

ORIGINAL ARTICLE

Early tumor shrinkage in patients with metastatic colorectal cancer receiving first-line treatment with cetuximab combined with either CAPIRI or CAPOX: An analysis of the German AIO KRK 0104 trial

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Abstract

Purpose. This study investigated the impact of early tumor shrinkage (ETS) on progression-free- (PFS) and overall survival (OS) in patients with metastatic colorectal cancer (mCRC) treated within the AIO KRK 0104 trial as first-line therapy. Moreover, correlations of ETS with clinical characteristics and prognostic markers were evaluated. **Patients and methods.** In total, 121 patients were included into this analysis. Patients were treated with cetuximab combined with either CAPIRI or CAPOX. ETS at six weeks was defined as a relative change of $\geq 20\%$ in the sum of the longest diameters of target lesions compared to baseline. Survival times were compared between patients with ETS $\geq 20\%$ versus no-ETS. **Results.** ETS $\geq 20\%$ was observed in 59% of all patients with *KRAS* wild-type tumors. In these patients ETS $\geq 20\%$ was associated with higher overall response rate (82% vs. 19%, $p < 0.001$). Also, PFS (8.9 vs. 4.7 months, $p < 0.001$) and OS (31.6 vs. 15.8 months, $p = 0.005$) were significantly superior in ETS $\geq 20\%$ of patients compared to no-ETS. In patients with *KRAS* mutant mCRC ETS $\geq 20\%$ neither had an effect on PFS nor OS. Cetuximab-induced skin toxicity correlated with the occurrence of ETS $\geq 20\%$ ($p = 0.002$). **Conclusion.** In patients with *KRAS* wild-type tumors treated with cetuximab plus capecitabine-based chemotherapy ETS $\geq 20\%$ is an important predictor of favorable outcome.

Mutations in the *KRAS* proto-oncogene have been identified as negative predictors of response to anti-EGFR antibodies such as cetuximab or panitumumab leading to an exclusion of affected patients from anti-EGFR therapy [1–7]. Nevertheless, even in first-line trials response to anti-EGFR-based treatment is limited to less than 60% of all patients with *KRAS* wild-type (wt) tumors [3–5]. Therefore, additional biological or clinical markers are needed to identify those patients that are most likely to benefit from anti-EGFR treatment. Recently, Piessevaux and coworkers demonstrated that early tumor shrinkage (ETS) $\geq 20\%$ was associated with prolonged overall survival times (OS) in patients with *KRAS* wt tumors receiving cetuximab-based first-line therapy. They analyzed ETS $\geq 20\%$ after

treatment duration of eight weeks and selected $\geq 20\%$ tumor reduction in diameter as a cut-off differentiating early response in shrinkers from non-shrinkers [8]. In patients with *KRAS* wt tumors ETS $\geq 20\%$ was associated with long-term survival, showing a significantly greater effect in patients that received chemotherapy plus cetuximab compared to patients that were treated with chemotherapy alone. This finding was underlined by significant treatment interaction testing. Therefore, the authors concluded that ETS $\geq 20\%$ might be an indicator of cetuximab-related antitumor activity in patients with *KRAS* wt metastatic colorectal cancer (mCRC). Other authors demonstrated that the prognostic value of ETS in mCRC-patients receiving chemotherapy alone depends on the ETS

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cut-off: greater ETS was clearly associated with longer survival [9].

Previously reported data from the COIN study suggested that the combination of cetuximab with capecitabine might be less effective than combinations with an infusional fluoropyrimidine [10]. The present analysis therefore asks the question if $ETS \geq 20\%$ predicts progression-free survival (PFS) and OS in patients receiving cetuximab plus capecitabine-based regimens. In the present investigation, we evaluated patients with mCRC that received cetuximab in combination with capecitabine plus oxaliplatin (CAPOX) or plus irinotecan (CAPIRI) as first-line treatment. On the one hand, $ETS \geq 20\%$ was correlated with KRAS mutation occurring in the tumor, while on the other hand, patient-related parameters such as skin toxicity and patient characteristics were analyzed in the context of ETS-prediction.

$ETS \geq 20\%$ represents a post-randomization marker that was assessed six weeks after the start of systemic treatment in this trial. Therefore, a potential guarantee-time bias as described by Anderson and coworkers [11] was addressed by a landmark analysis.

Methods

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. 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 [12].

Study design and treatment schedule

The AIO KRK 0104 study was designed as an open-label, randomized phase II study which 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 (i.e. oral capecitabine 800 mg/m² twice daily on days 1 through 14, followed by a one-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 (i.e. capecitabine 1000 mg/m² twice daily on days 1 through 14,

followed by a one-week rest period plus oxaliplatin 130 mg/m² as a 120-minute intravenous infusion on day 1). Treatment cycles were repeated every three weeks until disease progression or unacceptable toxicity [13,14]. A final update on survival data was done in June 2011 [14].

Patients

One hundred and twenty-one of the 146 patients that were evaluated for KRAS/BRAF mutations within the AIO KRK 0104 trial [14] were included in this analysis. Twenty-five patients were not included in this analysis due to early progression/death in 10 patients and in 15 patients due to withdrawal of informed consent, serious adverse events within the first weeks of therapy or protocol violations concerning response evaluation.

End points

The present investigation was performed as an exploratory analysis. Radiological tumor response [complete remission (CR), partial remission (PR), stable disease (SD), progressive disease (PD)] was assessed according to RECIST (version 1.0) criteria. Response evaluation was performed at six-week intervals. PFS was defined as the interval between randomization and first documentation of progression or death; OS was calculated as the time between randomization and death due to any reason. Patients alive were censored at the last time point of patient contact.

ETS in this trial was defined as a reduction of $\geq 20\%$ in diameter if a single lesion was observed. In case of more than one lesion ETS was calculated based on the sum of lesions. We evaluated ETS at six weeks when patients of the AIO KRK 0104 trial were treated with two cycles of chemotherapy plus cetuximab. An alteration of two weeks was tolerated.

Statistical analysis

Data were summarized by properly chosen measures of location and spread for continuous variables and by proportions for discrete variables. Fisher's exact-tests and χ^2 -tests were applied to estimate differences in response or baseline characteristics. Differences in OS and PFS were estimated using the Kaplan-Meier method and were compared between the groups by log-rank tests. Further, differences in PFS and OS were analyzed using Cox regressions. All statistical analyses were performed with SPSS version 20, IBM, New York, USA and R (version 2.13.0; The R Foundation for Statistical Computing/R Development Core Team, GNU General Public License). The present analysis included only patients that were evaluable for ETS after six weeks of systemic treatment. This approach of a landmark analysis according to the

proposition by Anderson and coworkers [11] was chosen to eliminate a potential guarantee-time bias. Since no patients were 'lost for analysis' between start of treatment and ETS assessment this procedure excludes an impact of guarantee time bias on survival.

Results

Study population

This exploratory analysis includes 121 patients who received cetuximab plus CAPOX or cetuximab plus CAPIRI as first-line treatment of mCRC. Baseline characteristics of the whole patient population were recently published [14]. Patient characteristics according to the analyzed subgroups are shown in Table I.

In the AIO KRK 0104 trial *KRAS* wt tumors seemed more frequent within the group of ETS $\geq 20\%$ than in no-ETS patients (71% vs. 53%, $p = 0.06$). Favorable baseline characteristics were a little more frequent in our ETS $\geq 20\%$ population than in the no-ETS population. These trends were seen for liver metastasis, liver limited metastasis, lymph node metastases, prior adjuvant treatment and multi organ involvement.

Cetuximab-associated skin toxicity of any grade (I–III) correlated well with ETS (100% of ETS $\geq 20\%$ patients vs. 86% of no-ETS patients, $p = 0.002$). None of eight patients without any cetuximab-based skin toxicity developed ETS $\geq 20\%$ (Table I). If skin toxicity was correlated as grade 0–1 versus grade 2–4,

Table I. Patient characteristics.

Parameters	Early tumor shrinkage ($\geq 20\%$)		No early tumor shrinkage ($< 20\%$)		p-value
	No	%	No	%	
No of patients	63	52	58	48	
Age, years					
Median	63		60		0.20
Range	32–75		38–77		
Sex					
Female	19	30	19	33	0.85
Male	44	70	39	67	
Karnofsky PS					
100	26	42	23	40	0.69
90	23	38	16	28	
80	10	16	15	26	
70	3	5	3	5	
Not reported	1		1		
Primary tumor site					
Colon	42	67	37	64	0.33
Rectum	19	30	21	36	
Colon + Rectum	2	3	0	0	
Prior adjuvant therapy					
Chemotherapy	7	11	15	26	0.06
Radiotherapy	6	10	6	10	1.0
Disease site					
Liver	59	94	48	83	0.09
Liver only metastasis	30	48	18	31	0.12
Lung	21	33	22	38	0.70
Lymph node	16	25	27	47	0.02
Bone	1	2	2	3	0.61
Peritoneum	5	8	6	10	0.76
1 organ involved	31	49	22	38	0.25
2 organs involved	21	33	18	31	
3 organs involved	10	16	12	21	
4 organs involved	1	2	5	9	
5 organs involved	0	0	1	2	
> 2 disease sites	11	17	18	31	0.09
Treatment-arm					
CAPIRI	28	44	37	64	0.05
CAPOX	35	56	21	36	
KRAS					
Wild-type	45	71	31	53	0.06
Mutant	18	29	27	47	
Cetuximab-related skin toxicity of any grade					
Skin toxicity	63	100	50	86	0.002
No skin toxicity	0	0	8	14	

Characteristics of patients, percentages based on non-missing data. P-values: χ^2 -test/Fisher's exact test, except age: independent samples: Mann-Whitney U-test.

Table II. Parameters of treatment response.

Parameter	All patients		KRAS WT cohort	
	Early tumor shrinkage	No early tumor shrinkage	Early tumor shrinkage	No early tumor shrinkage
Number of patients	63	58	45	31
ORR-Recist 1.0 (%)	84	24	82	19
p (Fisher's exact test)	< 0.001		< 0.001	
Median PFS (months) 95% CI	8.6	5.1	8.9	4.7
p (log-rank) HR (95% CI)	7.4–9.8	4.3–6.0	7.1–10.6	4.0–5.5
	< 0.001		< 0.001	
	0.50 (0.34–0.73)		0.37 (0.23–0.60)	
Median OS (months) 95% CI	28.7	17.0	31.6	15.8
p (log-rank) HR (95% CI)	22.6–34.7	8.9–25.1	26.6–35.5	8.5–23.1
	0.023		0.005	
	0.63 (0.43–0.94)		0.48 (0.29–0.82)	

CI, confidence interval; HR, hazard ratio by cox-regression; ORR, overall response rate; OS, overall survival; PFS, progression-free survival.

significance was lost. No correlation of intensity of skin-toxicity and ETS $\geq 20\%$ could be detected.

Impact of ETS on treatment efficacy in the AIO KKR 0104 trial

In our study cohort, ETS $\geq 20\%$ was observed in 52% (63/121) of all patients and was associated with longer median PFS [8.6 vs. 5.1 months, $p < 0.001$, hazard ratio (HR): 0.50 (95% CI 0.34–0.73)] and longer median OS [28.7 vs. 17.0 months, $p = 0.023$, HR: 0.63 (95% CI 0.43–0.94)] (Table II).

Impact of ETS on treatment efficacy with respect to KRAS mutation

Taking *KRAS* mutation into account, the rate of ETS $\geq 20\%$ was 59% (45/76) in patients with

KRAS wt tumors and 40% (18/45) in patients with *KRAS* mutant mCRC. ETS $\geq 20\%$ translated into a beneficial outcome only in patients with *KRAS* wt tumors, but not in patients bearing *KRAS* mutant tumors. PFS and OS in the *KRAS* wt-population reached 8.9 vs. 4.7 months [$p < 0.001$, HR: 0.37 (95% CI, 0.23–0.60)] and 31.6 vs. 15.8 months [$p = 0.005$, HR: 0.48 (95% CI 0.29–0.82)] in patients with ETS $\geq 20\%$ vs. no-ETS (Table II, Figures 1 and 2).

PFS and OS in patients with *KRAS* mutant mCRC were neither associated with significantly improved PFS [7.5 vs. 5.8 months, $p = 0.73$, HR: 0.90 (95% CI 0.49–1.67)], nor with longer OS (19.7 vs. 28.7 months, $p = 0.81$, HR: 1.09 (95% CI 0.57–2.05)] (Figures 3 and 4).

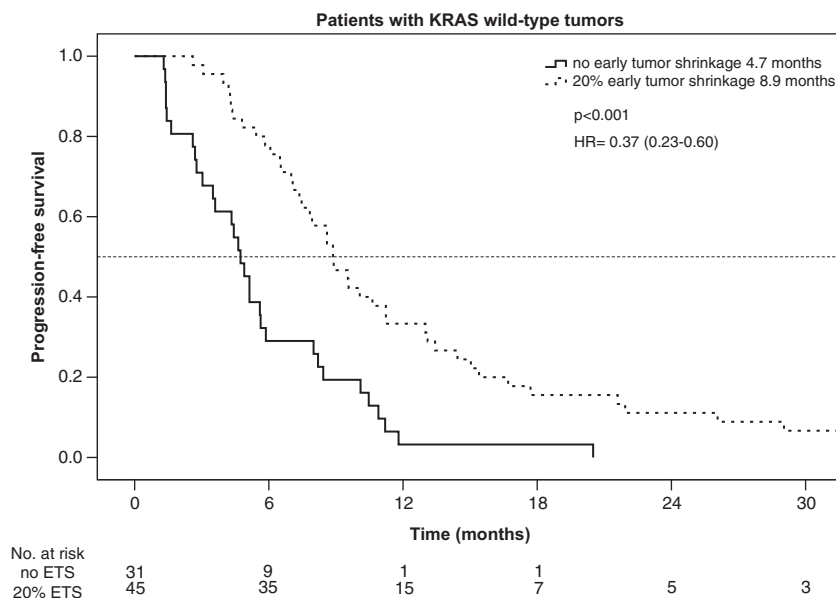


Figure 1. Progression-free survival – *KRAS*-Wt population in the AIO KKR 0104 trial according to early tumor shrinkage.

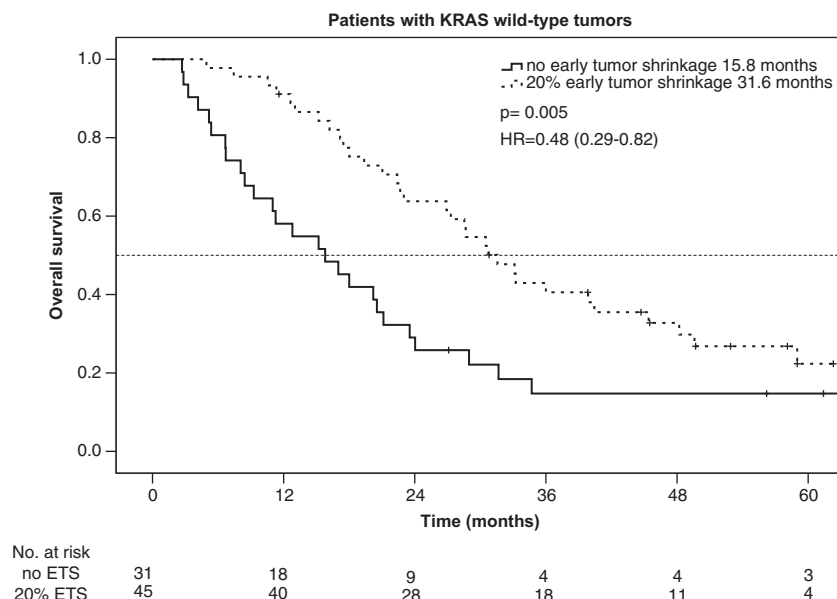


Figure 2. Overall survival – *KRAS*-WT population of the AIO KRK 0104 trial according to early tumor shrinkage.

Discussion

KRAS mutation is an established negative predictor of treatment response to anti-EGFR agents in mCRC. Accordingly, the use of anti-EGFR antibodies such as cetuximab is limited to patients with *KRAS* wt tumors. However, even in first-line treatment in patients with *KRAS* wt mCRC, response rates following anti-EGFR-antibody-based therapy did not exceed 60% [3–5] and therefore, research regarding predictive markers beyond *KRAS* is ongoing. Changes of the initial tumor size observed at the first reevaluation (ETS) are known prognostic parameters for outcome of patients with mCRC receiving chemotherapy and depend on the respective cut-off value [9]. In patients with *KRAS* wt mCRC receiving cetuximab-based therapy, $\text{ETS} \geq 20\%$ was found to correlate significantly with PFS and OS in first-line treatment [8] and at a cut-off of $> 10\%$ also in pre-treated patients [15].

In the AIO KRK 0104 trial, 59% of patients with *KRAS* wt tumors developed $\text{ETS} \geq 20\%$ at the time of first tumor-reevaluation, which was scheduled six weeks after the start of treatment. These 59% compare well with the frequencies observed within the CRYSTAL-trial-62% (FOLFIRI plus cetuximab) and the OPUS-study (FOLFOX4 plus cetuximab)-69% where eight-week intervals for reevaluation were used.

In patients with *KRAS* wt mCRC the differences in outcome observed in the AIO KRK 0104 trial between $\text{ETS} \geq 20\%$ versus no-ETS appear moderate with regard to PFS (8.9 vs. 4.7 months, $\Delta \text{PFS} = 4.2$ months, HR: 0.37) but translate into a relative prolongation of OS (31.6 vs. 15.8 months, $\Delta \text{OS} = 15.8$ months, HR: 0.48) of similar extent.

This observation compares well to the data from the OPUS- and CRYSTAL-trial concerning effects on PFS ($\Delta \text{PFS} = 6.8$ and 6.2 months), and OS ($\Delta \text{OS} = 11.4$ and 10.3 months) by $\text{ETS} \geq 20\%$ in patients with *KRAS* wt tumors that received cetuximab-based treatment [8] (Table III).

It is clearly of great interest to clarify the relation of $\text{ETS} \geq 20\%$ to baseline characteristics. Concerning this question the present analysis is highly limited by its retrospective and exploratory nature based on subgroup analyses and low patient numbers. However, a positive trend might suggest that $\text{ETS} \geq 20\%$ patients are more likely to have liver metastasis and no metastasis in lymph nodes as well as being untreated with adjuvant chemotherapy. This information on patient characteristics and $\text{ETS} \geq 20\%$ has not been reported in other cetuximab-based first-line trials such as OPUS and CRYSTAL [8].

A correlation of EGFR-antibody-related skin-toxicity and outcome has been observed in various trials [5,6]. Therefore, a correlation of skin-toxicity and $\text{ETS} \geq 20\%$ as observed in our study might have been expected as both markers are known to correlate with favorable outcome in mCRC patients treated with cetuximab. In the present analysis, all patients with $\text{ETS} \geq 20\%$ also presented skin-toxicity (grades 1–4). However, 14% of no-ETS patients had no skin toxicity ($p = 0.002$). These data indicate that skin toxicity does not guarantee $\text{ETS} \geq 20\%$ but lack of skin toxicity highly correlates with no-ETS.

The prognostic/predictive role of $\text{ETS} \geq 20\%$ in patients with mCRC that received cetuximab-based first-line therapy was only observed in patients with *KRAS* wt tumors in the AIO KRK 0104 trial and was not evident in patients with *KRAS* mutation.

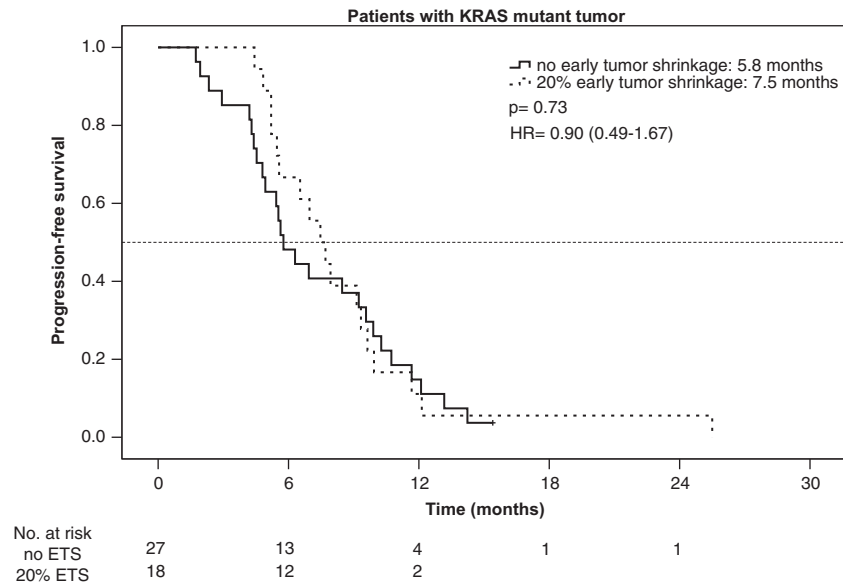


Figure 3. Progression-free survival – *KRAS*-mutant population in the AIO KRK 0104 trial according to early tumor shrinkage.

Our results are, of course, limited by small sample size and a biologic ratio concerning the lack of prognostic power of $ETS \geq 20\%$ in *KRAS* mutant mCRC is not obvious. However, Tejpar and coworkers demonstrated a similar effect in patients with *KRAS* p.G13D mutant mCRC showing a significantly increased response rate undergoing cetuximab-based first-line therapies (40.5 vs. 22.0%) without substantial benefit in terms of OS (HR: 0.89) [16].

In the AIO KRK 0104 trial, $ETS \geq 20\%$ appears as an early and powerful indicator of PFS and OS. This effect was limited to patients with *KRAS* wt tumors. However, the correlation of ETS (evaluated by various cut-off levels) with outcome has also been

observed in unselected patients treated with chemotherapy alone [9]. Therefore, differences in treatment (use of anti-EGFR agents) may require different cut-offs levels for ETS (according to the individual effect of the regimens on response to therapy) to obtain optimal separation of prognostic subgroups.

While $ETS \geq 20\%$ may clearly indicate patients benefitting from therapy, it is more difficult to draw conclusions for no-ETS patients. This is specifically important since no-ETS is not a homogeneous group, but consists of patients developing new lesions, patients progressing during treatment and patients having minor responses (ETS of 0–20%). The characterization of these subgroups requires prospectively

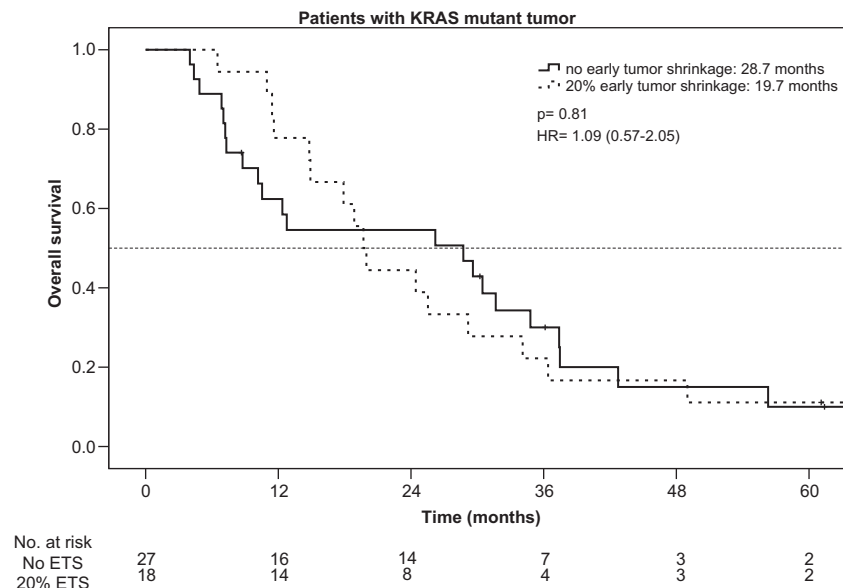


Figure 4. Overall survival – *KRAS*-mutant population of the AIO KRK 0104 trial according to early tumor shrinkage.

Table III. ETS in KRAS wt-mCRC: CRYSTAL-, OPUS- and AIO KRK 0104 trial.

KRAS wt-mCRC	CRYSTAL FOLFIRI + Cet	OPUS FOLFOX + Cet	AIO KRK0104 CAPOX/CAPIRI + Cet
ETS of all patients	62%	69%	59%
PFS in ETS-patients	14.1 months	11.9 months	8.9 months
Δ PFS (ETS-no-ETS)	6.8 months	6.2 months	4.2 months
OS in ETS-patients	30.0 months	26.0 months	31.6 months
Δ OS (ETS-no-ETS)	11.4 months	10.3 months	15.8 months

ETS, early tumor shrinkage; Cet, cetuximab; OS, overall survival; PFS, progression-free survival.

planned evaluation in clinical trials. Since ETS $\geq 20\%$ has proven its power as surrogate marker of favorable outcome in various cohorts, ETS could be of interest for designing clinical trials that need to separate patients into prognostic subgroups during the trial.

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