Upfront Modified Fluorouracil, Leucovorin, Oxaliplatin, and Irinotecan Plus Panitumumab Versus Fluorouracil, Leucovorin, and Oxaliplatin Plus Panitumumab for Patients With RAS/BRAF Wild-Type Metastatic Colorectal Cancer: The Phase III TRIPLETE Study by GONO

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PURPOSE To verify whether the intensification of the upfront chemotherapy backbone with a modified schedule of modified fluorouracil, leucovorin, oxaliplatin, and irinotecan (mFOLFOXIRI) increases the activity of fluorouracil, leucovorin, and oxaliplatin when both regimens are combined with panitumumab as initial treatment for RAS and BRAF wild-type (wt) metastatic colorectal cancer (mCRC).

METHODS TRIPLETE was a prospective, open-label, phase III trial in which previously untreated patients with unresectable RAS and BRAF wt mCRC were randomly assigned 1:1 to modified FOLFOX/panitumumab (control group) or mFOLFOXIRI/panitumumab (experimental group) up to 12 cycles, followed by fluorouracil/-leucovorin/panitumumab until disease progression. The primary end point was objective response rate (ORR) according to RECIST 1.1. Hypothesizing an ORR of 60% in the control group, 432 cases provided 90% power to a two-sided chi-square test for heterogeneity with a two-sided alpha error of .05 to detect ≥ 15% differences between arms (ClinicalTrials.gov identifier: NCT03231722).

RESULTS From September 2017 to September 2021, 435 patients were enrolled (control group/experimental group: 217/218) in 57 Italian sites. One hundred sixty (73%) patients treated with mFOLFOXIRI plus panitumumab and 165 (76%) patients treated with modified FOLFOX/panitumumab achieved RECIST response (odds ratio 0.87, 95% CI, 0.56 to 1.34, P = .526). No differences in early tumor shrinkage rate (57%/58%, P = .878) and deepness of response (median: 48%/47%, P = .845) were reported, nor in R0 resection rate (25%/29%, P = .317). No significant difference between arms was reported in terms of progression-free survival (median progression-free survival: 12.7 in the experimental group vs 12.3 months in the control group, hazard ratio: 0.88, 95% CI, 0.70 to 1.11, P = .277).

CONCLUSION The intensification of the upfront chemotherapy backbone in combination with panitumumab does not provide additional benefit in terms of treatment activity at the price of increased gastrointestinal toxicity in patients with RAS and BRAF wt mCRC.

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INTRODUCTION

The combination of two cytotoxic drugs, fluorouracil, leucovorin, and oxaliplatin (FOLFOX) or fluorouracil, leucovorin, and irinotecan (FOLFIRI), with an anti–epidermal growth factor receptor (EGFR) antibody (cetuximab or panitumumab) is an upfront option for patients with unresectable RAS and BRAF wild-type (wt) metastatic colorectal cancer (mCRC).1,2

An intensified upfront chemotherapy backbone, the triplet fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFIRI), in combination with bevacizumab significantly improved response rate, progression-free
**CONTEXT**

**Key Objective**
Does modified fluorouracil, leucovorin, oxaliplatin, and irinotecan (mFOLFOXIRI) plus panitumumab provide higher activity than fluorouracil, leucovorin, and oxaliplatin (FOLFOX) plus panitumumab in patients with unresectable RAS and BRAF wild-type metastatic colorectal cancer? The phase III randomized TRIPLETE study aims at answering this question.

**Knowledge Generated**
The intensification of the upfront chemotherapy backbone with mFOLFOXIRI in combination with panitumumab does not provide any benefit in ORR and progression-free survival compared with FOLFOX and panitumumab in RAS and BRAF wild-type metastatic colorectal cancer and is associated with increased gastrointestinal toxicity. FOLFOX plus panitumumab allows achieving remarkable activity and efficacy results, thus supporting patients’ selection according to the primary tumor side and RAS and BRAF mutational status to optimize the efficacy of anti–epidermal growth factor receptor (EGFR)-based first-line treatments.

**Relevance**
Our results do not support the use of the triplet in combination with anti-EGFRs and highlight that patients’ selection according to RAS and BRAF mutational status and primary tumor location may optimize the efficacy of anti–EGFR-based first-line treatments.

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**METHODS**

**Study Design and Participants**
TRIPLETE is a prospective, open-label, multicenter, randomized phase III study that included patients with mCRC recruited from 57 Oncology Units in Italy (Data Supplement, online only). Eligible patients, stratified according to Eastern Cooperative Oncology Group performance status (ECOG PS; 0-1 v 2), primary tumor location (right [from cecum to transverse colon] versus left [from splenic flexure to rectum]), and liver-only metastases (yes v no) were randomly assigned by minimization to receive FOLFOX plus panitumumab (control group) or mFOLFOXIRI plus panitumumab (experimental group) in a 1:1 ratio.

Main inclusion criteria were as follows: histologically confirmed colorectal adenocarcinoma; RAS (KRAS and NRAS exons 2, 3, and 4) and BRAF codon 600 wt status of primary tumor and/or related metastasis assessed by local laboratory; age between 18 and 75 years; an ECOG PS of 0-2 if age ≥ 70 years or 0 if age 71-75 years; unresectable and measurable metastatic disease according to RECIST version 1.1; and adequate bone marrow, hepatic, and renal function. Main exclusion criteria were as follows: any previous treatment for metastatic disease; adjuvant treatment with oxaliplatin; adjuvant treatment with fluoropyrimidine monotherapy completed < 6 months before relapse; and peripheral neuropathy of grade 2 or higher according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.0.

Modified FOLFOX plus panitumumab consisted of a 30- to 60-minute intravenous infusion of panitumumab at 6 mg/kg, followed by a 120-minute infusion of oxaliplatin at 85 mg/m² given concurrently with leucovorin at 200 mg/m², followed by bolus infusion of FU at 400 mg/m², followed...
by a 48-hour continuous infusion of FU at 2,400 mg/m², starting on day 1. Cycles were repeated once every 14 days. mFOLFOXIRI plus panitumumab was administered as a 30- to 60-minute intravenous infusion of panitumumab at 6 mg/kg, followed by a 60-minute infusion of irinotecan at 150 mg/m², followed by a 120-minute infusion of oxaliplatin at 85 mg/m² given concurrently with leucovorin at 200 mg/ m², followed by a 48-hour continuous infusion of FU at 2,400 mg/m², starting on day 1. Cycles were repeated once every 14 days. In both groups, treatment was administered up to 12 cycles, followed by maintenance with FU/leucovorin and panitumumab every 14 days, until progressive disease, patient’s refusal, unacceptable adverse events, or consent withdrawal.

All tumor assessments were based on investigator-reported measurements and were performed according to RECIST 1.1 by means of computed tomography scans repeated every 8 weeks. The assessment of surgical resectability by an experienced and dedicated local multidisciplinary team was recommended at every tumor assessment. In the case of surgical radical resection of residual metastases, postoperative therapy with the same preoperative regimen was planned up to 12 cycles.

Adverse events were graded according to the NCI-CTCAE version 4.0. Treatment modifications were allowed according to the study protocol. The use of granulocyte colony-stimulating factor was not recommended as primary prophylaxis.

The Protocol (online only) was approved by the local ethics committees at participating centers, and the study was conducted in accordance with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. All patients provided their written informed consent to study procedures before enrollment. The study Protocol is available in the Data Supplement.

The trial is registered with ClinicalTrials.gov identifier: NCT03231722.

Study End Points

The primary end point was objective response rate (ORR) defined as the percentage of patients achieving a complete or partial response, according to RECIST 1.1 criteria, during the whole treatment, including both the induction and the maintenance phases, on the basis of investigator-reported measurements.

Secondary end points included safety, PFS (defined as the time from random assignment to the first documentation of disease progression, according to RECIST version 1.1, or death from any cause, whichever occurred first; patients who were alive and progression-free at the time of the

FIG 1. CONSORT diagram. *Patients included in the intention-to-treat population. 4 Patients included in the safety population. FOLFOX, fluorouracil, leucovorin, and oxaliplatin; mFOLFOXIRI, modified fluorouracil, leucovorin, oxaliplatin, and irinotecan.
analysis were censored at the date of the last tumor assessment; no censoring for secondary surgery or treatment interruption because of any cause was made), early tumor shrinkage (ETS) rate (defined as the percentage of patients achieving a ≥ 20% decrease in the sum of the diameters of the RECIST target lesions after 8 weeks from treatment start compared with baseline), deepness of response (DoR; defined as the relative change in the sum of the longest diameters of the RECIST target lesions at the nadir, in the absence of new lesions or progression of nontarget lesions, compared with baseline), R0 resection rate (defined as the proportion of patients undergoing secondary resection of metastases with no macroscopic or microscopic residual tumor), and OS (defined as the time from random assignment to death because of any cause, not yet mature at the time of the analysis).

Statistical Analysis

The primary analysis of ORR and all efficacy analyses were performed in the intention-to-treat population, including all randomly assigned patients. Adverse events were assessed in the safety population, including patients who received at least one dose of the study treatment.

The chi-square test for heterogeneity and the odds ratio (OR) with 95% CIs were used to compare the ORR between treatment groups. Under the assumption of an ORR in the control group equal to 60%,12,13 a sample size of 432 cases, randomly assigned in a 1:1 ratio, provided approximately 90% power to a two-sided chi-square test for heterogeneity at the 0.05 significance level, to detect $15\%$ differences in ORR between arms.

R0 resection rate of metastases, ETS, and DoR in the two groups were compared with a chi-square test or Mann-Whitney test when appropriate; ORs and 95% CIs were estimated with a logistic regression model.

The median period of follow-up was calculated according to the reverse Kaplan-Meier method. Distribution of time-to-event variables for PFS was estimated using the Kaplan-Meier product limit method. The log-rank test was used as primary analysis for treatment groups’ comparison. Hazard ratios (HRs) with 95% CIs were estimated with a Cox proportional hazards model. The proportional hazards assumption was graphically assessed by a log($-$log) plot (Data Supplement). Since it was violated, the 26-month restricted mean survival time for each treatment group and the between-group difference were reported as post hoc analysis.

Stratified analyses of ORR and PFS were also performed. Exploratory subgroup analyses were conducted by interaction tests to determine the consistency of the treatment effect according to key baseline characteristics.

All statistical tests were two-sided, and P values $\leq$.05 were deemed significant. Statistical analyses were performed using SAS version 9.4 and R version 4.1.1.

### TABLE 1. Baseline Characteristics of Patients in the Intention-to-Treat Population

| Characteristic | Control Group (n = 217) | Experimental Group (n = 218) |
|---------------|------------------------|-----------------------------|
| Age, years (IQR) | 59 (51-65) | 59 (51-64) |
| Age, years ≤ 70 | 199 (92) | 203 (93) |
| Age, years > 70 | 18 (8) | 15 (7) |
| Sex | | |
| Male | 138 (64) | 136 (62) |
| Female | 79 (36) | 82 (38) |
| ECOG PS | | |
| 0 | 174 (80) | 183 (84) |
| 1 | 42 (19) | 34 (15) |
| 2 | 1 (1) | 1 (1) |
| Prior adjuvant chemotherapy | | |
| Yes | 5 (2) | 12 (6) |
| No | 212 (98) | 206 (94) |
| Primary tumor site | | |
| Left colon or rectum | 191 (88) | 192 (88) |
| Right colon | 26 (12) | 26 (12) |
| Resected primary tumor | | |
| Yes | 93 (43) | 111 (51) |
| No | 124 (57) | 107 (49) |
| Time to metastases | | |
| Synchronous | 192 (88) | 189 (87) |
| Metachronous | 25 (12) | 29 (13) |
| No. of metastatic sites | | |
| 1 | 104 (48) | 103 (47) |
| > 1 | 113 (52) | 115 (53) |
| Liver-only disease | | |
| Yes | 81 (37) | 86 (39) |
| No | 136 (63) | 132 (61) |
| Mucinous histology | | |
| Yes | 10 (5) | 21 (10) |
| No | 133 (61) | 140 (64) |
| MMR status | | |
| Proficient MMR | 145 (67) | 162 (74) |
| Deficient MMR | 2 (1) | 6 (3) |
| Missing data | 70 (32) | 50 (23) |

NOTE. Data are No. (%) unless otherwise noted. The control group indicates FOLFOX plus panitumumab. The experimental group indicates mFOLFOXIRI plus panitumumab.

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; FOLFOX, fluorouracil, leucovorin, and oxaliplatin; IQR, interquartile range; mFOLFOXIRI, modified fluorouracil, leucovorin, oxaliplatin, and irinotecan; MMR, mismatch repair.
RESULTS

From September 2017 to September 2021, 435 patients were randomly assigned to the control (n = 217) or the experimental group (n = 218; Fig 1) and were included in the intention-to-treat population. Four hundred thirty-one patients (213 in the control group and 218 in the experimental group) received at least one dose of the study treatment and were included in the safety population (Fig 1).

The cutoff date for the present analysis was March 7, 2022. Patient- and tumor-related characteristics at baseline were well balanced between groups (Table 1). All patients were White, and the median age was 59 (interquartile range [IQR], 51-65) years. Most patients had an ECOG PS of 0 (82%), presented with synchronous metastases (88%) and a left-sided primary tumor (88%). Overall, 52% of patients had multiple metastatic sites and 38% showed liver-only disease (Table 1).

One hundred sixty (73%) of 218 patients in the experimental group achieved response versus 165 (76%) of 217 patients in the control group (OR: 0.87 [95% CI, 0.56 to 1.34]; \( P = .526 \)). Fifteen (7%) complete responses and 145 (66%) partial responses were observed in the experimental group versus 15 (7%) complete and 150 (69%) partial responses in the control group (Fig 2A). After adjustment for stratification factors, no difference between arms was observed (OR: 0.83 [95% CI, 0.53 to 1.29]; \( P = .407 \)). The subgroup analyses revealed no significant interaction effect between treatment arms and clinical factors at baseline except for sex (\( P \) for interaction = .014) and primary tumor site (\( P \) for interaction = .03; Fig 3).

Two hundred fifty-one (58%) patients achieved ETS with no difference between groups (57% in the experimental group v 58% in the control group; OR 0.97 [95% CI, 0.66 to 1.42]; \( P = .878 \); Fig 2B). Similar results were shown for median DoR that was 48% (IQR: 32%-60%) in the experimental group and 47% (IQR: 30%-62%) in the control group (\( P = .845 \)); Fig 4).

R0 resection rate was not significantly different between the two treatment groups both in the overall population (54 [25%] in the experimental arm v 63 [29%] in the control arm, OR 0.81 [95% CI, 0.53 to 1.23]; \( P = .317 \)) and in the liver-only subgroup (36 [42%] of 86 v 35 [43%] of 81, OR 0.95 [95% CI, 0.51 to 1.75]; \( P = .860 \)). At a median follow-up of 26.5 (IQR: 13.7-35.9) months, 305 (70%) events of disease progression occurred (148 [68%] of 218 patients in the experimental group and 157 [72%] of 217 patients in the control group). The median PFS was 12.7 months (95% CI, 11.1 to 15.5) in
the experimental group and 12.3 months (95% CI, 11.1 to 14.3) in the control group (HR, 0.88; 95% CI, 0.70 to 1.11; log-rank test \( P = .277 \); Fig 5). As the proportional hazards assumption was violated (Data Supplement), the 26-month restricted mean survival time was post hoc calculated and it was 14.3 months (95% CI, 13.1 to 15.4) in the experimental group and 13.6 months (95% CI, 12.6 to 14.7) in the control group, with a difference of 0.62 months (95% CI, −0.99 to 2.22; \( P = .451 \)). After adjustment for stratification factors, no difference between arms was observed in terms of PFS (HR, 0.89; 95% CI, 0.71 to 1.11; stratified log-rank test \( P = .369 \)). No significant interaction effect was shown between treatment arms and analyzed subgroups (Data Supplement).

The median number of cycles administered per patient as induction treatment was 9 (IQR, 6-12) in both arms. The median relative dose intensity was 81% for FOLFOX plus panitumumab (IQR: 70%-92%) and 75% for mFOLFOXIRI plus panitumumab (IQR: 63%-86%). In the control group, the median relative dose intensities of fluorouracil continuous infusion, fluorouracil bolus infusion, and oxaliplatin were 82%, 79%, and 82%, respectively. One hundred fifty-seven (72%) and 133 (62%) patients required at least one dose reduction in the experimental and control group, respectively.

Treatment was delayed because of any reason in 194 (89%) and 175 (82%) patients in the experimental and control arm, respectively.

Adverse events are shown in Table 2. Grade 3-4 adverse events were reported in 151 (69%) of 218 patients in the experimental group and in 121 (57%) of 213 patients in the control group. The most frequent all-cause grade 3-4 events were neutropenia (70 [32%] in the experimental group vs 42 [20%] in the control group), diarrhea (51 [23%] vs 14 [7%]), rash acniform (42 [19%] vs 61 [29%]),
stomatitis (15 [7%] v 14 [7%]), hypokalemia (16 [7%] v 8 [4%]), and fatigue (16 [7%] v 4 [2%]).

Serious adverse events occurred in 72 (33%) and 44 (21%) patients in the experimental and control group, respectively. Three deaths because of treatment-related adverse events (sepsis in one patient and diarrhea in two patients) were reported in the experimental group (1%) versus none in the control group.

DISCUSSION

The TRIPLETE study did not meet its primary end point, failing to demonstrate improved activity with a modified schedule of FOLFOXIRI compared with FOLFOX when combined with the anti-EGFR monoclonal antibody panitumumab as initial therapy of patients with unresectable RAS and BRAF wt mCRC. In the past few years, the use of anti–EGFR-based first-line regimens in patients with RAS wt mCRC increased worldwide and several post hoc subgroup analyses of controlled trials led to improvement in the selection of patients who are most likely to benefit from this treatment option beyond RAS mutational status. In fact, the limited benefit achieved with the addition of anti-EGFR agents to standard chemotherapy in the BRAF V600–mutant subgroup led to restriction of their upfront use to patients with RAS and BRAF wt mCRC.14,15 Moreover, consistent results from subgroup analyses of randomized trials of chemotherapy plus anti-EGFR versus chemotherapy alone or plus bevacizumab showed a significant interaction between the anti-EGFR effect and the primary tumor location.16,17 A clinically relevant PFS and OS benefit from the upfront use of anti-EGFRs was shown among patients with RAS wt tumors originating from the left side of the colon, thus making FOLFOX or FOLFIRI plus cetuximab or panitumumab a preferred upfront option for these patients.2,18 Conversely, patients with right-sided tumors were mostly excluded from anti–EGFR-based upfront therapies, and this was supported by the acknowledgment of a higher prevalence in these tumors of other rare molecular alterations predictive of intrinsic resistance to anti-EGFRs.19 When the TRIPLETE study was designed, the differential efficacy of anti-EGFR agents according to the primary tumor location was not established, whereas the negative prognostic impact of the right-sidedness was well known,20 so that the primary tumor side was used as a stratification

![Graph showing change from baseline (%)](image)

**FIG 4.** Deepness of response. The control group indicates FOLFOX plus panitumumab. The experimental group indicates mFOLFOXIRI plus panitumumab. FOLFOX, fluorouracil, leucovorin, and oxaliplatin; mFOLFOXIRI, modified fluorouracil, leucovorin, oxaliplatin, and irinotecan.
factor to avoid relevant unbalances between arms but not as an eligibility criterion. However, because of the above-mentioned evidence, the percentage of patients with left-sided tumors in the study population was as high as 88%. As a consequence, we observed an ORR in the FOLFOX plus panitumumab group of 76% that was significantly higher than that planned in the null hypothesis (60%), on the basis of the results of the pivotal PRIME study.13

Despite acknowledging all the methodological limitations of cross-trials comparisons, our results with FOLFOX plus panitumumab in a large (n = 217) and prospective cohort of clinically and molecularly selected patients seem to favorably compare with those reported among patients with left-sided RAS wt tumors treated with doublets plus anti-EGFRs in other pivotal trials, where ORRs ranged from 64% to 73%.16 The growing amount of evidence about the role of several rare molecular alterations as predictors of intrinsic resistance to anti-EGFRs21 and the widespread NGS panels allowing extensive tumor molecular characterization probably led to an hyperselection of enrolled patients beyond RAS and BRAF mutational status. Centralized translational analyses on both tissue and blood samples to verify this hypothesis are currently ongoing.

Moreover, patients included in our trial were clinically selected for being able to receive an intensified treatment. In fact, 82% had an ECOG PS of 0, and the median age was quite low (59 years).

In our study, although the intensification of the chemotherapy backbone was associated with a very high ORR (73%), even higher among patients with left-sided tumors (77%), it did not provide any advantage in any measure of treatment activity. The ORR in our cohort of 218 patients treated at 57 Italian centers was lower than the 87% ORR reported for 63 RAS wt patients treated at 21 German centers in the mFOLFOXIRI plus panitumumab arm of the phase II randomized VOLFI study.9 The ability to induce a rapid and relevant tumor shrinkage was regarded as the strongest point for the combination of the triplet with an anti-EGFR, and we chose ORR as the primary end point of this phase III trial. Despite acknowledging that prolonging OS is the ultimate goal of systemic treatments in the metastatic setting, the choice of OS as the primary end point of the study would have hampered its feasibility. ORR was preferred because of its reliable association with OS in previous trials investigating anti-EGFR-based regimens, which was not demonstrated for PFS.22-26 In particular, among patients with RAS wt tumors enrolled in the FIRE-3 study comparing FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab, a significant advantage in favor of the anti-EGFR arm was shown in terms of both centrally assessed ORR (72.0% v 56.1%, P = .0029) and OS (32.5 v 26.1 months; HR, 0.75; 95% CI, .63 to .90).
and, in particular, of diarrhea (23%), even if reduced doses of irinotecan (150 mg/m² once every 2 weeks) and FU (2,400 mg/m² once every 2 weeks) were adopted. Similar results were reported in the VOLFI study, where grade 3 diarrhea was reported in 25% of patients, with the same dose of irinotecan and a higher dose of FU (3,000 mg/m² once every 2 weeks).9 Conversely, in our previous MACBETH study, where irinotecan was further reduced to 130 mg/m² once every 2 weeks and FU was administered at 2,400 mg/m² once every 2 weeks grade 3, diarrhea occurred in 18% of patients.7

In conclusion, the intensification of the upfront chemotherapy backbone in combination with panitumumab in patients with RAS and BRAF wt and mostly (88%) left-sided mCRC does not provide any benefit in terms of treatment activity at the price of a non-negligible increase in gastrointestinal toxicity. FOLFOX plus panitumumab achieves an ORR as high as 76% with a median PFS of 12.3 months, thus supporting patients’ selection according to the primary tumor side and RAS and BRAF mutational status to optimize the efficacy of anti-EGFR-based first-line treatments.

### TABLE 2. All-Cause Adverse Events, Occurring During First-Line Therapy in the Safety Population, According to the Treatment Group

| Adverse Event                  | Control Group (n = 213) | Experimental Group (n = 218) |
|-------------------------------|-------------------------|------------------------------|
|                               | Grade 1-2 | Grade 3-4 | Grade 1-2 | Grade 3-4 |
| Any event                     | 86 (40)   | 121 (57)  | 59 (27)   | 151 (69)  |
| Anemia                        | 54 (25)   | 2 (1)     | 87 (40)   | 6 (3)     |
| Thrombocytopenia              | 64 (30)   | 2 (1)     | 62 (28)   | 2 (1)     |
| Nausea                        | 71 (33)   | 4 (2)     | 102 (47)  | 11 (5)    |
| Vomiting                      | 25 (12)   | 2 (1)     | 48 (22)   | 5 (2)     |
| Diarrhea                      | 71 (33)   | 14 (7)    | 106 (49)  | 51 (23)   |
| Stomatitis                    | 82 (38)   | 14 (7)    | 81 (37)   | 15 (7)    |
| Neutropenia                   | 43 (20)   | 42 (20)   | 62 (28)   | 70 (32)   |
| Febrile neutropenia           | —         | 7 (3)     | —         | 11 (5)    |
| Neurotoxicity                 | 96 (45)   | 8 (4)     | 95 (44)   | 5 (2)     |
| Fatigue                       | 91 (43)   | 4 (2)     | 108 (50)  | 16 (7)    |
| Anorexia                      | 22 (10)   | 0 (0)     | 35 (16)   | 5 (2)     |
| Fever                         | 27 (13)   | 1 (1)     | 39 (18)   | 1 (1)     |
| Alopecia                      | 3 (1)     | —         | 4 (2)     | —         |
| Hand-foot syndrome            | 40 (19)   | 5 (2)     | 27 (12)   | 0 (0)     |
| Rash acneiform                | 128 (60)  | 61 (29)   | 130 (60)  | 42 (19)   |
| Hypomagnesemia                | 38 (18)   | 3 (1)     | 59 (27)   | 3 (1)     |
| Hypokalemia                   | 35 (16)   | 8 (4)     | 49 (22)   | 16 (7)    |
| Hypocalcemia                  | 20 (9)    | 0 (0)     | 18 (8)    | 1 (1)     |
| Infusion-related reaction     | 18 (8)    | 4 (2)     | 17 (8)    | 2 (1)     |

NOTE. Data are No. (%). The table lists all grade 1-2, 3, and 4 events that occurred in any treatment group. The control group indicates FOLFOX plus panitumumab. The experimental group indicates mFOLFOXIRI plus panitumumab.

Abbreviations: FOLFOX, fluorouracil, leucovorin, and oxaliplatin; mFOLFOXIRI, modified fluorouracil, leucovorin, oxaliplatin, and irinotecan.
Upfront mFOLFOXIRI/Panitumumab for Patients With RAS/BRAF wt mCRC

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DISCLAIMER
The corresponding author had full access to all study data and had the final responsibility for the decision to submit for publication. Amgen had no role in the design and conduct of the trial; collection, management, analysis, and interpretation of the data; or the decision to submit the manuscript for publication.

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