Fluorouracil, Leucovorin, and Irinotecan Plus Cetuximab Versus Cetuximab as Maintenance Therapy in First-Line Therapy for *RAS* and *BRAF* Wild-Type Metastatic Colorectal Cancer: Phase III ERMES Study

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ABSTRACT

PURPOSE The intensity of anti-EGFR–based first-line therapy for *RAS/BRAF* wild-type (wt) metastatic colorectal cancer (mCRC), once disease control is achieved, is controversial. A de-escalation strategy with anti-EGFR monotherapy represents a potential option to maintain efficacy while reducing cytotoxicity.

METHODS In this multicenter, open-label, phase III trial, patients with untreated *RAS/BRAF* wt mCRC were randomly assigned to receive either fluorouracil, leucovorin, and irinotecan/cetuximab (FOLFIRI/Cet) until disease progression (arm A) or FOLFIRI/Cet for eight cycles followed by Cet alone (arm B). The coprimary end points were a noninferior progression-free survival (PFS) in the modified per-protocol (mPP) population (>eight cycles) and a lower incidence of grade (G) 3-4 adverse events (AEs) for arm B compared with arm A.

RESULTS Overall, 606 patients were randomly assigned, with 300 assigned to arm A and 306 to arm B. The median follow-up was 22.3 months. In the mPP population, 291 events occurred with a PFS of 10 versus 12.2 months for arms B and A, respectively (P of noninferiority = .43). In the intention-to-treatment (ITT, ≥one cycle) population, 503 events occurred with a PFS of 9 versus 10.7 months (P = .39). The overall survival was 35.7 versus 30.7 months (P = .119) and 31.0 versus 25.2 months (P = .32) in the mPP and ITT population, respectively. Arm B had lower G3-4 AEs during the maintenance period than arm A (20.2% *v* 35.1%).

CONCLUSION The ERMES study did not demonstrate noninferiority of maintenance with Cet alone. Despite a more favorable safety profile, maintenance with single-agent Cet after induction with FOLFIRI/Cet cannot be recommended for all patients but could represent an option in selected cases.

ACCOMPANYING CONTENT

Data Supplement

Protocol

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INTRODUCTION

Colorectal cancer (CRC) is the third most common malignancy worldwide and the second leading cause of cancer-related mortalities. It is the most common cause of malignancy-related death in men age 20-49 years.[1] Stage is the pivotal predictor of survival in CRC, with a 5-year survival rate of approximately 14% for metastatic disease.[2] Systemic chemotherapy is still the mainstay of treatment for mismatch repair proficient stage IV disease. For patients not showing symptom progression on first-line chemotherapy, maintenance therapy should be considered.[3] Maintenance therapy is a strategy based on de-escalation of drug intensity aimed at reducing side effects and improving patients' quality of life (QoL) without jeopardizing efficacy. Fluoropyrimidine monotherapy,[4] or in combination with bevacizumab,[5-9] is the preferred maintenance option after induction with oxaliplatin-based chemotherapy plus bevacizumab.[3] Instead, maintenance treatment after anti-epidermal growth factor receptor (EGFR)–based first-line therapy is controversial. Indeed, there are no phase III data supporting this strategy, while evidence relies only on phase II trials.[10-18] According to the ESMO guidelines, owing to the absence of cumulative side effects, first-line treatment with fluorouracil, leucovorin, and irinotecan (FOLFIRI) may be continued until disease progression.[3] Major tumor shrinkage is seen within the first

CONTEXT

Key Objective

Is cetuximab (Cet) monotherapy maintenance noninferior to fluorouracil, leucovorin, and irinotecan plus Cet until disease progression in terms of progression-free survival and for reducing the incidence of grade 3-4 adverse events in patients with *RAS* and *BRAF* wild-type (wt) metastatic colorectal cancer (mCRC)?

Knowledge Generated

The ERMES trial did not meet its primary objective, but it showed an improvement in the toxicity profile of the experimental arm, comparable response rates between the arms, and the absence of detrimental signals in terms of overall survival for chemotherapy de-escalation.

Relevance *(E.M. O'Reilly)*

Maintenance therapy plays a role in the treatment of selected patients with mCRC. In this non-inferiority phase III trial, the value of maintenance Cet following cytotoxic therapy was not established in *RAS/BRAF* wt disease. Alternative maintenance strategies are under investigation.*

*Relevance section written by *JCO* Associate Editor Eileen M. O'Reilly, MD.

3-4 months of treatment,[11] so continued exposure to combined antineoplastic therapy might not improve disease control but rather cause more side effects in addition to the inevitable progression of the disease. ERMES was a phase III trial designed to test whether maintenance therapy with cetuximab (Cet) monotherapy after induction with first-line FOLFIRI plus Cet might represent a valid option in the continuum of care of patients with *RAS* and *BRAF* wild-type (wt) metastatic colorectal cancer (mCRC).

METHODS

Patient Selection

ERMES was a multicenter, open-label, randomized, phase III noninferiority trial. The complete study protocol is available online (protocol of the ERMES trial). Key eligibility criteria are reported in a previous paper.[19] Population included patients diagnosed with previously untreated, histologically proven unresectable mCRC, with centrally confirmed *RAS* and *BRAF* wt status on the primary tumor or related metastasis (local assessment was accepted for AIOM-SIAPEC–certified centers). Patients who completed adjuvant therapy at least 6 months before entering the study were eligible. The study protocol was approved by the ethics committee of the coordinating center (Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Prot. 23942/14) and from each participating center. All patients provided written informed consent before study entry. This trial was conducted in accordance with the Declarations of Helsinki.

Study Design

The study design is illustrated in Figure 1. Eligible patients were randomly assigned with a 1:1 ratio to receive either the standard or the experimental treatment (arm A *v* arm B). Standard treatment consisted of FOLFIRI plus Cet while experimental treatment included FOLFIRI plus Cet for eight cycles, followed by Cet monotherapy. Detailed treatment schedules are reported in the previous paper.[19] Stratification factors for centralized random assignment included age (<65 *v* ≥65 years), Eastern Cooperative Group performance status (0-1 *v* 2), liver-only disease (yes *v* no), and exposure to prior adjuvant treatment (yes *v* no). Treatment was continued until disease progression, death, unacceptable toxicity, or consent withdrawal. At the time of disease progression, infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX) plus bevacizumab was recommended as second-line therapy.

Imaging and Toxicity Assessment

Efficacy and safety assessments were carried out as previously described.[19] Chest and abdomen contrast-enhanced computed tomography scans were repeated every 8 weeks from random assignment to disease progression or death, and tumor assessment was performed according to the RECIST criteria (ver 1.1).[20] Toxicity (including Cet-related skin adverse events) was recorded and graded throughout the whole treatment (including both induction and maintenance phases) according to the National Cancer Institute-Common Terminology Criteria for Adverse Events (NCI-CTCAE) version 4.03. The Dermatology Life Quality Index and EORTC QLQ C30 questionnaires were administered at baseline and at weeks 8, 16, 24, and 32 to assess patients' QoL. Translational analyses were planned for both baseline formalin-fixed paraffin-embedded (FFPE) tumor tissue samples and circulating tumor DNA from liquid biopsies performed at the following time points: baseline, 8 weeks, disease progression, and 3 months after disease progression.

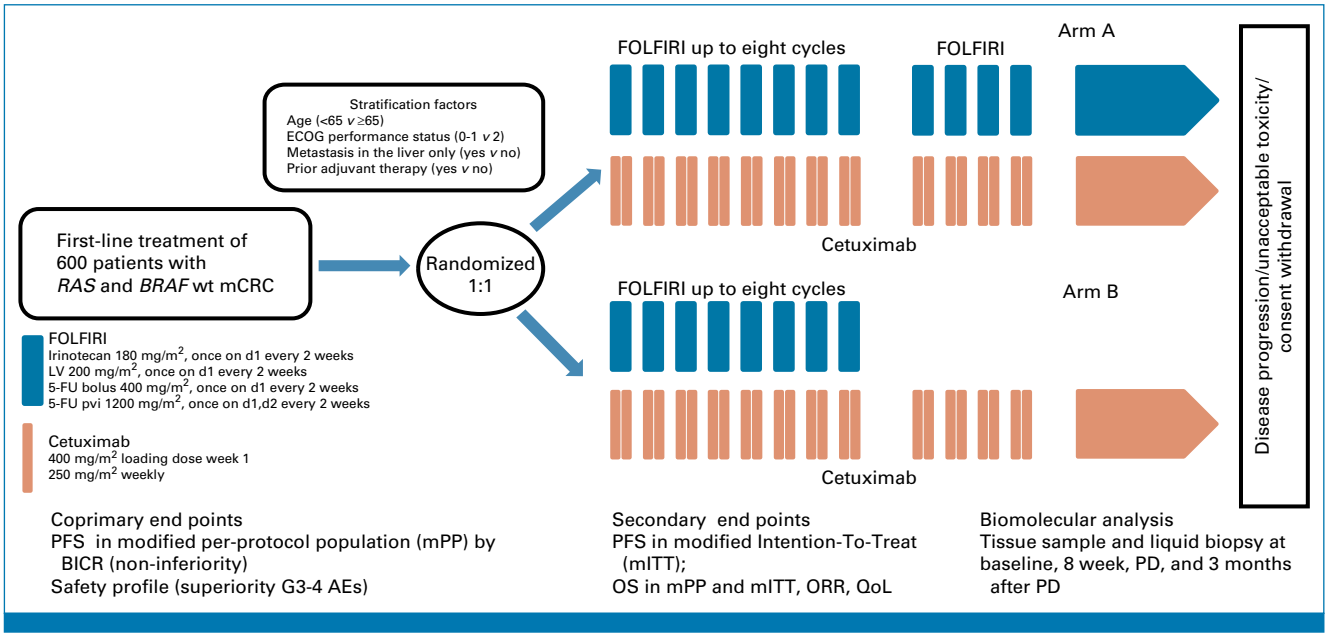

FIG 1. Study design. FU, fluorouracil; AEs, adverse events; BICR, blind independent central review; ECOG, Eastern Cooperative Group; ETS, early tumor shrinkage; FOLFIRI, fluorouracil, folic acid and irinotecan; LV, folinic acid; mCRC, metastatic colorectal cancer; mITT, modified intention to treat; mPP, modified per-protocol; ORR, over response rate; OS, overall survival; PD, progression disease; PFS, progression-free survival; QoL, quality of life.

Objectives and End Points

The objective of this study was to demonstrate the noninferior efficacy and superior safety profile of the experimental treatment when compared with the standard treatment. The trial had two coprimary end points: progression-free survival (PFS) from random assignment and toxicity rate. PFS was defined as the time from random assignment (before the start of induction therapy) to disease progression or death from any cause. The determination of the clinical response or disease progression was based on investigator-reported measurements. A blinded independent central review was preplanned. The toxicity rate was defined as the percentage of patients with treatment-related AEs graded 3-4 based on NCI-CTCAE version 4.03. Secondary end points are detailed in the previous paper[19] and include overall response rate (ORR), overall survival (OS), early tumor shrinkage (ETS), incidence of Cet-related skin toxicity, safety profile, QoL, and translational analyses which included molecular profiles assessed by next-generation sequencing on FFPE tumor tissue samples and liquid biopsies. Specific secondary end points, including ETS, QoL, and translational analyses, will be presented in separate publications.

Sample Size Estimation

Detailed sample size estimation was previously reported.[19] In brief, the statistical hypothesis was based on the CRYSTAL trial,[21] which reported a median PFS of 11.4 months with an upper 95% CI boundary for the hazard ratio (HR) of 0.76 in *RAS* wt patients who received FOLFIRI plus Cet continuously. Thus, in agreement with the European Medicines Agency Guideline on the Choice of the Noninferiority Margin, a noninferiority margin of 1.33 (=1/0.75) for the HR of arm B versus arm A was considered appropriate. The null hypothesis of inferiority HR for PFS of arm B versus arm A is ≥1.33 was tested in the modified per-protocol (mPP) population versus the alternative hypothesis of noninferiority HR is 1. Three-hundred and eighty-six events were needed to reach a power of 80% (under the alternative hypothesis) at a one-sided significance level of 0.025.

Concerning the coprimary end point toxicity rate, assuming a rate of grade (G) 3-4 AEs of 50%-80% in arm A (79.3% was observed in the CRYSTAL trial),[21] a sample size of 300 patients for each treatment arm would yield a power of 80% to detect a reduction of 10%-12% of patients experiencing G3-4 AEs, with a two-sided Fisher exact test at a significance level of 0.05.

Statistical Analyses

In agreement with the principles of noninferiority trials, the primary analysis was performed in the mPP population. In addition, the analysis was repeated for the modified intention-to-treatment (modified intention-to-treat [mITT]) population. The HR for PFS was estimated using a stratified Cox proportional hazard model. Moreover, unstratified HR was estimated, and multivariate Cox models were applied. The

same statistical methods specified for PFS were also applied to OS. Differences in incidence rate of any G3-4 AEs were compared between the two arms using a two-sided Fisher exact test. The two coprimary endpoints (PFS and toxicity rate) were compared between the two arms using a fixed-sequence testing procedure to control for a family-wise type I error rate of 0.05 in a strong sense.[19] According to this sequence, only if the first null hypothesis of inferiority is rejected at a one-sided significance level of 0.025, the second null hypothesis will be tested at a significance level of 0.05 in a confirmatory analysis.[22] For statistical analysis of primary end point (PFS), a *P* value of noninferiority was used. For secondary end point analysis, a *P* value of superiority was used.

The associated exact two-sided 95% CI (Clopper-Pearson) was calculated for the response rate. Odds ratios and associated 95% CI were calculated using the stratified Cochran-Mantel-Haenszel procedure with the stratification factors used at random assignment with a significance level set at 0.05.

RESULTS

Between May 2015 and March 2020, 606 patients were randomly assigned. Of them, 593 patients who received at least one treatment cycle were included in the mITT population. A total of 296 and 297 patients were assigned to arms A and B, respectively. Of them, 154 and 183 patients in arms A and B, respectively, received treatment beyond cycle 8, constituting a mPP population of 337 patients. The dropout rate was approximately 40% in each arm, and approximately 20% of the patients were excluded because of conversion to surgery (Fig 2; Data Supplement, Table S1 [online only]).

Table 1 summarizes the patient and disease characteristics of the mPP population. Notably, despite the dropout, the characteristics were well balanced between the two arms, including nonstratification factors such as primary tumor location, primary tumor resection, and number of metastatic sites, without statistical differences.

The median follow-up in the mPP population was 22.4 months (95% CI, 20.89 to 25.07).

Primary End Points: PFS and Safety in mPP Population

In total, 291 PFS events were observed in the mPP population. The PFS was 10.0 and 12.2 months in arms B and A, respectively (HR, 1.3; 95% CI, 1.03 to 1.64). The first primary end point was not met: the upper limit of 95% CI HR crosses the noninferiority boundary set at 1.33, with a noninferiority *P* value of .43 (Fig 3). In the subgroup analysis for PFS in the mPP population, better performance of the standard arm versus the experimental arm was reported in all subgroups (Fig 4). A quantitative positive interaction was reported only in the subgroup for primary tumor location, with a major benefit in favor of arm A reported for right-sided tumor (interaction $P = .04$).

For the second coprimary end point, Table 2 summarizes treatment toxicity, reporting the rate of G3-4 AEs during

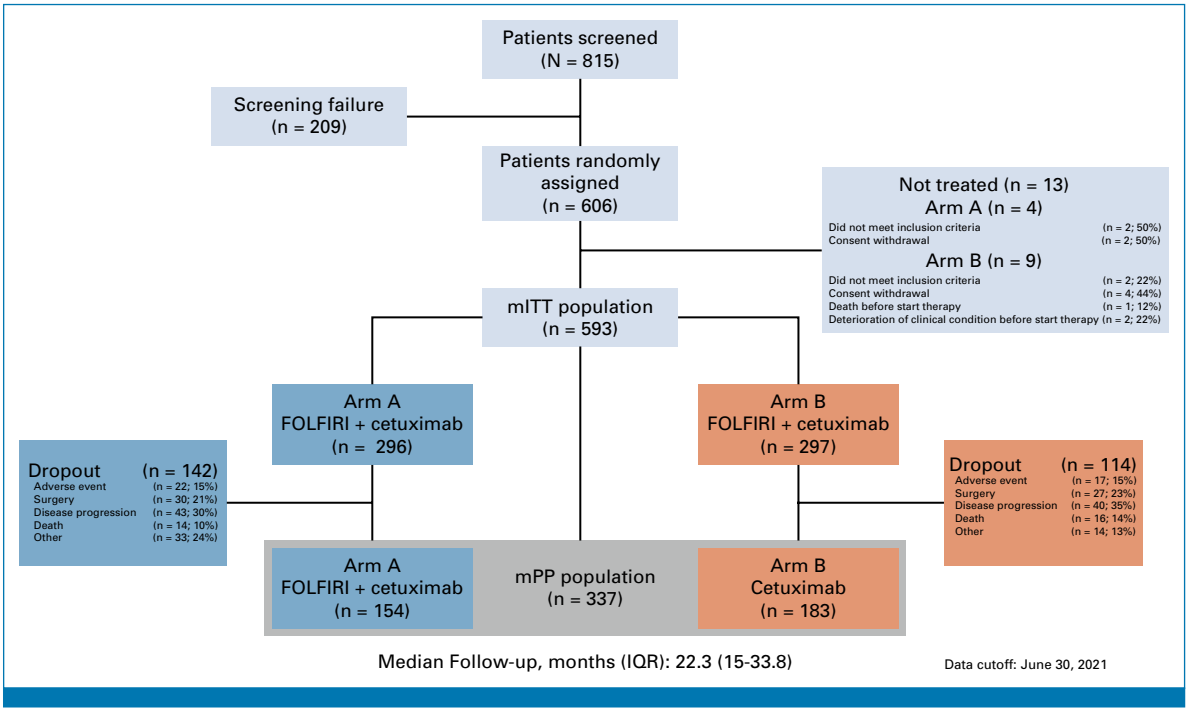

FIG 2. CONSORT diagram. FOLFIRI, fluorouracil, folic acid, and irinotecan; mITT, modified intention to treat; mPP, modified per protocol.

TABLE 1. Patient and Disease Characteristics for Arm A (FOLFIRI plus Cet until disease progression) Versus Arm B (FOLFIRI plus Cet for eight cycles followed by Cet monotherapy) in mPP Population

Parameter	Arm A (n = 154)	Arm B (n = 183)
Age, years, median (min-max)	62.7 (34-79)	65 (22-82)
Sex, No. (%)		
Male	99 (64.3)	126 (68.9)
Female	55 (35.7)	57 (31.2)
ECOG-PS, No. (%)		
Grade 0	119 (77.3)	145 (79.2)
Grade 1	35 (22.7)	36 (19.7)
Grade 2	0	2 (1.1)
Prior adjuvant therapy, No. (%)		
Yes	43 (27.9)	51 (27.9)
No	111 (72.1)	132 (72.1)
Metastasis in the liver only, No. (%)		
Yes	18 (11.7)	15 (8.2)
No	136 (88.3)	168 (91.8)
Metastatic sites (1 *v* >1), No. (%)		
1	125 (81.2)	145 (79.2)
>1	29 (18.8)	38 (20.8)
Prior surgery, No. (%)		
Yes	94 (61)	112 (61.2)
No	50 (32.5)	57 (31.2)
NA	10 (6.5)	14 (7.7)
Primary tumor location, No. (%)		
Right	32 (21)	33 (18)
Left	103 (67)	135 (74)
NA	19 (12)	15 (8)

Abbreviations: Cet, cetuximab; ECOG, Eastern Cooperative Group; FOLFIRI, fluorouracil, folic acid and irinotecan; mPP, modified per protocol; NA, not available; PS, performance status.

both the induction and maintenance phases. Arm B showed a better safety profile with lower G3-4 AEs rate during the entire treatment (52% in arm A *v* 50.3% in arm B) and specifically in the maintenance phase (35.1% in arm A *v* 20.2% in arm B). In the maintenance phase, the reduction of AEs was observed in all system organ classes, notably in classes of clinical interest (arm A *v* arm B): diarrhea (5.2% *v* 0.6%), oral mucositis (2.0% *v* 0.6%), decreased neutrophil count (7.1% *v* 0.6%), and skin and subcutaneous tissue disorders (18.2% *v* 14.2%). Since the first coprimary end point was not reached, no statistical analysis was performed. All AEs observed during the entire treatment are summarized in Data Supplement (Table S2).

Secondary End Points

The analysis of ORR according to RECIST 1.1 during the whole period did not show statistically significant differences between the two groups (67.5% in arm A; 71.6% in arm B; Data Supplement, Fig S1).

A total of 185 OS events (54.9%) were observed in the mPP population. The OS was 35.7 months (95% CI, 30.62 to 40.16) in arm B and 30.7 months (95% CI, 25.26 to 34.63) in arm A (HR, 0.79; 95% CI, 0.59 to 1.06; $P = .119$; Fig 5). Subgroup analysis of OS in patients with mPP is shown in the Data Supplement (Fig S2).

A total of 503 PFS events were observed in the mITT population. The PFS was 9 and 10.7 months in arm B and A, respectively (HR, 1.1; 95% CI, 0.92 to 1.31; $P = .305$; Data Supplement, Fig S3a). The subgroup analysis for PFS in the mITT population is shown in the Data Supplement (Fig S4). Overall, 303 OS events (56.2%) were observed in the mITT population. OS was 31.0 months (95% CI, 27.33 to 35.49) in arm B and 25.2 months (95% CI, 22.03 to 32.96) in arm A (HR, 0.89; 95% CI, 0.71 to 1.10; $P = .3$; Data Supplement, Fig S3b). The subgroup analysis for OS in the intention-to-treatment arm is reported in the Data Supplement (Fig S5).

Dose intensity in both arms is reported in the Data Supplement (Table S3). Data regarding second-line treatment

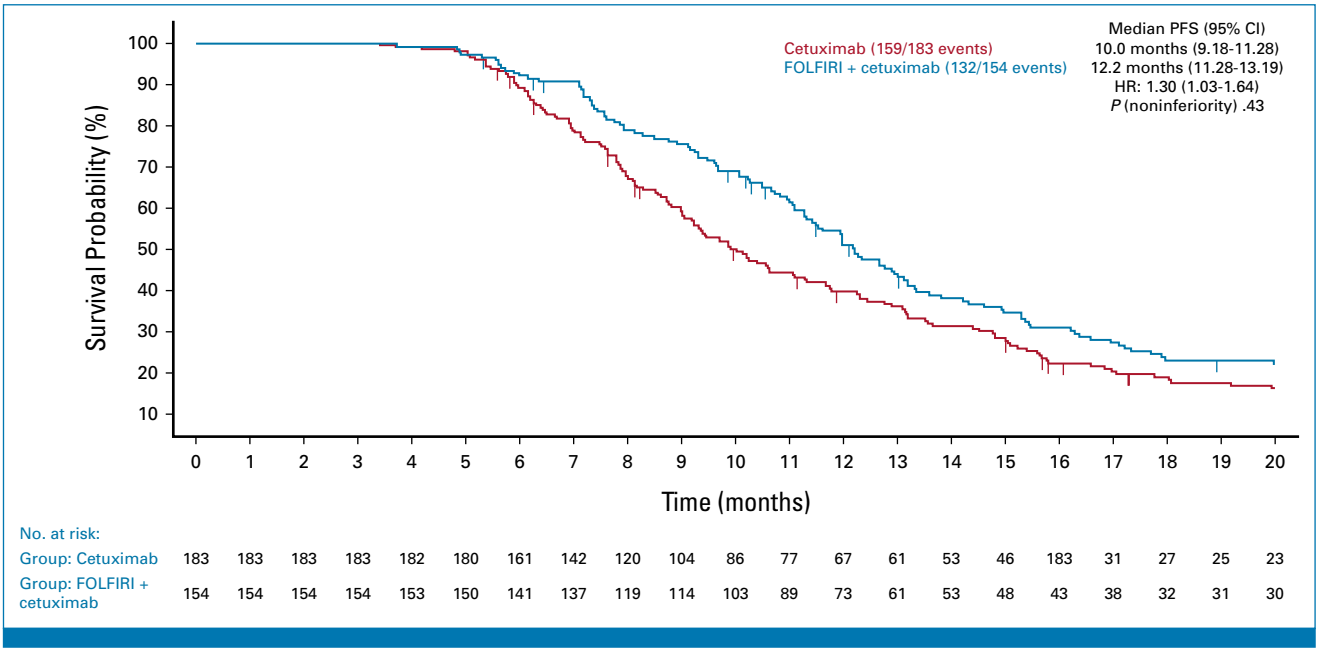

FIG 3. Kaplan-Meier estimates of PFS in mPP population for arm A (FOLFIRI plus Cet until disease progression, n = 154) compared with arm B (FOLFIRI plus Cet for eight cycles followed by Cet monotherapy, n = 183). Indicated HRs derived from Cox regression testing. *P* values derived from log-rank tests. Cet, cetuximab; FOLFIRI, fluorouracil, folic acid, and irinotecan; HR, hazard ratio; mPP, modified per protocol; PFS, progression-free survival.

administered after disease progression were available for approximately 30% of patients in the mPP population and are reported in the Data Supplement (Table S4).

DISCUSSION

The ERMES study is the first phase III trial to evaluate the efficacy and safety profile of maintenance monotherapy with Cet after 4 months of induction with FOLFIRI plus Cet in a population of patients with *RAS* and *BRAF* wt mCRC.

Previous evidence from the TIME-PRODIGE 28,[23] MACRO-2,[13] PANAMA,[10,11] and VALENTINO[15,16] phase II trials regarding the choice of optimal maintenance treatment remains undefined. The TIME-PRODIGE 28 showed a clinically meaningful benefit in terms of PFS and OS in favor of Cet maintenance compared with observation after induction with FOLFIRI plus Cet in patients with *RAS* and *BRAF* wt mCRC. However, the study did not meet the primary end point since the 6 months PFS rate for Cet was <40%.[23] Although the MACRO-2 trial showed a probable noninferiority of Cet as maintenance after induction with FOLFOX plus Cet compared with continuation of treatment until progression,[13] in the VALENTINO[15,16] and PANAMA[10,11] trials, continuation of folinic acid and fluorouracil (FA/FU) plus panitumumab compared with two different monotherapies, panitumumab or FA/FU, appeared to be the best treatment option.

The statistical design of the ERMES study was based on two coprimary end points: noninferiority in terms of PFS of Cet monotherapy compared with FOLFIRI plus Cet until disease progression and superiority of toxicity profile in terms of reduction of G3-4 AEs. These end points were evaluated in the mPP population, which included patients exposed to at least nine cycles of therapy, where the two arms diverged in the treatment schedule. The ERMES study did not demonstrate noninferiority in terms of PFS of Cet monotherapy compared with FOLFIRI plus Cet.

The results of the ERMES trial should be received with the awareness that the statistical power of the study was affected by the high number of dropouts, because of the higher-than-expected rate of patients exiting the study before nine cycles of therapy. This event was mainly linked to a significantly higher rate of surgery for liver metastases and a higher rate of progression in the first 4 months of therapy. This latter aspect may be intrinsic to the nature of the ERMES as a de-escalation pragmatic study. Indeed, the awareness of being able to expose patients to de-escalated cytotoxic therapy may have conditioned investigators to enroll, within the study inclusion criteria, a frailer population. This emerges from the significant presence of comorbidities in the enrolled patients (Data Supplement, Table S4). This reduced statistical power because of the high dropout rate represents a limitation of the study since it might have impaired achieving the primary end point. However, the results of the ERMES study display wide internal and external consistency and allow multiple inferences. Specifically, while diverging from the results of the MACRO-2 study, in which maintenance with Cet monotherapy reached noninferiority for

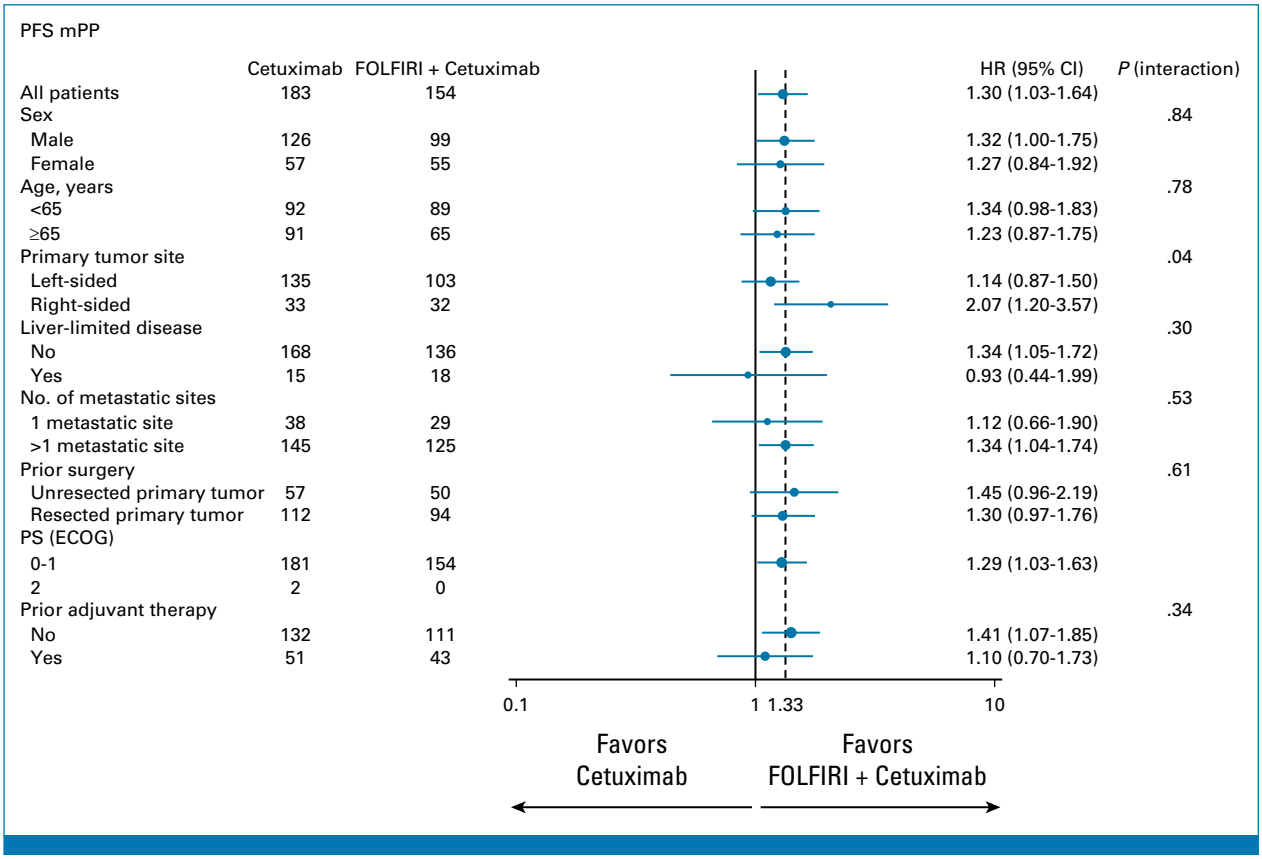

FIG 4. Subgroup analysis of PFS in mPP population for arm A (FOLFIRI plus Cet until disease progression, n = 154) compared with arm B (FOLFIRI plus Cet for eight cycles followed by Cet monotherapy, n = 183). Forest plot with indicated analyses. HRs for progression or death with 95% CI. *P* of interaction is reported. Cet, cetuximab; FOLFIRI, fluorouracil, folic acid, and irinotecan; HR, hazard ratio; mPP, modified per protocol; PFS, progression-free survival; PS, performance status.

PFS compared with FOLFOX plus Cet, results of the ERMES study are consistent with those of the VALENTINO trial,[15,16] in which panitumumab monotherapy did not reach noninferiority compared with FA/FU plus panitumumab. Moreover, median PFS are consistent between the two studies.

Subgroup analysis for primary end point confirmed a better performance of the standard arm for all subgroups. Notably, a statistically significant positive quantitative interaction was observed for primary tumor location. In fact, patients with right-sided tumors presented a benefit from continuing FOLFIRI plus Cet until disease progression. This observation

TABLE 2. Grade 3-4 AEs of Interest With Onset During Whole and Maintenance Period (full analysis set population)

	Arm A (n = 154), %		Arm B (n = 183), %	
AE	Entire Treatment Period	Maintenance Period	Entire Treatment Period	Maintenance Period
All G3-4 AEs	52.0	35.1	50.3	20.2
Anemia	0	0	1.1	1.1
Febrile neutropenia	5.2	1.3	2.2	0
Neutrophil count decreased	14.9	7.1	9.3	0.6
Diarrhea	10.4	5.2	7.7	0.6
Oral mucositis	5.2	2.0	1.6	0.6
Fatigue	4.6	3.3	0.6	0
Hypomagnesemia	2.0	1.3	1.1	0.6
Skin disorders	26.6	18.2	26.8	14.2

Abbreviations: AEs, adverse events; G, grade.

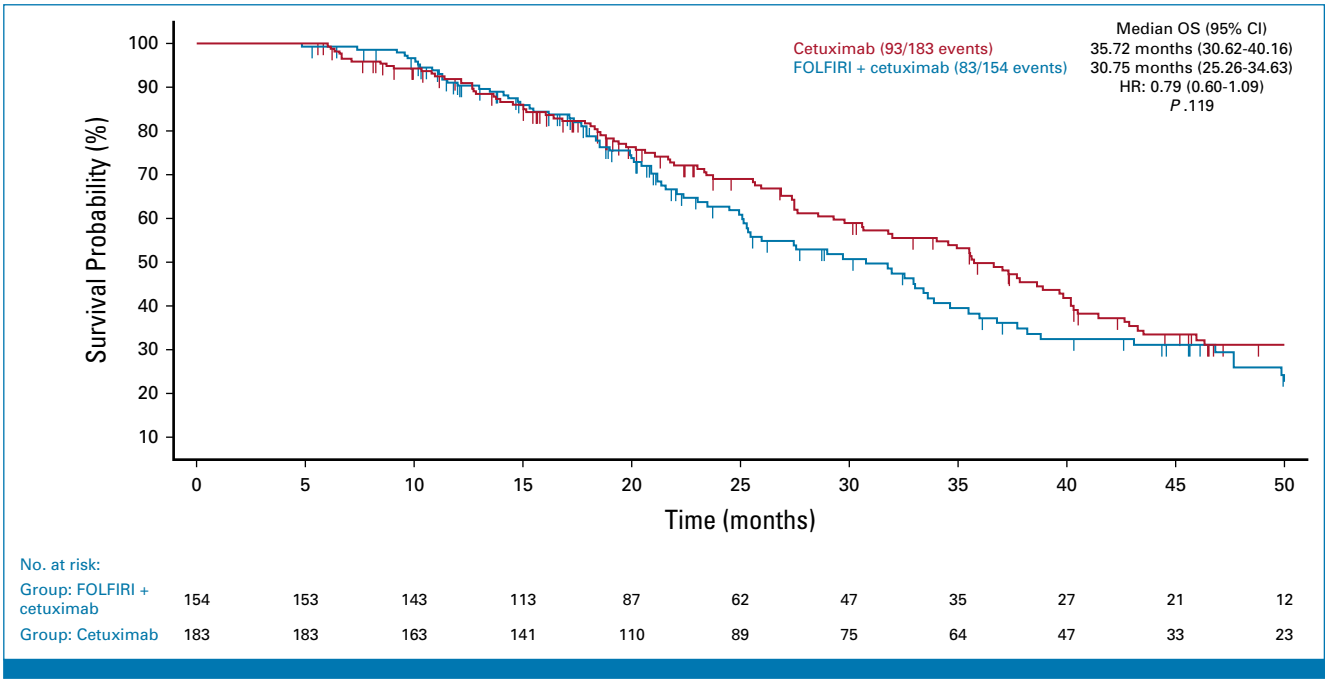

FIG 5. Kaplan-Meier estimates of OS in mPP population for arm A (FOLFIRI plus Cet until disease progression, n = 154) compared with arm B (FOLFIRI plus Cet for eight cycles followed by Cet monotherapy, n = 183). Indicated HRs derived from Cox regression testing. *P* values derived from log-rank tests. Cet, cetuximab; FOLFIRI, fluorouracil, folic acid, and irinotecan; HR, hazard ratio; mPP, modified per protocol; OS, overall survival.

should be interpreted with caution because of the exploratory nature of this subset analysis and may require further validation.

Although noninferiority for PFS was not reached, the toxicity profile was clinically better in the experimental arm with Cet monotherapy compared with the standard arm. Indeed, after eight cycles of induction, a numerical reduction in G3-4 AEs was observed for all toxicities of clinical interest in the experimental arm compared with the standard arm. According to the statistical design, statistical analysis of the safety coprimary end point could not be performed since the primary end point was not achieved.

Focusing on the secondary end points, it is noteworthy that the ORR overlapped between the two treatment arms. This was expected given that major tumor shrinkage is observed within the induction phase which was the same for the two arms.[19] This evidence is consistent with results of the VALENTINO trial, which reported no significant difference between arms in terms of ORR. Moreover, ORRs observed in both arms (67.5% in arm A; 71.6% in arm B) are consistent with those observed in recent trials of similar setting.[24] Concerning OS, it is important to highlight that the study is not powered to report statistically significant differences for this end point. Keeping in mind this limitation, we observed that both in the mPP and mITT populations, the experimental arm reaches a numerically higher median OS compared with the standard arm. Evidence of OS benefit, irrespective of comparable PFS, has been reported in the setting of first-line treatment for *RAS* wt mCRC by head-to-head trials comparing anti-EGFR–based versus bevacizumab-based therapy.[25-27] To date, the roots for this evidence are not clear. It has been postulated that higher ORR and ETS and greater deepness of response (DoR) could support this benefit.[28,29] In the ERMES trial, no difference in terms of ORR was observed between arms, and simultaneously, no improvement in ETS or DoR is expected for the experimental arm, which received the same dose intensity for the first 4 months (thus no difference in ETS is expected) and a reduced dose intensity in the maintenance period (thus an equivalent or inferior DoR is expected) with respect to the standard arm. Moreover, rates of patients who underwent surgery with curative intent were comparable between arms. Therefore, the OS benefit observed in the experimental arm of ERMES trial does neither seem to rely on the response rate nor the conversion to surgery. On the contrary, postprogression survival might be related to the second and subsequent lines of treatment.[30] Despite the limited availability of data concerning second-line treatment (around 30%), interestingly, the rate of second-line treatment was higher in the experimental arm than the standard arm (Data Supplement, Table S5). The safer toxicity profile and longer chemotherapy-free interval might have favorably affected subsequent treatment.

In conclusion, the study did not meet the primary end point. Thus, treatment with FOLFIRI plus Cet should be continued until disease progression or patient tolerance is achieved. However, given the better safety profile, RR, and signal on OS, a de-escalation strategy may remain an option in selected cases owing to patient preference or tolerability. Preplanned translational analyses are ongoing, and results are expected to improve the selection of patients who would benefit the most from treatment de-escalation.

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DISCLAIMER

Merck KGaA, Darmstadt, Germany (CrossRef Funder ID:10.13039/100009945) had no role in the design and conduct of the trial, collection, management, analysis, and interpretation of the data, or in the decision to submit the manuscript for publication. Merck KGaA, Darmstadt, Germany reviewed the manuscript for medical accuracy only before journal submission. The authors are fully responsible for the content of this manuscript and the views and opinions are described in the publication solely reflect those of the authors. A. O. and C. B. had full access to all the study data. C. P., A. O., and C. B. were responsible for the decision to submit this manuscript for publication.

EQUAL CONTRIBUTION

C.P. and A.O. contributed equally to this work.

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DATA SHARING STATEMENT

With respect to clinical trials, Fondazione Policlinico Agostino Gemelli IRCCS Roe, acting as the legal sponsor, is committed to providing information about its results to researchers with the goal of facilitating scientific progress. The information that will be considered for disclosure includes individual participant data that underlie the results reported in this article (text, tables, figures, and appendices). In addition, the study protocol and statistical analysis plan can be made available. All shared data must be anonymized to protect the privacy of the patients who participated in the trial, in accordance with applicable laws and regulations and in compliance with the International Council for Harmonization and Good Clinical Practice. Researchers should provide a scientifically sound proposal directed at direzione.scientifica@policlinicogemelli.it for approval to gain access to the requested data. Shared data are used only to achieve the aims of the approved proposal.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Fluorouracil, Leucovorin, and Irinotecan Plus Cetuximab Versus Cetuximab as Maintenance Therapy in First-Line Therapy for *RAS* and *BRAF* Wild-Type Metastatic Colorectal Cancer: Phase III ERMES Study

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