

Cetuximab Plus Capecitabine and Irinotecan Compared With Cetuximab Plus Capecitabine and Oxaliplatin As First-Line Treatment for Patients With Metastatic Colorectal Cancer: AIO KRK-0104—A Randomized Trial of the German AIO CRC Study Group

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ABSTRACT

Purpose

The AIO KRK-0104 randomized phase II trial investigated the efficacy and safety of cetuximab combined with capecitabine and irinotecan (CAPIRI) or capecitabine and oxaliplatin (CAPOX) in the first-line treatment of metastatic colorectal cancer (mCRC).

Patients and Methods

A total of 185 patients with mCRC were randomly assigned to cetuximab (400 mg/m² day 1, followed by 250 mg/m² weekly) plus CAPIRI (irinotecan 200 mg/m², day 1; capecitabine 800 mg/m² twice daily days 1 through 14, every 3 weeks; or cetuximab plus CAPOX (oxaliplatin 130 mg/m² day 1; capecitabine 1,000 mg/m² twice daily day 1 through 14, every 3 weeks). The primary study end point was objective response rate (ORR).

Results

In the intention-to-treat patient population (n = 177), ORR was 46% (95% CI, 35 to 57) for CAPIRI plus cetuximab versus 48% (95% CI, 37 to 59) for CAPOX plus cetuximab. Analysis of the *KRAS* gene mutation status was performed in 81.4% of the intention to treat population. Patients with *KRAS* wild-type in the CAPIRI plus cetuximab arm showed an ORR of 50.0%, a PFS of 6.2 months and an OS of 21.1 months. In the CAPOX plus cetuximab arm, an ORR of 44.9%, a PFS of 7.1 months and an OS of 23.5 months were observed. While ORR and PFS were comparable in *KRAS* wild-type and mutant subgroups, a trend toward longer survival was associated with *KRAS* wild-type. Both regimens had manageable toxicity profiles and were safe.

Conclusion

This randomized trial demonstrates that the addition of cetuximab to CAPIRI or CAPOX is effective and safe in first-line treatment of mCRC. In the analyzed regimens, ORR and PFS did not differ according to *KRAS* gene mutation status.

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INTRODUCTION

Median survival of metastatic colorectal cancer (mCRC) has been greatly improved by the introduction of the topoisomerase-I inhibitor irinotecan and the third-generation platinum compound oxaliplatin.¹⁻⁵ Modern chemotherapy regimens combine infusional fluorouracil (FU) and folinic acid with either irinotecan (FOLFIRI) or oxaliplatin (FOLFOX). A further landmark in the treatment of mCRC was the development of oral fluoropyrimidine derivatives. Capecitabine is a rationally designed prodrug, which is converted to FU predominantly in tumor cells. The combination of capecitabine with oxaliplatin (CAPOX) was compared with infusional FU-, folinic acid-, and oxaliplatin-containing regimens in a number of phase III trials.⁶⁻⁸ Data across these trials consistently demonstrated similar efficacy outcomes, with CAPOX offering the advantage of more convenient oral fluoropyrimidine administration. While also the combination of capecitabine and irinotecan

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(CAPIRI) was shown to be effective, data from earlier trials showed diverse results as far as its safety profile was concerned.⁹⁻¹¹ However, a recent phase III trial investigating CAPIRI in a large cohort of patients indicated that the regimen was effective and safe.¹²

Cetuximab, a chimeric antibody directed against the epidermal growth factor receptor (EGFR), is active as a single agent as well as in combination with irinotecan when applied in irinotecan-refractory mCRC.¹³ Recently, a phase III trial (CRYSTAL) and a large phase II trial (OPUS) confirmed the efficacy of cetuximab combined with FOLFIRI or FOLFOX in the first-line treatment of mCRC.^{14,15}

In the process of defining biomarkers that predict response to anti-EGFR treatment, analysis of the *KRAS* gene mutational status has become a standard of care. The *KRAS* gene encodes a G protein that links ligand-dependent activation to intracellular pathways of the EGFR signaling cascade. The most common mutations involve codons 12 and 13 and cause constitutive activation of *KRAS*-associated signaling.¹⁶⁻¹⁸ Several large trials investigating anti-EGFR treatment strategies provided convincing evidence that *KRAS* mutations are associated with inefficacy of anti-EGFR directed treatment.^{14,15,19}

The AIO (Arbeitsgemeinschaft Internistische Onkologie) KRK-0104 study was designed as a multicenter randomized phase II study to investigate the efficacy and safety of cetuximab in combination with CAPIRI or CAPOX for the first-line treatment of patients with mCRC.

PATIENTS AND METHODS

Patients and Eligibility Criteria

Eligible patients were 18 to 75 years of age and had stage IV, histologically confirmed colorectal adenocarcinoma. Other key eligibility criteria included a Karnofsky performance status $\geq 70\%$, life expectancy ≥ 3 months, adequate organ function, and at least one unidimensionally measurable lesion. Immunohistochemical testing of EGFR expression performed at the participating centers was also required as an inclusion criterion. Exclusion criteria included surgery or radiation therapy within 4 weeks before study entry, prior treatment with topoisomerase-1 inhibitors or anti-EGFR agents, and prior cytotoxic treatment for CRC (except adjuvant chemotherapy ≥ 6 months before random assignment).

The study protocol was approved by ethics committees of all participating centers. All patients provided written informed consent before study entry.

Study Design and Treatment Schedule

The AIO KRK-0104 study was designed as an open-label, randomized phase II study. It was conducted at 35 centers in Germany. Random assignment was centrally performed by fax. In both study arms, cetuximab was given at an initial dose of 400 mg/m² as a 120-minute infusion, followed by weekly infusions of 250 mg/m² over 60 minutes. Patients in arm A received chemotherapy with CAPIRI (ie, oral capecitabine 800 mg/m² twice daily on days 1 through 14, followed by a 1-week rest period plus irinotecan 200 mg/m² as a 30-minute intravenous infusion on day 1). In patients older than 65 years, doses were further reduced by 20%. Patients in arm B received chemotherapy with CAPOX (ie, capecitabine 1,000 mg/m² twice daily on days 1 through 14, followed by a 1-week rest

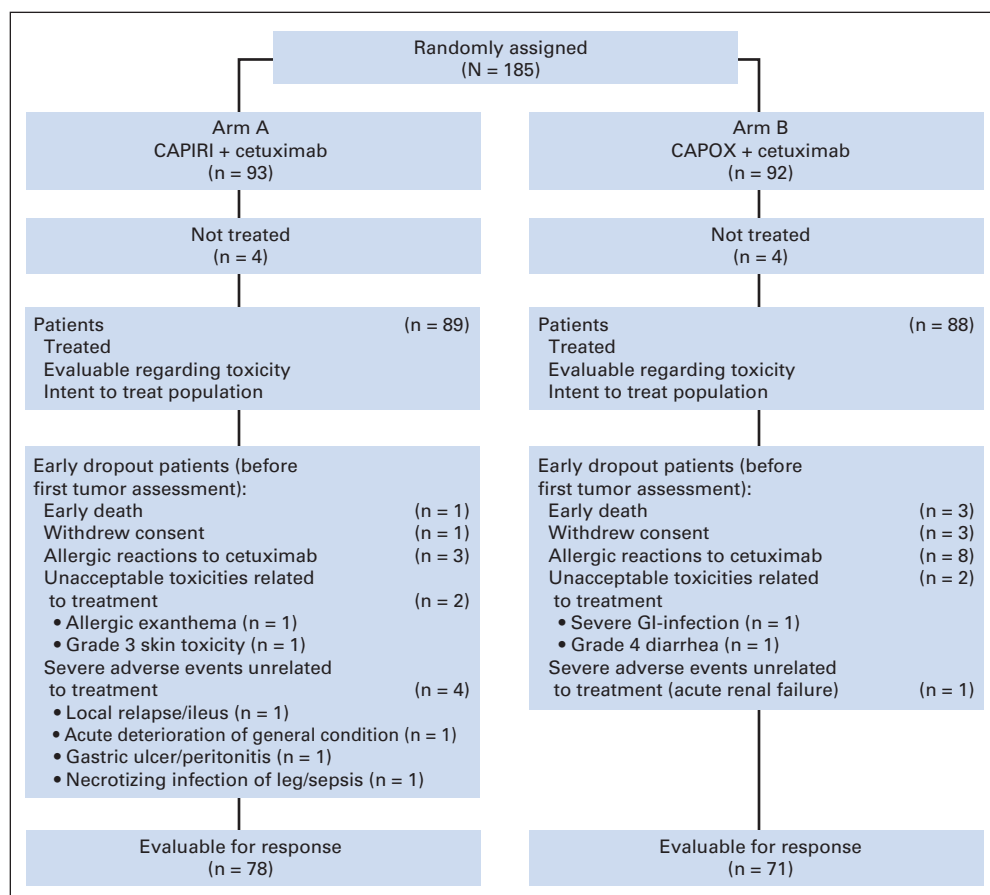


Fig 1. CONSORT diagram. CAPIRI, capecitabine and irinotecan; CAPOX, capecitabine and oxaliplatin.

period plus oxaliplatin 130 mg/m² as a 120-minute intravenous infusion on day 1). Treatment cycles were repeated every 3 weeks until disease progression or unacceptable toxicity. Adverse events were assessed according to National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0.

Tumor Assessments

Tumor response was evaluated every two cycles (6 weeks) by the investigators with the use of consistent imaging techniques (computed tomography or magnetic resonance imaging) according to Response Evaluation Criteria in Solid Tumors. All patients were observed for survival every 3 months for a minimum of 2 years. The intention-to-treat (ITT) population comprised all patients who had received at least one application of chemotherapy. The assessable population was defined by patients receiving study treatment beyond the first tumor assessment.

Statistical Analysis

The primary study end point was the overall rate of radiologic tumor response (ORR; complete plus partial response) in the ITT patient population. The sample size determination was initially based on an optimal two-stage Simon design in order to discriminate in each arm between an expected ORR of 50% and a futile rate of 30%, with both type I and II errors set at 0.1. After sufficient efficacy with regard to the two-stage design was documented, the sample size was increased to 2 × 84 patients in a protocol amendment to allow a more precise estimation of the ORR, with a width of the 95% CI of approximately ± 10%.

Secondary end points included time to progression (defined as the time interval from first study treatment [day 1, cycle 1] until the first detection of progressive disease), disease control rate (complete remission plus partial remission plus stable disease), and the evaluation of grade 3 and 4 toxicities.

Table 1. Baseline Patient Demographics and Clinical Characteristics (intent-to-treat population)

Characteristic	CAPIRI + Cetuximab		CAPOX + Cetuximab		Total	
	No.	%	No.	%	No.	%
No. of patients	89		88		177	
Age, years						
Median		63		62		63
Range		32-75		38-77		32-77
> 65	33	37.1	31	35.2	64	36.2
Sex						
Female	26	29.2	25	28.4	51	28.8
Male	63	70.8	63	71.6	126	71.2
Karnofsky PS, %						
100	30	33.7	32	36.4	62	35.0
90	27	30.3	34	38.6	61	34.5
80	25	28.1	15	17.1	40	22.6
70	5	5.6	7	8.0	12	6.8
Not reported	2	2.3	0	0.0	2	1.1
Primary tumor site						
Colon	53	59.6	60	68.2	113	63.8
Rectum	36	40.4	25	28.4	61	34.5
Colon and rectum	0	0.0	3	3.4	3	1.7
Prior therapy						
Adjuvant chemotherapy	21	23.6	14	15.9	35	19.8
Radiotherapy	12	13.5	6	6.8	18	10.2
Disease sites						
Liver	73	82.0	80	90.9	153	86.4
Liver only metastases	32	36.0	37	42.1	69	39.0
Lung	33	37.1	29	33.0	62	35.0
Lymph node	29	32.6	29	33.0	58	32.8
Peritoneum	11	12.4	11	12.5	22	12.4
Other	26	29.2	15	17.0	41	23.2
No. of disease sites						
1	36	40.4	40	45.5	76	42.9
2	31	34.8	26	29.5	57	32.2
3	14	15.7	16	18.2	30	16.9
> 3	8	9.0	6	6.8	14	7.9
EGFR status						
Positive	66	74.2	60	68.2	126	71.2
Negative	21	23.6	26	29.5	47	26.6
Unknown	2	2.3	2	2.3	4	2.3
KRAS status						
Wild-type	40	44.9	49	55.7	89	50.3
Mutant	33	37.1	22	25.0	55	31.1
Unknown	16	18.0	17	19.3	33	18.6

Abbreviations: CAPIRI, capecitabine plus irinotecan; CAPOX, capecitabine plus oxaliplatin; PS, performance status; EGFR, epidermal growth factor receptor.

KRAS Mutation Detection

KRAS testing was performed in a German reference laboratory for KRAS analysis (University of Munich, Department of Pathology). After dissection of tumor-containing areas, DNA was isolated using Qiagen DNA Micro-Amp-kits (Qiagen, Hilden, Germany). Detection of mutations in codons 12 and 13 of the KRAS proto-oncogene was then performed by pyrosequencing using Qiagen's PyroMark Gold kits together with a Q24 pyrosequencer device. This procedure resulted in a specificity of 0.98 and sensitivity of 0.99 for the detection of mutations in the KRAS proto-oncogene.

RESULTS

Patient Characteristics and Disposition

From September 2004 to December 2006, 185 patients were randomly assigned, 93 to cetuximab and CAPIRI (arm A) and 92 to cetuximab and CAPOX (arm B; Fig 1). Although standard inclusion and exclusion criteria were applied in this trial, four patients in each group did not receive any study therapy: three patients died before starting treatment, four patients withdrew consent, and one patient developed a serious adverse event and was lost to follow-up. Thus, the ITT population included 89 patients in arm A, and 88 patients in arm B. Of these 177 patients, 28 patients discontinued study treatment within the first two treatment cycles before the first scheduled tumor assessment (Fig 1). The most common reasons for early dropout were severe allergic/anaphylactic reactions related to cetuximab (three patients in arm A, and eight patients in arm B). All infusion-related allergic reactions occurred on day 1 during the first cetuximab infusion. Therefore, 149 patients (cetuximab plus CAPIRI, $n = 78$; cetuximab plus CAPOX, $n = 71$) received study treatment beyond the first tumor assessment and were evaluable for efficacy. There were no major imbalances between the two groups in terms of baseline demographic and clinical characteristics (Table 1; Appendix Tables A1 and A2, online only).

Treatment Exposure and Second-Line Treatment

Median treatment duration was similar in both arms with 4.2 months in the cetuximab plus CAPIRI arm versus 4.4 months in the cetuximab plus CAPOX arm. The most frequent reasons for treatment discontinuation were progression of disease (43.5%), adverse events related to study medication (17.5%), patient wish (11.9%), and

surgical resection and/or radiofrequency ablation (7.9%; Appendix Table A3, online only). The median number of treatment cycles was six in both groups. Doses of study drugs had to be reduced frequently in both treatment arms. Dose reduction was necessary in 31.8% compared to 44.4% of treatment cycles in arms A and B, respectively ($P < .001$). However, the number of delayed cycles was similar in both groups (17.3% in arm A, v 16.6% in arm B, $P = .814$; Table 2).

There were no major imbalances between the treatment groups with respect to the use of second-line therapy (85.4% of patients in arm A compared to 86.4% in arm B). Second-line therapy was FU/capecitabine-based in 66.3% versus 67.0%, oxaliplatin-based in 50.6% versus 22.7%, irinotecan-based in 12.4% versus 38.6%, cetuximab-based in 11.2% versus 14.8%, and bevacizumab-based in 24.7% versus 25.0% of patients in the CAPIRI plus cetuximab versus CAPOX plus cetuximab arms, respectively.

The number of patients receiving all five active drugs (FU/capecitabine, irinotecan, oxaliplatin, cetuximab, bevacizumab) during the course of mCRC therapy was comparable between arms A and B (43.8% v 43.2%).

Efficacy

The overall response rate in the ITT population was 46.1% in the cetuximab plus CAPIRI group (95% CI, 35.4% to 57.0%), and 47.7% in the cetuximab plus CAPOX group (95% CI, 37.0% to 58.7%; Table 3). In the assessable patient population of 149 patients, ORRs of 52.6% (95% CI, 40.9% to 64.0%) and 59.2% (95% CI, 46.8% to 70.7%) were achieved in arms A and B, respectively. The disease control rate in this patient population reached 84.6% (95% CI, 74.7% to 91.8%) in arm A compared to 95.8% (95% CI, 88.1% to 99.8%) in arm B. Median time to remission was short in both arms (1.7 v 1.5 months).

Within the trial, 36.2% of patients were older than 65 years (33 patients in arm A, and 31 patients in arm B, ITT population). These patients received the CAPIRI regimen with a 20% dose reduction. The ORR in these older patients was 42.4% (95% CI, 25.5% to 60.8%) versus 45.2% (95% CI, 27.3% to 64%), and the disease control rate was 66.7% (95% CI, 48.2% to 82%) versus 71% (95% CI, 52% to 85.8%) for the CAPIRI plus cetuximab versus CAPOX plus cetuximab groups.

Table 2. Treatment Administration

Parameter	CAPIRI + Cetuximab		CAPOX + Cetuximab		Total	
	No.	%	No.	%	No.	<i>P</i>
No. of patients	89		88		177	
Duration of therapy, months						
Median		4.2		4.4		4.3
Range		0-19.5		0-17.3		0-19.5
No. of treatment cycles per patient						
Median		6		6		6
Range		1-26		1-23		1-26
Evaluable treatment cycles	617		536			
Cycles with dose reduction*	196	31.8	238	44.4		< .001
Cycles with treatment delay†	107	17.3	89	16.6		.814

Abbreviations: CAPIRI, capecitabine plus irinotecan; CAPOX, capecitabine plus oxaliplatin.

*Defined as < 90% of scheduled doses for cetuximab, irinotecan, oxaliplatin, or capecitabine.

†Defined as treatment cycles exceeding 24 days.

Table 3. Best Response During Treatment (intent-to-treat population and assessable patients, *KRAS* wild-type and mutant population)

	CAPIRI + Cetuximab		CAPOX + Cetuximab	
ITT Population	No.	%	No.	%
No. of patients	89		88	
Complete response	3	3.4	5	5.7
Partial response	38	42.7	37	42.0
Stable disease	25	28.1	26	29.5
Progressive disease	12	13.5	3	3.4
Response rate*	41	46.1	42	47.7
95% CI		35.4 to 57.0		37.0 to 58.7
Disease control rate†	66	74.2	68	77.3
95% CI		63.8 to 82.9		67.1 to 85.5

	KRAS Status							
	Wild-Type		Mutant		Wild-Type		Mutant	
	No.	%	No.	%	No.	%	No.	%
No. of patients	40		33		49		22	
Complete response	1	2.5	1	3.0	4	8.2	1	4.5
Partial response	19	47.5	15	45.5	18	36.7	10	45.5
Stable disease	10	25.0	11	33.3	13	26.5	9	40.9
Progressive disease	6	15.0	3	9.1	3	6.1	0	0
Not assessable‡	4	10.0	3	9.1	11	22.4	2	9.1
Response rate*	20	50.0	16	48.5	22	44.9	11	50.0
95% CI		33.8 to 66.2		30.5 to 66.5		30.5 to 59.3		27.3 to 72.7
Disease control rate†	30	75.0	27	81.8	35	71.4	20	90.9
95% CI		61.0 to 89.0		67.9 to 95.7		58.3 to 84.5		77.9 to 104.0

Abbreviations: ITT, intent-to-treat; CAPIRI, capecitabine and irinotecan; CAPOX, capecitabine and oxaliplatin.

*Complete plus partial response.

†Complete plus partial response plus stable disease.

‡Not assessable, early dropout patients prior to first tumor assessment.

Tumor samples suitable for the analysis of *KRAS* mutation status were obtained from 144 (81.4%) of 177 patients. For remaining patients samples were either not sufficient in size or not available. Response rates were independent of the *KRAS* status (wild-type versus

mutant) in arm A (50.0% *v* 48.5%) and arm B (44.9% *v* 50.0%; Table 3). Likewise, *KRAS* status also had little effect on progression-free survival (PFS) in arm A (6.2 *v* 5.8 months) and arm B (7.1 *v* 6.5 months; Table 4). There was a trend toward longer median overall

Table 4. Treatment Efficacy

ITT Population (n = 177)	CAPIRI + Cetuximab (n = 89)		CAPOX + Cetuximab (n = 88)	
	Median (months)	95% CI (months)	Median (months)	95% CI (months)
Time to remission	1.7	1.2 to 7.1	1.5	1.5 to 6.3
Remission duration	5.8	5.0 to 7.7	7.5	6.1 to 8.2
Time to progression	6.3	5.5 to 7.8	7.7	6.5 to 9.2
Time to treatment failure	4.7	4.3 to 5.5	5.1	4.5 to 6.3
Progression-free survival	6.1	5.4 to 7.7	7.1	5.6 to 9.1
Overall survival	21.1	17.1 to 28.7	25.5	19.4 to 33.8

<i>KRAS</i> wild-type (n = 89)	CAPIRI + Cetuximab (n = 40)		CAPOX + Cetuximab (n = 49)	
	Median (months)	95% CI (months)	Median (months)	95% CI (months)
Progression-free survival	6.2	3.7 to 8.8	7.1	4.8 to 9.0
Overall survival	21.1	17.1 to 25.2	23.5	15.9 to 31.0

<i>KRAS</i> mutant (n = 55)	CAPIRI + Cetuximab (n = 33)		CAPOX + Cetuximab (n = 22)	
	Median (months)	95% CI (months)	Median (months)	95% CI (months)
Progression-free survival	5.8	4.1 to 7.4	6.5	4.6 to 8.5
Overall survival	17.9	12.9 to 22.9	18.8	0.0 to 39.8

Abbreviations: ITT, intent-to-treat; CAPIRI, capecitabine plus irinotecan; CAPOX, capecitabine plus oxaliplatin.

survival in the *KRAS* wild-type compared to the mutant subgroup in arm A (21.1 v 17.9 months) and arm B (23.5 v 18.8 months; Fig 2). Similar results were obtained when the effect of *KRAS* status was evaluated in the assessable population who had received cetuximab until first restaging (data not shown).

Safety

Overall, the toxicity profile of both combinations was manageable (Table 5). In terms of grade 3/4 hematologic adverse events, patients treated with cetuximab plus CAPIRI displayed higher rates of anemia (3.4% v 0%; $P = .12$), leucopenia (5.6% v 3.4%; $P = .72$), and neutropenia (9% v 1.1%; $P = .03$). However, the statistically significantly higher rate of neutropenia did not result in an increased incidence of neutropenic fever in the cetuximab plus CAPIRI arm. Neutropenic fever was rare across the entire study (1.1% v 0% in arm A v B).

Cetuximab-related acneiform exanthema/desquamation occurred in most patients in both treatment groups (82% in arm A v

84.1% in arm B) reaching grade 3/4 severity in 12.4% versus 20.5% of patients ($P = .16$). Grade 3/4 diarrhea occurred in 15.7% of patients receiving cetuximab plus CAPIRI, compared to 19.3% of patients receiving cetuximab plus CAPOX. As expected, oxaliplatin-induced sensory neurotoxicity was a clinically meaningful adverse event in the cetuximab plus CAPOX treatment group; 69.3% of patients in arm B developed sensory neurotoxicity of all grades, and 14.8% of patients developed grade 3 neurotoxicity. Hand-foot syndrome was reported less often than expected in both treatment arms: in arm A, 22.5% of patients reported hand-foot syndrome of all grades, compared to 30.7% of patients in arm B.

DISCUSSION

To our knowledge, the AIO KRK-0104 phase II study of the German AIO CRC Study Group is the first randomized trial to investigate cetuximab plus CAPIRI and cetuximab plus CAPOX. Even though the trial was not designed to directly compare the two treatment arms,

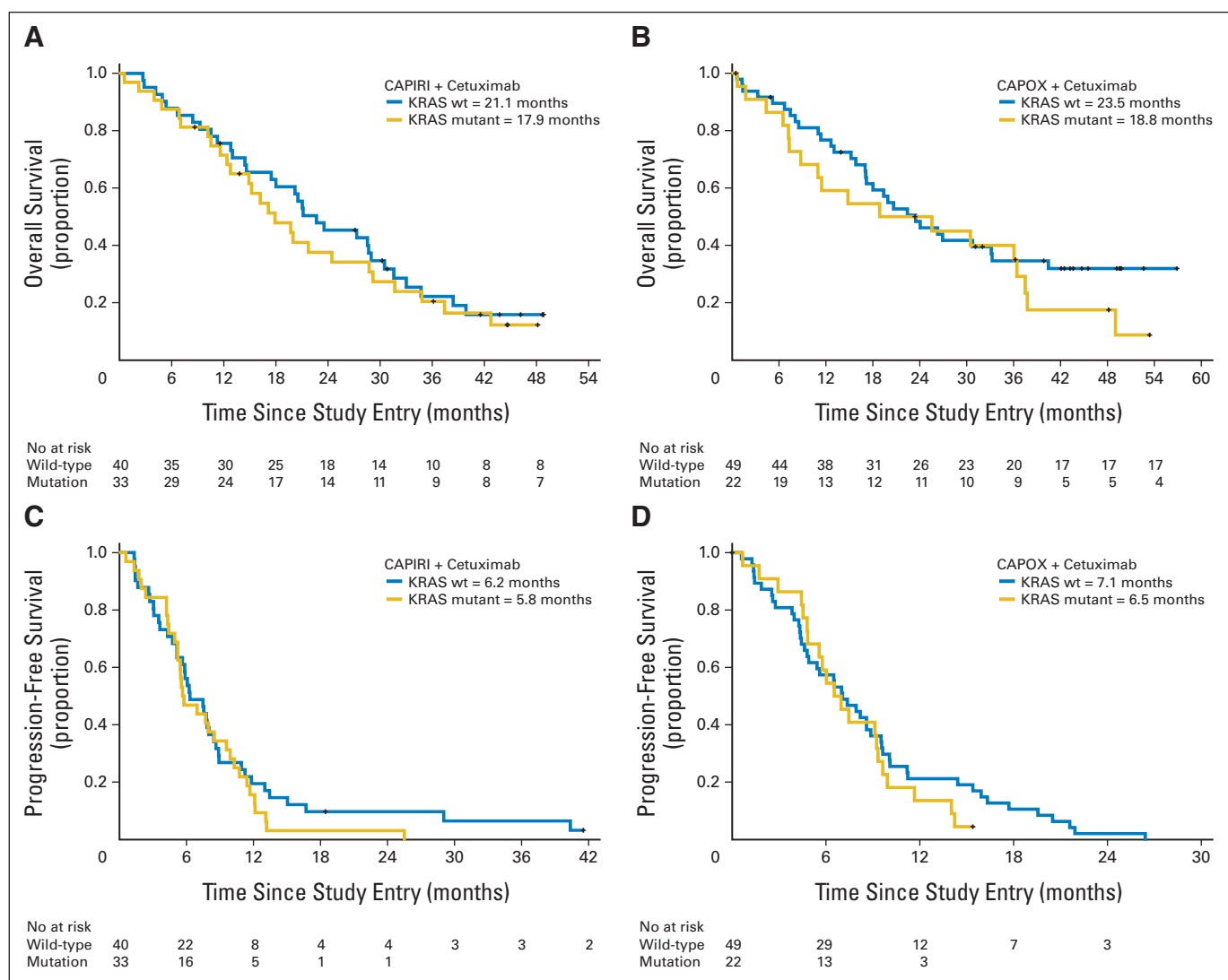


Fig 2. Overall survival (A, B) and progression-free survival (C, D) for patients with *KRAS* wild-type (wt) and mutant in the capecitabine and irinotecan (CAPIRI) plus cetuximab and the capecitabine and oxaliplatin (CAPOX) plus cetuximab treatment arms.

Table 5. Hematologic and Nonhematologic Grade 3/4 Toxicities

Grade 3/4 Toxicity	CAPIRI + Cetuximab		CAPOX + Cetuximab		P
	No.	%	No.	%	
No. of patients	89		88		
Hematologic adverse events					
Anemia	3	3.4	0	0	.12
Thrombopenia	0	0.0	3	3.4	.06
Leucopenia	5	5.6	3	3.4	.72
Neutropenia	8	9.0	1	1.1	.03
Neutropenic fever	1	1.1	0	0.0	.50
Infection	3	3.4	5	5.7	.50
Nonhematologic adverse events					
Exanthema/desquamation	11	12.4	18	20.5	.16
Nail changes	1	1.1	3	3.4	.37
Skin other	4	4.5	5	5.7	.75
Hand-foot syndrome*	11	12.4	20	22.7	.08
Nausea	6	6.7	8	9.1	.59
Vomiting	1	1.1	3	3.4	.37
Diarrhea	14	15.7	17	19.3	.56
Constipation	1	1.1	1	1.1	1.00
Stomatitis	1	1.1	0	0.0	.50
Neurotoxicity, sensory	1	1.1	13	14.8	< .01
Fatigue/asthenia	4	4.5	6	6.8	.54
Pain	8	9.0	4	4.6	.37
Allergic reaction	3	3.4	8	9.1	.43

Abbreviations: CAPIRI, capecitabine plus irinotecan; CAPOX, capecitabine plus oxaliplatin.

*Grade 2/3 events.

evaluation of ORR, the primary end point of this trial, indicated that both regimens were similarly effective. In the ITT analysis, ORR was 46.1% for cetuximab plus CAPIRI and 47.7% for cetuximab plus CAPOX, which favorably compares with previously reported results from phase II studies.^{20,21} The observed ORR were greater than 50% only among assessable patients (52.6% v 59.2%). The CRYSTAL trial had shown that superior remission induction in the cetuximab-containing arm translated into a higher rate of surgery for metastases (7.0% v 3.7%).¹⁴ In this trial, secondary resection and/or radiofrequency ablation was documented in 7.9% of patients.

A retrospective analysis of the *KRAS* status was performed in 81.4% of the ITT population. It was not expected to note that in this trial *KRAS* status had no impact on ORR as comparable remission rates were observed for patients with *KRAS* wild-type and mutant tumors in the CAPIRI plus cetuximab arm (50.0% v 48.5%) and the CAPOX plus cetuximab arm (44.9% v 50.0%). This result was also maintained when both study arms were analyzed together (data not shown). In the CRYSTAL trial, and likewise also in the OPUS trial, patients with *KRAS* wild-type treated with cetuximab-based combination therapy achieved markedly superior response rates than *KRAS*-mutant subgroups.^{22,23}

Again, in this trial only slight differences in PFS were observed in *KRAS* wild-type versus mutant subgroups receiving CAPIRI plus cetuximab (6.2 v 5.8 months) or CAPOX plus cetuximab (7.1 v 6.5 months). In comparison, more favorable PFS times were reported in *KRAS* wild-type than in mutant subgroups in the CRYSTAL trial (9.9 v 7.4 months) and the OPUS trial (8.3 v 5.5 months).^{22,23}

Median overall survival for patients with *KRAS* wild-type in this trial was well in the expected range and reached 21.1 months for cetuximab plus CAPIRI and 23.5 months for cetuximab plus CAPOX

which compares favorably with the results previously reported in the CRYSTAL (23.5 months) and OPUS trials (22.8 months).

Although *KRAS* status affected neither ORR nor PFS in our trial, longer survival times were observed for patients with *KRAS* wild-type compared with *KRAS* mutant status in the cetuximab plus CAPIRI group (21.1 v 17.9 months) and the cetuximab plus CAPOX group (23.5 v 18.8 months). In the absence of superior efficacy data in patients with *KRAS* wild-type, this result may point to the positive prognostic effect of *KRAS* wild-type in this particular setting of palliative treatment.

Clearly, our study is too small to allow a meaningful conclusion from the *KRAS* analysis. However, our data complement the COIN trial results which suggest that the addition of cetuximab to CAPOX may not improve treatment efficacy in patients with *KRAS* wild-type compared to *KRAS* mutant.²⁴ In our study, this effect is clearly not related to the choice of the chemotherapeutic combination partner irinotecan or oxaliplatin. While consistently positive data were obtained for the combination of cetuximab plus FOLFIRI (CRYSTAL trial) and FOLFOX (OPUS and COIN trial), capecitabine and cetuximab do not seem to be favorable combination partners. As opposed to the COIN trial, however, we did not observe increased nonhematologic or gastrointestinal toxicity with either treatment arm.²⁵ Therefore, our data do not support the argument that cetuximab and capecitabine are less effective solely based on increased and overlapping toxicity profiles. This raises the question if there may be a mechanistic basis for an inhibitory interaction between both agents.

The AIO KRK-0604 randomized phase II trial was based on an identical chemotherapy backbone (CAPIRI v CAPOX) as our study, but, instead of cetuximab, added bevacizumab in both arms. Median PFS in the AIO KRK-0604 trial was substantially longer than in our study and reached 12.1 months for the bevacizumab plus CAPIRI arm

and 10.4 months for the bevacizumab plus CAPOX arm.²⁶ One explanation may be that anti-EGFR directed and antiangiogenic strategies have different effects on PFS. Another argument is the shorter duration of first-line treatment in our trial (six cycles in both arms) compared to the AIO KRK-0604 trial (eight to nine cycles). End of treatment was predominantly caused by disease progression, adverse events related to study medication, and patient wish. In contrast to the AIO KRK-0604 study, de-escalation to capecitabine plus antibody was not allowed within our study protocol. In addition, our study had to report a high early dropout rate, and a high rate of infusion-related events (Fig 1). Even though antiallergic premedication with antihistamine agents was specified in the study protocol, the 6.2% incidence of severe cetuximab-related infusion reactions was higher than expected. As a consequence, we offered patients intensified premedication with additional application of dexamethasone before the first infusion of cetuximab.

Except for the high incidence of cetuximab-related allergic reactions, the safety profiles documented in our study did not reveal excessive toxicity. Both treatment regimens had manageable toxicities and were safe. Earlier trials evaluating combined chemotherapy with capecitabine and irinotecan had shown high incidences of severe gastrointestinal adverse effects with grade 3/4 diarrhea documented in up to 36% of patients. It was therefore suggested to apply reduced doses of capecitabine and irinotecan for subsequent trials.^{11,27} We used doses reduced by 20% in the CAPIRI arm (ie, capecitabine 800 mg/m², irinotecan 200 mg/m², and an additional 20% dose reduction in patients > 65 years) compared to earlier trials. With these dose reductions, there was no evidence of increased gastrointestinal toxicity even in combination with cetuximab. Grade 3/4 diarrhea occurred in 15.7% of patients receiving cetuximab plus CAPIRI, and in 19.3% of patients receiving cetuximab plus CAPOX. The reduced dose of capecitabine in the CAPIRI arm led to a lower rate of grade 2 to 3 hand-foot syndrome compared to the CAPOX arm (12.4% v 22.7%). Accordingly, the rate of adverse events in our study did not exceed the rates that would be expected from the regimen components in each of the two treatment arms. Even though patient numbers are small, the additional 20% dose reduction in older patients did not appear to compromise efficacy parameters.

Taking together the three latest trials investigating capecitabine combined with irinotecan (ie, CAIRO1, AIO KRK-0604, and our trial), there is convincing data demonstrating that the safety profile of CAPIRI is clinically manageable, even in combination with targeted agents.^{12,26}

In conclusion, this trial demonstrates that the regimens combining cetuximab with CAPIRI or CAPOX have similar activity. They are safe treatment options for first-line therapy of mCRC. The question why *KRAS* gene mutation status did not correlate with ORR and PFS in this study needs to be addressed by future investigations.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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