

Extended RAS Analysis of the Phase III EPIC Trial: Irinotecan + Cetuximab Versus Irinotecan as Second-Line Treatment for Patients with Metastatic Colorectal Cancer

ALBERTO SOBRERO,^a HEINZ-JOSEF LENZ,^b CATHY ENG,^c WERNER SCHEITHAUER,^d GARY MIDDLETON,^e WENFENG CHEN,^f REGINA ESSER,^g JOHANNES NIPPGEN,^f HOWARD BURRIS^h

^aIRCCS San Martino Policlinico, Genoa, Italy; ^bKeck School of Medicine of the University of Southern California, Los Angeles, California, USA; ^cUniversity of Texas MD Anderson Cancer Center, Houston, Texas, USA; ^dMedical University of Vienna, Vienna, Austria; ^eCollege of Medical and Dental Sciences, University of Birmingham, Birmingham, United Kingdom; ^fMerck Serono Co., Ltd., China, an affiliate of Merck KGaA, Darmstadt, Germany; ^gMerck KGaA, Darmstadt, Germany; ^hTennessee Oncology Sarah Cannon Research Institute, Nashville, Tennessee, USA

Disclosures of potential conflicts of interest may be found at the end of this article.

Key Words. Cetuximab • Irinotecan • Metastatic colorectal cancer • EPIC • RAS

ABSTRACT

Background. The multicenter, open-label, randomized, phase III EPIC study (EMR 062202-025) investigated cetuximab plus irinotecan versus irinotecan in patients with epidermal growth factor receptor–detectable metastatic colorectal cancer (mCRC) that progressed on first-line fluoropyrimidine- and oxaliplatin-based chemotherapy; we report the outcomes of patients with RAS-wild-type (wt) disease.

Materials and Methods. Available DNA samples from RAS-unselected patients ($n = 1,164$ of 1,298 [89.7%]) were reanalyzed for RAS mutations using beads, emulsion, amplification, and magnetics. Baseline characteristics, efficacy, safety, and poststudy therapy were assessed. RAS-wt status was defined as a mutated RAS allele frequency of $\leq 5\%$, with all relevant alleles being analyzable.

Results. Baseline characteristics were comparable between the groups ($n = 452$ patients with RAS-wt mCRC; cetuximab plus irinotecan $n = 231$, irinotecan $n = 221$) and between

the RAS-wt and RAS-unselected populations. In the cetuximab plus irinotecan versus irinotecan arms, median overall survival was 12.3 versus 12.0 months, median progression-free survival (PFS) was 5.4 versus 2.6 months, and objective response rate (ORR) was 29.4% versus 5.0%, respectively. Quality of life (QoL) was improved in the cetuximab plus irinotecan arm. Serious adverse events occurred in 45.4% (cetuximab plus irinotecan) and 42.4% (irinotecan) of patients. In total, 47.1% of patients in the irinotecan arm received subsequent cetuximab therapy.

Conclusion. PFS, ORR, and QoL were improved with cetuximab plus irinotecan as a second-line treatment in patients with RAS-wt mCRC, confirming that cetuximab-based therapy is suitable in this population. Almost half of patients in the irinotecan arm received poststudy cetuximab, masking a potential overall survival benefit of cetuximab addition. *The Oncologist* 2021;26:e261–e269

Implications for Practice: Cetuximab is approved for the treatment of RAS–wild-type metastatic colorectal cancer (mCRC). In this retrospective analysis of the phase III EPIC study (cetuximab plus irinotecan vs. irinotecan alone as second-line treatment in patients with RAS-unselected mCRC), the subgroup of patients with RAS–wild-type mCRC who received cetuximab plus irinotecan had improved progression-free survival, objective response rate, and quality of life compared with the RAS-unselected population. These findings suggest that cetuximab-based therapy is a suitable second-line treatment for patients with RAS–wild-type mCRC.

Correspondence: Howard Burris, M.D., Department of Medical Oncology, Tennessee Oncology Sarah Cannon Research Institute, 1100 Charlotte Avenue, Suite 800, Nashville, Tennessee 37203, USA. Telephone: 1-615-969-0322; e-mail: howard.burris@sarahcannon.com. Received August 10, 2020; accepted for publication October 23, 2020; published Online First on December 14, 2020. <http://dx.doi.org/10.1002/onco.13591>

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INTRODUCTION

Colorectal cancer (CRC) is the fourth most common cancer and the second leading cause of cancer-related deaths globally, with approximately 1.8 million new cases and almost 900,000 deaths annually [1].

Cetuximab, an immunoglobulin G subtype 1 monoclonal antibody targeting the epidermal growth factor receptor (EGFR) [2], in combination with oxaliplatin- or irinotecan-based doublet chemotherapy, is a first-line standard-of-care treatment for patients with *RAS*-wild-type (wt) metastatic CRC (mCRC) [3–5]. Later-line therapies in mCRC tend to include a biological agent in combination with chemotherapy and are selected based on which prior therapies the patient has received [6].

The randomized phase III study EPIC (Erbix plus Irinotecan for the Treatment of mCRC; EMR 062202-025), initiated in May 2003, was designed to determine whether the combination of cetuximab and irinotecan as a second-line therapy would result in longer overall survival (OS) than that with irinotecan alone in irinotecan-naïve patients with mCRC unselected for *RAS* mutational status. The original findings of the EPIC trial revealed statistically significantly improved progression-free survival (PFS) and objective response rate (ORR) with cetuximab plus irinotecan compared with irinotecan, but there was no difference in OS [2]. The observed improvement in PFS and ORR suggests that cetuximab provides tumor control and thus has clinically relevant therapeutic benefit in this patient population. The lack of improvement in OS upon the addition of cetuximab to irinotecan may be attributed to the high crossover rate in the irinotecan arm because cetuximab was already approved in the third- and later-line setting when the EPIC trial was conducted.

At the time this study was initiated, tumor EGFR expression was considered the only potentially relevant biomarker of response for anti-EGFR inhibitors. This assumption has now been dispelled, and evidence of EGFR expression is no longer an eligibility requirement for anti-EGFR therapy [3–5]. Instead, *RAS* mutations have been established as a much more evidence-based predictive biomarker [7]. Retrospective analyses of pivotal studies with cetuximab plus chemotherapy, such as CRYSTAL and OPUS, found that ORR, PFS, and OS were significantly improved in patients with *RAS*-wt tumors compared with those in patients with *RAS*-mutant tumors [8, 9]; thus, extended *RAS* testing was included in treatment guidelines and product labels [4–5, 10, 11], and the phase III TAILOR trial became the first to prospectively enroll a *RAS*-wt population [12].

Because the EPIC trial was conducted before *RAS* was identified as a relevant biomarker for selecting patients for cetuximab treatment, a retrospective analysis of the *RAS*-wt population was necessary to confirm the increased benefit of cetuximab-based therapy as a standard second-line treatment for patients with *RAS*-wt mCRC. We retrospectively analyzed the outcomes of patients with *RAS*-wt mCRC in the EPIC study population. An analysis of the *KRAS*-mutant population, a small proportion of the total population ($n = 108$ [8.3%]), has been reported previously [13].

MATERIALS AND METHODS

EPIC was a multicenter, open-label, randomized, phase III study that enrolled patients from 221 sites globally. Eligibility criteria have been described previously [2]. Briefly, eligible patients had histologically documented mCRC and immunohistochemical evidence of EGFR expression. Disease progression or discontinuation due to toxicity within 6 months of the last dose of first-line fluoropyrimidine and oxaliplatin-based treatment for metastatic disease was required. Patients who had previously received irinotecan or anti-EGFR therapies were not eligible. Patients were randomly assigned 1:1 to receive cetuximab plus irinotecan or irinotecan. The primary endpoint was OS; secondary endpoints included PFS, ORR, and quality of life (QoL). The trial was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the ethics committees of all participating centers, and all patients provided written informed consent.

Treatment

Patients assigned to the cetuximab plus irinotecan arm received an initial cetuximab dose of 400 mg/m² (2-hour i.v. infusion) and then 250 mg/m² (1-hour i.v. infusion) weekly. Pretreatment with an antihistamine was required prior to the first dose of cetuximab and was administered at the investigator's discretion prior to subsequent doses. Irinotecan was administered at 350 mg/m² (90-minute i.v. infusion; 300 mg/m² for patients aged ≥ 70 years, those with Eastern Cooperative Oncology Group performance status [ECOG PS] of 2, or those with prior pelvic/abdominal irradiation) every 3 weeks in both treatment arms, starting 1 hour after completing cetuximab infusion for patients in the cetuximab arm. Patients received treatment until disease progression, unacceptable toxicity, or withdrawal of consent. There were no poststudy treatment limitations (supplemental online Methods).

Extended RAS Analysis

For retrospective biomarker analysis, available DNA samples were reanalyzed for mutations in *KRAS* and *NRAS* exons 2, 3, and 4 using BEAMing (beads, emulsion, amplification, magnetics) technology. *RAS*-wt status was defined as having all relevant alleles analyzable and a sum of mutated *RAS* allele frequencies across all tested mutations of $\leq 5\%$. The number of DNA samples included in this analysis was higher than the number of tumor samples available for the earlier retrospective analysis of the EPIC trial by *KRAS* status, which analyzed samples from U.S. sites only (23% of all randomized patients) and was therefore not representative of the overall study population [13]. Baseline characteristics, efficacy, safety, and poststudy therapy were also assessed (additional information for assessments and statistical analysis are provided in the supplemental online Methods).

RESULTS

Baseline Characteristics

From May 2003 to February 2006, 1,298 *RAS*-unselected patients with EGFR-detectable mCRC who had previously progressed on first-line fluoropyrimidine and oxaliplatin–

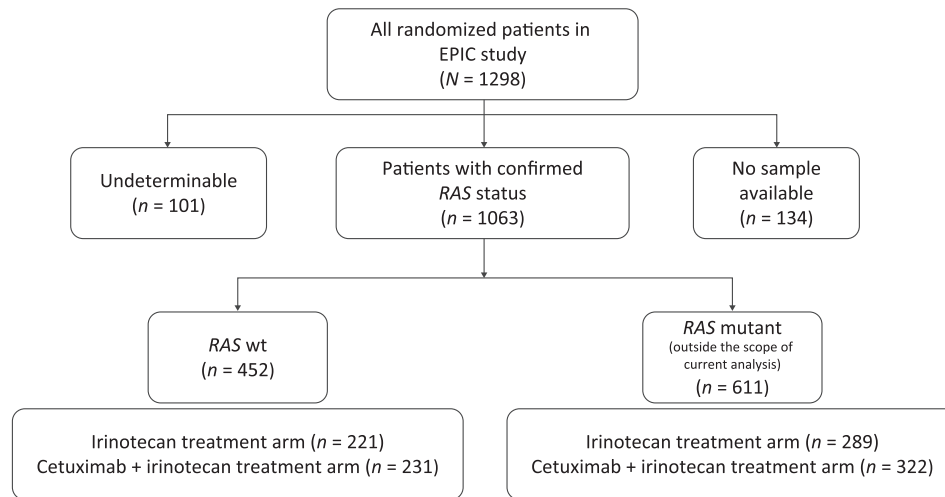


Figure 1. Patient disposition. Abbreviation: wt, wild type.

based chemotherapy were enrolled (Fig. 1). Among the enrolled patients, *RAS* status could not be determined in 101 patients (7.8%), and 134 patients (10.3%) had no sample available. Of the 452 patients with *RAS*-wt mCRC who were randomized, 446 (98.7%) received treatment: 229 of 231 patients (99.1%) in the cetuximab plus irinotecan arm and 217 of 221 patients (98.2%) in the irinotecan arm. Among patients in the cetuximab plus irinotecan and irinotecan arms, only 27 patients (11.7%) and 28 patients (12.7%), respectively, had received previous bevacizumab therapy; bevacizumab had not been approved in many participating countries at the time of this study.

Baseline characteristics in the randomized population were comparable to those of the unselected population and reasonably balanced between treatment arms within the *RAS*-wt subgroup (Table 1). Most patients in the *RAS*-wt subgroup were men (62.8%) and had an ECOG PS of 0 or 1 (93.5%). Median age was 61 years, and 38.7% were aged >65 years.

Treatment Adherence and Exposure

Patients in the *RAS*-wt group received irinotecan for a median duration of 18.0 weeks (range, 0.7–89.1) in the cetuximab plus irinotecan arm and 10.0 weeks (range, 1.1–71.0) in the irinotecan arm; the median cumulative irinotecan doses were 1,798.4 mg/m² (range, 266.1–7,204.8) and 1,056.8 mg/m² (range, 173.6–7,150.3), respectively. Median duration of cetuximab treatment was 19.0 weeks (range, 0.7–97.9), and median cumulative dose was 4,524.0 mg/m² (range, 159.6–22,086.3). In the cetuximab plus irinotecan arm, 79.0% of patients received ≥80% of the planned dose intensity of irinotecan versus 85.7% of patients in the irinotecan arm. For cetuximab treatment, ≥80% of the planned dose intensity was administered in 72.9% of patients.

In the irinotecan arm, 104 patients (47.1%) received cetuximab in a subsequent line of therapy after the EPIC study; 90 (40.7%) received cetuximab plus irinotecan (Fig. 2). In the cetuximab plus irinotecan arm, 26 patients (11.3%) received cetuximab after the study.

Efficacy

Median OS was 12.3 versus 12.0 months (hazard ratio [HR], 0.91; 95% confidence interval [CI], 0.71–1.17; *p* = .4645) in the cetuximab plus irinotecan versus irinotecan arms, respectively (Table 2; Fig. 3A); median PFS was 5.4 versus 2.6 months (HR, 0.57; 95% CI, 0.46–0.69; *p* < .0001; Table 2; Fig. 3B). ORR was higher in the cetuximab plus irinotecan arm than in the irinotecan arm: 29.4% versus 5.0% (odds ratio [OR], 8.12; 95% CI, 4.04–17.40; *p* < .0001) (Table 2). An analysis of OS by poststudy treatment within the *RAS*-wt population showed improved median OS in patients who received poststudy cetuximab compared with those not receiving cetuximab or any subsequent therapy in both treatment arms (Fig. 2; supplemental online Table 1). In the cetuximab plus irinotecan arm, median OS in patients who had previously received bevacizumab (*n* = 27) versus those without prior bevacizumab therapy (*n* = 204) was 10.2 (95% CI, 4.53–14.09) versus 12.8 months (95% CI, 11.47–15.70), respectively. In the irinotecan arm, median OS was not estimable (95% CI, 11.73 months–not estimable) in patients who had received previous bevacizumab (*n* = 28) versus 11.8 months (95% CI, 9.00–13.31) in patients without prior bevacizumab therapy (*n* = 193). ORR in patients who had previously received bevacizumab was 18.5% in the cetuximab plus irinotecan arm (*n* = 27) and 3.6% in the irinotecan arm (*n* = 28).

Safety

Adverse events (AEs) in the *RAS*-wt population were consistent with the safety profile observed in the overall EPIC safety population and in other cetuximab studies [2, 8, 9], and no new or unexpected safety signals were observed in either treatment arm. In the cetuximab plus irinotecan and irinotecan arms, 76.4% and 61.8% of patients, respectively, experienced a grade ≥ 3 treatment-emergent AE. Grade ≥ 3 treatment-related AEs (TRAEs) were observed in 67.7% and 45.2% of patients in the cetuximab plus irinotecan versus irinotecan arms, respectively; the most common grade 3/4 TRAEs (occurring in ≥20 patients in any treatment arm)

Table 1. Baseline characteristics of the RAS-wt and RAS-unselected populations in the EPIC study

Characteristic	RAS-wt		Total (n = 452), n (%)	RAS-unselected [2] Total (n = 1,298), n (%)
	Irinotecan (n = 221), n (%)	Cetuximab plus irinotecan (n = 231), n (%)		
Sex				
Female	74 (33.5)	86 (37.2)	160 (35.4)	482 (37.1)
Male	147 (66.5)	145 (62.8)	292 (64.6)	816 (62.9)
Median age (range), years	60.0 (23–82)	61.0 (33–85)	61.0 (23–85)	62 (21–90)
ECOG PS				
0	112 (50.7)	126 (54.5)	238 (52.7)	664 (51.2)
1	101 (45.7)	90 (39.0)	191 (42.3)	555 (42.8)
2	7 (3.2)	15 (6.5)	22 (4.9)	70 (5.4)
Not reported	1 (0.5)	0	1 (0.2)	9 (0.7)
Prior therapy				
Radiotherapy	44 (19.9)	46 (19.9)	90 (19.9)	249 (19.2)
Adjuvant	19 (8.6)	15 (6.5)	34 (7.5)	102 (7.9)
Metastatic	8 (3.6)	17 (7.4)	25 (5.5)	70 (5.4)
Neoadjuvant	18 (8.1)	17 (7.4)	35 (7.7)	90 (69.3)
Chemotherapy	221 (100)	231 (100)	452 (100)	1,298 (100)
Adjuvant	55 (24.9)	54 (23.4)	109 (24.1)	646 (49.8)
Metastatic	219 (99.1)	231 (100)	450 (99.6)	1,289 (99.3)
Neoadjuvant	14 (6.3)	17 (7.4)	31 (6.9)	80 (6.2)
First-line therapy				
Fluoropyrimidine	216 (97.7)	225 (97.4)	441 (97.6)	1,266 (97.5)
Oxaliplatin	219 (99.1)	229 (99.1)	448 (99.1)	1,280 (98.6)
Reason for discontinuation				
Disease progression	143 (64.7)	144 (62.3)	287 (63.5)	843 (64.9)
Toxicity	29 (13.1)	36 (15.6)	65 (14.4)	207 (15.9)
Other	44 (19.9)	45 (19.5)	89 (19.7)	225 (17.3)
Unknown	3 (1.4)	5 (2.2)	8 (1.8)	11 (0.8)
Tumor type				
Colon	160 (72.4)	149 (64.5)	309 (68.4)	902 (69.5)
Rectum	61 (27.6)	82 (35.5)	143 (31.6)	395 (30.4)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.1)
Number of disease sites				
1	69 (31.2)	81 (35.1)	150 (33.2)	415 (32.0)
≥ 2	150 (67.9)	149 (64.5)	299 (66.2)	871 (67.1)
Missing	2 (0.9)	1 (0.4)	3 (0.7)	12 (0.9)
EGFR-positive CRC				
Yes	221 (100)	230 (99.6)	451 (99.8)	1,275 (98.2)
No	0 (0.0)	1 (0.4)	1 (0.2)	2 (0.2)
Liver metastases				
Yes	170 (76.9)	176 (76.2)	346 (76.5)	989 (76.2)
No	49 (22.2)	54 (23.4)	103 (22.8)	297 (22.9)

Abbreviations: CRC, colorectal cancer; ECOG PS, Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; wt, wild type.

were diarrhea (32.3% vs. 17.1%) and neutropenia (20.5% vs. 14.3%). In the cetuximab plus irinotecan arm, grade ≥ 3 drug-related skin reactions were observed in 12.2% of patients, and grade ≥ 3 acne-like dermatitis occurred in 1.7%. These TRAEs account for the overall higher TRAE rate in the cetuximab plus irinotecan group.

Serious TRAEs occurred in 29.3% and 21.2% of patients in the cetuximab plus irinotecan and irinotecan arms, respectively. Cetuximab-related serious AEs (SAEs) occurred in 14.4% of patients in the cetuximab plus irinotecan arm. Irinotecan-related SAEs were observed in 26.6% versus 21.2% of patients in the cetuximab plus irinotecan versus

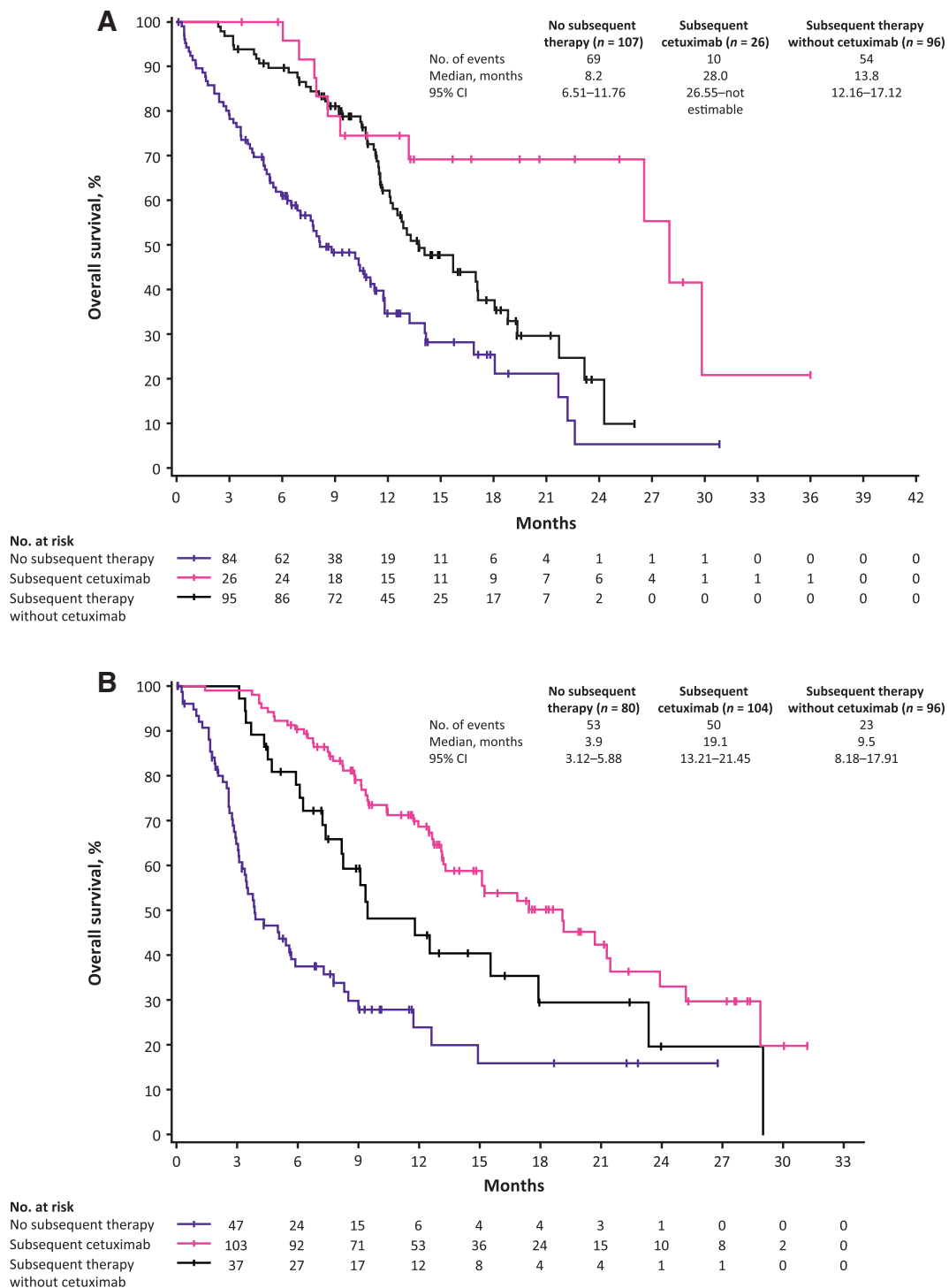


Figure 2. Overall survival by subsequent therapy in the RAS-wild-type population. **(A):** In the cetuximab plus irinotecan arm of the EPIC study. **(B):** In the irinotecan arm of the EPIC study. Abbreviation: CI, confidence interval.

irinotecan arms, respectively. The most common grade ≥ 3 serious TRAEs (occurring in $\geq 5\%$ of patients) in both treatment arms were febrile neutropenia and diarrhea. Furthermore, serious TRAEs leading to death occurred in eight patients in the cetuximab plus irinotecan arm and were cetuximab-related in five patients (dyspnea [$n = 1$], disease progression [$n = 1$], cardiac failure and renal failure [$n = 1$],

vomiting and sudden death [$n = 1$], sepsis [$n = 1$]) and irinotecan-related in seven patients (diarrhea, cardiac failure and renal failure [$n = 1$], pneumonia aspiration and respiratory arrest [$n = 1$], disease progression [$n = 1$], gastroenteritis [$n = 1$], neutropenia [$n = 1$], vomiting and sudden death [$n = 1$], intestinal perforation, peritonitis and sepsis [$n = 1$]) versus three patients in the irinotecan arm

Table 2. Summary of efficacy results in the RAS-wt and RAS-unselected populations in the EPIC study

	RAS-wt population		RAS-unselected population [2]	
	Irinotecan (n = 221)	Cetuximab plus irinotecan (n = 231)	Irinotecan (n = 650)	Cetuximab plus irinotecan (n = 648)
Median duration of therapy (range), weeks				
Cetuximab	NA	19.0 (0.7–97.9)	NA	14.0 (0.7–97.9)
Irinotecan	10.0 (1.1–71.0)	18.0 (0.7–89.1)	9.9 (0.4–71.0)	13.1 (0.7–89.1)
OS				
Number of events, n (%)	126 (57.0)	133 (57.6)	429 (66.0)	445 (68.8)
Median (95% CI), months	12.0 (9.36–14.92)	12.3 (11.37–14.09)	9.99 (9.13–11.33)	10.71 (9.59–11.30)
HR (95% CI)	0.91 (0.71–1.17)		0.975 (0.854–1.114)	
Log-rank p value	.4645		.7114	
PFS				
Number of events, n (%)	201 (91.0)	212 (91.8)	598 (92.0)	610 (94.1)
Median (95% CI), months	2.6 (2.30–2.83)	5.4 (4.24–5.75)	2.56 (2.1–2.69)	3.98 (3.15–4.14)
HR (95% CI)	0.57 (0.46–0.69)		0.692 (0.617–0.776)	
Log-rank p value	<.0001		<.0001	
Response				
Primary definition, n (%)				
Complete response	0	4 (1.7)	1 (0.2)	9 (1.4)
Partial response	11 (5.0)	64 (27.7)	26 (4.0)	97 (15.0)
Stable disease	100 (45.2)	90 (39.0)	271 (41.7)	292 (45.1)
Progressive disease	71 (32.1)	46 (19.9)	243 (37.4)	174 (26.9)
Not assessable	39 (17.6)	27 (11.7)	109 (16.8)	76 (11.7)
ORR (CR + PR), n (%) [95% CI]	11 (5.0) [2.51–8.73]	68 (29.4) [23.63–35.77]	27 (4.2) [2.75–5.99]	106 (16.4) [13.59–19.44]

Abbreviations: CI, confidence interval; CR, complete response; HR, hazard ratio; NA, not applicable; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; wt, wild type.

(febrile neutropenia [$n = 1$]; intestinal obstruction [$n = 1$]; neutropenia [$n = 1$]). AEs resulting in discontinuation of cetuximab occurred in 20.5% of patients in the cetuximab plus irinotecan arm. AEs leading to irinotecan discontinuation were similar in both arms (22.3% vs. 19.4% in the cetuximab plus irinotecan vs. irinotecan arms).

QoL

Compliance rates for the QoL questionnaire in the RAS-wt population at baseline were 86.1% and 90.0% in the cetuximab plus irinotecan and irinotecan arms, respectively. The on-study completion rate subsequently decreased over time, stabilizing at approximately 50% at week 21 in each arm and remaining at this level until weeks 51 and 45 in the cetuximab plus irinotecan and irinotecan arms, respectively. Patients who completed the QoL assessment questionnaire answered 96.7% to 100% of the questions. Baseline scores were similar between treatment arms for 13 of 15 QoL scales. For the symptom scale fatigue and the single item insomnia, differences from baseline scores favored cetuximab plus irinotecan over irinotecan ($p < .1$). A longitudinal model (truncated at week 45) was used to compare change from baseline scores over time between treatment arms. During the course of the study, improved

QoL was reported by patients in the cetuximab plus irinotecan arm compared with those in the irinotecan arm for several multi-item and single-item scales (supplemental online Table 2). The model also showed advantages for cetuximab treatment for two functioning scales (physical functioning and role functioning), two symptom scales (fatigue and nausea/vomiting), and two single-item scales (pain and appetite loss), all in favor of the combination treatment ($p < .05$). A trend for improved cognitive functioning, global health status, and constipation was also observed in the cetuximab plus irinotecan arm ($p < .1$). The remaining multi-item and single-items scales showed no significant differences between the two treatment arms.

DISCUSSION

This retrospective analysis of the RAS-wt population of the EPIC study reiterates that the addition of cetuximab to irinotecan did not prolong OS—consistent with results of the primary analysis in the non-biomarker-defined population [2] as well as those of a previous subgroup analysis in the KRAS-wt population [13]. The lack of change in OS is possibly due to the high rate of poststudy crossover to cetuximab therapy in patients in the irinotecan arm, as

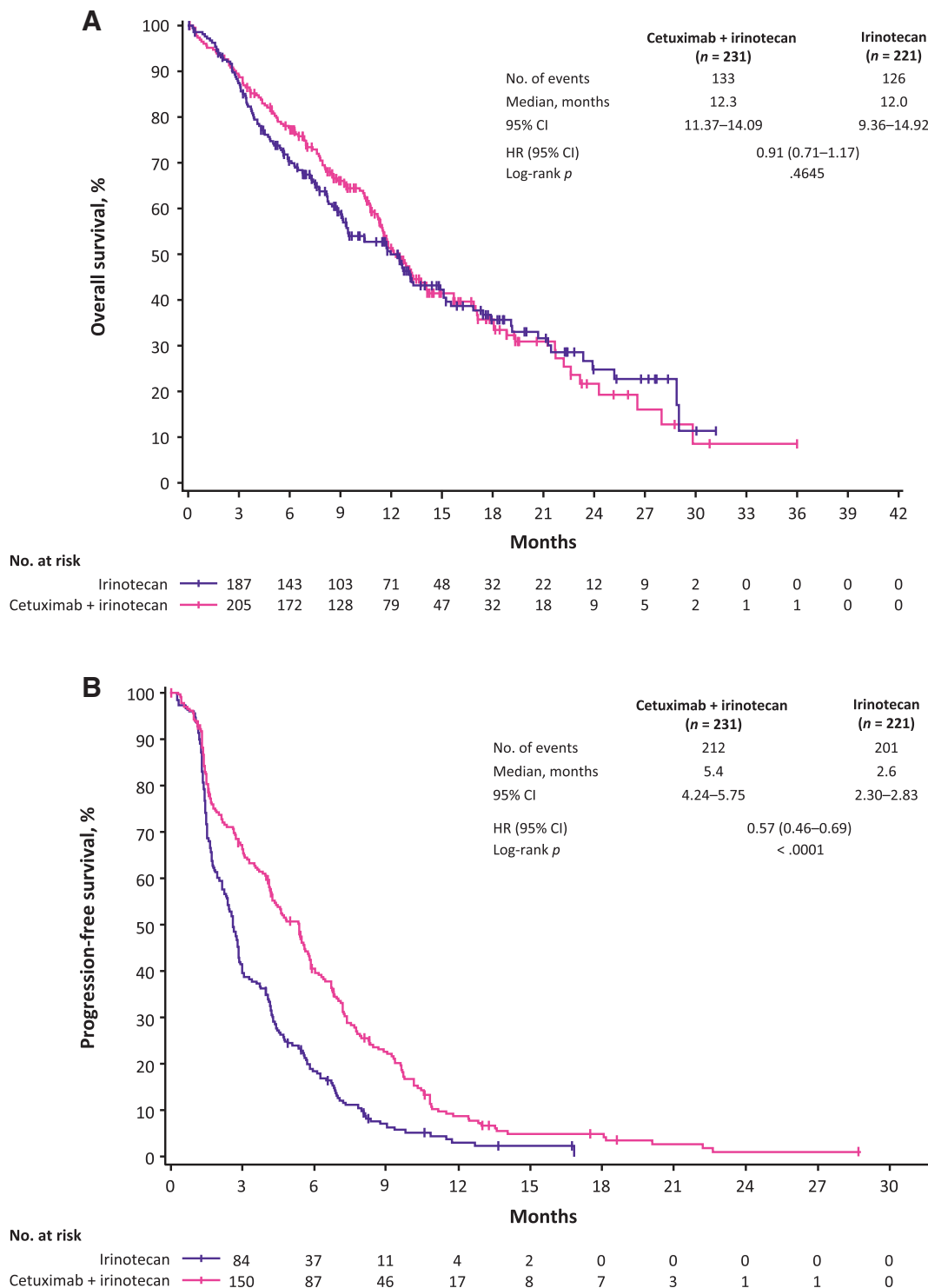


Figure 3. Survival in the *RAS*-wild-type population of the EPIC study. **(A):** Overall survival. **(B):** Progression-free survival. Abbreviations: CI, confidence interval; HR, hazard ratio.

suggested by Sobrero et al [2]. Indeed, nearly half of the patients with *RAS*-wt tumors in the irinotecan arm received cetuximab in a subsequent line of therapy after the study, potentially masking any OS benefit of the addition of cetuximab to irinotecan. This hypothesis is supported by results from the CO.17 study of cetuximab versus best supportive care (BSC) in pretreated advanced *RAS*- and *BRAF*-wt CRC, in which OS was significantly improved with cetuximab compared with BSC (10.1 vs. 4.8 months), with

only 7.0% of patients who received BSC subsequently receiving cetuximab [14, 15].

Interestingly, patients in both treatment arms of EPIC who received poststudy cetuximab had improved OS compared with those who received a subsequent therapy without cetuximab or no poststudy therapy, suggesting that the administration of cetuximab at any point in the second or later line may improve survival. Furthermore, these data suggest that cetuximab-based therapy may be a suitable

standard treatment in the rechallenge setting (i.e., retreatment with cetuximab after progression in a subsequent therapy line without cetuximab) as well as beyond progression for patients with *RAS*-wt mCRC. Thus, although guidelines recommend the use of cetuximab in the first-line treatment setting [3–5], data from this trial support the use of cetuximab in second or subsequent line treatment settings. Of note, limitations of this analysis include a potential bias because of the differences in the proportion of subsequent therapies with and without cetuximab in the two treatment arms. Another possible bias arises from the observation that patients who live longer are more likely to receive cetuximab in any subsequent therapy line.

In contrast to OS, PFS was more than doubled and ORR was approximately sixfold higher in the cetuximab plus irinotecan arm than in the irinotecan arm ($p < .0001$ each), and this improvement was more prominent than that in the primary analysis [2] and in the analysis of the *KRAS*-wt population [13]. These results suggest that second-line cetuximab may have a clinically meaningful therapeutic benefit in patients with mCRC—considering their survival prognosis of approximately 1 year, which is supported by the improvements observed in the patients' QoL. Furthermore, patients who received cetuximab continued treatment for longer, likely because of the prolonged PFS. In both this retrospective analysis and the initial results of the EPIC study [2], the longer PFS and higher ORR observed upon the addition of cetuximab to irinotecan may be a better indicator of the additional benefit conferred by cetuximab than OS, because these endpoints are directly related to the study period and are therefore unaffected by subsequent therapies and are clinically relevant in patients with mCRC.

Similar to the results of the primary analysis of the EPIC study, no new or unexpected safety signals in the *RAS*-wt population were observed in either treatment arm. Furthermore, the improved QoL, as demonstrated for several single- and multi-item scales in the cetuximab plus irinotecan arm compared with that in the irinotecan arm, is also reflected in the observed treatment duration, which was almost twice as long in the cetuximab plus irinotecan arm than in the irinotecan arm. Although an analysis for efficacy in left-sided versus right-sided tumors was not feasible in this retrospective study because of missing data on primary tumor location, the ORR for the *RAS*-wt population in this study was among the highest observed to date in the second-line setting when compared with that reported for other regimens, such as bevacizumab plus oxaliplatin, fluorouracil, and leucovorin (FOLFOX4), as reported for the E3200 study (ORR, 22.7%) [16], and panitumumab plus combination chemotherapy (ORR, 41% for panitumumab plus 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) vs. 10% for FOLFIRI in patients with *RAS*-wt tumors) [17]. Notably, although ORR and PFS increased from 16.4% to 29.4% and from 4.0 to 5.4 months, respectively, in the *RAS*-unselected and the *RAS*-wt populations with cetuximab plus irinotecan, the efficacy outcomes for patients receiving irinotecan did not differ between the *RAS*-unselected and *RAS*-wt populations (PFS, 2.6 months in both populations; ORR: 4.2% and 5.0%, respectively). These findings, as well as the improved QoL observed in the cetuximab plus

irinotecan arm, further confirm the increased efficacy of cetuximab in patients with *RAS*-wt tumors in second-line treatment and confirm that *RAS* testing is predictive of clinical benefit.

CONCLUSION

This retrospective analysis of *RAS*-wt patients enrolled in the EPIC study emphasizes the role of cetuximab-based therapy as a standard second-line treatment for patients with *RAS*-wt mCRC.

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AUTHOR CONTRIBUTIONS

Conception/design: Alberto Sobrero, Heinz-Josef Lenz, Regina Esser, Johannes Nippgen, Howard Burris

Provision of study material or patients: Cathy Eng, Werner Scheithauer, Gary Middleton, Howard Burris

Collection and/or assembly of data: Cathy Eng, Werner Scheithauer, Gary Middleton, Howard Burris

Data analysis and interpretation: Alberto Sobrero, Heinz-Josef Lenz, Cathy Eng, Gary Middleton, Wenfeng Chen, Regina Esser, Johannes Nippgen, Howard Burris

Manuscript writing: Alberto Sobrero, Heinz-Josef Lenz, Cathy Eng, Gary Middleton, Wenfeng Chen, Regina Esser, Johannes Nippgen, Howard Burris

Final approval of manuscript: Alberto Sobrero, Heinz-Josef Lenz, Cathy Eng, Werner Scheithauer, Gary Middleton, Wenfeng Chen, Regina Esser, Johannes Nippgen, Howard Burris

DISCLOSURES

Alberto Sobrero: Amgen, Bayer, Bristol Myers Squibb, Celgene, Eli Lilly & Co., EMD Serono (an affiliate of Merck KGaA, Darmstadt, Germany), Roche, Sanofi, Takeda (C/A); **Heinz-Josef Lenz:** Bayer, Bristol Myers Squibb, EMD Serono, Roche (C/A), Bayer, Bristol Myers Squibb, EMD Serono, Roche, Takeda (H), Bayer, EMD Serono (other—travel support); **Cathy Eng:** Bayer, LSK Global PS, Roche, Sirtex, Taiho (C/A); **Wenfeng Chen:** Merck Serono Co., Ltd., China, an affiliate of Merck KGaA, Darmstadt, Germany (E); **Regina Esser:** Merck KGaA (Darmstadt, Germany) (E, OI); **Johannes Nippgen:** Merck Serono Co., Ltd., China, an affiliate of Merck KGaA, Darmstadt, Germany (E); **Howard Burris:** AstraZeneca, Celgene, Daiichi Sankyo, FORMA Therapeutics, Incyte, Pfizer (C/A), Agios, AstraZeneca, Arch, Array BioPharma, Arvinas, Bayer, BIND Therapeutics, BioAtla, BioMed Valley, Boehringer-Ingelheim, Bristol Myers Squibb, CicloMed, CytomX, eFFECTOR, Eli Lilly & Co., Roche/Genentech, Gilead Sciences, GlaxoSmithKline, Harpoon Therapeutics, Incyte, Janssen, Jounce Therapeutics, Kymab, MacroGenics, MedImmune, Merck KGaA, Millennium Pharmaceuticals, Mirna Therapeutics, Moderna, Novartis, Pfizer, Revolution Medicine, Seattle Genetics, Tesaro, TG Therapeutics, Verastem, Vertex Pharmaceuticals (RF—institution), HCA/Sarah Cannon (OI). The other authors indicated no financial relationships. (C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

REFERENCES

1. Bray F, Ferlay J, Soerjomataram I et al. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68: 394–424.
2. Sobrero AF, Maurel J, Fehrenbacher L et al. EPIC: Phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. *J Clin Oncol* 2008;26:2311–2319.
3. Van Cutsem E, Cervantes A, Adam R et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol* 2016;27:1386–1422.
4. NCCN Clinical Practice Guidelines in Oncology: Colon Cancer. Version 3.2019. Available at https://www.nccn.org/professionals/physician_gls/pdf/colon.pdf. Accessed November 4, 2019.
5. NCCN Clinical Practice Guidelines in Oncology: Rectal Cancer. Version 3.2019. Available at https://www.nccn.org/professionals/physician_gls/pdf/rectal.pdf. Accessed November 4, 2019.
6. Goldberg RM, Montagut C, Wainberg ZA et al. Optimising the use of cetuximab in the continuum of care for patients with metastatic colorectal cancer. *ESMO Open* 2018;3:e000353.
7. Martins M, Mansinho A, Cruz-Duarte R et al. Anti-EGFR therapy to treat metastatic colorectal cancer: Not for all. In: Jordan P, ed. *Targeted Therapy of Colorectal Cancer Subtypes*. Cham, Switzerland: Springer Nature Switzerland AG; 2018;1110:113–131.
8. Van Cutsem E, Lenz HJ, Köhne CH et al. Fluorouracil, leucovorin, and irinotecan plus cetuximab treatment and RAS mutations in colorectal cancer. *J Clin Oncol* 2015;33:692–700.
9. Bokemeyer C, Köhne CH, Ciardiello F et al. FOLFOX4 plus cetuximab treatment and RAS mutations in colorectal cancer. *Eur J Cancer* 2015;51:1243–1252.
10. Erbitux (cetuximab) [package insert]. Indianapolis, IN: Eli Lilly and Company; 2019.
11. Erbitux (cetuximab) [summary of product characteristics]. Darmstadt, Germany: Merck KGaA; 2019.
12. Qin S, Li J, Wang L et al. Efficacy and tolerability of first-line cetuximab plus leucovorin, fluorouracil, and oxaliplatin (FOLFOX-4) versus FOLFOX-4 in patients with RAS wild-type metastatic colorectal cancer: The open-label, randomized, phase III TAILOR trial. *J Clin Oncol* 2018;36: 3031–3039.
13. Langer C, Kopit J, Awad M et al. Analysis of K-RAS mutations in patients with metastatic colorectal cancer receiving cetuximab in combination with irinotecan: Results from the EPIC trial. *Ann Oncol* 2008;19(suppl 8):385Pa.
14. Loree JM, Dowers A, Tu D et al. Expanded RAS and BRAF V600 testing as predictive biomarkers for single agent cetuximab in the randomized phase III CO.17 trial. *J Clin Oncol* 2019; 37(suppl 4):537a.
15. Jonker JJ, O'Callaghan CJ, Karapetis CS et al. Cetuximab for the treatment of colorectal cancer. *N Engl J Med* 2007;357:2040–2048.
16. Giantonio BJ, Catalano PJ, Meropol NJ et al. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: Results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol* 2007;25: 1539–1544.
17. Peeters M, Oliner KS, Price TJ et al. Analysis of KRAS/NRAS mutations in a phase III study of panitumumab with FOLFIRI compared with FOLFIRI alone as second-line treatment for metastatic colorectal cancer. *Clin Cancer Res* 2015;21: 5469–5479.



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