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ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

ORIGINAL ARTICLE

Re-treatment with panitumumab followed by regorafenib versus the reverse sequence in chemorefractory metastatic colorectal cancer patients with *RAS* and *BRAF* wild-type circulating tumor DNA: the PARERE study by GONO☆

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Available online 18 October 2025

Background: Re-treatment with anti-epidermal growth factor receptor (EGFR) monoclonal antibodies offers a promising approach to extend the continuum of care of patients with *RAS* and *BRAF* wild-type (wt) metastatic colorectal cancer (mCRC) with no mutations of resistance in their circulating tumor DNA (ctDNA) at the time of treatment re-exposure.

Patients and methods: PARERE (NCT04787341) is an open-label, multicenter, randomized phase II trial investigating the optimal sequencing of panitumumab and regorafenib in chemorefractory *RAS* and *BRAF* wt mCRC patients, who previously derived benefit from first-line anti-EGFR-containing regimens, then received at least one intervening anti-EGFR-free line of treatment, and were prospectively selected for the absence of *RAS* and *BRAF* mutations in their ctDNA. Eligible patients were randomly assigned 1 : 1 to receive anti-EGFR re-treatment with panitumumab followed by regorafenib after progression (arm A) versus the reverse sequence (arm B). The primary endpoint was overall survival (OS).

Results: Between December 2020 and December 2024, 428 patients underwent molecular screening, and 213 with *RAS*/*BRAF* ctDNA wt were randomized (arm A/B = 106/107). At a median follow-up of 31.9 months, no difference in terms of OS was observed between treatment arms, with a median OS of 11.7 and 11.6 months in arms B and A, respectively (hazard ratio 1.13, 85% confidence interval 0.90-1.41, $P = 0.441$). However, re-treatment with panitumumab was associated with higher objective response rate (ORR; first ORR: 16% versus 2%, $P = 0.003$; second ORR: 18% versus 0%, $P = 0.013$) and disease control rate (DCR; first DCR: 61% versus 36%, $P < 0.001$; second DCR: 62% versus 38%, $P = 0.003$), and longer progression-free survival (PFS; first PFS: 4.2 versus 2.4 months, $P = 0.103$; second PFS: 3.9 versus 2.7 months, $P = 0.019$) than regorafenib, regardless of the sequence of the study treatments.

Conclusions: Anti-EGFR re-treatment should be regarded as an option in the continuum of care of chemorefractory mCRC patients with *RAS* and *BRAF* wt tumors, with no alterations of acquired resistance in their ctDNA.

Key words: metastatic colorectal cancer (mCRC), anti-EGFR, rechallenge, liquid biopsy, panitumumab, regorafenib

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☆Note: This study was presented at the ESMO Congress 2025, 17-21 October 2025, Berlin, Germany.

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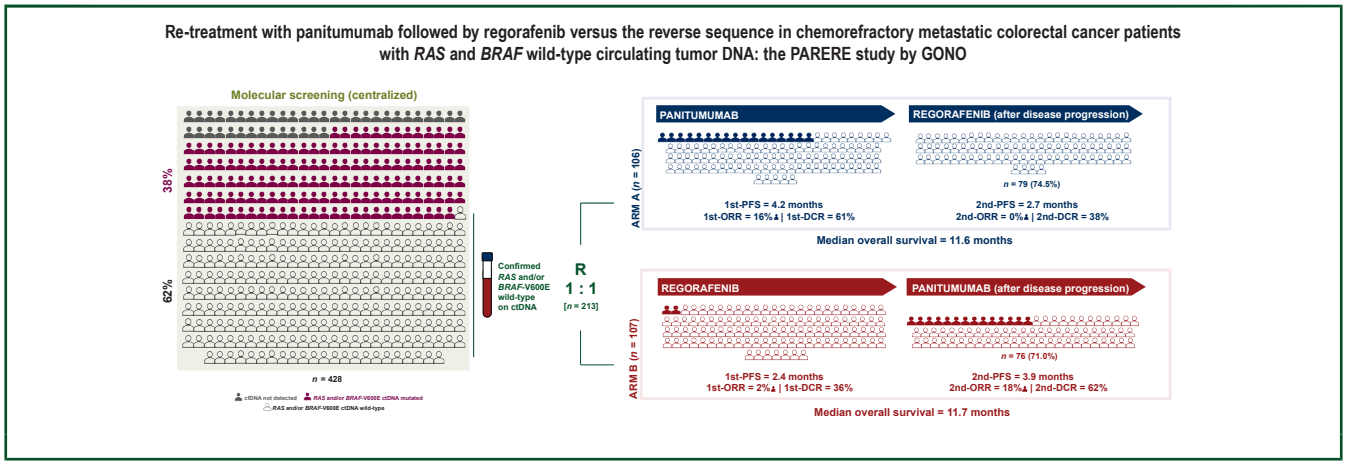
GRAPHICAL ABSTRACT



INTRODUCTION

After progressing to systemic therapies—including fluoropyrimidines, oxaliplatin, irinotecan, antiangiogenic agents, and anti-epidermal growth factor receptor (EGFR) monoclonal antibodies (mAbs)—a not negligible percentage of metastatic colorectal cancer (mCRC) patients (40%-50% according to data from clinical trials and 20%-35% according to real-world data) is still amenable to receive subsequent treatments.[1-3]

In the chemorefractory setting, the multitargeted tyrosine kinase inhibitor regorafenib was the first drug to demonstrate efficacy as single agent in phase III randomized trials,[4,5] then followed by the novel fluoropyrimidine trifluridine—tipiracil (FTD—TPI).[6,7] Over the past decade, further therapeutic options have emerged in this setting, thus making the choice of the most effective treatment a challenging issue for medical oncologists.[1,8,9] Nevertheless, for the all-comers population, these systemic therapies generally provide limited benefit, with response rates ranging from 1% to 5% and median durations of overall survival (mOS) around 7-10 months.[4,5,9,10]

In a chemorefractory, anti-EGFR-naive, *RAS* wild-type (wt) population, the Japanese phase II randomized REVERCE study demonstrated a longer OS from the sequential treatment with regorafenib followed by cetuximab ± irinotecan after disease progression versus the reverse strategy.[11]

However, in the *RAS* and *BRAF* wt subgroup, anti-EGFR agents are now generally administered in combination with a chemotherapy backbone in the first-line setting, especially in the case of left-sided primary tumors.[10,12,13] Nevertheless, under the selective pressure of the targeted treatment, acquired resistance frequently arises, mainly driven by the activation of key downstream signaling pathways, via *RAS* and/or *BRAF* mutations (∼10%-30% of cases) or other point mutations in the antibody-binding site of the EGFR extracellular domain (EGFR-ECD, ∼25%).[14-19]

Notably, these resistance mechanisms may exponentially decay after treatment withdrawal,[20] thus potentially restoring tumor sensitivity to EGFR blockade and offering the rationale for reusing the same biologic agents in the late-line setting. This hypothesis was firstly supported by the liquid biopsy-based *post hoc* analyses of phase II single-arm clinical trials,[21-23,24,26,27] revealing lack of benefit from anti-EGFR re-treatment in patients harboring *RAS* or *BRAF* mutations in their circulating tumor DNA (ctDNA), and more recently confirmed by prospective trials enrolling only patients with *RAS* and *BRAF* wt ctDNA.[23,28,29] However, no randomized trials were available.

Based on these findings, the PARERE study was designed to validate the role of the liquid biopsy-guided anti-EGFR re-treatment and to assess its proper placement in the therapeutic route of *RAS* and *BRAF* wt chemorefractory mCRC patients.

PATIENTS AND METHODS

Study design and participants

PARERE (NCT04787341) was an open-label, multicenter, randomized phase II study that enrolled patients from 37 Italian oncology units.

The main inclusion criteria were histologically confirmed diagnosis of *RAS* and *BRAF* wt mCRC; Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤1; previous treatment with—or absolute contraindications to—fluoropyrimidines, oxaliplatin, irinotecan, and anti-angiogenic agents (bevacizumab or aflibercept); Response Evaluation Criteria In Solid Tumors (RECIST) response or disease stabilization for at least 6 months during a previous first-line anti-EGFR-based treatment; at least one intervening line of anti-EGFR-free therapy; and a time interval of at least 4 months from the last anti-EGFR administration.

Eligible patients were prospectively selected for the absence of *RAS* (codons 12, 13, 59, 61, 117, and 146 of

KRAS and *NRAS* genes) and *BRAF*-V600E mutations in their ctDNA and randomly assigned in a 1 : 1 ratio to receive anti-EGFR re-treatment with panitumumab followed by regorafenib after disease progression (arm A, control) versus the reverse sequence (arm B, experimental).

Randomization was stratified according to baseline ECOG PS: 0 versus 1.

The study was conducted in accordance with the principles of Good Clinical Practice and approved by the institutional review board at each participating center. All participants provided written informed consent to study procedures before enrollment.

Treatments

Panitumumab was administered at a dose of 6 mg/kg i.v., day 1 every 2 weeks and regorafenib at 160 mg/day orally for 3 weeks followed by 1 week rest every 28 days in both treatment arms. Alternative personalized starting doses of regorafenib (i.e. 80 mg/day or 120 mg/day) were permitted at investigators' choice to be possibly escalated to 160 mg/day based on individual patients' tolerance, as per clinical practice.

All treatments were administered until disease progression, unacceptable toxicity, or patients' refusal.

Assessments

Molecular analyses on tissue samples to determine *RAS* and *BRAF* wt status [as well as mismatch repair (MMR) and human epidermal growth factor receptor 2 (HER2) testing when available] were locally carried out as per clinical practice in participating centers.

Conversely, ctDNA was centrally analyzed at the Department of Diagnostic Pathology and Laboratory Medicine, Fondazione IRCCS Istituto Nazionale dei Tumori (Milan, Italy) using the Oncomine™ Colon cell-free (cf)DNA Assay (Thermo Fisher Scientific, Inc., Waltham, MA) able to detect single-nucleotide variants and short indels in 14 CRC-related genes: *AKT1*, *APC*, *BRAF*, *CTNNB1*, *EGFR*, *ERBB2*, *FBXW7*, *GNAS*, *KRAS*, *MAP2K1*, *NRAS*, *PIK3CA*, *SMAD4*, and *TP53*.

Tumor imaging [contrast-enhanced chest and abdominal computed tomography (CT) scan or abdomen magnetic resonance imaging and chest CT, if contrast-enhanced CT scan was contraindicated] was conducted at baseline, and every 8 weeks until the second evidence of disease progression.

Radiographic assessments were locally carried out according to RECIST v1.1.

Adverse events were recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events version 5.0.

Endpoints

The primary endpoint was OS, defined as the time from randomization to the date of death due to any cause, censoring at the last follow-up patients alive and without progressive disease at the time of data cut-off.

Secondary endpoints included first progression-free survival (PFS), defined as the time from randomization to the first documentation of objective disease progression or death due to any cause; second PFS, defined as the time from the beginning of any treatment received after the first evidence of disease progression to the documentation of objective disease progression or death from any cause; first and second objective response rate (ORR, defined as the percentage of patients who achieved partial or complete response according to RECIST v1.1) and disease control rate (DCR; first and second DCR, defined as the percentage of patients who achieved partial or complete response, or stable disease according to RECIST v1.1) during the first and the second treatment received; and safety, defined as the percentage of patients experiencing any-grade and grade >2 treatment-related adverse events.

Statistical analysis

Considering an expected mOS of 9 months with panitumumab followed by regorafenib (arm A), 155 events were required to detect a hazard ratio (HR) of 0.69 in favor of the reverse sequence (regorafenib followed by panitumumb, arm B), with a two-sided log-rank test, type I error, and power of 0.15% and 80%, respectively.

The cut-off date for this analysis was 7 August 2025.

All randomized patients were included in the intention-to-treat (ITT) population.

OS, second PFS, second ORR, and second DCR were also reported in the per-protocol population, including patients who received at least one cycle of both study treatments according to their randomization arm; patients not experiencing disease progression to first-line therapies at the data cut-off were censored at the date of the last disease assessment.

Safety was assessed in all enrolled patients who received at least one dose of the study treatment.

Distribution of time-to-event variables was estimated using the Kaplan—Meier method; HRs and 85% confidence intervals (CIs) for OS and 95% CIs for secondary endpoints were estimated using Cox proportional hazards models and compared using two-sided log-rank tests stratified by ECOG PS, as used for randomization.

The ORR, DCR, and toxicity rates were compared with the χ^2 test or Fisher's exact test, when appropriate; the corresponding exact two-sided 95% CIs were calculated based on the binomial distribution.

Statistical analyses were carried out using SAS (version 9.2) and R (version 4.4.2).

RESULTS

Molecular screening with liquid biopsy

Between December 2020 and December 2024, 428 molecular screenings were centrally carried out and cell-free DNA was evaluable in 387 (90.4%) cases (Figure 1), with a median turnaround time of 12 days (95% CI 11-13 days).

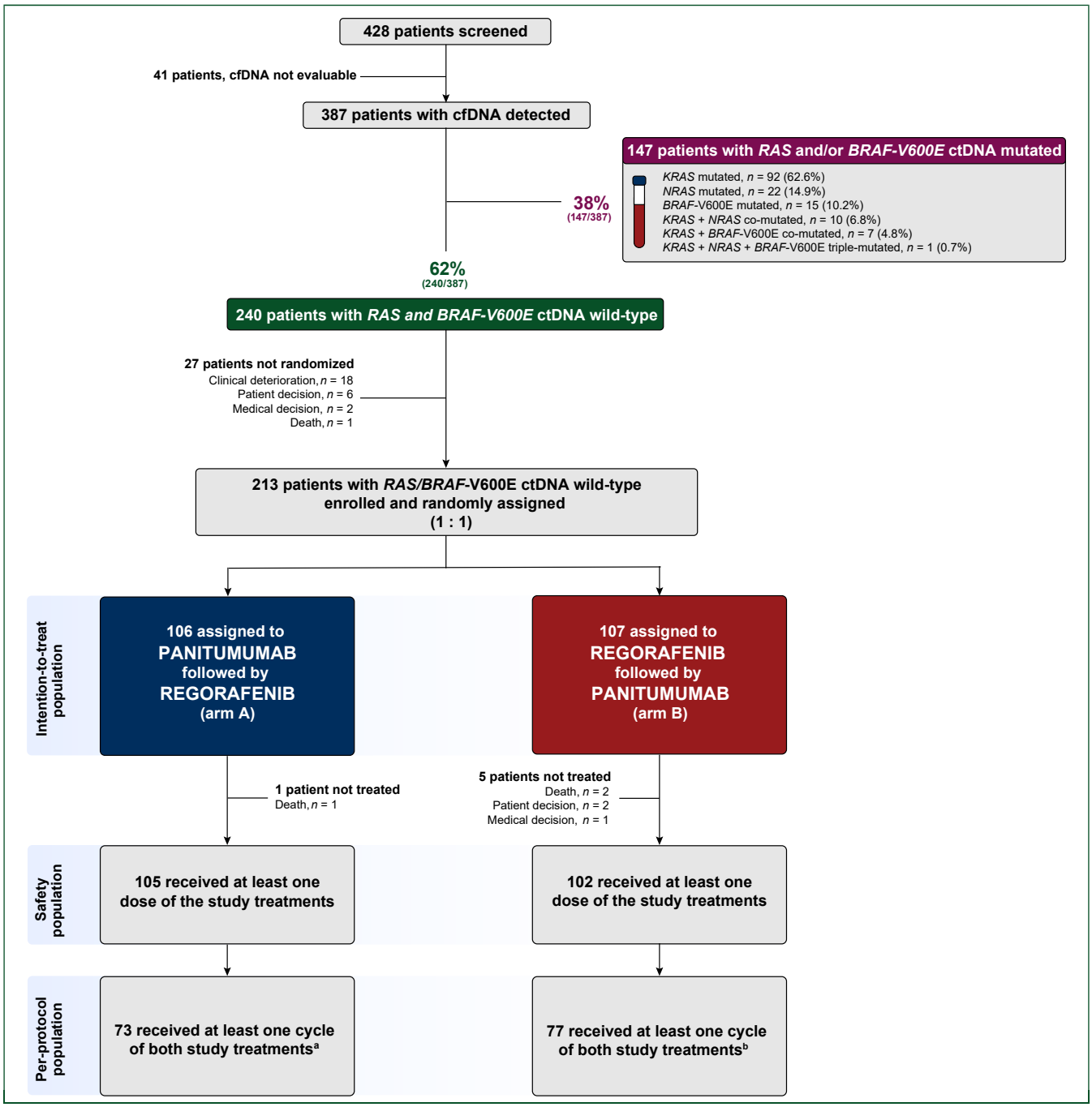


Figure 1. CONSORT diagram.
cfDNA, cell-free DNA; ctDNA, circulating tumor DNA.
[a]Two patients not experiencing disease progression to panitumumab at the data cut-off. [b]Three patients not experiencing disease progression to regorafenib at the data cut-off.

In 147 (38.0%) out of 387 cases, *RAS* and/or *BRAF*-V600E mutation were found, with mutations affecting codon 61 of both *KRAS* and *NRAS* being the most common (Figure 2A). The median variant allele fractions of *KRAS*, *NRAS*, and *BRAF*-V600E ctDNA mutations were 0.61% [interquartile range (IQR) 0.23%-2.04%], 0.79% (IQR 0.29%-3.66%), and 0.30% (IQR 0.19%-2.8%), respectively.

As compared with the *RAS*/*BRAF*-V600E wt ctDNA group, a higher percentage of patients in the *RAS/BRAF*-V600E mut ctDNA group had experienced first-line disease progression while on treatment or within 3 months after the last administration of anti-EGFR (74.2% versus 60.4%, $P = 0.006$; Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.10.002) and a shorter anti-EGFR-free interval had elapsed (11.2 versus 14.3 months, $P = 0.004$; Figure 2B). No difference was found in the first-line outcome in terms of median PFS or ORR, or the number of prior anti-EGFR-free lines of therapy (Supplementary Table S1, available at https://doi.org/10.1016/j.annonc.2025.10.002).

Moreover, samples with *RAS*/*BRAF*-V600E mut ctDNA were more likely to present co-mutations on *MAP2K1*

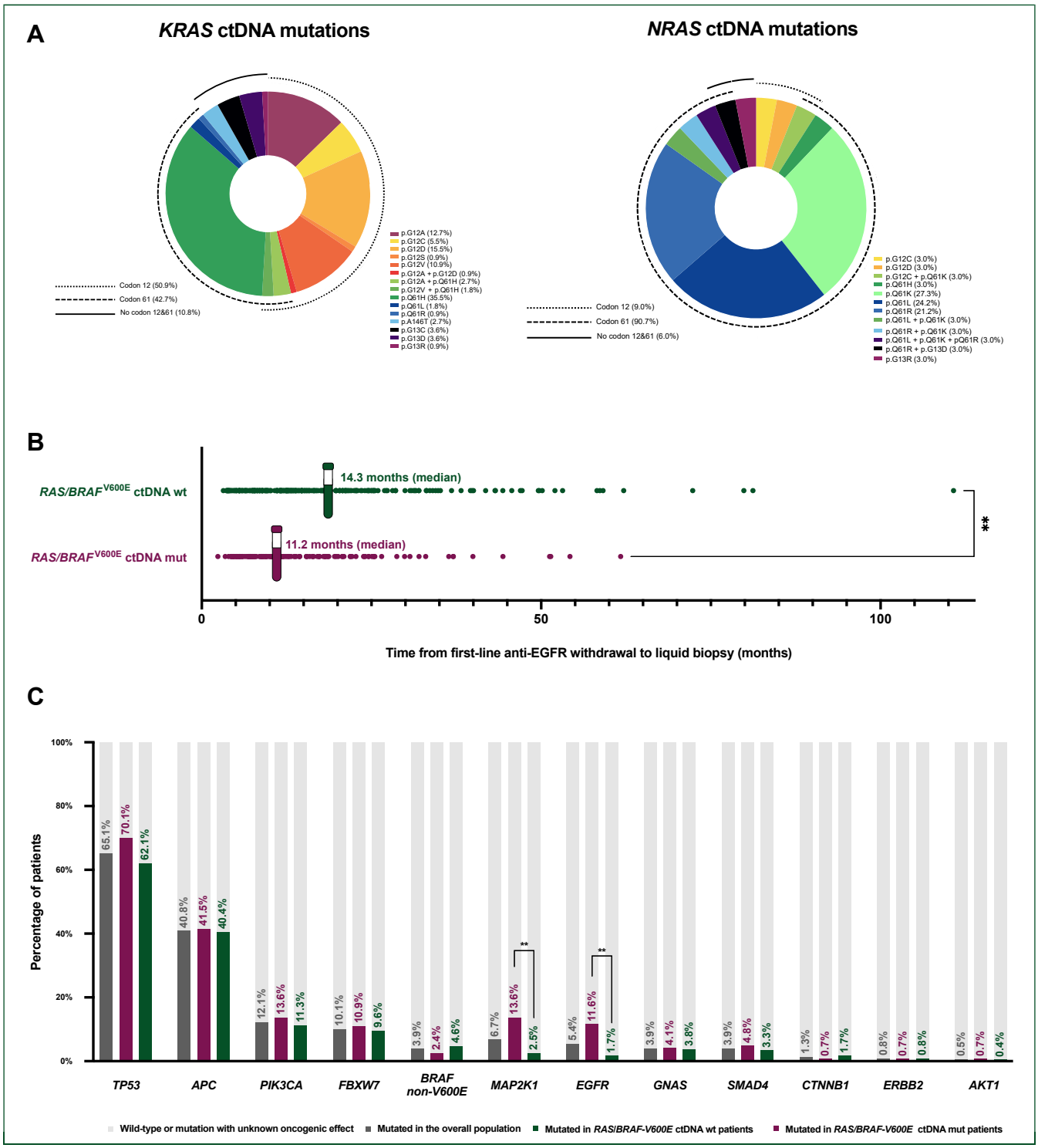


Figure 2. Molecular screening with liquid biopsy. (A) Distribution of *KRAS* and *NRAS* ctDNA mutations in patients screened within the PARERE trial. (B) Median time from first-line anti-EGFR withdrawal and liquid biopsy screening between *RAS/BRAF*-V600E ctDNA wt and ctDNA mut. (C) Frequency of genomic alterations identified by NGS on baseline ctDNA of screened patients in the overall ($n = 387$), *RAS/BRAF*-V600E ctDNA mut ($n = 147$), and *RAS/BRAF*-V600E ctDNA wt ($n = 240$) populations. ctDNA, circulating tumor DNA; EGFR, epidermal growth factor receptor; mut, mutated; NGS, next-generation sequencing; wt, wild-type.

(13.6% versus 2.5%, $P < 0.001$) and *EGFR* (11.6% versus 1.7%, $P < 0.001$) genes (Figure 2C).

Patients

Two hundred and thirteen (88.8%) out of 240 *RAS/BRAF*-V600E ctDNA wt patients were randomly assigned to panitumumab followed by regorafenib (arm A, $n = 106$) or to regorafenib followed by panitumumab (arm B, $n = 107$) (ITT population; Figure 1).

Two hundred and seven patients received at least one dose of the first study treatment (safety population; 105 in arm A and 102 in arm B) and 150 (70.4%) patients entered

https://doi.org/10.1016/j.annonc.2025.10.002

the per-protocol population (73 in arm A and 77 in arm B), receiving at least one dose of both study treatments or not experiencing disease progression during or after the first study treatment ($n = 145$) (Figure 1).

Patients' and disease characteristics of the ITT population are summarized in Table 1.

The median age of the study population was 62 years [61 years (IQR 52-68 years) and 64 years (IQR 58-74 years) in arms A and B, respectively].

The majority of patients had an ECOG PS of 0 (70.8% in arm A and 68.2% in arm B), a left-sided primary tumor (92.5% and 88.8%), presented with more than one site of metastatic disease (83.0% and 86.8%), and had previously received a median of two lines of therapy in both treatment arms (Table 1).

MMR/microsatellite instability (MSI) and HER2 status on tumor tissue were assessed in 204 (95.8%) and 121 (56.8%) cases, respectively. Three (1.5%) MMR-deficient/MSI-high and six (5.0%) HER2-positive patients were included.

Efficacy

At a median follow-up of 31.9 months (IQR 17.8-44.7 months), 169 (79.3%) OS events were observed [84 (79.2%) in arm A; 85 (79.4%) in arm B].

The median OS was 11.6 months and 11.7 months in arms A and B, respectively (HR 1.13, 85% CI 0.90-1.41, log-rank test $P = 0.441$; Figure 3A). No OS difference was evident also in the per-protocol population (median OS 16.7 and 16.1 months in arms A and B, respectively; HR 1.07, 85% CI 0.81-1.41, $P = 0.730$; Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2025.10.002).

Patients treated with panitumumab first (arm A) experienced longer first PFS (4.2 versus 2.4 months; HR 1.26, 95% CI 0.95-1.66, $P = 0.103$) and higher first ORR (16% versus 2%, $P = 0.003$) and DCR (61% versus 36%, $P < 0.001$) than those treated with regorafenib first (arm B) (Figure 3B and Table 2). Median treatment duration was 3.8 months with panitumumab (IQR 1.94-5.75 months) and 2.1 months with regorafenib (IQR 1.61-4.38 months).

Seventy-nine (74.5%) out of 106 patients randomized in arm A and 76 (71.0%) out of 107 patients randomized in arm B were assigned to the second treatment after first disease progression.

Patients treated with panitumumab after disease progression (arm B) reported longer second PFS (3.9 versus 2.7 months; HR 0.67, 95% CI 0.48-0.94, $P = 0.019$) and higher second ORR (18% versus 0%, $P = 0.013$) and second DCR (62% versus 38%, $P = 0.003$) than those treated with regorafenib (arm A) (Figure 3C and Table 2), with a median treatment duration of 2.2 months (IQR 1.71-3.36 months) and 3.5 months (IQR 1.54-5.49 months) with regorafenib and panitumumab, respectively.

Similar findings were reported in the per-protocol populations (Supplementary Figure S1, available at https://doi.org/10.1016/j.annonc.2025.10.002, and Table 2).

No significant interaction was found between all analyzed clinical characteristics and treatment effect, with the exception of significantly lower OS benefit from arm A (panitumumab first) among patients with an anti-EGFR-free interval $\leq$6 months [P for interaction (P_{int}) = 0.041; Figure 4A]. Consistent results were reported in terms of first PFS ($P_{int} = 0.005$; Figure 4B). A heterogeneous effect of treatment strategies on OS was reported also according to sex, with higher benefit from arm A among females ($P_{int} = 0.018$).

Molecular hyperselection

Two hundred and twelve out of 213 randomized patients had a full coverage in relevant gene regions included in the Oncomine™ panel. Nineteen (9.0%) patients harbored at least one mutation potentially associated with resistance to anti-EGFR mAbs[30,31] in their ctDNA (gene-altered ctDNA population; Supplementary Figure S2, available at https://doi.org/10.1016/j.annonc.2025.10.002)—*AKT1*, *MAP2K1*, *EGFR*, *ERBB2*, non-*BRAF*-V600E class I or II, and *PIK3CA* exon 20 oncogenic mutations.

In a *post hoc* exploratory analysis, no difference in efficacy and activity parameters between panitumumab and regorafenib was reported in the gene-altered ctDNA population, while the benefit from panitumumab re-treatment over regorafenib was more evident in the ctDNA negatively hyperselected population (Supplementary Figure S3 and Table S2, available at https://doi.org/10.1016/j.annonc.2025.10.002).

Out of 110 patients with known MMR-proficient/microsatellite stable and HER2-negative tumors, efficacy results were consistent with those in the ITT population, with numerically longer first and second PFS, higher first and second ORR with panitumumab, and no OS difference (Supplementary Figure S4 and Table S2, available at https://doi.org/10.1016/j.annonc.2025.10.002).

Safety

Grade 3 and 4 events of any cause occurred in 45 (43.0%) and 52 (51.0%) patients in arms A and B, respectively ($P = 0.268$).

Grade $\geq$3 acneiform skin rash was more frequent with panitumumab than with regorafenib in both treatment arms (19.2% versus 2.9% as first treatment, $P < 0.001$—13.7% versus 0% as second treatment, $P = 0.002$) (Figure 5).

In arm B, 96 (94.1%) of 102 patients started regorafenib after randomization at a reduced dosage [88 (86.3%) at 80 mg/day and 8 (7.8%) at 120 mg/day] and 26 of them (27.1%) escalated to 160 mg/day. Similarly, in arm A, 68 [95.8%] of 71 patients started regorafenib as second treatment with a dose reduction [61 (85.9%) at 80 mg/day and 7 (9.9%) at 120 mg/day] and 19 of them (27.9) were able to escalate to the full dosage.

Compared with panitumumab, regorafenib was significantly associated with a higher incidence of grade $\geq$3 adverse events, including hypertension (13.7% versus 1.0%

Table 1. Baseline characteristics of the intention-to-treat population

	Panitumumab followed by regorafenib (arm A; *n* = 106)	Regorafenib followed by panitumumab (arm B; *n* = 107)
Age, median (IQR), years	61 (52-68)	64 (58-74)
<65 years, *n* (%)	67 (63.2)	54 (50.5)
≥65 years, *n* (%)	39 (36.8)	53 (49.5)
Sex, *n* (%)		
Female	39 (36.8)	46 (43.0)
Male	67 (63.2)	61 (57.0)
ECOG performance status, *n* (%)		
0	75 (70.8)	73 (68.2)
1	31 (29.2)	34 (31.8)
Location of primary tumor, *n* (%)		
Left or rectum	98 (92.5)	95 (88.8)
Right	8 (7.5)	12 (11.2)
Surgery on primary tumor, *n* (%)		
Yes	82 (77.4)	86 (80.4)
No	24 (22.6)	21 (19.6)
Time to metastases, *n* (%)		
Synchronous	78 (73.6)	76 (71.0)
Metachronous	28 (26.4)	31 (29.0)
Previous adjuvant chemotherapy, *n* (%)		
No	82 (77.4)	84 (78.5)
Yes	24 (22.6)	23 (21.5)
First-line anti-EGFR received, *n* (%)		
Panitumumab	69 (65.1)	74 (69.2)
Cetuximab	37 (34.9)	33 (30.8)
Objective response to first-line anti-EGFR-containing regimes, *n* (%)		
Yes	84 (79.2)	86 (80.4)
No	22 (20.8)	21 (19.6)
No. of previous lines for the metastatic disease, median (IQR)	2 (2-3)	2 (2-3)
No. of anti-EGFR-free lines of therapy, *n* (%)		
1 line	80 (75.5)	81 (75.7)
>1 line	26 (24.5)	26 (24.3)
Anti-EGFR-free interval, median (IQR), months	15.0 (10.1-24.7)	14.6 (9.3-23.4)
>6, *n* (%)	99 (93.4)	98 (91.6)
≤6, *n* (%)	7 (6.6)	9 (8.4)
>18, *n* (%)	45 (42.5)	41 (38.3)
≤18, *n* (%)	61 (57.5)	66 (61.7)
Re-treatment strategy, *n* (%)		
Reintroduction[a]	42 (39.6)	46 (43.0)
Rechallenge[a]	64 (60.4)	61 (57.0)
No. of metastatic sites, *n* (%)		
Multiple	88 (83.0)	93 (86.8)
Single	18 (17.0)	14 (13.2)
Liver-only disease, *n* (%)		
Yes	12 (11.3)	9 (8.5)
No	94 (88.7)	97 (91.5)
Liver metastases, *n* (%)		
Yes	76 (71.7%)	78 (72.9%)
No	30 (28.3%)	29 (27.1%)
Other oncogenic mutations in cfDNA, *n* (%)		
Yes	88 (83.0)	84 (79.2)
No	18 (17.0)	22 (20.8)
Unknown	—	1
MMR and MSI status on tumor tissue, *n* (%)		
MSI-high or dMMR	3 (2.9)	0 (0.0)
MSS/MSI-low or pMMR	99 (97.1)	102 (100.0)
Unknown	4	5
HER2 status on tumor tissue, *n* (%)		
Positive	5 (7.6)	1 (1.8)
Negative	61 (92.4)	54 (98.2)
Unknown	40	52

cfDNA, cell-free DNA; dMMR, mismatch repair-deficient; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; IQR, interquartile range; MMR, mismatch repair system; MSI, microsatellite instability; pMMR, mismatch repair-proficient.
[a]Disease progression occurring during or within (rechallenge) versus after (reintroduction) 3 months after the prior last anti-EGFR administration.

as first treatment, $P < 0.001$—10% versus 0% as second treatment, $P = 0.006$), fatigue (9.8% versus 2.9% as first treatment, $P = 0.047$), and hand–foot skin reaction (5.9% versus 0% as first treatment, $P = 0.013$) (Figure 5).

Subsequent therapies

Overall, of the 99 (46.5%) out of 213 randomized patients, 54 (51.0%) in arm A and 45 (44.0%) in arm B received at least another line of systemic therapy after progressing to their respective second study treatment (Supplementary Figure S5, available at https://doi.org/10.1016/j.annonc.2025.10.002).

The most common subsequent therapy was FTD–TPI ± bevacizumab in both treatment arms [83.3% (45/54) in arm A; 75.6% (34/45) in arm B], followed by chemotherapy rechallenge [11.1% (6/54) in arm A; 22.2% (10/45) in arm B].

No numerical imbalances were observed between treatment arms in terms of subsequent therapies.

Notably, eight patients (six in arm A and two in arm B) were re-exposed to further anti-EGFR-based treatments.

DISCUSSION

Several single-arm phase II trials showed that a re-treatment strategy with anti-EGFRs could be a promising approach in chemorefractory *RAS* and *BRAF* wt mCRC patients not bearing in their ctDNA genetic mechanisms of acquired resistance to this class of drugs.[21,23,32-34] However, the lack of evidence from randomized clinical trials elucidating the potential benefit from this strategy versus a standard of care in the later-line settings blunted the use of this therapeutic approach in clinical practice. Accordingly, PARERE aimed at quantifying the magnitude of benefit from the reuse of an anti-EGFR—panitumumab—as compared with regorafenib, a standard-of-care option in chemorefractory mCRC, in a molecularly selected population. It is noteworthy that PARERE demonstrated that ctDNA-guided anti-EGFR re-treatment is superior to

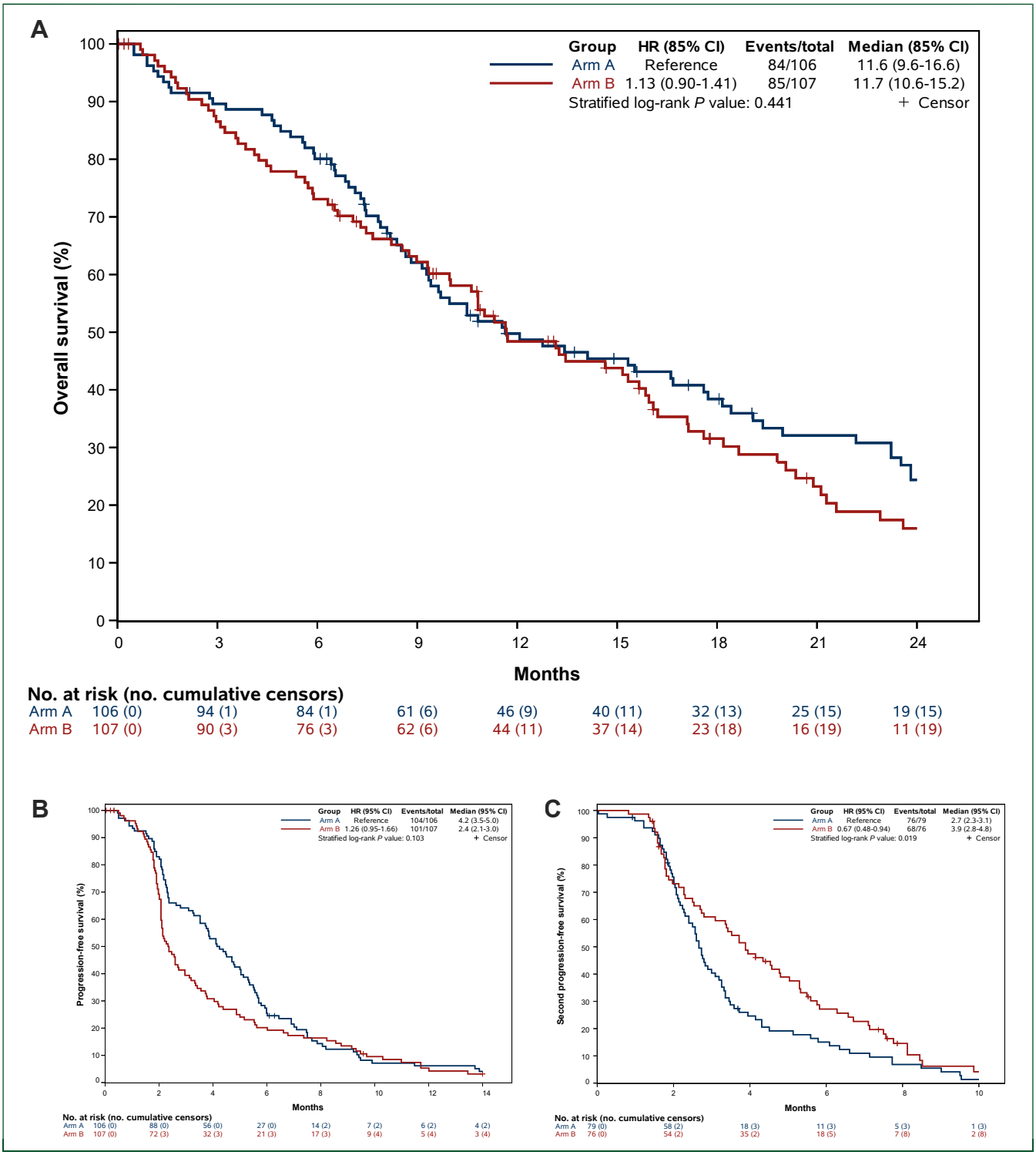


Figure 3. Overall survival and Progression-free survivals in the intention-to-treat population. Kaplan—Meier estimates of overall survival (A), first progression-free survival (B), and second progression-free survival (C) in the intention-to-treat population. Arm A, re-treatment with panitumumab followed by regorafenib at disease progression; arm B, regorafenib followed by re-treatment with panitumumab at disease progression. Crosses denote censored patients.
CI, confidence interval; HR, hazard ratio.

regorafenib in terms of ORR, DCR, and PFS and is associated with a more manageable safety profile, regardless of the planned sequence of administration of the two drugs. Since panitumumab was given in both the arms, the trial could not aim at demonstrating an OS advantage for anti-EGFR versus regorafenib but just to compare the two sequences. In fact, despite an initial survival advantage was observed with early initiation of anti-EGFR re-treatment (arm A), no significant difference in OS was ultimately detected. This finding may be partially explained by the benefit observed in second PFS for arm B—when patients previously treated with regorafenib were able to be re-treated with panitumumab after first disease progression—thus possibly diluting the OS benefit between

Table 2. Activity outcomes in the intention-to-treat and per-protocol populations

	Panitumumab[a] (arm A; ITT *N* = 106)	**Regorafenib (arm B; ITT *N* = 107)**	
First ORR, *n* (%)	17 (16)	2 (2)	OR 0.10, 95% CI 0.02-0.44, $P = 0.003$[b]
First DCR, *n* (%)	65 (61)	38 (36)	OR 0.35, 95% CI 0.20-0.61, $P < 0.001$[b]
	Regorafenib[a] (arm A; ITT *N* = 79)	**Panitumumab (arm B; ITT *N* = 76)**	
Second ORR, *n* (%)	0 (0)	14 (18)	OR 36.9, 95% CI 2.16-630.51, $P = 0.013$[b]
Second DCR, *n* (%)	30 (38)	47 (62)	OR 2.65, 95% CI 1.38-5.06, $P = 0.003$[b]
	Regorafenib[a] (arm A; PP *N* = 71)	**Panitumumab (arm B; PP *N* = 74)**	
Second ORR, *n* (%)	0 (0)	14 (19)	OR 34.27, 95% CI 2.00-586.58, $P = 0.015$[b]
Second DCR, *n* (%)	27 (38)	47 (64)	OR 2.84, 95% CI 1.45-5.56, $P = 0.002$[b]

CI, confidence interval; DCR, disease control rate; ITT, intention-to-treat population; OR, odds ratio; ORR, objective response rate; PP, per-protocol population.
[a]Reference.
[b]Wald χ^2 test.

both treatment strategies. Furthermore, the absence of significant differences in terms of subsequent therapies may further support this interpretation.

With regard to the choice of regorafenib in the treatment sequence, it should be underlined that, when PARERE was designed, data neither from the SUNLIGHT trial, which established FTD—TPI + bevacizumab as a new standard of care in third line,[9] nor from the FRESCO2 trial, which lead to the approval of fruquintinib in the chemorefractory scenario,[8] had been published yet. In the same setting, the only registered alternative to regorafenib during most time of the trial accrual was FTD—TPI monotherapy, whose efficacy seems similar to regorafenib, according to cross-trial comparisons and also in the SORGATT trial,[35] with a different safety profile.[4-7] Therefore, though acknowledging that the therapeutic algorithm of chemorefractory mCRC has recently been reshaped in the very last years,[1] regorafenib is still an option in the advanced lines of mCRC care.

The findings from PARERE should be interpreted in the current framework of other studies addressing anti-EGFR re-treatment in chemorefractory mCRC patients. In particular, two clinical trials recently randomized patients with *RAS* wt tumors to anti-EGFR re-treatment with cetuximab plus irinotecan-based chemotherapy versus investigator's choice. In the phase II CITRIC trial, only patients with no mutations in *RAS*, *BRAF*, and *EGFR-ECD* in their ctDNA were randomized.[25] Despite being less powered (only 58 patients were enrolled), the magnitude of benefit from cetuximab + irinotecan in terms of ORR (13% versus 0%) and PFS (median: 4.4 versus 2.2 months) was similar to PARERE, therefore supporting the external validity of our findings.[25] In the phase III FIRE-4 trial, the potential benefit of anti-EGFR re-treatment was likely masked by the absence of a centralized ctDNA screening before randomization and by the inclusion of patients who were unlikely truly chemorefractory, as suggested by the overperformance of the control arm (ORR 11%, mPFS 4.6 months, OS 15.1 months), where patients mostly received chemotherapy doublets ± antiangiogenics (76%).[36]

With regard to the role of molecular selection by liquid biopsy, PARERE provides the strongest evidence available so far on the percentage of patients who are excluded from anti-EGFR re-treatment for molecular reasons (38%), the actual persistence in later lines of mechanisms of acquired resistance (i.e. the high prevalence of codon 61 mutations in *RAS* genes and the co-occurrence of multiple alterations), thus emphasizing the selection by liquid biopsy—when available—as preferable, rather than clinical criteria alone. This given, we acknowledge that, despite molecular selection, >40% of patients did not derive any benefit from panitumumab, suggesting that ctDNA profiling as a selection tool from anti-EGFR re-treatment can be improved. To this objective, an intriguing hypothesis is supported by an exploratory analysis of the Japanese REMARRY and PURSUIT trials,[34] where the benefit from anti-EGFR re-treatment was modest when alterations of resistance occurred during the initial anti-EGFR-based therapy and then decayed over time. Conversely, higher benefit was observed among patients with no alterations of resistance at any time point, especially expanding the search for alterations of resistance beyond *RAS* and *BRAF* mutations (negative hyperselection).[34] While the collection of ctDNA samples at the time of disease progression to the first-line anti-EGFR-based therapy was not scheduled in PARERE, as it was deemed hardly feasible in a large multicentric academic trial, our findings seem to underline the relevance of the anti-EGFR-free interval duration. In fact, subgroup analyses suggest that anti-EGFR re-treatment might not be a good choice when the anti-EGFR-free interval is ≤6 months, though in the absence of *RAS* or *BRAF*-V600E ctDNA mutations, with coherent results in terms of first PFS and OS. Consistently with the Japanese trials, we also observed in a randomized setting that the benefit from anti-EGFR re-treatment, as compared with regorafenib, was mainly restricted to negatively hyperselected patients, with no difference between the two strategies in case of alterations potentially associated with anti-EGFR resistance. We acknowledge that the next-generation sequencing panel used for ctDNA screening in PARERE (Oncomine™) was designed to detect only single-nucleotide variants and short indels in a smaller number of genes than those included in the PRESSING panel and other studies exploring the same concept.[30,31,37,38]

PARERE also aimed at addressing the question of the best treatment sequence between anticipation and delay of anti-EGFR re-treatment, with respect to regorafenib. Even if we could not identify a clearly preferable treatment

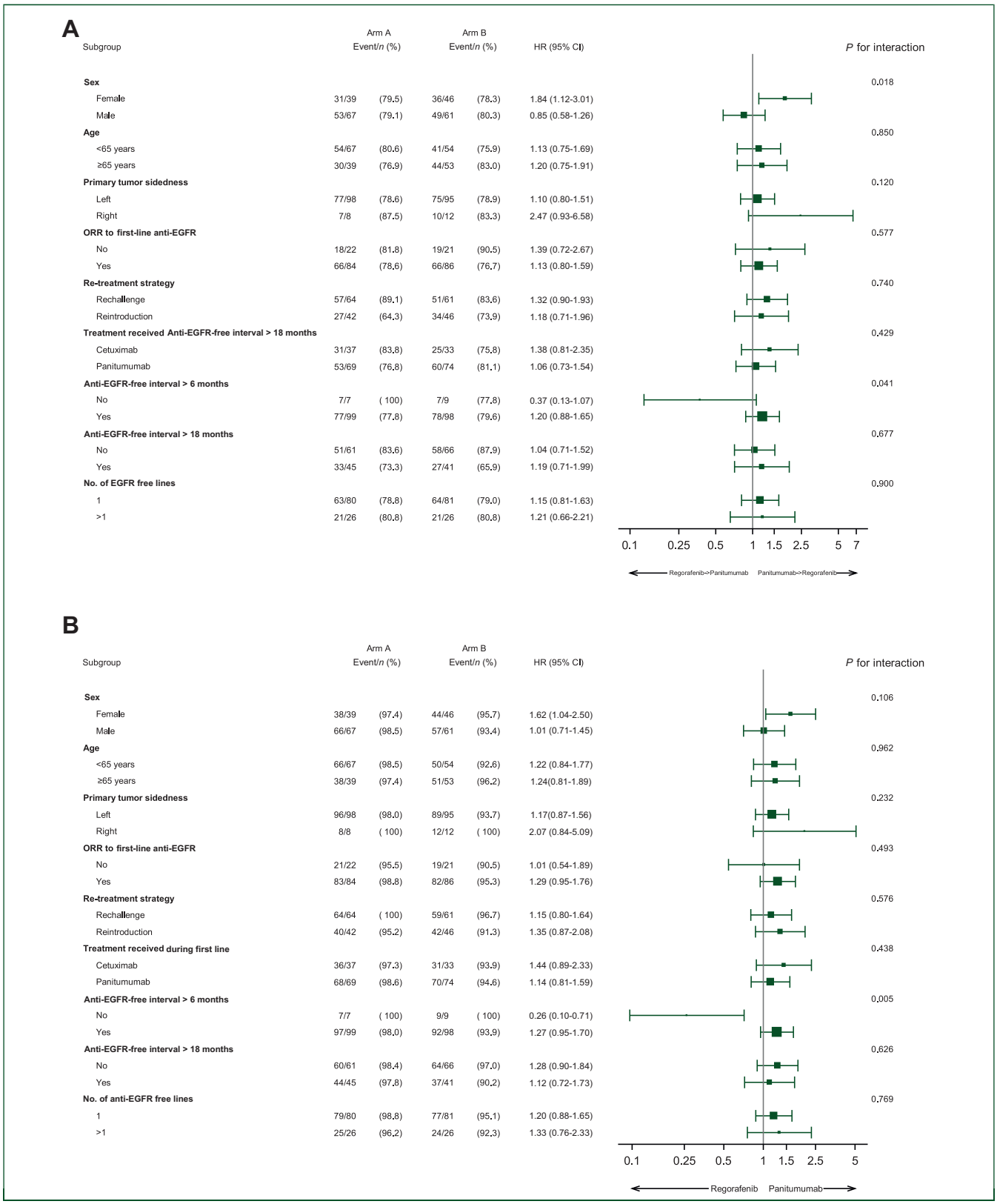


Figure 4. Subgroup analyses for overall survival and first progression-free survival in the intention-to-treat population. Forest plots analyses of overall survival (A) and first progression-free survival (B) according to clinical characteristics in the intention-to-treat population. The size of the square symbols indicates the size of the subgroups investigated.
CI, confidence interval; HR, hazard ratio.

sequence, we believe that the most pragmatic choice in a therapeutic scenario of heavy chemo-refractoriness is to address the attrition rate across later lines of treatment, linked to the high risk of clinical deterioration, anticipating, rather than postponing, the administration of the most effective approach in the sequence, i.e. the anti-EGFR

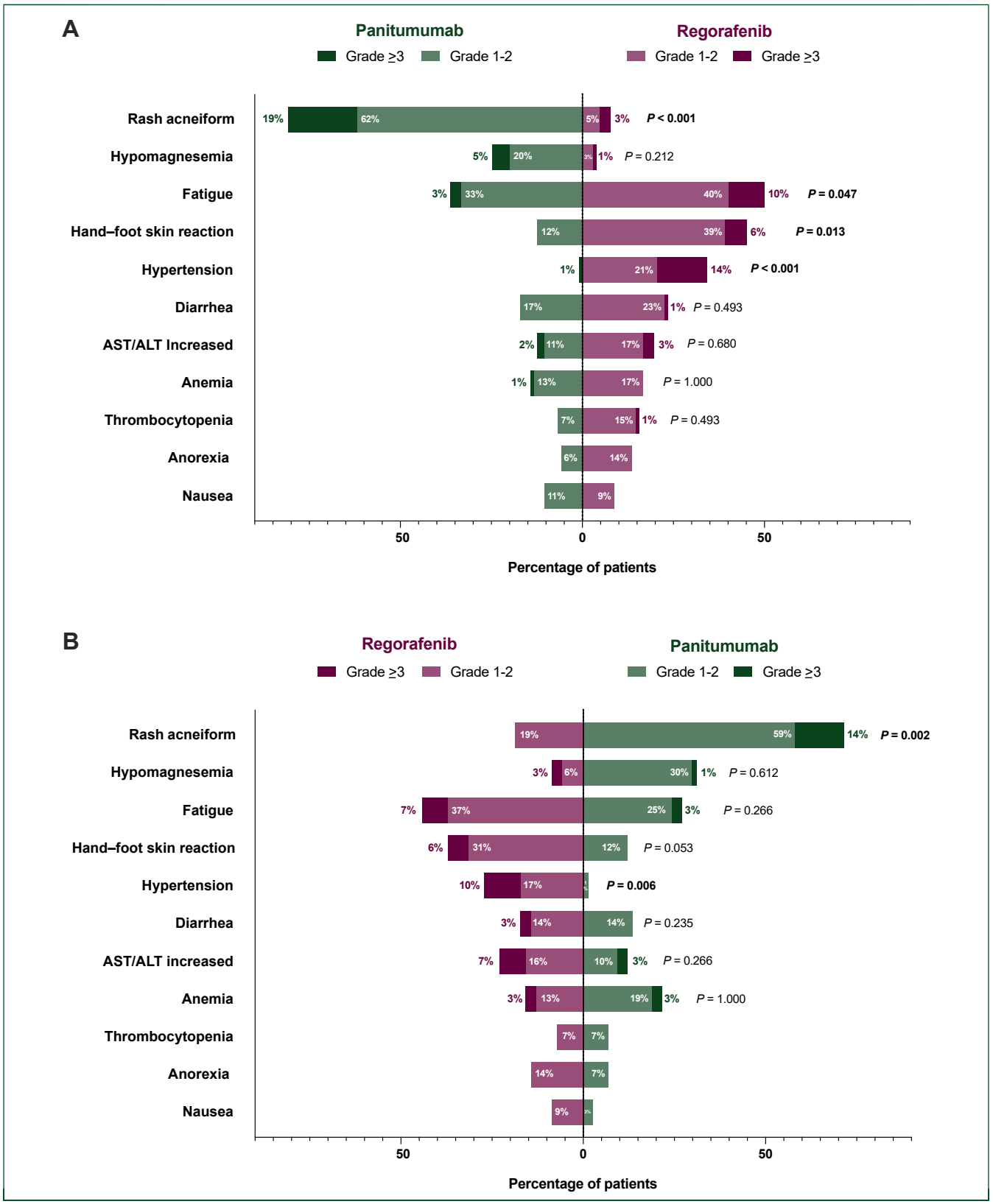


Figure 5. Safety. Tornado plots of aAll-cause adverse events occurring during first (A) and second (B) study treatments.
ALT, alanine aminotransferase; AST, aspartate aminotransferase.

re-treatment that demonstrated a clear PFS and activity benefit, except for the subgroup of patients with an anti-EGFR-free interval $\leq$6 months.

In conclusion, based on the results of the PARERE trial, anti-EGFR re-treatment should be regarded as an option in the continuum of care of chemorefractory mCRC patients

https://doi.org/10.1016/j.annonc.2025.10.002

with *RAS* and *BRAF* wt tumors, selected by liquid biopsy. Since FTD—TPI + bevacizumab is today the third-line standard of care for most patients based on a large phase III trial,[9] anti-EGFR re-treatment might be generally considered after disease progression to this therapy. None the less, if tumor shrinkage is a compelling need, as in the case of symptomatic lesions or lesions at risk of becoming symptomatic soon, or in the presence of contraindications to the addition of the antiangiogenic, anticipating anti-EGFR re-treatment might be clinically sound, if at least 6 months have elapsed from the last anti-EGFR administration in the first-line setting.

ACKNOWLEDGEMENTS

The authors thank all participating patients, their families, and caregivers for their involvement in this trial and all Italian GONO Foundation investigators and site personnel from participating sites.

GONO Foundation Investigators (collaborators): Vincenzo Formica, Angelo Martignetti, Domenico Cristiano Corsi, Elena Fea, Elena Parlagreco, Alessandra Gennari, Rossana Berardi, Francesca Simionato, Elisa Sperti, Alessandro Pastorino, Editta Baldini, Emanuela Dell'Aquila, Emiliano Tamburini, Gemma Zucchelli, Angela Buonadonna, Rita Chiari, Saverio Cinieri, Alberto Ballestrero, Rosa Berenato, Myriam Katja Paris, Samanta Cupini, Michele Ghidini, Michela Frisinghelli, and Claudia Sonaglio.

FUNDING

This work was supported by the GONO Foundation and partially supported by Amgen and Bayer (no grant number). The funding sources had no role in the design of this trial and its execution, analyses, interpretation of the data, or decision to submit results. CC, MMG, and VC received support at UNIPI by the European Union—NextGenerationEU through the Italian Ministry of University and Research under PNRR - M4C2-I1.3 Project PE_00000019 'HEAL ITALIA' [grant number CUP: I53C22001440006]. The views and opinions expressed are those of the authors only and do not necessarily reflect those of the European Union or the European Commission. Neither the European Union nor the European Commission can be held responsible for them.

DISCLOSURE

FPi: research funding (to institution) from Lilly, BMS, Incyte, AstraZeneca, Amgen, Agenus, Rottapharm, Johnson & Johnson, GSK, and Tempus; personal honoraria as an invited speaker from BeOne, Daiichi-Sankyo, Seagen, Astellas, Ipsen, AstraZeneca, Servier, Bayer, Takeda, Johnson&Johnson, BMS, MSD, Amgen, Merck Serono, Pierre Fabre, Incyte, and AstraZeneca; advisory/consultancy from BMS, MSD, Amgen, Pierre Fabre, Johnson&Johnson, Servier, Bayer, Takeda, Astellas, GSK, Daiichi-Sankyo, Pfizer, BeOne, Jazz Pharmaceuticals, Incyte, Rottapharm, Merck Serono, Italfarmaco, Gilead, AstraZeneca, Agenus, and Revolution Medicine; travel expenses from Amgen, Merck Serono, Pierre Fabre, Servier, Astellas, Incyte, and Johnson&Johnson. SL: honoraria for advisory boards/speakers bureau from Amgen, Merck Serono, Eli Lilly Co, Roche, Eli Lilly Co, Bristol-Myers Squibb, Servier, and Merck Serono; and research funding from Amgen and Merck Serono. SDD: consulting or advisory role for Amgen, Merck Serono, Servier, and Bayer; and travel, accommodations, expenses from Bayer. EF: honoraria for advisory boards from Merck-Pierre Fabre. MS: advisory board and speakers' bureau from Amgen, Merck, Servier, Daiichi-Sankyo, AstraZeneca, and MSD. LS is supported by the AIRC under My First Grant (MFAG27367), outside the submitted work, and reports consulting or advisory role for Pierre Fabre, AstraZeneca, Bayer, Servier, Merck, Amgen, GSK, Incyte, Leopharma, MSD, and Takeda. GR: speaking bureau from Accademia di Medicina; and advisory/consultancy from Amgen and AstraZeneca. DR: speaking bureau from Amgen, Pierre Fabre, Bayer, Takeda, and MSD. CC: advisory board or consultant role with AstraZeneca, Bicara Therapeutics, BMS, GSK, Lilly, Merck, Mirati, MSD, Nordic Pharma, Roche, Pfizer, Pierre Fabre, Revolution Medicine, Rottapharm, Takeda, and Tempus; invited speaker with compensation for Amgen, Bayer, Merck Serono, MSD, Pierre Fabre, Servier, and Takeda; and research grants from Amgen, Merck, Pierre Fabre, Roche, Seagen (Pfizer), Servier, and Tempus. All other authors have declared no conflicts of interest.

REFERENCES

1. Ciracì P, Studiale V, Taravella A, Antoniotti C, Cremolini C. Late-line options for patients with metastatic colorectal cancer: a review and evidence-based algorithm. *Nat Rev Clin Oncol*. 2025;22(1):28-45.
2. Rossini D, Germani MM, Lonardi S, et al. Treatments after second progression in metastatic colorectal cancer: a pooled analysis of the TRIBE and TRIBE2 studies. *Eur J Cancer*. 2022;170:64-72.
3. Modest DP, Stintzing S, von Weikersthal LF, et al. Impact of subsequent therapies on outcome of the FIRE-3/AIO KRK0306 trial: first-line therapy with FOLFIRI plus cetuximab or bevacizumab in patients with KRAS wild-type tumors in metastatic colorectal cancer. *J Clin Oncol*. 2015;33(32):3718-3726.
4. Grothey A, Van Cutsem E, Sobrero A, et al. Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet*. 2013;381(9863):303-312.
5. Li J, Qin S, Xu R, et al. Regorafenib plus best supportive care versus placebo plus best supportive care in Asian patients with previously treated metastatic colorectal cancer (CONCUR): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol*. 2015;16(6):619-629.
6. Mayer RJ, Van Cutsem E, Falcone A, et al. Randomized trial of TAS-102 for refractory metastatic colorectal cancer. *N Engl J Med*. 2015;372(20):1909-1919.
7. Xu J, Kim TW, Shen L, et al. Results of a randomized, double-blind, placebo-controlled, phase III trial of trifluridine/tipiracil (TAS-102) monotherapy in Asian patients with previously treated metastatic colorectal cancer: the TERRA study. *J Clin Oncol*. 2018;36(4):350-358.
8. Dasari A, Lonardi S, Garcia-Carbonero R, et al. Fruquintinib versus placebo in patients with refractory metastatic colorectal cancer (FRESCO-2): an international, multicentre, randomised, double-blind, phase 3 study. *Lancet*. 2023;402(10395):41-53.
9. Prager GW, Taieb J, Fakih M, et al. Trifluridine—tipiracil and bevacizumab in refractory metastatic colorectal cancer. *N Engl J Med*. 2023;388(18):1657-1667.

10. Cervantes A, Adam R, Roselló S, et al. Metastatic colorectal cancer: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Ann Oncol*. 2023;34(1):10-32.
11. Shitara K, Yamanaka T, Denda T, et al. REVERCE: a randomized phase II study of regorafenib followed by cetuximab versus the reverse sequence for previously treated metastatic colorectal cancer patients. *Ann Oncol*. 2019;30(2):259-265.
12. Rossini D, Boccaccino A, Carullo M, et al. Primary tumour side as a driver for treatment choice in RAS wild-type metastatic colorectal cancer patients: a systematic review and pooled analysis of randomised trials. *Eur J Cancer*. 2023;184:106-116.
13. Yoshino T, Hooda N, Younan D, et al. A meta-analysis of efficacy and safety data from head-to-head first-line trials of epidermal growth factor receptor inhibitors versus bevacizumab in adult patients with RAS wild-type metastatic colorectal cancer by sidedness. *Eur J Cancer*. 2024;202:113975.
14. Misale S, Yaeger R, Hobor S, et al. Emergence of KRAS mutations and acquired resistance to anti-EGFR therapy in colorectal cancer. *Nature*. 2012;486(7404):532-536.
15. Benvenuti S, Sartore-Bianchi A, Di Nicolantonio F, et al. Oncogenic activation of the RAS/RAF signaling pathway impairs the response of metastatic colorectal cancers to anti-epidermal growth factor receptor antibody therapies. *Cancer Res*. 2007;67(6):2643-2648.
16. Diaz LA, Williams RT, Wu J, et al. The molecular evolution of acquired resistance to targeted EGFR blockade in colorectal cancers. *Nature*. 2012;486(7404):537-540.
17. Montagut C, Argilés G, Ciardiello F, et al. Efficacy of Sym004 in patients with metastatic colorectal cancer with acquired resistance to anti-EGFR therapy and molecularly selected by circulating tumor DNA analyses: a phase 2 randomized clinical trial. *JAMA Oncol*. 2018;4(4):e175245.
18. Parseghian CM, Sun R, Woods M, et al. Resistance mechanisms to anti-epidermal growth factor receptor therapy in *RAS/RAF* wild-type colorectal cancer vary by regimen and line of therapy. *J Clin Oncol*. 2023;41(3):460-471.
19. Raghav K, Ou FS, Venook AP, Innocenti F, Sun R, Lenz HJ, Kopetz S. Acquired genomic alterations on first-line chemotherapy with cetuximab in advanced colorectal cancer: circulating tumor DNA analysis of the CALGB/SWOG-80405 trial (Alliance). *J Clin Oncol*. 2023;41(3):472-478.
20. Parseghian CM, Loree JM, Morris VK, et al. Anti-EGFR-resistant clones decay exponentially after progression: implications for anti-EGFR re-challenge. *Ann Oncol*. 2019;30(2):243-249.
21. Cremolini C, Montagut C, Ronga P, et al. Rechallenge with anti-EGFR therapy to extend the continuum of care in patients with metastatic colorectal cancer. *Front Oncol*. 2023;12:946850.
22. Cremolini C, Rossini D, Dell'Aquila E, et al. Rechallenge for patients with *RAS* and *BRAF* wild-type metastatic colorectal cancer with acquired resistance to first-line cetuximab and irinotecan: a phase 2 single-arm clinical trial. *JAMA Oncol*. 2019;5(3):343-350.
23. Sartore-Bianchi A, Pietrantonio F, Lonardi S, et al. Circulating tumor DNA to guide rechallenge with panitumumab in metastatic colorectal cancer: the phase 2 CHRONOS trial. *Nat Med*. 2022;28(8):1612-1618.
24. Ohhara Y, Shinozaki E, Osawa H, et al. Liquid biopsy for optimizing the rechallenge of cetuximab in metastatic colorectal cancer: additional study of E-rechallenge trial. *J Clin Oncol*. 2019;37(4):585.
25. Vivas CS, Barrull JV, Rodriguez CF, et al. 511MO Third line rechallenge with cetuximab (Cet) and irinotecan in circulating tumor DNA (ctDNA) selected metastatic colorectal cancer (mCRC) patients: the randomized phase II CITRIC trial. *Ann Oncol*. 2024;35(2):S433-S434.
26. Kagawa Y, Kotani D, Bando H, et al. Plasma RAS dynamics and anti-EGFR rechallenge efficacy in patients with RAS/BRAF wild-type metastatic colorectal cancer: REMARRY and PURSUIT trials. *J Clin Oncol*. 2022;40(suppl 16):3518.
27. Sunakawa Y, Nakamura M, Ishizaki M, et al. RAS mutations in circulating tumor DNA and clinical outcomes of rechallenge treatment with anti-EGFR antibodies in patients with metastatic colorectal cancer. *JCO Precis Oncol*. 2020;(4):898-911.
28. Ciardiello D, Martinelli E, Troiani T, et al. Anti-EGFR rechallenge in patients with refractory ctDNA RAS/BRAF wt metastatic colorectal cancer: a nonrandomized controlled trial. *JAMA Netw Open*. 2024;7(4):e245635.
29. Parseghian CM, Vilar Sanchez E, Sun R, et al. Phase 2 study of anti-EGFR rechallenge therapy with panitumumab with or without trametinib in advanced colorectal cancer. *J Clin Oncol*. 2022;40(suppl 16):3520.
30. Cremolini C, Morano F, Moretto R, et al. Negative hyper-selection of metastatic colorectal cancer patients for anti-EGFR monoclonal antibodies: the PRESSING case-control study. *Ann Oncol*. 2017;28(12):3009-3014.
31. Shitara K, Muro K, Watanabe J, et al. Baseline ctDNA gene alterations as a biomarker of survival after panitumumab and chemotherapy in metastatic colorectal cancer. *Nat Med*. 2024;30(3):730-739.
32. Ciardiello D, Famiglietti V, Napolitano S, et al. Final results of the CAVE trial in RAS wild type metastatic colorectal cancer patients treated with cetuximab plus avelumab as rechallenge therapy: neutrophil to lymphocyte ratio predicts survival. *Clin Colorectal Cancer*. 2022;21(2):141-148.
33. Napolitano S, Ciardiello D, De Falco V, et al. Panitumumab plus trifluridine/tipiracil as anti-EGFR rechallenge therapy in patients with refractory RAS wild-type metastatic colorectal cancer: overall survival and subgroup analysis of the randomized phase II VELO trial. *Int J Cancer*. 2023;153(8):1520-1528.
34. Kagawa Y, Taniguchi H, Kotani D, et al. Longitudinal ctDNA monitoring and prediction of anti-EGFR rechallenge outcomes in RAS/BRAF wild-type metastatic colorectal cancer (mCRC): the REMARRY & PURSUIT trials. *J Clin Oncol*. 2025;43:3514.
35. Ducreux MP, Ben Abdelghani M, Tougeron D, et al. 3O PRODIGE 68 - UCGI 38 - SOREGATT: a randomized phase II study comparing the sequences of regorafenib (reg) and trifluridine/tipiracil (t/t) after failure of standard therapies in patients (pts) with metastatic colorectal cancer (mCRC). *Ann Oncol*. 2024;35(1):S3.
36. Weiss L, Heinemann V, Weikersthal L, et al. FIRE-4 (AIO KRK-0114): randomized study evaluating the efficacy of cetuximab re-challenge in patients with metastatic RAS wild-type colorectal cancer responding to first-line treatment with FOLFIRI plus cetuximab. *J Clin Oncol*. 2025;43(suppl 16):3513.
37. Morano F, Corallo S, Lonardi S, et al. Negative hyperselection of patients with *RAS* and *BRAF* wild-type metastatic colorectal cancer who received panitumumab-based maintenance therapy. *J Clin Oncol*. 2019;37(33):3099-3110.
38. Weiss L, Stintzing S, Stahler A, et al. Molecular hyperselection for optimal choice of first-line targeted therapy independent of primary tumor sidedness: an exploratory analysis of the randomized FIRE-3 study performed in RAS wild-type metastatic colorectal cancer. *Eur J Cancer*. 2025;221:115399.