Maintenance Therapy With Panitumumab Alone vs Panitumumab Plus Fluorouracil-Leucovorin in Patients With *RAS* Wild-Type Metastatic Colorectal Cancer
A Phase 2 Randomized Clinical Trial

Filippo Pietrantonio, MD; Federica Morano, MD; Salvatore Corallo, MD; Rosalba Miceli, PhD; Sara Lonardi, MD; Alessandra Raimondi, MD; Chiara Cremolini, MD; Lorenza Rimassa, MD; Francesca Bergamo, MD; Andrea Sartore-Bianchi, MD; Marco Tampellini, MD; Patrizia Racca, MD; Matteo Clavarezza, MD; Rosa Berenato, MD; Marta Caporale, MD; Maria Antista, MD; Monica Niger, MD; Valeria Smiroldo, MD; Roberto Murialdo, MD; Alberto Zaniboni, MD; Vincenzo Adamo, MD; Gianluca Tomasello, MD; Monica Giordano, MD; Fausto Petrelli, MD; Raffaella Longarini, MD; Saverio Cinieri, MD; Alfredo Falcone, MD; Vittorina Zagonel, MD; Maria Di Bartolomeo, MD; Filippo de Braud, MD

IMPORTANCE Few studies are available on the role of maintenance strategies after induction treatment regimens based on anti–epidermal growth factor receptors, and the optimal regimen for an anti–epidermal growth factor receptors–based maintenance treatment in patients with *RAS* wild-type metastatic colorectal cancer is still to be defined.

OBJECTIVE To determine whether maintenance therapy with single-agent panitumumab was noninferior to panitumumab plus fluorouracil and leucovorin after a 4-month induction treatment regimen.

DESIGN, SETTING, AND PARTICIPANTS This open-label, randomized phase 2 noninferiority trial was conducted from July 7, 2015, through October 27, 2017, at multiple Italian centers. Patients with *RAS* wild-type, unresectable metastatic colorectal adenocarcinoma who had not received previous treatment for metastatic disease were eligible. Induction therapy consisted of panitumumab plus FOLFOX-4 (panitumumab, 6 mg/kg, oxaliplatin, 85 mg/m² at day 1, leucovorin calcium, 200 mg/m², and fluorouracil, 400-mg/m² bolus, followed by 600-mg/m² continuous 24-hour infusion at days 1 and 2, every 2 weeks). Cutoff date for analyses was July 30, 2018.

INTERVENTIONS Patients were randomized (1:1) to first-line panitumumab plus FOLFOX-4 for 8 cycles followed by maintenance therapy with panitumumab plus fluorouracil-leucovorin (arm A) or panitumumab (arm B) until progressive disease, unacceptable toxic effects, or consent withdrawal. The minimization method was used to stratify randomization by previous adjuvant treatment and number of metastatic sites.

MAIN OUTCOMES AND MEASURES The prespecified primary end point was 10-month progression-free survival (PFS) analyzed on an intention-to-treat basis with a noninferiority margin of 1.515 for the upper limit of the 1-sided 90% CI of the hazard ratio (HR) of arm B vs A.

RESULTS Overall, 229 patients (153 male [66.8%]; median age, 64 years [interquartile range (IQR), 56-70 years]) were randomly assigned to arm A (n = 117) or arm B (n = 112). At a median follow-up of 18.0 months (IQR, 13.1-23.3 months]), a total of 169 disease progression or death events occurred. Arm B was inferior (upper limit of 1-sided 90% CI of the HR, 1.857). Ten-month PFS was 59.9% (95% CI, 51.5%-69.8%) in arm A vs 49.0% (95% CI, 40.5%-59.4%) in arm B (HR, 1.51; 95% CI, 1.11-2.07; *P* = .01). During maintenance, arm A had a higher incidence of grade 3 or greater treatment-related adverse events (36 [42.4%] vs 16 [20.3%]) and panitumumab-related adverse events (27 [31.8%] vs 13 [16.4%]), compared with arm B.

CONCLUSIONS AND RELEVANCE In patients with *RAS* wild-type metastatic colorectal cancer, maintenance therapy with single-agent panitumumab was inferior in terms of PFS compared with panitumumab plus fluorouracil-leucovorin, which slightly increased the treatment toxic effects.

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Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Filippo Pietrantonio, MD, Department of Medical Oncology, Fondazione IRCCS Istituto Nazionale dei Tumori, via Giacomo Venezian 1, 20133 Milan, Italy (filippo.pietrantonio@istitutotumori.mi.it).

The treatment landscape of unresectable metastatic colorectal cancer (mCRC) has relevantly changed after the introduction of biological agents and the development of continuum of care strategies. The decision-making process on the optimal intensity and duration of first-line treatment in patients with mCRC is based on literature data, treatment tolerability, patients' preferences, and costs.[1]

In pivotal trials of chemotherapy doublets with or without biological agents,[2-5] treatment continuation was scheduled until progressive disease or unacceptable toxic effects. A negative effect on quality of life of this approach is caused by oxaliplatin-related cumulative neurotoxicity.[6,7] This evidence paved the way to maintenance or intermittent strategies in patients achieving disease control after combination chemotherapy with or without bevacizumab.[6-12] Available evidence indicates that de-escalating chemotherapy intensity in the maintenance setting significantly reduces the toxicity burden, without impairing survival outcomes.[6,7] Indeed, fluorouracil and leucovorin-based maintenance treatment achieves noninferior progression-free survival (PFS) compared with no de-escalation,[6] while improving the duration of disease control compared with treatment holidays.[8,10,12] According to current guidelines,[1] after a 4- to 6-month induction treatment with bevacizumab plus doublet or triplet[13] regimens, bevacizumab plus a fluoropyrimidine is regarded as the optimal maintenance regimen.

An anti-epidermal growth factor receptor (EGFR) agent added to doublet chemotherapy is currently recommended as a first-line treatment option for patients with *RAS* wild-type mCRC.[1,14-16] However, the optimal duration of anti-EGFR-based upfront treatment is still to be defined because, to date, little evidence-based data are available on the role of maintenance[17,18] or intermittent[19,20] strategies after anti-EGFR-based induction regimens. We investigated whether, after 4-month induction therapy with panitumumab plus oxaliplatin-based doublet chemotherapy, maintenance treatment with panitumumab was noninferior to panitumumab plus fluorouracil-leucovorin in patients with *RAS* wild-type mCRC.

Methods

Study Design and Patient Selection

The VALENTINO study was an open-label, randomized, multicenter phase 2 noninferiority trial whose participants were similar to those in trials that established efficacy of first-line doublets plus anti-EGFRs.[2-5] The study protocol is found in Supplement 1. Inclusion criteria consisted of histologically confirmed colorectal adenocarcinoma; being 18 years or older; Eastern Cooperative Oncology Group performance status of 0 to 1; no previous treatment for advanced disease; *RAS* wild-type status locally assessed at local centers according to European Union–approved standard methods; disease judged unresectable by the local multidisciplinary team; measurable or evaluable lesions according to Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1; and adequate bone marrow, liver, and renal function. We excluded patients who had received adjuvant oxaliplatin-based chemotherapy and experienced a relapse during treatment or within 12 months from

Key Points

Question Is maintenance therapy with single-agent panitumumab noninferior to panitumumab plus fluorouracil and leucovorin after a 4-month induction treatment with panitumumab plus FOLFOX-4 in patients with previously untreated *RAS* wild-type metastatic colorectal cancer?

Findings In this open-label, phase 2 randomized clinical trial of 229 patients, maintenance therapy with single-agent panitumumab alone was inferior to panitumumab plus fluorouracil-leucovorin in terms of 10-month progression-free survival (49.0% vs 59.9%).

Meaning The continuation of single-agent anti–epidermal growth factor receptor treatment in the maintenance setting will likely achieve inferior progression-free survival compared with the continuation of chemotherapy plus an anti–epidermal growth factor receptor agent in a phase 3 confirmation trial.

treatment completion (or within 6 months in the case of adjuvant fluoropyrimidine monotherapy). Other exclusion criteria consisted of clinically relevant cardiovascular disease, concurrent active malignant neoplasms (except for those disease free for more than 5 years), or other significant comorbidities that could affect patients' outcomes; pregnancy, lactation, or childbearing potential; and not using or not willing to use medically approved contraception. Institutional review board and ethics committee approval was obtained from all participating centers (eMethods in Supplement 2). All the patients provided written informed consent before any study-related procedures. This study followed the Consolidated Standards of Reporting Trials (CONSORT) reporting guideline.

Treatment Plan and Randomization

Data were collected from July 7, 2015, through October 27, 2017. Patients were randomly assigned (1:1) to panitumumab plus FOLFOX-4 (panitumumab, 6 mg/kg [1-hour infusion for the first administration; 30-minute infusion thereafter], oxaliplatin, 85 mg/m² at day 1, and leucovorin calcium, 200 mg/m², and fluorouracil, 400-mg/m² bolus followed by 600-mg/m² continuous 24-hour infusion at days 1 and 2, every 2 weeks), for 8 cycles, followed by panitumumab plus fluorouracil-leucovorin (arm A) or panitumumab (arm B). Both maintenance treatments were continued until progressive disease, consent withdrawal, unacceptable toxic effects, or death (eFigure 1 in Supplement 2). Treatment group allocation was performed with a minimization algorithm implementing a random component. Stratification factors were number of metastatic sites (1 vs ≥2) and previous adjuvant therapy (no vs yes).

Study Assessments

Disease evaluation was performed by means of computed tomography of the thorax and abdomen or magnetic resonance imaging scans at screening and every 8 weeks thereafter until progressive disease or death. Tumor response was classified according to RECIST, version 1.1, as complete response, partial response, stable disease, or progressive disease. Complete response and partial response should have been confirmed by 2 assessments not less than 4 weeks apart. Patients who discontinued study

treatment without progressive disease had tumor assessments every 8 weeks until progressive disease or study withdrawal. Treatment safety was assessed during the induction and maintenance phases according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 4.03. The protocol recommended preemptive treatment of skin rash with doxycycline at the dose of 100 mg/d for 5 consecutive days, given every other cycle starting at cycle 1, day 1. Quality of life was investigated through the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaires C30 and CR29 and EuroQOL (European quality of life) 5-dimension questionnaires at baseline and every 8 weeks until progressive disease. Quality-of-life data will be analyzed when most patients will conclude treatment and will be presented in a separate publication. *BRAF* codon 600 mutations were centrally confirmed, as previously described.[21]

Outcomes

The primary end point was PFS. The aim was to compare 10-month PFS in the 2 treatment arms. Progression-free survival was assessed locally as the interval from randomization to first objective documentation of progressive disease or death due to any cause, whichever occurred first (censoring at last follow-up for patients alive and without progressive disease). Secondary end points were safety, overall survival, overall response rate, disease control rate, duration of response, and quality of life. Overall survival was the interval from randomization to death due to any cause (censoring at last follow-up for patients alive). Overall response rate was defined as the proportion of patients achieving an objective response (complete or partial), and disease control rate was defined as the proportion of patients achieving a complete or a partial response or stable disease. Duration of response was defined as the interval from first documented response to progressive disease or death due to any cause, whichever occurred first (censoring at the date of last follow-up for patients alive and without progressive disease).

Statistical Analysis

Activity and efficacy analyses were performed for the intention-to-treat population (all randomized patients) and for the per protocol population (including patients with complete or partial response or stable disease after induction who received ≥1 maintenance cycle). Safety analyses were performed for patients who received at least 1 induction cycle. Sample size was calculated taking into account the 10.1-month median PFS reported by the PRIME trial (Panitumumab Randomized Trial In Combination With Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy) in the patient subgroup with *RAS* wild-type tumors.[2] A sample of 224 patients, 112 per arm, recruited during a 2-year period would achieve 90% power to detect 50% PFS in arm A and a maximum difference of 15% less in arm B (1-sided α = 0.1, with a 15% dropout rate taken into account). These assumptions would imply a noninferiority limit equal to 1.515 for the PFS hazard ratio (HR) of arm B vs A, that is, how much A can exceed B, with B still being considered noninferior to A. The null hypothesis for proving noninferiority was HR (B vs A) of at least 1.515 (B is inferior to A);

the alternative hypothesis, was HR (B vs A) of less than 1.515 (B is not inferior to A). The null hypothesis would have been rejected in favor of the alternative if the upper limit of the 1-sided 90% CI for HR, estimated in a Cox proportional hazards regression model stratified by prior adjuvant therapy (no or yes) and number of disease sites (1 or ≥2), was lower than 1.515. Overall survival and PFS curves were estimated in the 2 treatment arms by the Kaplan-Meier method and compared using the log-rank test. Binomial 2-sided 95% CIs were calculated for overall response rate and disease control rate. The Mantel-Haenszel method was applied to estimate the pooled odds ratio (OR) of response in arm B vs A across the strata determined according to the stratification factors and tested using the Cochran Mantel-Haenszel test. Duration of response and median duration of response were estimated by the Kaplan-Meier method and compared using the log-rank test. Subgroup analyses were performed by estimating Kaplan-Meier curves according to treatment arm in each subgroup; Cox proportional hazards regression models with interaction treatment × subgroup were fitted to estimate HRs and corresponding 95% CIs. Median follow-up was calculated by the reverse Kaplan-Meier approach. A stratified univariable Cox proportional hazards regression model was fitted to estimate the HR of arm B vs A for overall survival.

All tests were 2 sided at α = .05, with the exception of the 1-sided test of noninferiority for PFS. The analyses were performed using SAS software, version 9.1 (SAS Institute, Inc), and R software, version 3.4.1 (R Foundation for Statistical Computing).

Results
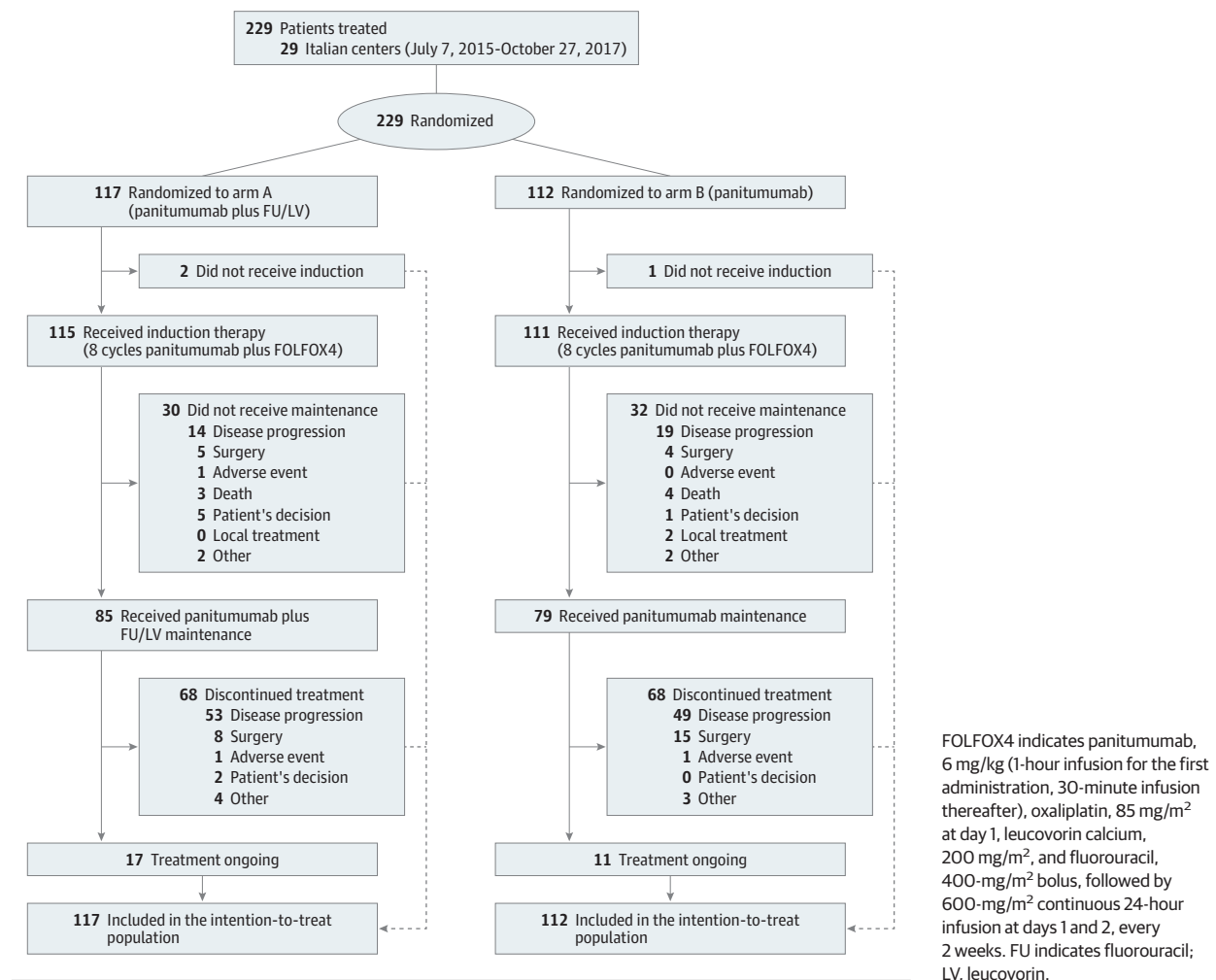
Patient Populations

From July 7, 2015, through October 27, 2017, 229 patients (153 male [66.8%] and 76 female [33.2%]; median age, 64 years [interquartile range (IQR), 56-70 years]) were randomized to arm A (n = 117) or arm B (n = 112). Patients' demographic and disease characteristics were well balanced in both arms (eTable 1 in Supplement 2). Three patients were randomized but did not receive study treatment. The main reasons for treatment discontinuation were progressive disease in 135 (59.7%), resection for metastases in 32 (14.2%), adverse events in 3 (1.3%), deaths in 7 (3.1%), and patient or investigator decision or other reasons in 21 (9.3%) (Figure 1).

Efficacy

The cutoff date for analyses was July 30, 2018. The median treatment duration was 7.4 months (IQR, 4.3-12.4 months) for the overall population, 8.4 months (IQR, 4.7-14.0 months) for arm A, and 7.0 months (IQR, 4.0-10.5 months) for arm B. Progression-free survival events occurred in 169 (including 15 deaths in the absence of progression), consisting of 83 in arm A (including 6 deaths) and 86 in arm B (including 9 deaths); median follow-up was 18.0 months (IQR, 13.1-23.3 months).

The null hypothesis of inferiority of arm B vs arm A could not be rejected because the upper limit of the 1-sided 90% CI of the HR was 1.857 and exceeded the 1.515 noninferiority boundary. In arm A, 10-month PFS was 59.9% (95% CI, 51.5%-

Figure 1. Consort Diagram of the Study

229 Patients treated
29 Italian centers (July 7, 2015-October 27, 2017)

229 Randomized

117 Randomized to arm A (panitumumab plus FU/LV)

112 Randomized to arm B (panitumumab)

2 Did not receive induction

1 Did not receive induction

115 Received induction therapy (8 cycles panitumumab plus FOLFOX4)

111 Received induction therapy (8 cycles panitumumab plus FOLFOX4)

30 Did not receive maintenance
  14 Disease progression
  5 Surgery
  1 Adverse event
  3 Death
  5 Patient's decision
  0 Local treatment
  2 Other

32 Did not receive maintenance
  19 Disease progression
  4 Surgery
  0 Adverse event
  4 Death
  1 Patient's decision
  2 Local treatment
  2 Other

85 Received panitumumab plus FU/LV maintenance

79 Received panitumumab maintenance

68 Discontinued treatment
  53 Disease progression
  8 Surgery
  1 Adverse event
  2 Patient's decision
  4 Other

68 Discontinued treatment
  49 Disease progression
  15 Surgery
  1 Adverse event
  0 Patient's decision
  3 Other

17 Treatment ongoing

11 Treatment ongoing

117 Included in the intention-to-treat population

112 Included in the intention-to-treat population

FOLFOX4 indicates panitumumab, 6 mg/kg (1-hour infusion for the first administration, 30-minute infusion thereafter), oxaliplatin, 85 mg/m² at day 1, leucovorin calcium, 200 mg/m², and fluorouracil, 400-mg/m² bolus, followed by 600-mg/m² continuous 24-hour infusion at days 1 and 2, every 2 weeks. FU indicates fluorouracil; LV, leucovorin.

69.8%) and median PFS was 12.0 months (95% CI, 10.4-14.5 months). In comparison, 10-month PFS was 49.0% (95% CI, 40.5%-59.4%) and median PFS was 9.9 months (95% CI, 8.4-11.0 months) in arm B (log-rank test, P = .006) (**Figure 2**A and eTable 2 in Supplement 2). The HR of arm B vs arm A from the univariable Cox proportional hazards regression model stratified by prior adjuvant therapy and number of disease sites was 1.51 (95% CI, 1.11-2.07; P = .009) (eTable 2 in Supplement 2).

The overall number of deaths was 74, including 40 in arm A and 34 in arm B. Overall survival at the median follow-up of 18 months was 66.4% (95% CI, 57.1%-77.2%) in arm A and 62.4% (95% CI, 52.3%-74.4%) in arm B (HR, 1.13; 95% CI, 0.71-1.81; P = .60) (Figure 2B and eTable 2 in Supplement 2).

There was no significant difference between arms in terms of overall response rate and disease control rate (eTable 2 in Supplement 2). Overall response rate was 66.7% (95% CI, 57.4%-75.1%) in arm A and 67.0% (95% CI, 57.4%-75.6%) in arm B; the pooled OR for overall response rate in arm B vs A was 1.07 (95% CI, 0.61-1.86) (P = .82). Disease control rate was 82.9% (95% CI, 74.8%-89.2%) in arm A and 83.9% (95% CI, 75.8%-90.2%) in arm B; the pooled OR for disease control rate in arm B vs A was 1.06 (95% CI, 0.52-2.15; P = .87). In the 153
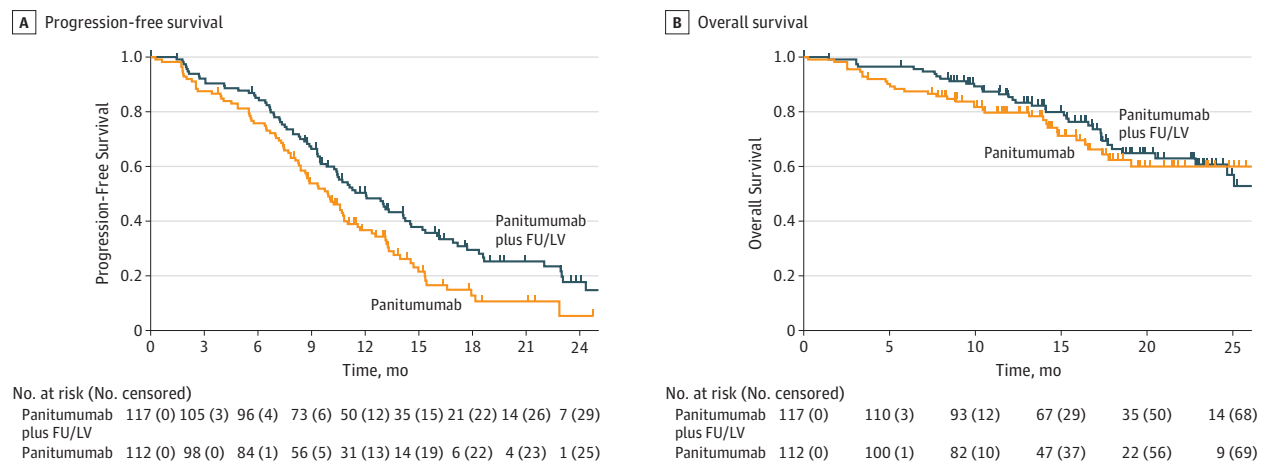
patients achieving RECIST response, median duration of response was 10.9 months (IQR, 5.8-21.0 months) in arm A and 9.0 months (IQR, 5.9-14.7 months) in arm B (P = .16) (eFigure 2 in Supplement 2).

The forest plots showing treatment HR and 95% CI according to stratification factors and other prognostic variables are shown in **Figure 3** (for PFS) and eFigure 3 in Supplement 2 (for overall survival). The per protocol population included 164 patients, 85 in arm A and 79 in arm B. Median follow-up was 17.9 months (IQR, 13.1-23.3 months). In arm A, 10-month PFS was 70.3% (95% CI, 61.2%-80.8%) and median PFS was 14.1 months (95% CI, 11.3-17.2 months). In arm B, 10-month PFS was 59.0% (95% CI, 49.0%-71.0%); median PFS was 10.8 months (95% CI, 9.9-13.3 months); and HR was 1.50 (95% CI, 1.03-2.19; P = .04) (eFigure 4A in Supplement 2). For overall survival, HR was 0.95 (95% CI, 0.50-1.82; P = .88) (eFigure 4B in Supplement 2).

Safety

Dose delays and reductions are reported in eMethods in Supplement 2. In the safety population of 226 patients, adverse events of at least grade 3 occurred in 52 patients (31.7%), including 36 (42.4%) in arm A and 16 (20.3%) in arm B. In arm A, an

Figure 2. Kaplan-Meier Curves for Progression-Free Survival (PFS) and Overall Survival According to Treatment Arm

A Progression-free survival

B Overall survival

No. at risk (No. censored)

| Panitumumab plus FU/LV | 117 (0) | 105 (3) | 96 (4) | 73 (6) | 50 (12) | 35 (15) | 21 (22) | 14 (26) | 7 (29) |
| Panitumumab | 112 (0) | 98 (0) | 84 (1) | 56 (5) | 31 (13) | 14 (19) | 6 (22) | 4 (23) | 1 (25) |

No. at risk (No. censored)

| Panitumumab plus FU/LV | 117 (0) | 110 (3) | 93 (12) | 67 (29) | 35 (50) | 14 (68) |
| Panitumumab | 112 (0) | 100 (1) | 82 (10) | 47 (37) | 22 (56) | 9 (69) |

Data are shown in the intention-to-treat population at the date of first data cutoff (July 30, 2018). Ten-month PFS was 59.9% (95% CI, 51.5%-69.8%) vs 49.0% (95% CI, 40.5%-59.4%) in arm A vs arm B. The hazard ratio (HR) of arm B vs arm A was 1.51 (95% CI, 1.11-2.07; *P* = .009). Overall survival at the median

follow-up of 18 months was 66.4% (95% CI, 57.1%-77.2%) vs 62.4% (52.3%-74.4%) in arm A vs arm B (HR, 1.13; 95% CI, 0.71-1.81; *P* = .60). FU indicates fluorouracil; LV, leucovorin.

increased incidence of diarrhea (any grade, 21 [24.7%] vs 8 [10.1%]; grade ≥3, 4 [4.7%] vs 1 [1.3%]) and stomatitis (any grade, 28 [32.9%] vs 6 [7.6%]; grade ≥3, 6 [7.1%] vs 1 [1.3%]) occurred compared with arm B. Panitumumab-related toxic effects (mainly skin rash, paronychia, hypomagnesemia, and conjunctivitis) were reported in most patients, although the rates were higher in arm A vs B (any grade, 65 [76.5%] vs 33 [41.8%]; grade ≥3, 27 [31.8%] vs 13 [16.5%]). Patients experienced neurotoxic effects of any grade in 84 cases (37.2%) and of grade 3 or higher in 7 (3.1%). Notably, 3 patients died of sepsis during the induction phase (eTable 2 in Supplement 2).

Discussion

The rationale of a maintenance strategy with anti-EGFRs in absence of the fluoropyrimidine backbone is supported by the single-agent efficacy of such drugs in patients with molecularly selected mCRC. The MACRO-2 trial[17] suggested the noninferiority in terms of 9-month PFS of maintenance treatment with cetuximab alone compared with continuation of modified FOLFOX-6 plus cetuximab, even though the trial was conducted in patients with *KRAS* exon 2 wild-type mCRC. Such limitation and the small sample size highlighted the need for larger studies restricted to *RAS* wild-type mCRC. The VALENTINO phase 2 study prospectively enrolled patients with *RAS* wild-type mCRC and showed that maintenance therapy with single-agent panitumumab was inferior in terms of PFS compared with panitumumab plus fluorouracil-leucovorin, which slightly increased the treatment toxicity. Even if we adopted a large noninferiority margin as high as 1.515, this reinforces the clear PFS inferiority of single-agent panitumumab as maintenance treatment, so that a subsequent phase 3 trial would have an extremely low probability of meeting a primary end point of noninferiority.

The PFS benefit of adding fluorouracil-leucovorin to panitumumab in the maintenance setting did not differ according to main subgroups, including those with poorer prognosis and primary resistance to anti-EGFR agents, such as right-sided primary tumors or *BRAF*-mutated ones.[16,22] The prevalence of right-sided tumors was only 17%, and that of *BRAF*-mutated tumors was only 4%, therefore lower than expected in the *RAS* wild-type population, showing an increased refinement of patients' selection in the clinical practice. Even if the absence of a panitumumab-free arm did not allow us to perform predictive analyses, PFS in these 2 subgroups was particularly poor in arm B (Figure 2). The clinical importance of further investigating anti-EGFR-based maintenance in these patient subgroups is modest because anti-EGFR agents are not commonly used in the upfront treatment of most patients with *BRAF*-mutated or right-sided (*RAS* wild-type) mCRC.[1,14]

Our results are biologically sound for at least 2 reasons. First, several patients with *RAS* wild-type mCRC are primarily resistant to EGFR inhibition owing to the presence of EGFR-independent oncogenic drivers other than *RAS* and *BRAF* mutations, specific gene expression profiles, and overexpression of specific microRNAs such as microRNA 31-3p.[16,22-24] Therefore, in this clinically and biologically heterogeneous patient population, single-agent anti-EGFRs may represent a suboptimal maintenance treatment option compared with chemotherapy continuation. Second, in tumors with initial sensitivity to EGFR inhibition, acquired resistance may be delayed by the synergistic effect of the combined chemotherapeutic agent. In our study, the duration of response curves were similar in both arms to 6 months but progressively diverged over time (eFigure 2 in Supplement 2), suggesting the presence of a patient subgroup achieving long-term response with the combination of panitumumab and fluorouracil-leucovorin.

Maintenance treatment with single-agent panitumumab had less toxic effects, although the safety profile was clearly

Figure 3. Forest Plots of Progression-Free Survival by Patient Subgroups Within the Intention-to-Treat Population

Characteristic	No. of Events/Patients		Median PFS (95% CI), mo		HR (95% CI)	
	Panitumumab Plus FU/LV	Panitumumab	Panitumumab Plus FU/LV	Panitumumab		
Sex						
Female	27/38	30/38	10.72 (8.59-18.40)	10.00 (7.17-13.20)	1.44 (0.85-2.43)	
Male	56/79	56/74	12.07 (10.43-16.00)	9.74 (8.65-12.60)	1.58 (1.08-2.31)	
Age, y						
<65	45/59	45/64	11.02 (9.47-14.20)	10.59 (8.26-13.30)	1.21 (0.79-1.84)	
≥65	38/58	41/48	13.03 (10.43-22.00)	9.13 (8.39-12.60)	2.01 (1.28-3.15)	
ECOG performance status						
0	57/84	60/81	13.13 (10.46-16.00)	10.07 (8.85-13.20)	1.49 (1.03-2.15)	
1	26/33	26/31	9.84 (7.20-16.20)	7.40 (4.08-12.40)	1.80 (1.03-3.14)	
Prior adjuvant treatment						
Yes	9/17	16/19	24.34 (22.93-NA)	8.85 (4.08-15.40)	4.47 (1.93-10.32)	
No	74/100	70/93	10.53 (9.47-13.10)	9.93 (8.65-11.60)	1.26 (0.91-1.76)	
Primary tumor resected						
Yes	49/73	55/72	13.03 (11.02-17.20)	10.03 (8.29-12.60)	1.86 (1.25-2.77)	
No	34/44	31/40	10.34 (7.34-14.20)	9.38 (8.26-13.30)	1.13 (0.69-1.84)	
Liver metastases only						
Yes	28/42	27/39	12.07 (9.47-16.90)	10.69 (9.74-14.70)	1.13 (0.67-1.92)	
No	55/75	59/73	11.45 (9.51-15.40)	8.72 (7.40-12.40)	1.85 (1.26-2.70)	
Synchronous metastases						
Yes	68/94	66/83	10.53 (9.47-13.10)	9.38 (8.29-10.80)	1.48 (1.05-2.09)	
No	15/23	20/29	22.01 (14.11-NA)	11.58 (7.83-NA)	1.91 (0.97-3.77)	
Number of metastatic sites						
1	40/62	48/64	14.14 (11.28-22.00)	10.59 (8.75-13.20)	1.67 (1.08-2.57)	
≥2	43/55	40/48	9.51 (7.96-13.00)	8.72 (6.45-12.60)	1.50 (0.97-2.32)	
Primary tumor site						
Right colon	15/19	19/21	8.63 (5.86-NA)	6.97 (4.51-8.88)	2.10 (1.06-4.16)	
Left colon or rectum	68/98	67/91	12.86 (10.53-15.20)	10.69 (9.74-13.13)	1.45 (1.03-2.05)	
***BRAF* status**						
Wild-type	31/113	79/103	12.04 (10.39-14.60)	10.07 (8.75-11.70)	1.50 (1.09-2.06)	
Mutated	2/4	7/9	8.42 (2.73-NA)	5.59 (1.78-NA)	1.14 (0.22-5.92)	
All patients	83/117	86/112	12.00 (10.40-14.50)	9.90 (8.40-11.00)	1.51 (1.11-2.07)	

ECOG indicates Eastern Cooperative Oncology Group; FU, fluorouracil; HR, hazard ratio; LV, leucovorin. Dashed line indicates predefined noninferiority boundary (HR, 1.515).

manageable in both treatment arms. Indeed, preemptive therapy for toxic effects on the skin was recommended by our study to decrease the incidence of skin rash of grade 3 or higher according to the literature.[24] The incidence of 26.5% (60 patients) in the VALENTINO study favorably compares with 37% reported in the PRIME trial.[2] Most importantly, the extremely low incidence of grade 3 neurotoxic effects (3.1%) is in line with other academic trials scheduling early discontinuation of oxaliplatin treatment after a preplanned number of cycles.[8,13,19,25]

Among postinduction strategies aimed at improving quality of life, intermittent treatments have been investigated by dedicated clinical trials. These strategies may have a remarkable clinical value in patients with low disease burden and in those who achieve the rapid and deep tumor responses typically associated with anti-EGFR-based first-line regimens.[26] Among the few available evidences for such strategies in the era of biological agents,[19,20] the randomized noncomparative phase 2 COIN-B study[19] was conducted in patients with *KRAS* exon 2 wild-type mCRC and showed that treatment holidays followed by reinduction therapy at progressive disease and maintenance therapy with cetuximab alone may achieve

noninferior failure-free survival compared with historical data. However, in the comparative analysis, a treatment break was associated with inferior overall survival and postinduction PFS compared with maintenance therapy with cetuximab.

Limitations

Our study has some limitations. First, the control arm (panitumumab plus fluorouracil-leucovorin) could have been regarded as experimental. Indeed, discontinuing oxaliplatin treatment after a preplanned number of cycles has improved tolerability, with clearly acceptable loss of efficacy.[6,7] The available evidence on anti-EGFR-based treatments is limited to the randomized phase 2 SAPPHIRE study,[18] showing similar 9-month PFS when de-escalating to panitumumab plus fluorouracil-leucovorin or continuing panitumumab plus modified FOLFOX-6 therapy. Second, the lack of a single-agent fluorouracil-leucovorin arm hampered the chance of assessing the specific effect of continuing panitumumab in the maintenance setting, as investigated by the ongoing randomized phase 2 PanaMa study.[27] Third, in our study, randomization was planned before starting induction treatment, and patients who

could not proceed to the randomly assigned maintenance strategy were included in the intention-to-treat analysis. However, the results obtained in the per protocol and intention-to-treat populations were highly consistent. Finally, the reintroduction of FOLFOX-4 plus panitumumab after progressive disease during the maintenance phase was not scheduled by our study. Indeed, the negative data on continuation of anti-EGFR-based treatment beyond progression are consistent with the well-described emergence of tumor clones with genomic resistance to EGFR inhibition.[28,29]

Conclusions

Despite the noninferiority design and the sample size, this study clearly demonstrates the inferiority of maintenance treatment with single-agent panitumumab compared with panitumumab plus fluorouracil-leucovorin. Even if panitumumab plus fluorouracil-leucovorin were to be regarded as the optimal maintenance strategy after an oxaliplatin-based induction treatment, this conclusion cannot be generalized for a combination chemotherapy including irinotecan, because the issue of cumulative toxic effects is less clinically significant. Most important, even if the VALENTINO study planned the discontinuation of oxaliplatin treatment after a fixed 4-month induction, the clinical decision making on treatment de-escalation and its timing should be dynamically managed by physicians by taking into account several factors, such as available evidence, patient preference, baseline patient- and disease-related characteristics, specific drug toxicities, and response to induction treatment.

Author Affiliations: Oncology and Hemato-oncology Department, University of Milan, Milan, Italy (Pietrantonio, Sartore-Bianchi, de Braud); Department of Medical Oncology, Fondazione Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Istituto Nazionale dei Tumori, Milan, Italy (Pietrantonio, Morano, Corallo, Raimondi, Caporale, Antista, Niger, Di Bartolomeo, de Braud); Clinical Epidemiology and Trial Organization, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy (Miceli); Unit of Medical Oncology 1, Department of Clinical and Experimental Oncology, Istituto Oncologico Veneto, IRCCS, Padua, Italy (Lonardi, Bergamo, Zagonel); Unit of Medical Oncology, Azienda Ospedaliero-Universitaria (AOU) Pisana, Department of Translational Research and New Technologies in Medicine, University of Pisa, Pisa, Italy (Cremolini, Falcone); Medical Oncology and Hematology Unit, Humanitas Cancer Center, Humanitas Clinical and Research Center, Rozzano, Italy (Rimassa, Smiroldo); Niguarda Cancer Center, Grande Ospedale Metropolitano Niguarda, Milan, Italy (Sartore-Bianchi); Department of Oncology, AOU San Luigi di Orbassano, University of Torino, Orbassano, Italy (Tampellini); Colorectal Cancer Unit, Medical Oncology Division 1, AOU Città della Salute e della Scienza, Torino, Italy (Racca); Medical Oncology Unit, Ente Ospedaliero Ospedali Galliera, Genoa, Italy (Clavarezza); Medical Oncology Unit A.O. Papardo and Department of Human Pathology, University of Messina, Messina, Italy (Berenato, Adamo); Department of Internal Medicine, University of Genoa and IRCCS AOU San Martino-IST, Genoa, Italy (Murialdo); Medical Oncology Unit, Fondazione Poliambulanza, Brescia, Italy (Zaniboni); Medical Oncology Unit, Azienda Socio-Sanitaria Territoriale (ASST) Ospedale di Cremona, Cremona, Italy (Tomasello); Medical Oncology Unit, Azienda Socio Sanitaria Territoriale Lariana, Como, Italy (Giordano); Medical Oncology Unit, Oncology Department, ASST Bergamo Ovest, Treviglio, Italy (Petrelli); Medical Oncology Unit,

Azienda Ospedaliera San Gerardo, Monza, Italy (Longarini); Medical Oncology Unit, Ospedale Antonio Perrino, Brindisi, Italy (Cinieri).

Oftalmico, Milan, Italy; Alessandro Bertolini, MD, Department of Medical Oncology, Azienda Socio-Sanitaria Territoriale (ASST) della Valtellina e Alto Lago, Sondrio, Italy; Letizia Procaccio, MD, Department of Clinical and Experimental Oncology, Istituto Oncologico Veneto, IRCCS, Padua, Italy; Carlotta Antoniotti, MD, Unit of Medical Oncology, Azienda Ospedaliero-Universitaria (AOU) Pisana, Department of Translational Research and New Technologies in Medicine, University of Pisa, Pisa, Italy; Maria Giulia Zampino, MD, Gastrointestinal Unit, Istituto Europeo di Oncologia, Milan, Italy; Mario Airoldi, MD, Department of Medical Oncology, AOU Città della Salute e della Scienza di Torino, Turin, Italy; Graziella Pinotti, MD, Department of Medical Oncology, Ospedale di Circolo, Varese, Italy; Daniele Fagnani, MD, Department of Medical Oncology, ASST di Vimercate, Vimercate, Italy; Clara Natoli, Department of Medical Oncology, Facoltà di Medicina e Chirurgia Università degli Studi G. D'Annunzio, Chieti, Italy; Antonio Nuzzo, MD, Department of Medical Oncology, Ospedale Civico Renzetti, Lanciano, Italy; Enrico Cortesi, MD, Department of Medical Oncology B, Policlinico Umberto I, Sapienza Università di Roma, Rome, Italy; Lorenzo Antonuzzo, MD, Department of Medical Oncology, AOU Careggi, Florence, Italy; Francesco Leone, MD, Gastrointestinal Unit, Fondazione del Piemonte per l'Oncologia–IRCC di Candiolo, Candiolo, Italy; Mario Roselli, MD, Department of Medical Oncology, Policlinico Univeritario Tor Vergata, Rome, Italy; and Samantha Di Donato, MD, Department of Medical Oncology, Azienda Unita' Sanitaria Locale Toscana Centro, Ospedale di Prato, Prato, Italy.

Data Sharing Statement: See Supplement 3.

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