Impact of exact segment by segment primary tumor location status on anti-EGFR antibody first-line treatment efficacy in RAS/BRAF wild-type and BRAF mutant metastatic colorectal cancer. A pooled analysis of AIO studies FIRE-1, CIOX, FIRE-3, XELAVIRI, and VOLFI.

Annabel Helga Sophie Alig
Charite Universitatsmedizin Berlin Campus Charite Mitte: Charite Universitatsmedizin Berlin
https://orcid.org/0000-0002-3922-3450
Volker Heinemann
Klinikum der Universitat Munchen Campus Grosshadern: Klinikum der Universitat Munchen Standort Grosshadern
Michael Geissler
Stadtisches Klinikum Karlsruhe gGmbH
Ludwig Fischer von Weikersthal
Gesundheitszentrum St. Marien, Amberg
Thomas Decker
Oncological Practice, Ravensburg
Kathrin Heinrich
Klinikum der Universitat Munchen Campus Grosshadern: Klinikum der Universitat Munchen Standort Grosshadern
Swantje Held
ClinAssess GmbH, Leverkusen
Lena Weiss
Klinikum der Universitat Munchen Campus Grosshadern: Klinikum der Universitat Munchen Standort Grosshadern
Laura Elisabeth Fischer
Klinikum der Universitat Munchen Campus Grosshadern: Klinikum der Universitat Munchen Standort Grosshadern
Nicolas Moosmann
Krankenhaus Barmherzige Bruder Regensburg
Arndt Stahler
Charite Universitatsmedizin Berlin Campus Charite Mitte: Charite Universitatsmedizin Berlin

Ivan Jelas
Charite Universitatsmedizin Berlin Campus Charite Mitte: Charite Universitatsmedizin Berlin
Annika Kurreck
Charité Universitätsmedizin Berlin CVK: Charite Universitatsmedizin Berlin - Campus Virchow-Klinikum
Jana Kaethe Striefler
Charité Universitätsmedizin Berlin CVK: Charite Universitatsmedizin Berlin - Campus Virchow-Klinikum
Jobst Christian von Einem
Charite Universitatsmedizin Berlin Campus Charite Mitte: Charite Universitatsmedizin Berlin
Anke Claudia Reinacher-Schick
Saint Josef Hospital: Sankt Josef Krankenhaus
Andrea Tannapfel
Universitatsklinikum der Ruhr-Universitat Bochum
Clemens Giessen-Jung
University Hospital Munich Campus Grosshadern: Klinikum der Universitat Munchen Standort Grosshadern
Sebastian Stintzing
Charite Universitatsmedizin Berlin Campus Charite Mitte: Charite Universitatsmedizin Berlin
Dominik Paul Modest (dominik.modest@charite.de)
Charité University Medicine Berlin

Research

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Abstract

Background

Primary tumor location (left vs. right) has prognostic and predictive impact on the therapeutic management of metastatic colorectal cancer (mCRC) in particular in the context of anti-epithelial growth factor receptor (anti-EGFR) antibodies.

This analysis evaluates the relevance of exact segment-by-segment tumor location in patients with metastatic colorectal cancer on outcome and efficacy of anti-EGFR-antibodies.

Methods

This is a retrospective, pooled analysis of five randomized clinical trials (FIRE-1, CIOX, FIRE-3, XELAVIRI and VOLFI) treating metastatic colorectal cancer patients in a first-line setting, published between 2011-2019. Each trial was a multicentre, phase 2 or phase 3 trial in which patients with untreated metastatic colorectal cancer received chemotherapy regimens with or without monoclonal antibodies (anti-VEGF, anti-EGFR). Eligible were patients with histologically confirmed metastatic colorectal cancer in good performance status who were at least 18 years old. Individual data of 1809 patients with available exact primary tumor location were included into this analysis.

Prognostic and predictive effects of primary tumor location were evaluated in uni- and multivariate analyses using the Kaplan Meier method, log rank tests, Cox regressions and logistic regressions

Results

Exact primary tumor location is an important determinant of overall survival (OS) in mCRC patients ($P<0.001$). Multivariate analysis of RAS/BRAF wild-type metastatic colorectal cancer indicate that efficacy of anti-EGFR agents in terms of OS increases continuously from primary tumors located in the caecum (HR 2.63), ascending colon (HR 1.24), right flexure/transverse colon (HR 0.99), left flexure/descending colon (HR 0.91) to the sigmoid (HR 0.71) and rectum (HR 0.58), demonstrating significant benefit in sigmoid and rectal metastatic colorectal cancer, as well as clear detriment in caecum mCRC. Patients with BRAF V600E mutant disease arising from left-sided segments of the colorectum benefitted from EGFR-antibody treatment survival: hazard ratio for death in left-sided tumors: 0.42 (95% CI 0.19-0.92).

Conclusions

Primary tumor location of metastatic colorectal cancer affects prognosis. Anti-EGFR efficacy increases continuously from proximal to distal segments of the colorectum in metastatic colorectal cancer patients with RAS/BRAF wild-type and BRAF mutant tumors. Therefore, patients with BRAF mutant tumors of the distal segments may benefit from first-line Anti-EGFR-based therapy.

Trial registration

FIRE1	trial registration ID	n/a
CIOX	trial registration ID	NCT00254137
FIRE3	trial registration ID	NCT00433927
XELAVIRI	trial registration ID	NCT01249638
VOLFI	trial registration ID	NCT01328171

Background

Primary tumor location (PTL), usually defined as left- vs. right with a cut-off at the splenic flexure, is a prognostic and predictive biomarker in the treatment of metastatic colorectal cancer (mCRC) [1-4]. Patients presenting with right-sided mCRC have a dismal prognosis as compared to patients with left-sided mCRC. Additionally the PTL also appears to predict the efficacy of antibodies targeting the epidermal growth factor receptor (EGFR) with patients presenting with left-sided mCRC deriving a substantial benefit in overall survival (OS) with cetuximab or panitumumab therapy [1, 2].

Numerous efforts have been made to find a clear molecular correlate of clinical observations that have established primary tumor location as a tool for clinical decision-making. Although various molecular factors occurring with differing frequencies throughout the colon and rectum can be described [5-9], a usable classifier still has to be established. A key problem in the development of a molecular-based “right- vs- left mCRC” classifier might be that clear cut-offs cannot be found for most molecular markers and the biology of molecular differences throughout the colorectum underlies rather continuous changes than dichotomous distributions [6, 10].

Therefore, this pooled analysis of five randomized trials evaluates the impact of the exact location of the primary tumor (i.e. caecum, ascending colon, right flexure plus transverse colon, left flexure plus descending colon, sigmoid and rectum) in patients with mCRC breaking up the dichotomy of left- vs. right-sided colorectal cancer into six subgroups, acknowledging the continuum hypothesis [10]. We ask the question to which extent the exact location influences the prognosis also taking into account molecular subgroups as defined by (K)*RAS* and *BRAF* mutations. Moreover, the effect of anti-EGFR treatment according to exact PTL is explored in patients with *RAS/BRAF* wildtype and *BRAF V600E* mutant mCRC.
As this investigation is a retrospective and unplanned analysis our findings should be interpreted as such.

Methods

Trials

We performed a retrospective analysis of five trials addressing patients with previously untreated mCRC. Reports of the trials have been published previously [11–21]. All trials were conducted according to the Declaration of Helsinki and were approved by ethics committees. Table 1 provides an overview of the included studies.

Table 1
characteristics of the five studies included in the pooled analysis

	FIRE-1 [11, 17]	CIOX [14, 16]	FIRE-3 [12, 18–21]	XELAVIRI [13]	VOLFI [15]
Phase of study	III	II	III	III	II
Country	Germany	Germany	Germany / Austria	Germany	Germany
No. of centers	48	35	110 / 6	82	21
Recruiting period	07/2000–10/2004	09/2004–12/2006	01/2007–09/2012	12/2010–04/2016	06/2011–01/2016
Primary endpoint	PFS	ORR	ORR	TFS	ORR
Overall survival censored (%)	12.9	19.8	12.7	15.2	34.4
treatment arms arm A	FUFIRI	CAPIRI + Cet	FOLFIRI + Cet	FP + Bev -> PD -> FP + Iri + Bev	mFOLFOXIRI + Pani
arm B	mIROX	CAPOX + Cet	FOLFIRI + Bev	FP + Iri + Bev	FOLFOXIRI
Molecular subgroup allowed	all	all	All; KRAS exon 2 after 2009	all	KRAS exon 2 WT, RAS WT from 2014
Previous adjuvant chemotherapy allowed	yes (no TOP1 inhibitors, no platinum)	yes (no TOP1 inhibitors)	yes	yes	yes
Time between end of adjuvant therapy and relapse, months	6	6	6	6	6
RECIST version	- (WHO)	1.0	1.0	1.1	1.1
Trial finder registration	—	NCT00254137	NCT00433927	NCT01249638	NCT01328171

	FIRE-1 [11, 17]	CIOX [14, 16]	FIRE-3 [12, 18–21]	XELAVIRI [13]	VOLFI [15]
Eligibility criteria	18–75	18–75	18–75	≥ 18	≥ 18
Age, years	-	-	≤ 2	≤ 1	≤ 1
ECOG	≥ 70%	≥ 70%	-	-	-
Karnowsky index					

Patients An anonymized clinical database of the trials was established including the following information for each patient: trial, treatment arm, use of EGFR-antibody, age, sex, ECOG performance status, tumor characteristics (exact primary tumor site, metastatic sites), prior adjuvant treatment, molecular characteristics ((K)RAS and BRAF mutational status). Tumor samples assigned to each patient were tested for (K)RAS- and BRAF V600E-mutations as described previously [12-20].

Exact primary tumor location

Locations of the primary were extracted from the respective study report forms and differentiated into caecum, ascending colon, right flexure, transverse colon, left flexure, descending colon, sigmoid and rectum. Due to small numbers, tumors of the right flexure and transverse colon were analyzed as one group as well as tumors originating from the left flexure and the descending colon. Patients with more than one primary in more than one of these segments were excluded from the analysis of exact primary tumor location. Patients with tumors of the recto-sigmoid region were analyzed as sigmoid carcinoma.

Treatment

Treatment procedures were described in detail in the previous publications and are summarized in Table 1. Details concerning dosages are displayed in supplementary table 1. Treatments were stratified according to anti-EGFR antibody use vs. chemotherapy alone or bevacizumab-based therapy.

Definition of progression-free survival and overall survival

Progression-free survival (PFS) was defined as time from randomisation to first progression of disease or death from any cause (whatever occurred first). In addition, the XELAVIRI study defined PFS as time from randomisation until switching to a new anticancer drug. Overall survival (OS) was defined as time from randomisation to death from any cause. Objective response (OR) was evaluated according to classifications of the WHO (FIRE-1), RECIST 1.0 (CIOX, FIRE-3) or RECIST 1.1 (XELAVIRI, VOLFI).

Statistical analysis

All statistical analyses were performed using SAS software (version 9.4; SAS Institute, Cary, NC) and SPSS version 25.0 software (IBM Corporation, Amonk, NY, USA). Survival was expressed as medians including 95% confidence intervals by Kaplan Meier method and compared using log-rank tests.

Univariate and multivariate Cox regression analyses were used to conduct subgroup analyses. Additionally, Cox regression analyses with maximum-likelihood estimation were used for interaction testing. The two-sided significance level was set to 0.05 and estimates are reported with 95% confidence intervals.

Results

Patient and tumor characteristics

The study population consists of a total of 1809 patients with known exact primary tumor location, including 1333 patients with known molecular characteristics (of those: 717 patients with *RAS/BRAF* wildtype tumors, 514 patients with *RAS* mutant tumors, 102 patients with *BRAF V600E* mutant tumors). An overview of contributing studies and frequency of each location is shown in Supplementary Fig. 1. Baseline characteristics of patients and tumors are summarized in Table 2. Several characteristics are significantly associated with the exact PTL. Of note, the frequency of *BRAF* mutations ranged from 10–20% among the characterized tumor specimens in the right-sided locations, whereas only approximately 3% of sigmoid and rectal specimens harboured such a mutation. In contrast, the frequency of *RAS* mutations is also pronounced in right-sided tumors and appears to decrease from right to left, but peaking again in rectal tumors. A graphical overview of baseline and tumor characteristics of interest with significant differences according to exact PTL is provided as supplementary Fig. 2.

Table 2
Patient and tumor characteristics

characteristic	Caecum	C. asc.	R. flexure + C. trans.	L. flexure + C. desc.	Sigmoid	Rectum
	(n = 158)	(n = 186)	(n = 107)	(n = 126)	(n = 520)	(n = 712)
Study						
FIRE-1	30 (19.0%)	25 (13.4%)	27 (25.2%)	31 (24.6%)	121 (23.3%)	189 (26.5%)
CIOX	21 (13.3%)	21 (11.3%)	12 (11.2%)	12 (9.5%)	50 (9.6%)	61 (8.6%)
FIRE-3	51 (32.3%)	90 (48.4%)	30 (28.0%)	53 (42.1%)	231 (44.4%)	273 (38.3%)
XELAVIRI	47 (29.7%)	47 (25.3%)	33 (30.8%)	25 (19.8%)	83 (16.0%)	155 (21.8%)
VOLFI	9 (5.7%)	3 (1.6%)	5 (4.7%)	5 (4.0%)	35 (6.7%)	34 (4.8%)
RAS/BRAF status						
RAS/BRAF WT	40 (25.3%)	60 (32.3%)	37 (34.6%)	54 (42.9%)	250 (48.1%)	276 (38.8%)
RAS MT	67 (42.4%)	60 (32.3%)	30 (28.0%)	36 (28.6%)	102 (19.6%)	219 (30.8%)
BRAF MT	14 (8.9%)	25 (13.4%)	16 (15.0%)	11 (8.7%)	15 (2.9%)	21 (2.9%)
unknown	37 (23.4%)	41 (22.0%)	24 (22.4%)	25 (19.8%)	153 (29.4%)	196 (27.5%)
Antibody						
none	33 (20.9%)	28 (15.1%)	29 (27.1%)	34 (27.0%)	135 (26.0%)	196 (27.5%)
anti-EGFR	51 (32.3%)	62 (33.3%)	27 (25.2%)	44 (34.9%)	184 (35.4%)	236 (33.1%)
anti-VEGF	74 (46.8%)	96 (51.6%)	51 (47.7%)	48 (38.1%)	201 (38.7%)	280 (39.3%)
Sex						
male	92 (58.2%)	123 (66.1%)	65 (60.7%)	88 (69.8%)	347 (66.7%)	523 (73.5%)
female	66 (41.8%)	63 (33.9%)	42 (39.3%)	38 (30.2%)	173 (33.3%)	189 (26.5%)

characteristic	Caecum	C. asc.	R. flexure + C. trans.	L. flexure + C. desc.	Sigmoid	Rectum
Age (years) Median (range)	65 (31–87)	67 (32–84)	66 (22–88)	66 (25–84)	64 (32–81)	64 (27–86)
≤ 60	50 (31.6%)	53 (28.5%)	25 (23.4%)	38 (30.2%)	191 (36.7%)	261 (36.7%)
> 60-≤70	63 (39.9%)	75 (40.3%)	45 (42.1%)	54 (42.9%)	209 (40.2%)	296 (41.6%)
> 70	45 (28.5%)	58 (31.2%)	37 (34.6%)	34 (27.0%)	120 (23.1%)	155 (29.8%)
ECOG						
0	98 (62.0%)	95 (51.1%)	57 (53.3%)	65 (51.6%)	321 (61.7%)	449 (63.0%)
1	53 (33.5%)	78 (41.9%)	46 (43.0%)	54 (42.9%)	179 (34.4%)	234 (32.9%)
2	7 (4.4%)	13 (7.0%)	4 (3.7%)	5 (4.0%)	18 (3.5%)	25 (3.5%)
unknown	0 (0%)	0 (%)	0 (0%)	2 (1.6%)	2 (0.4%)	4 (5.6%)
Metastatic spread						
liver	122 (77.2%)	145 (78.0%)	89 (83.2%)	107 (85.0%)	450 (86.5%)	527 (74.1%)
liver-limited	54 (34.2%)	56 (30.1%)	40 (37.4%)	58 (46.0%)	199 (38.3%)	219 (30.8%)
lung	53 (33.5%)	63 (33.9%)	29 (27.1%)	28 (22.2%)	165 (31.7%)	328 (46.1%)
lymph nodes	51 (32.3%)	77 (41.4%)	39 (36.4%)	28 (22.2%)	139 (26.7%)	190 (26.7%)
peritoneum	24 (15.2%)	15 (8.1%)	9 (8.4%)	10 (7.9%)	35 (6.7%)	18 (2.5%)
No. of metastatic sites						
1	69 (43.7%)	76 (40.9%)	47 (44.0%)	68 (54.0%)	222 (42.7%)	296 (41.6%)
2	43 (27.2%)	65 (34.9%)	30 (28.0%)	34 (27.0%)	162 (31.2%)	227 (31.9%)
3	22 (13.9%)	27 (14.5%)	18 (16.8%)	13 (10.3%)	68 (13.1%)	113 (15.9%)

characteristic	Caecum	C. asc.	R. flexure + C. trans.	L. flexure + C. desc.	Sigmoid	Rectum
≥ 4	10 (6.3%)	12 (6.5%)	4 (3.7%)	4 (3.2%)	23 (4.4%)	29 (4.1%)
unknown	14 (8.9%)	6 (3.2%)	8 (7.5%)	7 (5.6%)	45 (8.7%)	47 (6.6%)
Onset of metastases						
synchronous	97 (61.4%)	130 (69.9%)	62 (58.0%)	79 (62.7%)	321 (61.7%)	395 (55.5%)
metachronous	30 (19.0%)	31 (16.7%)	27 (25.2%)	30 (23.8%)	114 (21.9%)	217 (30.5%)
unknown	31 (19.6%)	25 (13.4%)	18 (16.8%)	17 (13.5%)	85 (16.3%)	100 (14.0%)
Previous chemotherapy						
no	127 (80.4%)	160 (86.0%)	90 (84.1%)	105 (83.3%)	430 (82.7%)	469 (65.9%)
yes	31 (19.6%)	25 (13.4%)	17 (15.9%)	21 (16.7%)	90 (17.3%)	242 (34.0%)
unknown	0 (%)	1 (0.5%)	0 (%)	0 (%)	0 (%)	1 (0.1%)

Objective responses according to exact primary tumor location and molecular subgroups

Generally, irrespective of exact therapy, objective response rates (ORR) according to exact primary tumor location were neither significantly different in the full population nor in molecular subgroups, although numerically higher response rates in left-sided exact locations may be observed in patients with *RAS/BRAF* wildtype tumors as well as in *BRAF* mutant tumors. Rather low and homogeneous ORR ranging from 33% to 46% are observed in patients with *RAS* mutant mCRC when analyzed according to exact primary tumor location. Details are summarized in supplementary figure 3. Response rates differed in molecular subgroups in general with *RAS/BRAF* wildtype mCRC (60.5%) achieving higher rates as compared to *RAS* mutant mCRC (41.4%) and *BRAF* mutant mCRC (42.2%), $P<0.001$.

Prognostic impact of exact primary tumor location

In the analyzed population, the numerically longest PFS and OS are seen in patients with primary tumors located in the left flexure, descending colon and sigmoid. Among right-sided primaries no substantial differences were detected, despite primary tumors of right flexure/transverse colon mCRC trended to be associated with the numerically shortest survival. Kaplan Meier curves for all patients are indicated in Figure 1. Uni- and multivariate comparisons of exact primary tumor location with rectal primaries used as

reference confirmed right flexure/transverse colon mCRC as the subgroups with the worst and clearly impaired prognosis in both uni- and multivariate analysis of overall survival. This finding appears to be driven by the two subgroups of patients with mutant mCRC (*RAS* and *BRAF V600E*). Please refer to Suppl. Figure 4 for details.

Predictive impact of exact primary tumor location in patients with *RAS/BRAF* wildtype and BRAF mutant tumors

The predictive effect of exact primary tumor location for anti-EGFR was explored in uni- and multivariate analyses (Kaplan Meier estimates of overall survival in Figure 2; logistic and Cox regressions in Figure 3). ORR appeared to be influenced by exact primary tumor location with left sided locations being associated with a higher chance to achieve objective response to treatment. This observation was evident in both *RAS/BRAF* wildtype mCRC as well as in *BRAF* mutant mCRC. Clear benefit with anti-EGFR antibodies in terms of ORR was notably seen in left-sided mCRC with *BRAF* mutation in uni- as well as multivariate analyses.

In terms of PFS, a detrimental effect of anti-EGFR antibodies in patients with caecal *RAS/BRAF* wildtype mCRC as well as in patients caecal with *BRAF* mutant mCRC was demonstrated, whereas no significant differences in all other segments were evident with rather neutral (trend towards benefit in *BRAF* mutant mCRC) effects evolving with more distal primary tumor location. However, OS in *RAS/BRAF* wildtype mCRC appeared continuously improved with anti-EGFR antibodies the further distal the primary tumor was located. Whereas in patients with caecal primaries the usage of anti-EGFR antibodies resulted in a significant detrimental effect, neutral efficacy was seen in the continuity of the colon towards the sigmoid. The only subgroups demonstrating a clear benefit with anti-EGFR antibody treatment are patients with primaries located in sigmoid and rectal. Rectal PTL achieving the greatest benefit (hazard ratio for death: 0.58 (95% CI 0.43-0.77)). A similar pattern is observed in patients with *BRAF* mutant mCRC. An exploratory analysis in left- and right-sided *BRAF* mutant mCRC concerning anti-EGFR effects on OS suggests a significant benefit in favor of therapy with anti-EGFR antibodies in patients with left-sided, *BRAF* mutant mCRC. This is confirmed by both uni- and multivariate analysis and further confirmed by a significant interaction test (*P* for interaction=0.001). Please refer to Figures 2 and 3 for details. The interaction of PTL and anti-EGFR antibody efficacy is also present if the analysis is restricted to patients with *BRAF* mutant tumors from FIRE-3 and VOLFI representing the purest population as they contained direct randomization of anti-EGFR-antibodies (*P* for interaction: 0.003). Kaplan Meier curves of the FIRE-3/VOLFI subset are shown as Suppl. Figure 5. No trends towards favourable outcomes with the use of anti-EGFR antibodies were observed in patients with *RAS* mutant mCRC (data not shown).

Discussion

The presented analysis based on five randomized trials including data from 1809 individual patients represents a large and robust basis to evaluate the prognostic and predictive effects of the exact primary tumor location in mCRC.

Whereas the usual differentiation between left- vs. right colorectal cancer is a known predictor of OS in mCRC [1, 4, 22], our analysis suggests that certain differences between the exact segments may exist. Of interest, a clearly dismal prognosis (as compared to primary tumors of the rectum) was detected in patients with mCRC deriving from primaries of the right flexure/transverse colon. Similar trends of borderline significance in multivariate analyses were observed in patients with primaries in the caecum or ascending colon. Amongst patients with left-sided tumors, differences in outcome were not significantly different, although patients with rectal primaries appeared to achieve a numerically shorter OS as compared to patients with primaries of left flexure/descending colon and sigmoid. The small advantage of sigmoid vs. rectal carcinoma might be influenced by a smaller proportion of patients with *RAS* mutant mCRC in patients with sigmoid carcinoma (28% of tested specimens) as compared to patients with rectal cancer (42% of tested specimens) in context of a low frequency of *BRAF V600E* mutant tumors with dismal prognosis [23, 24] in both segments.

The effect of anti-EGFR antibodies did not impact on PFS in our cohort, illustrating - in accordance with previous publications - that PFS does not necessarily reflect the efficacy of these drugs [19, 25, 26] and anti-EGFR antibodies may rather impact response related endpoints and OS [15, 19, 27–29].

Clear effects of exact primary tumor location on overall survival were observed in patients with *RAS/BRAF* wildtype tumors. Interestingly, patients with primary tumors of the caecum derived a substantial disadvantage with anti-EGFR therapy, whereas substantial benefit was seen in patients with rectal cancers and - to a lesser extent - in patients with sigmoid primaries. Taken together, the data suggests a continuous increase of benefit from anti-EGFR antibodies from proximal (right) to distal (left) rather than the currently established dichotomous perspective of left (benefit from anti-EGFR) vs. right (no benefit from anti-EGFR) colorectal cancer [1, 2]. This perspective is supported by molecular analysis of colorectal tumors that rather proposes a continuum of biological changes from proximal to distal segments of colon and rectum [6, 10]. Based on these findings, treatment of rectal and sigmoid *RAS/BRAF* wildtype mCRC with anti-EGFR-antibodies appears a clinical necessity. Particularly, mCRC patients with primaries in the rectum may achieve an enormous advantage with anti-EGFR-targeted therapy, and patients with mCRC with primaries in the sigmoid achieve a clinically relevant advantage.

Interestingly, in patients with *BRAF* mutant mCRC a similar pattern of increasing anti-EGFR antibody therapy efficacy from proximal to distal was found in the segment by segment analysis. Whereas right-sided tumors achieved no benefit, left-sided tumors appeared to benefit from anti-EGFR therapy in our population. This finding was confirmed by a multivariate analysis and a significant interaction test.

The idea that left-sided *BRAF* mutant tumors may respond to anti-EGFR treatment is further supported by an increased ORR and prolonged OS in the absence of clinically relevant effects on PFS in this data set. This combination has been frequently observed in an evidently anti-EGFR sensitive population (i.e. *RAS/BRAF* wildtype mCRC) [1–3, 19].

Therefore, it could be hypothesized that *BRAF* mutation may not predict lack of anti-EGFR antibody efficacy. In turn, our findings suggest that patients with *BRAF* mutant mCRC arising from left-sided

primary tumors benefit to a similar extent from anti-EGFR antibodies as compared to *RAS/BRAF* wildtype tumors and should consecutively receive these drugs as part of first-line therapy. It needs to be noted that the sample size of this pooled analysis is too limited to draw definite conclusions on the benefit according to exact PTL (i.e. left flexure/descending colon, sigmoid and rectum).

Our findings are in contrast to reports that identified classical *BRAF V600E* mutations as likely negative predictors of anti-EGFR directed therapy [30–32]. However, it could be argued that these publications did not adjust their analyses for PTL and are consecutively biased by the relative over-representation of *BRAF* mutations in right-sided colon segments [33], a circumstance that is also present in our population. Consecutively, current guideline recommendations [34] do not recommend anti-EGFR-targeted antibodies as part of first-line therapy and cetuximab is currently used rather as combination partner for a *BRAF* inhibitor in refractory patients [35]. Accordingly, our finding in this particular subgroup challenges the actual treatment algorithm and needs confirmation from further trials with direct anti-EGFR-antibody randomisation such as CRYSTAL, PRIME, OPUS, CALGB/SWOG 80405 and PEAK [23, 36–38].

Challenging the idea of dichotomous left-right classification in mCRC, our hypothesis of a continuous increase in anti-EGFR therapy related benefit from proximal to distal parts of the colorectum supports the idea that the underlying molecular equivalent is likely a non-dichotomous biomarker (combination), potentially including EGFR- ligands, HER-3 messenger RNA or miR-31-3p [39–42].

Our pooled analysis is limited by its retrospective and exploratory design as well as by the low patient numbers in segments of the colon with an overall low frequency of primary tumors. Furthermore, a pool of five studies (of those two directly randomizing the anti-EGFR antibody) using various treatment regimens and therefore, containing heterogeneous populations may have invoked potential undetected biases.

Conclusions

In our analysis, the exact primary tumor location of mCRC impacts prognosis and is also associated with increasing anti-EGFR efficacy in a continuous pattern from proximal to distal segments of the colorectum in patients with *RAS/BRAF* wildtype tumors. Similarly, patients with *BRAF* mutant mCRC originating from distal segments of the colorectum may benefit from first-line anti-EGFR-based therapy.

List Of Abbreviations

anti-EGFR, anti-epithelial growth factor receptor; anti-VEGFR, anti–vascular endothelial growth factor; HR, hazard ratio; mCRC, metastatic colorectal cancer; OR, objective response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PTL, primary tumor location.

Declarations

Ethics approval and consent to participate

All trials were conducted according to the Declaration of Helsinki and were approved by ethics committees.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

Annabel Helga Sophie Alig:

Travel, Accommodations, Expenses: Pfizer, Roche, Eli Lilly, Novartis, PharmaMar

Consulting or Advisory Role: Roche

Volker Heinemann:

Honoraria: Roche, Celgene, Amgen, Sanofi, Merck, Sirtex Medical, Baxalta, Eli Lilly, Boehringer Ingelheim, Taiho Pharmaceutical, Servier

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Michael Geissler:

Consulting or Advisory Role: Amgen, Lilly, Merck and Serono

Travel, Accommodations, Expenses: Amgen

Ludwig Fischer von Weikersthal:

Honoraria: Novartis, Roche, Sanofi

Travel, Accommodations, Expenses: Amgen

Thomas Decker:

Consulting or Advisory Role: Novartis

Kathrin Heinrich:

Honoraria: Roche

Travel, Accommodations, Expenses: AMGEN, Celgene, Lilly

Swantje Held:

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Arndt Stahler:

Honoraria: Roche

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Ivan Jelas:

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Annika Kurreck:

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Conception and design: AHSA, VH, SS, DPM

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Data analysis and interpretation: All authors

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Accountable for all aspects of the work: All authors

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Figures

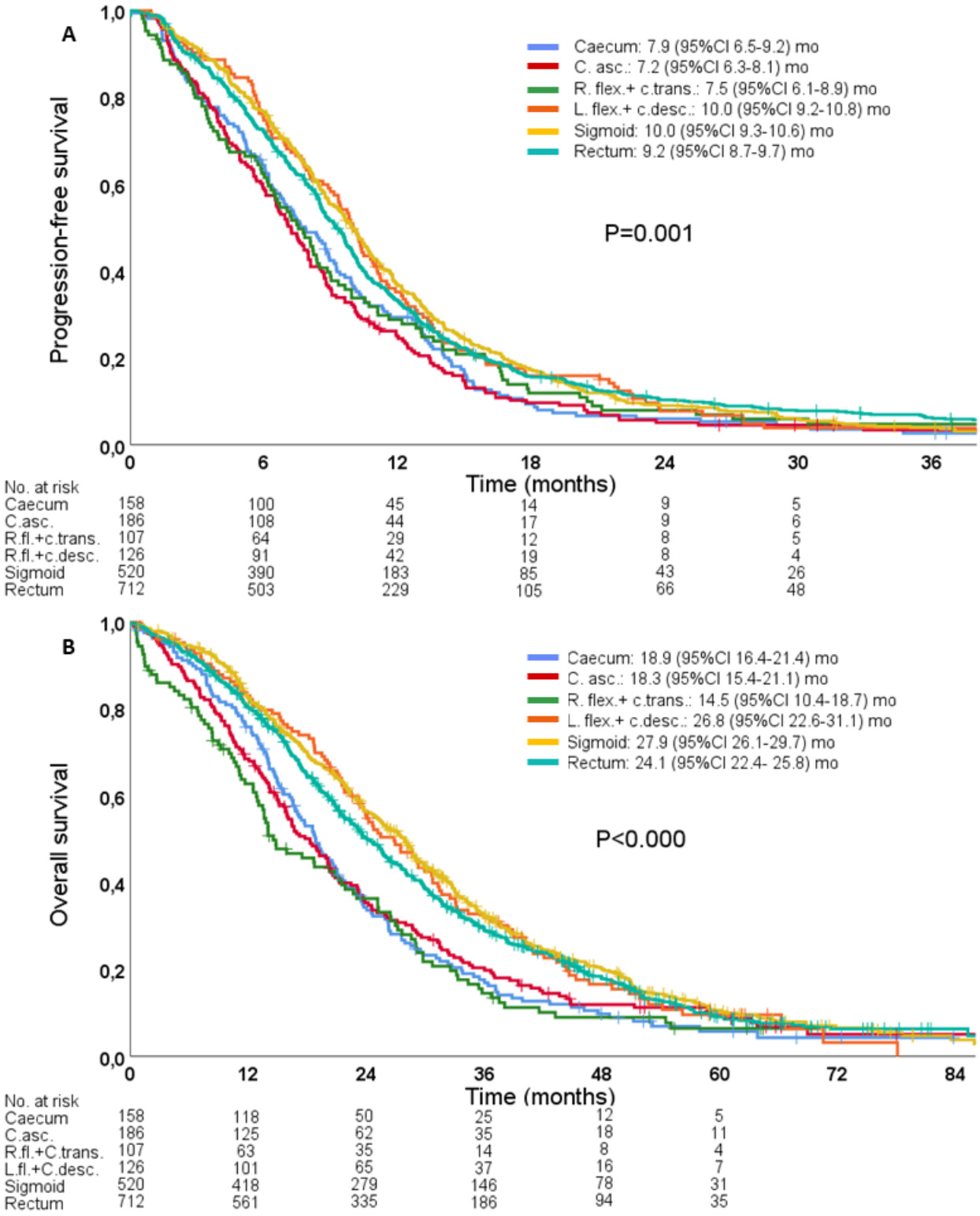

Figure 1

Kaplan Meier estimates of progression-free survival and overall survival according to exact PTL Legend: A) progression-free survival, B) Overall survival. C. asc.= ascending colon, r. flex./r.fl.=right flexure, l. flex/l.fl.=left flexure, c. trans=transverse colon, c. desc.=descending colon. P-values: log rank test.

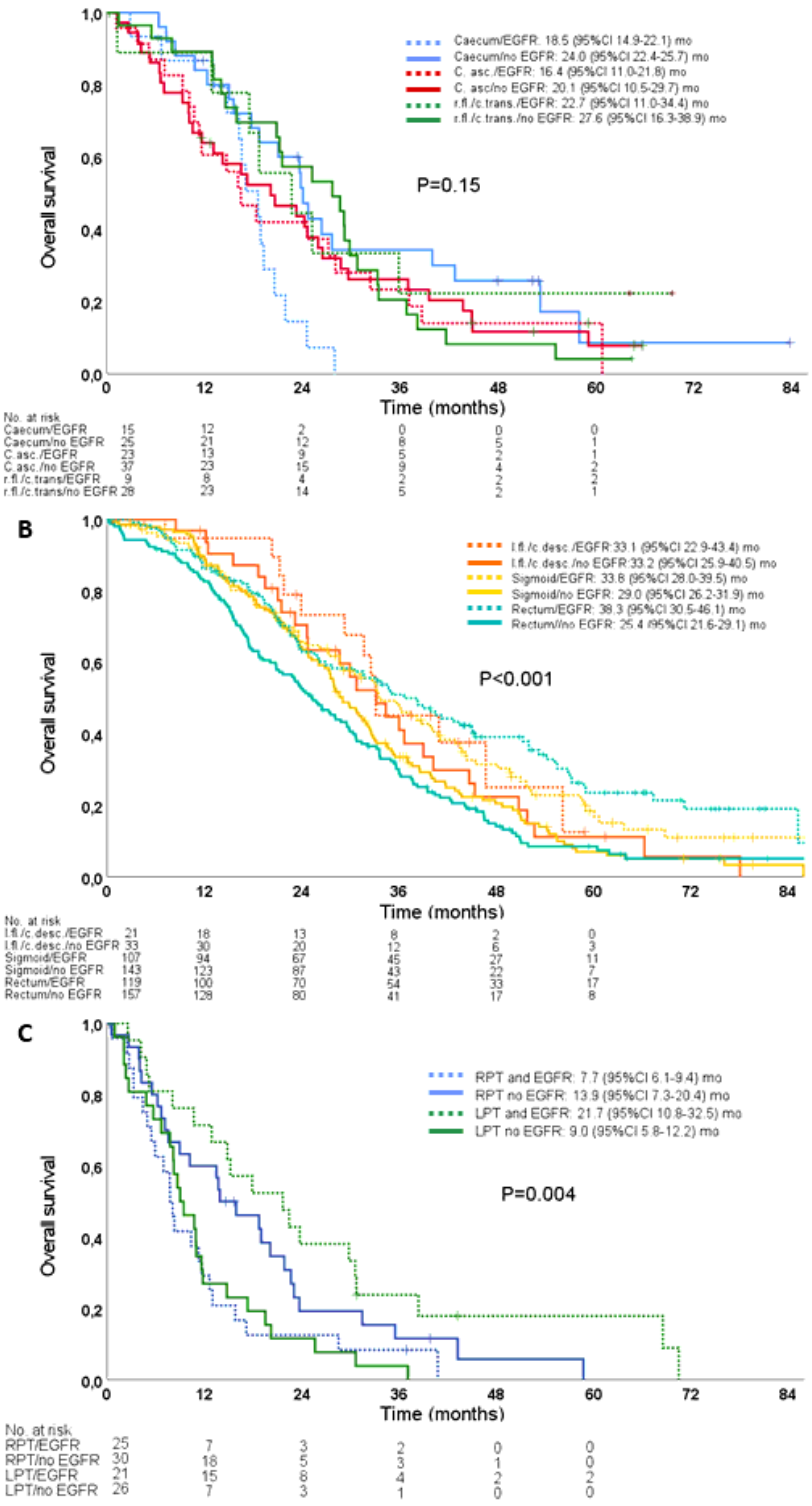

Figure 2

Kaplan Meier estimates of overall survival according to use of EGFR antibodies stratified by PTL Legend: A) RAS/BRAF WT right-sided primary tumor locations by EGFR-mAb use B) RAS/BRAF WT left-sided primary tumor locations by EGFR-mAb use, C) BRAF MT left- vs- right primary tumors by EGFR-mAb use.

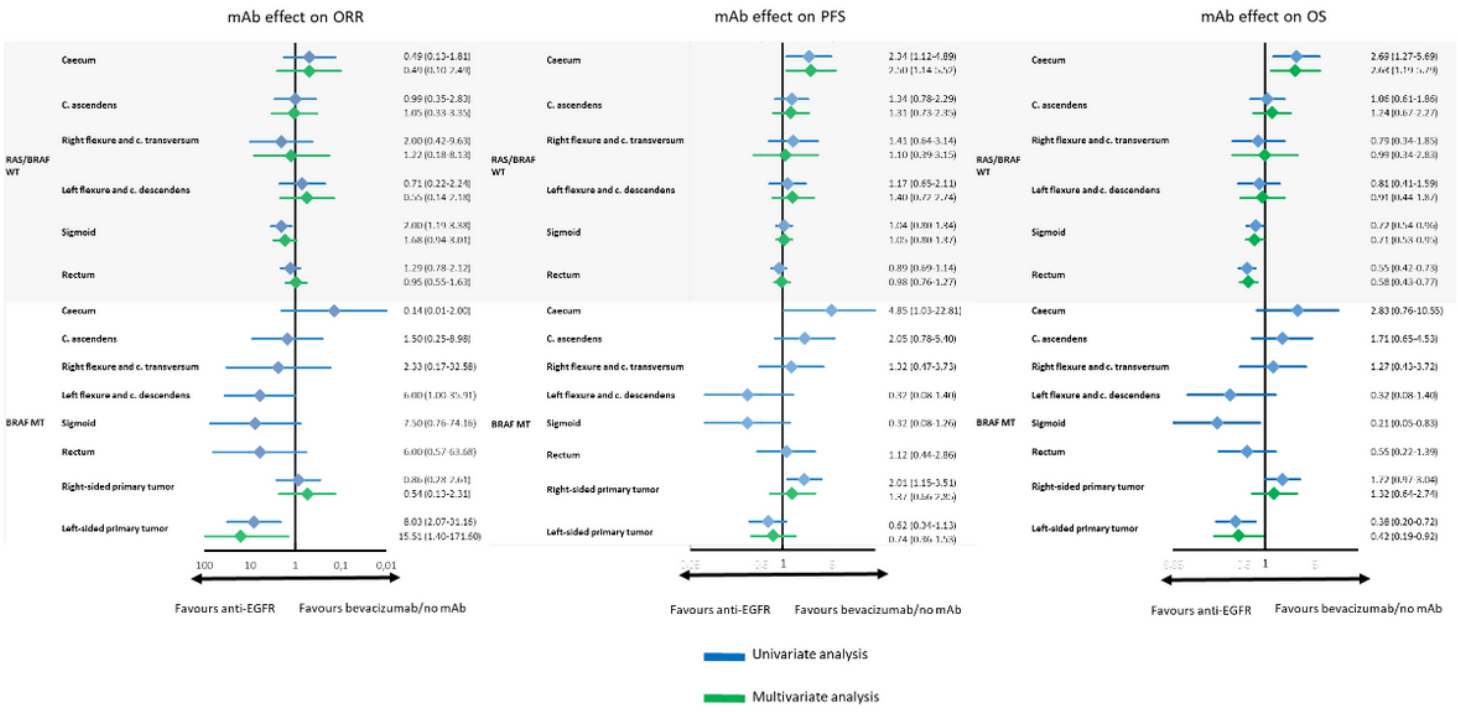

Figure 3

Forest plots of estimated anti-EGFR effect according to exact primary tumor location Legend: Uni- and multivariate analyses of anti-EGFR effect. Segment by segment analyses in patients with BRAF mutant mCRC were not performed due to insufficient numbers and resulting low fit of the models. Multivariate analyses of progression-free survival and overall survival included as factors: study, sex, age, ECOG performance status, liver-limited disease, peritoneal metastasis, prior adjuvant chemotherapy. Multivariate analyses of objective response rate included sex, age, ECOG performance status, liver-limited disease, peritoneal metastasis, prior adjuvant chemotherapy. ORR=objective response rate; PFS=progression free survival; OS=overall survival; mAb=monoclonal antibody

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