each subgroup are based on available data. DOR=duration of response. PFS=progression-free survival. OS=overall survival. MSI=microsatellite instability. NA=not applicable. NE=not estimable. *Proportion of patients with partial or complete response or stable disease for more than 4 months. †Medians are based on patients with a partial or complete response. ‡Time to event is estimated with the Kaplan-Meier method. §Specific mutations for *KRAS* and *PIK3CA* are shown in the appendix (p 3). ¶Two patients with mutated *PIK3CA* also had mutated *KRAS*; these patients had progressive disease as their best response. ‖One (4%) of 23 patients with left-sided colon cancer had *KRAS*-mutated disease. **Six (50%) of 12 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 metastatic colorectal cancer, one patient responded to treatment. ††Patient with transverse colon cancer had *KRAS* wild-type disease. ‡‡Six (30%) of 20 patients with rectal cancer had *KRAS*-mutated disease.

Table 2: **Clinical outcomes by subgroup**

before anti-EGFR treatment, seven (30%) patients achieved an objective response from pertuzumab plus trastuzumab treatment, versus four (57%) of seven patients with *KRAS* wild-type status determined after anti-EGFR therapy. Of note, clinical outcomes for patients with *PIK3CA*-mutated tumours are based on an analysis given a small subgroup (n=8). In patients with no *KRAS, PIK3CA*, or *BRAF* mutations (33 of 48 tested patients), 16 (48%) of 33 achieved an objective response and 22 (67%) had disease control. The single patient with a *BRAF* mutation had progressive disease as their best response.

Among the patients with right-sided colon tumours, fewer achieved an objective response or had disease control, and the median progression-free and overall survival was shorter than in patients with left-sided or rectal tumours (table 2). Notably, *KRAS* mutations were more common in right-sided (in six [50%] of 12 patients) than left-sided tumours (in one [4%] of 23 patients).

To investigate the association of *HER2* gene copy number with response in a post-hoc exploratory analysis, activity was assessed by NGS-derived copy number and *KRAS* status. In all patients, the median *HER2* copy number was 77 (IQR 16–126). In patients with wild-type *KRAS*, the median *HER2* copy number was 84 (IQR 16–133). Fewer patients with *KRAS* wild-type tumours with lower-than-median copy number achieved an objective response or had disease control than did those with higher-than-median or equal-to-median copy number (appendix pp 4, 9). In patients with *KRAS* mutations, median copy number was 67 (IQR 21–90); the single patient with an objective response in this group had 77 copies of *HER2*.

Since HER2 testing methods used for enrolment were not standardised in this study, a post-hoc analysis was done to assess activity in a patient subgroup with HER2 positivity determined via a single testing method. We observed that 13 (43%) of 30 patients with *KRAS* wild-type disease and *HER2* amplification determined by FoundationOne NGS—the most common method used locally or centrally in this analysis— achieved an objective response versus 17 (40%) of 43 patients who achieved an objective response in the *KRAS* wild-type population unselected for the HER2 testing method. Disease control was achieved in 13 (43%) of 30 patients with *KRAS* wild-type disease and *HER2* amplification

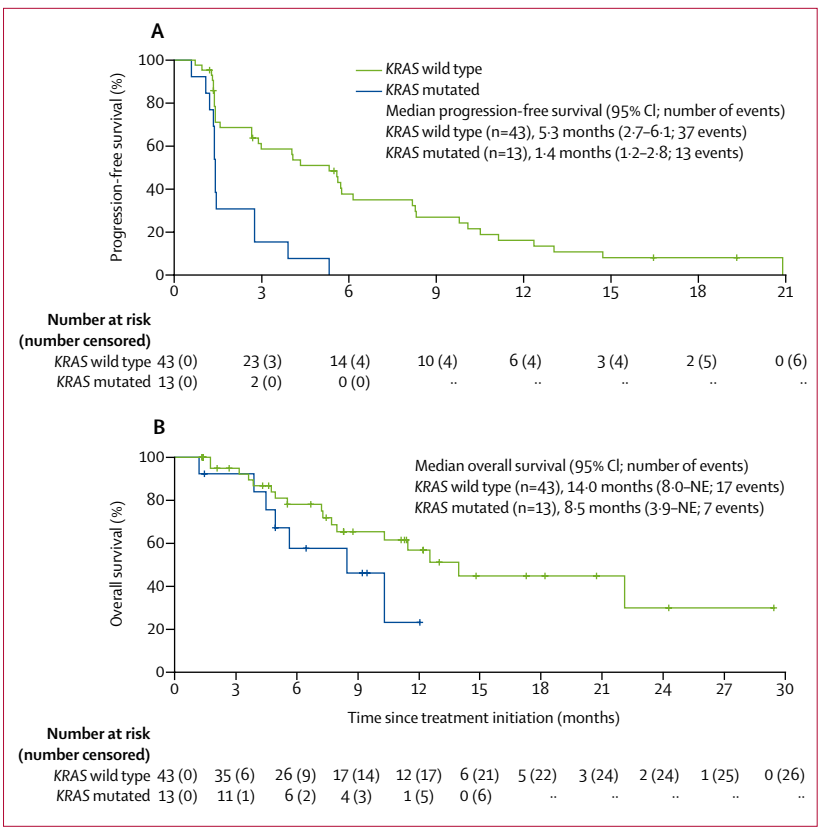

Figure 4: **Exploratory analysis of progression-free (A) and overall (B) survival by *KRAS* status**
NE=not estimable.

determined by FoundationOne NGS, versus 24 (56%) of 43 in the *KRAS* wild-type population unselected for the HER2 testing method.

Treatment-emergent adverse events were reported in 53 (93%) of 57 patients, serious treatment-emergent adverse events in ten (18%) patients, and grade 3–4 treatment-emergent adverse events in 21 (37%) patients. Three (5%) of 57 patients had a dose reduction because of adverse events (one patient with anaemia, two with weight loss) and one (2%) patient withdrew from treatment because of an adverse event (increase in bilirubin level). The most common all-grade treatment-emergent adverse events were diarrhoea (19 [33%] of 57 patients), fatigue (18 [32%]), and nausea (17 [30%]; table 3). The most common grade 3–4 treatment-emergent adverse events were hypokalaemia and abdominal pain (three [5%] patients each). Treatment-related treatment-emergent adverse events were reported in 43 (75%) patients. Two (4%) of these patients experienced serious drug-related treatment-emergent adverse events (one [2%] patient had an infusion-related reaction and one [2%] had chills). No patients had fatal treatment-emergent adverse events. 25 (44%) patients died during the study; death was due to disease progression in 22 (39%) patients and the cause was unknown in three (5%) patients.

Discussion

To the best of our knowledge, MyPathway is the first reported clinical trial to investigate the activity of pertuzumab plus trastuzumab—a regimen free of systemic chemotherapy—in patients with *HER2*-amplified metastatic colorectal cancer irrespective of *KRAS* status. In our analysis, objective responses were recorded in almost a third of patients, with responses lasting a median of 5·9 months (95% CI 2·8–11·1); four patients had response durations longer than 12 months. Disease control was recorded in 44% of patients and median progression-free survival was 2·9 months (95% CI 1·4–5·3). Median overall survival was 11·5 months (95% CI 7·7–not estimable), a duration that compares favourably with the overall survival observed in trials of other treatments for refractory metastatic colorectal cancer.[23] Patients with *KRAS* wild-type metastatic colorectal cancer had especially promising outcomes. Our data suggest promising activity and durable responses in heavily pretreated patients (median of four previous lines of therapy) with *HER2*-amplified metastatic colorectal cancer. Outcomes observed with pertuzumab plus trastuzumab are particularly striking when compared with the low proportion of patients with a response (<5%) from treatments currently indicated for metastatic colorectal cancer after the second line.[24]

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 effect on the efficacy of HER2-targeted treatments in patients with HER2-positive metastatic colorectal cancer 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 before MyPathway. 30% of 27 patients with HER2-positive, *KRAS* wild-type metastatic colorectal cancer treated with trastuzumab plus lapatinib in HERACLES achieved an objective response.[9] In MyPathway, 13 (23%) of 57 patients with *HER2*-amplified metastatic colorectal cancer had *KRAS* mutations. The proportion of patients with an objective response for this subgroup was only 8% (one of 13 patients), versus 40% (17 of 43 patients) in patients with wild-type *KRAS*, suggesting that patients with *HER2*-amplified, *KRAS* wild-type metastatic colorectal cancer derive a greater benefit from pertuzumab plus trastuzumab than those with *KRAS*-mutated metastatic colorectal cancer. Similarly, we observed that mutations in *PIK3CA* were associated with lower proportion of patients achieving an objective response (one [13%] of 8 patients) versus those with wild-type *PIK3CA* (17 [43%] of 40 patients).

Given the small size of the *PIK3CA*-mutated subgroup and the low number of patients with other *RAS/RAF* mutations, additional investigations will be required to verify the effect of mutations in these genes on HER2-targeted therapy. However, in an analysis[26] of circulating tumour DNA profiles to identify biomarkers of resistance

to lapatinib and trastuzumab in the HERACLES trial, alterations in *RAS*/*RAF* were recorded in six (86%) of seven patients who were refractory to treatment, but were observed in only three (14%) of 22 patients who had clinical benefit from lapatinib and trastuzumab. 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 might have a role in identifying markers of intrinsic and acquired resistance.

Patients with right-sided colorectal cancer have been reported to have a poorer prognosis than patients with left-sided colorectal cancer tumours.[27] In this study, we observed a lower prevalence of *HER2*-amplified right-sided tumours than of left-sided or rectal tumours. A lower proportion of patients with right-sided colon tumours had objective responses than those with left-sided or rectal tumours, and numerically shorter median progression-free survival and overall survival. However, right-sided tumours were also associated with a higher prevalence of *KRAS* mutations than were left-sided or rectal tumours (30%). As such, it remains to be seen whether pertuzumab plus trastuzumab activity differs by tumour sidedness, independent of *KRAS* status.

The assessment of HER2 status using FISH or CISH or immunohistochemistry is well established in breast[28] and gastric cancer[29] and has also been used for colorectal cancer.[30] In this study, 70% of patients had *HER2* amplification assessed by local NGS before 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 or CISH and NGS (local or central) testing, concordance for *HER2* amplification status was high (81%). The proportion of patients with *KRAS* wild-type metastatic colorectal cancer and FoundationOne NGS-determined *HER2* amplification who achieved an objective response was 43%, versus 40% in the overall *KRAS* wild-type population. These preliminary results suggest that NGS might be a viable approach to determine *HER2* amplification in patients with metastatic colorectal cancer. *HER2*-amplified patients were included in this report irrespective of HER2 overexpression, which was defined as more than 10% of cells with intense circumferential, basolateral, or lateral staining. Of note, HERACLES diagnostic criteria for HER2 positivity in colorectal cancer required HER2 overexpression in at least 50% of cells, or in more than 10% but less than 50% of cells if combined with *HER2* amplification.[30]

Our post-hoc analysis of activity by NGS-derived *HER2* copy number suggested that more patients with higher-than-median copy number achieved objective response than did those with lower copy number, which is consistent with results from HERACLES.[9] Of 16 responders with known *HER2* copy number in MyPathway, 12 had higher-than-median (≥74) copies. These and other data might position *HER2* copy number variation as an additional biomarker for treatment selection in patients with *HER2*-amplified metastatic colorectal cancer.

Taken together, these data support HER2 as a clinically relevant and actionable target in *HER2*-amplified, *KRAS* wild-type metastatic colorectal cancer. However, of eight patients with *HER2* amplification without overexpression,

	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%)	0
Dyspnoea	11 (19%)	1 (2%)	0
Vomiting	10 (18%)	1 (2%)	0
Infusion-related reaction	9 (16%)	1 (2%)	0
Increased blood alkaline phosphatase	7 (12%)	2 (4%)	0
Decreased appetite	8 (14%)	1 (2%)	0
Increased blood bilirubin	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
Increased aspartate aminotransferase	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
Lymphopenia	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
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%)

Data are n (%). Grade 1–2 adverse events occurring in at least 10% of patients and all grade 3 or worse adverse events are listed. There were no grade 5 treatment-emergent adverse events.

Table 3: **Treatment-emergent adverse events**

none achieved a response. Additional research is warranted to explore HER2 amplification and expression, HER2 expression levels, and their clinical significance in metastatic colorectal cancer.

The optimal HER2-targeted approach and sequencing of therapy for HER2-positive metastatic colorectal cancer is yet to be established. Although preclinical studies reported low activity for HER2-targeted monotherapy against colorectal cancer tumours, dual HER2-targeted combination regimens were associated with substantial reductions in tumour size.[6,8] A study in gastric cancer indicated that pertuzumab added to the current standard of care—trastuzumab plus chemotherapy[31]—did not confer an overall survival benefit (hazard ratio 0·84, 95% CI 0·71–1·00).[32] However, the combination of pertuzumab plus 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. Activity data for other HER2-targeted regimens are also expected from two new single-arm phase 2 trials: trastuzumab emtansine from HERACLES-RESCUE (NCT03418558), and pertuzumab plus trastuzumab emtansine from HERACLES-B (NCT03225937). Pertuzumab plus trastuzumab is also being investigated in the TRIUMPH trial (registration number not available), a multicentre phase 2 trial in Japan, accruing patients with HER2-positive metastatic colorectal cancer based on tissue analysis or circulating tumour DNA analysis.[33] The MyPathway strategy is also being investigated in a randomised trial (registered with NCI-SWOG, number S1613; NCT03365882) assessing pertuzumab plus trastuzumab versus cetuximab plus irinotecan in *RAS*/*BRAF* wild-type metastatic colorectal cancer. Finally, further research is needed to assess the role of continued HER2 blockade after progression on HER2-targeted therapy—a strategy that was observed to have anecdotal success in a case report of a patient with *HER2*-amplified colorectal cancer.[34]

In MyPathway, the combination of trastuzumab and pertuzumab was generally well tolerated. Diarrhoea, fatigue, and nausea were the most frequently reported adverse events and were generally low grade, consistent with known safety profiles for pertuzumab and trastuzumab in breast cancer. Pertuzumab binds to an EGFR heterodimerisation site on HER2 and, as such, is associated with anti-EGFR-related adverse events, such as diarrhoea, whereas fatigue and nausea are commonly attributed to trastuzumab treatment.[10,18] Individual grade 3 or 4 treatment-emergent adverse events were recorded in 6% or fewer of the analysis population.

Limitations of the current analysis include the absence of randomisation or of a control group; non-blinded investigator assessments; small patient cohorts in the subgroup analyses; local HER2 testing, with variability in permitted testing methods; optional co-mutation or microsatellite-instability testing done with site-determined methods; and the small number of archival samples available for central genomic, FISH or CISH, or immunohistochemistry retesting. Despite variability in testing approaches, pertuzumab plus trastuzumab conferred a promising overall proportion of patients with a response, suggesting that diverse methods can be used to identify patients who might benefit from HER2-targeted treatment. Additionally, data for *KRAS* and HER2 status were captured from assays on archival tissue obtained up to 37 months before enrolment in MyPathway. The potential subsequent development of *KRAS* mutations in tumours previously identified as *KRAS* wild-type could result in the underestimation of the proportion of patients with wild-type *KRAS* who achieved an objective response, as suggested by a small subgroup analysis showing an increased proportion of patients with an objective response in those with *KRAS* wild-type status determined after (*vs* before) anti-EGFR therapy. Finally, of seven patients still on study treatment at data cutoff, two patients had ongoing stable disease, which might also underestimate our assessment of the proportion of patients with objective response. MyPathway is an ongoing trial; when accrual to the HER2-positive basket cohort is complete, we expect to perform a final analysis of patients enrolled in this cohort, which will include patients with HER2-positive colorectal cancer as well as those with other HER2-positive cancers.

Results from MyPathway and HERACLES show the potential for dual HER2-targeted treatment in patients with HER2-positive metastatic colorectal cancer, and highlight the importance of molecular testing in this disease. Although the frequency of HER2 amplification or overexpression is low in this population, the prevalence of metastatic colorectal cancer and the promising proportion of patients with response from our study suggest that there is 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 for treatment. Pertuzumab plus trastuzumab is active in *HER2*-amplified, *KRAS* wild-type metastatic colorectal cancer, representing a therapeutic opportunity for this population, especially in patients refractory to or unable to tolerate chemotherapy. The activity data from this study suggests that early assessment of HER2 status, and earlier line use of HER2-targeted therapy, should be considered.

Contributors

FM-B, HH, CSwa, RK, HB, CSwe, RB, DRS, MSB, AS, KS, VC, and JH designed the study; FM-B, HH, KPSR, RRM, MF, AV, CSwa, RK, HB, CSwe, RB, DRS, MSB, SB, KS, VC, and JH interpreted the data; SB did the statistical analysis; and all the authors collected the data and wrote and revised the manuscript.

Declaration of interests

FM-B has served as a consultant for Dialecta and Sumitomo Dainippon; has served on advisory committees for Inflection Biosciences, Pieris, and DarwinHealth; and has 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; has served as a consultant for Acceleron Pharma, Bristol-Myers Squibb, Roche/Genentech, GlaxoSmithKline, Incyte, Lilly, Novartis, OncoMed, and TRACON Pharma; has received honoraria from Roche/Genentech and Lilly/ImClone; and has received travel, accommodation, and expense reimbursement from Roche/Genentech and TRACON Pharmaceuticals. HH's former institution (Duke University Medical Center, Durham, NC, USA) 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, and has received speaker fees from Amgen, Genentech, Sirtex, and Taiho and research support (paid to his institution) from Amgen, AstraZeneca, and Novartis. AV has received personal fees from AstraZeneca, Bristol-Myers Squibb, Roche/Genentech; grant funding from Amgen; and non-financial support from Caris Life Sciences. CSwa has received honoraria or consultant fees from Roche/Genentech, Ventana, Celgene, Pfizer, Novartis, and Bristol-Myers Squibb and grants from Pfizer and AstraZeneca, and owns stock in GRAIL, Epic Biosciences, Apogen Biotech, and Achilles Therapeutics (co-founder). RK has received grants from Incyte, Roche/Genentech, Merck Serono, Pfizer, Sequenom, Foundation Medicine, Guardant Health, and Konica Minolta and consulting fees from LOXO, X-Biotech, Actuate Therapeutics, Roche/Genentech, and NeoMed, and has an ownership interest in CureMatch. HB has received research funding for his institution from Roche/Genentech, Bristol-Myers Squibb, Incyte, Tarveda Therapeutics, Mersana Therapeutics, AstraZeneca, MedImmune, Macrogenics, Novartis, Boehringer Ingelheim, Eli Lilly, Seattle Genetics, AbbVie, Bayer, Celldex Therapeutics, Merck, Celgene, Agios Pharmaceuticals, and Jounce Therapeutics. CSwe 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. CSwe's institution has received research funding from Astellas Pharma, Exelixis, and Janssen Biotech. RB has served as a consultant for Roche/Genentech and has received honoraria from Genentech/Roche and Novartis and research funding from Puma Biotechnology. 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. DRS's 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, Oncogenex, OncoMed, Peregrine Pharmaceuticals, Pfizer, University of Texas Southwestern Medical Center—Simmons Cancer Center, and Verastem. MSB, SB, AS, KS, and VC are employed by and own stock in Roche/Genentech. JH has received research funding for his institution from Astellas Pharma, AstraZeneca, Celgene, Roche/Genentech, Johnson & Johnson, Lilly, and Novartis. All authors received non-financial support from Roche in the form of medical writing support for this manuscript. KPSR declares no competing interests.

Data sharing

Qualified researchers can request access to de-identified patient level data through the Clinical Study Data Request platform 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 can only do so via the Roche clinical study documents request form. Documents are made available on application, per scope and timing criteria as published on the Clinical Study Data Request platform.

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