European Journal of Cancer 70 (2017) 87–98

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejcancer.com

Original Research

The relevance of primary tumour location in patients with metastatic colorectal cancer: A meta-analysis of first-line clinical trials

Julian Walter Holch [a,b,*], Ingrid Ricard [c], Sebastian Stintzing [a,b], Dominik Paul Modest [a,b], Volker Heinemann [a,b]

[a] *Department of Medical Oncology, University Hospital Grosshadern, Ludwig-Maximilians-Universität München, Marchioninistrasse 15, 81377 Munich, Germany*
[b] *Comprehensive Cancer Center, University Hospital Grosshadern, Ludwig-Maximilians-Universität München, Marchioninistrasse 15, 81377 Munich, Germany*
[c] *Institute of Medical Informatics, Biometry, and Epidemiology, Ludwig-Maximilians-Universität München, Marchioninistrasse 15, 81377 Munich, Germany*

Received 16 September 2016; accepted 5 October 2016
Available online 29 November 2016

KEYWORDS
Metastatic colorectal cancer;
Primary tumour location;
Sidedness;
Prognostic biomarker;
Predictive biomarker;
Cetuximab;
Panitumumab;
Bevacizumab;
Anti-EGFR;
Anti-VEGF

Abstract ***Background:*** Retrospective subgroup analyses suggest that primary tumour location (PTL) has a prognostic importance and relates to response to targeted therapy.
Methods: We conducted a meta-analysis of first-line clinical trials available up to October 2016, which assessed the relevance of PTL in patients with metastatic colorectal cancer (mCRC). Right- and left-sided colorectal cancers were differentiated (RC and LC).
Results: In 13 first-line randomised controlled trials and one prospective pharmacogenetic study, RC was associated with a significantly worse prognosis compared with LC (hazard ratio [HR] for overall survival: 1.56; 95% confidence interval [CI]: 1.43–1.70; $P < 0.0001$). A meta-analysis of PRIME and CRYSTAL study suggests that PTL was predictive of survival benefit from addition of anti-EGFR antibody to standard chemotherapy in patients with RAS wild-type tumour (overall survival, HR for LC: 0.69; 95% CI: 0.58–0.83; $P < 0.0001$ and HR for RC: 0.96; 95% CI: 0.68–1.35; $P = 0.802$). A meta-analysis of FIRE-3/AIO KRK0306, CALGB/SWOG 80405 and PEAK study indicates that patients with RAS wild-type LC had a significantly greater survival benefit from anti-EGFR treatment compared with anti-VEGF treatment when added to standard chemotherapy (HR 0.71; 95% CI: 0.58–0.85;

* *Corresponding author*: Department of Medical Oncology and Comprehensive Cancer Center, Ludwig-Maximilians-Universität München, Marchioninistrasse 15, 81377, Munich, Germany. Fax: +49 89 4400 78698.
E-mail addresses: julian.holch@med.uni-muenchen.de (J.W. Holch), ricard@ibe.med.uni-muenchen.de (I. Ricard), sebastian.stintzing@med.uni-muenchen.de (S. Stintzing), dominik.modest@med.uni-muenchen.de (D.P. Modest), volker.heinemann@med.uni-muenchen.de (V. Heinemann).

http://dx.doi.org/10.1016/j.ejca.2016.10.007

P = 0.0003). By contrast, in patients with RC, benefit from standard therapy was poor and bevacizumab-based treatment was numerically associated with longer survival (HR 1.3; 95% CI: 0.97–1.74; P = 0.081).
Conclusions: The present meta-analysis demonstrates that PTL is prognostic in mCRC. Further, it supports the conclusion that patients with left-sided RAS wild-type mCRC should be preferentially treated with an anti-EGFR antibody. In right-sided mCRC, chemotherapy plus bevacizumab is a treatment option, but optimal treatment has yet to be defined.

1. Background

Tumours arising from different regions of the colon are clinically and molecularly distinct [1–5]. Beside differences in the luminal content (e.g. bacterial flora), this might reflect also the ontogenesis with left-sided colon tumours (LC) deriving from the embryonic hindgut and right-sided colon tumours (RC) deriving from the embryonic midgut [6,7]. As the embryological demarcation line at the distal third of the colon transversum is difficult to determine in retrospective analyses, the splenic flexure was used for differentiation of LC and RC in most of the available clinical reports. Characteristics of LC and RC differ substantially in several aspects. RC is more often found in female patients, it is more frequently characterised by higher TNM stage at first diagnosis, by mucinous histology and greater immunogenicity. It more frequently shows microsatellite instability due to a genetic or epigenetic inactivation of DNA mismatch-repair enzymes. In addition, RC more often shows activating mutations of RAS, BRAF and PIK3CA genes. In contrast, LC is characterised by a more frequent occurrence of chromosomal instability and a gene expression profile corresponding to an activation of the epithelial growth factor receptor (EGFR) pathway [1,8,9].

The differing molecular characteristics translate into a differential clinical outcome with RC displaying a markedly worse prognosis [1,8,10–21]. Nevertheless, primary tumour location (PTL) has not been used as a stratification factor in clinical trials so far.

Besides its prognostic relevance, several retrospective analyses suggest that PTL may also be predictive of treatment benefit from targeted therapy with anti-EGFR and anti-VEGF directed agents [11,19,21–26]. However, differences in study results may be attributable to sample size, heterogeneity in treatment and limited information on molecular and pathological features [14–16,27]. On this basis, the present study performed a meta-analysis of prospective clinical trials. The aims were to evaluate the prognostic and predictive relevance for targeted therapy with anti-EGFR and anti-VEGF antibodies in patients with mCRC.

2. Material and methods

2.1. Search strategy and selection criteria

A PubMed-based search including the following search terms was conducted in October 2016: colon cancer, colorectal cancer, metastatic colorectal cancer, mCRC as well as primary tumour location, left-sided tumour, right-sided tumour, sidedness. Relevant MeSH terms (Medical Subject Headings) were used where possible. No restrictions were placed on the searches. The titles and abstracts of all remaining citations were reviewed and irrelevant citations were discarded. Potentially relevant studies were retrieved in full text and assessed. Hand searches of the reference lists of the relevant reports were carried out to identify any relevant studies that were missed with the search strategy. Further, major oncological conferences such as the American Society of Clinical Oncology, European Society for Medical Oncology and World Gastrointestinal Cancer Conferences were searched manually. If multiple reports referred to the same data, the report containing the most recent data was included into the analyses. From the results obtained, first-line randomised controlled trials (RCTs) and prospective clinical trials evaluating the relevance of PTL in mCRC were selected for a meta-analytic evaluation.

2.2. Objectives

The primary objective of the meta-analysis was to evaluate the impact of PTL on overall survival (OS) and progression-free survival (PFS) in relation to the applied treatment. Overall response rate (ORR) was considered where data were available.

2.3. Analyses

Time to event outcomes (OS and PFS) were reported using medians and HRs with corresponding 95% CIs and P-values where available. For ORR, medians and odds ratios (ORs) along with 95% CIs and P-values

were reported where available. For the investigation of the impact of PTL on OS and PFS, both stratified and unstratified HRs were used, where data were available. The standard error estimates were derived from the 95% CIs. Fixed-effects (FE) models (unconditional maximum-likelihood method) and random-effects (RE) models (restricted maximum-likelihood method) were used to calculate the weighted overall HR on study-level trial data. The inverse variance of each study was used as the weight. The presence of publication and reporting bias was evaluated through the examination of funnel plots and the implementation of file drawer analyses (Rosenthal's method). Leave-one-out meta-analyses were performed as sensitivity analyses. Heterogeneity among the evaluated trials was assessed by comparing results of the FE and RE analyses. Further, the Cochran's Q-test and the I^2 statistics were computed. To evaluate an interaction effect between the relevance of PTL and treatment with anti-EGFR/anti-VEGF antibody, meta-regressions were performed. Also, follow-up time and time of recruitment were integrated in the meta-regressions to identify a potential bias. To this end, the variables recruitment and follow-up were centred to the mean before inclusion as continuous parameters in the models. If follow-up time was not mentioned explicitly, it was derived from the corresponding Kaplan–Meier plots.

The significance level was set to 0.05. All considered tests were two-sided. The analyses were performed using R 3.2.2 with the packages forestplot and metafor.

3. Results

3.1. Overview of the included trials

In a total of 13 first-line RCTs and one prospective pharmacogenetic study (PROVETTA), the role of PTL was investigated (Table 1). In these studies, the weighted overall HRs for PTL with regard to OS and PFS were evaluated (Fig. 1).

For a total of seven trials, the impact of PTL on OS and PFS within the different treatment arms was evaluable (Supplementary Fig. S1). Supplementary Table S1 shows the corresponding survival times.

Five trials reported detailed outcome of the differential treatment arms according to PTL subgroup (Table 2). Of these trials, two meta-analyses were performed according to the comparators used. First, a meta-analysis of CRYSTAL and PRIME study evaluated the predictive relevance of PTL for anti-EGFR therapy combined with standard chemotherapy (Fig. 2). Second, a meta-analysis of CALGB/SWOG 80405, FIRE-3 and PEAK study evaluated the impact of PTL on therapy with either anti-EGFR or anti-VEGF antibody combined with standard chemotherapy (Fig. 3).

For analyses evaluating the prognostic relevance of PTL (Fig. 1), the presence of a publication and reporting bias was evaluated by examination of funnel plots (Supplementary Fig. S3). The implementation of the file drawer analyses (Rosenthal's method) revealed a fail-safe number for all meta-analyses of at least 100. Leave-one-out meta-analyses were performed as sensitivity analyses. A significant impact of a single trial on the overall result was excluded with this approach.

3.2. Prognostic implications of PTL

In the evaluable studies, RC was documented in an average of 27% of the patients (18.2–41.0%). OS in patients with RC was generally poor and remained below 20 months in several studies investigating chemotherapy with and without targeted therapy (Table S1). In both FE and RE models of the meta-analysis evaluating OS, HRs were significantly adverse for RC in comparison to LC (Fig. 1A). This effect was also evident with regard to PFS (Fig. 1B). Further, the prognostic effect was similarly evident when the differential effect of PTL on outcome was considered for each treatment arm of the studies, where data were available (Supplementary Fig. S1).

Albeit the majority of the evaluated trials consistently reported a worse outcome for patients with RC, a significant heterogeneity was observed in the meta-analysis. To explain this heterogeneity, meta-regressions were performed for both OS and PFS (Supplementary Fig. S1 and S2). Beside treatment with cetuximab or bevacizumab, the follow-up intervals as well as the period of patient recruitment have been included here. The only significant predictor in these models was the use of cetuximab (in conjunction with chemotherapy) as compared with no cetuximab use (resulting in chemotherapy treatment plus bevacizumab or chemotherapy only). With the inclusion of this variable, the majority of the heterogeneity between the analysed trials ($I^2 = 46.9\%$ for OS; $P = 0.032$) could be explained resulting in a residual heterogeneity of 7.7% ($P = 0.249$). As a result of the meta-regressions, the difference in terms of OS and PFS between LC and RC was significantly greater in cetuximab-treated patients ($P = 0.005$). Of note, bevacizumab use and the other analysed variables had no significant impact on the prognostic relevance of PTL.

3.3. Predictive implications of PTL for anti-EGFR therapy

To analyse the predictive implications of PTL on targeted therapy with anti-EGFR antibody, a meta-analysis on two trials was performed (CRYSTAL and PRIME). The meta-analysis evaluated the treatment effects on OS, PFS and ORR comparing anti-EGFR therapy plus standard chemotherapy with chemotherapy only (Fig. 2). For OS, PFS and ORR, the analysis

Table 1
Summary of studies included in the meta-analysis.

Study	Biomarker population	Treatment arms	Number of patients	Percentage of patients with RC	Demarcation line of PTL	Year of initial publication	Recruitment	Follow-up (months)
NO16966 [16]	(K)RAS/BRAF unselected	CapOx/FOLFOX CapOx/FOLFOX + bev	1268	26.3	Splenic flexure	2008	2004–2005	57
FIRE-1 [12]	(K)RAS/BRAF unselected	FuFIRI mIrOx	423	19.4	Splenic flexure	2011	2000–2004	60
FOCUS [15]	(K)RAS/BRAF unselected	FU IrFu OxFu	1390	n.r.	n.r.	2009	2000–2003	150
AVF2107g [16]	(K)RAS/BRAF unselected	IFL IFL + bev	559	36.9	Splenic flexure	2004	2000–2002	33
AGITG MAX [14]	(K)RAS/BRAF unselected	Cap Cap + bev Cap + Mito + bev	440	28.2	Transverse colon (excluded)	2010	2005–2007	42
PROVETTA [16]	(K)RAS/BRAF unselected	FOLFIRI + bev	200	28.0	Splenic flexure	n.r.	n.r.	54
MAVERICC [30]	KRAS WT/ BRAF unselected	FOLFOX + bev FOLFIRI + bev	376	41.0	n.r.	n.r.	n.r.	18.4
FIRE-2 [13]	KRAS WT/ BRAF unselected	CapOx + cet CapIri + cet	146	31.5	Splenic flexure	2011	2004–2006	60
JACCRO-CC 05/06 [18]	KRAS WT/ BRAF unselected	FOLFOX/SOX + cet	110	18.2	Splenic flexure	2016	2010–2013	48
CRYSTAL [21]	RAS WT/ BRAF unselected	FOLFIRI FOLFIRI + cet	364	23.1	Splenic flexure	2009	2004–2005	60
PRIME [29]	RAS WT/ BRAF unselected	FOLFOX FOLFOX + pani	416	21.2	Splenic flexure	2010	2006–2008	68
CALGB/SWOG 80405 [19]	RAS WT/ BRAF unselected	FOLFOX/FOLFIRI + bev FOLFOX/FOLFIRI + cet	474	31.4	Transverse colon (excluded)	n.r.	2005–2012	108
FIRE-3 [21]	RAS WT/ BRAF unselected	FOLFIRI + cet FOLFIRI + bev	394	22.3	Splenic flexure	2014	2007–2012	72
PEAK [29]	RAS WT/ BRAF unselected	FOLFOX + bev FOLFOX + pani	143	25.2	Splenic flexure	2014	2009–2011	68

Abbreviations: PTL, primary tumour location; LC, left-sided colorectal cancer; RC, right-sided colorectal cancer; WT, wild-type; Cap, capecitabine; F(U), fluorouracil; FOL, folinic acid; I(RI), irinotecan; OX, oxaliplatin; Mito, mitomycin C; S, teysuno (S1); L, leucovorin; bev, bevacizumab; cet, cetuximab; pani, panitumumab; n.r., not reported.

revealed a significant benefit from first-line anti-EGFR treatment only for patients with RAS wild-type LC. The interaction between PTL and treatment benefit from anti-EGFR antibody was evaluated by comparison of HRs for RC and LC using a meta-regression (Supplementary Figure S4). A trend for interaction was observed only for OS (P = 0.10), but not for PFS (P = 0.3) and ORR (P = 0.2).

3.4. Impact of PTL on targeted therapy with either anti-EGFR or anti-VEGF antibody

To further analyse the impact of PTL on targeted therapy, a meta-analysis on three trials was performed evaluating PTL in the comparative setting of first-line anti-EGFR versus anti-VEGF antibody in combination with standard chemotherapy: FIRE-3, CALGB/SWOG 80405 and PEAK. In RAS wild-type LC, the meta-analysis revealed a significant benefit from first-line anti-EGFR treatment with regard to OS and ORR, but not for PFS (Fig. 3). In RC, by contrast, the HRs favoured bevacizumab-based treatment in the head-to-head comparison with anti-EGFR antibody. The results were significant for PFS (HR: 1.53; 95% CI: 1.16–2.01; P = 0.003), whereas results for OS did not reach the level of significance (HR: 1.3; 95% CI = 0.97–1.74; P = 0.081). Of note, the overall odds ratio for ORR numerically favoured anti-EGFR–based treatment in patients with RC. The meta-regression evaluating the interaction between PTL and treatment with either anti-VEGF or anti-EGFR antibodies showed a significant interaction for OS (P < 0.001) and PFS (P < 0.001), but not for ORR (P = 0.41; Supplementary Figure S5). Considering

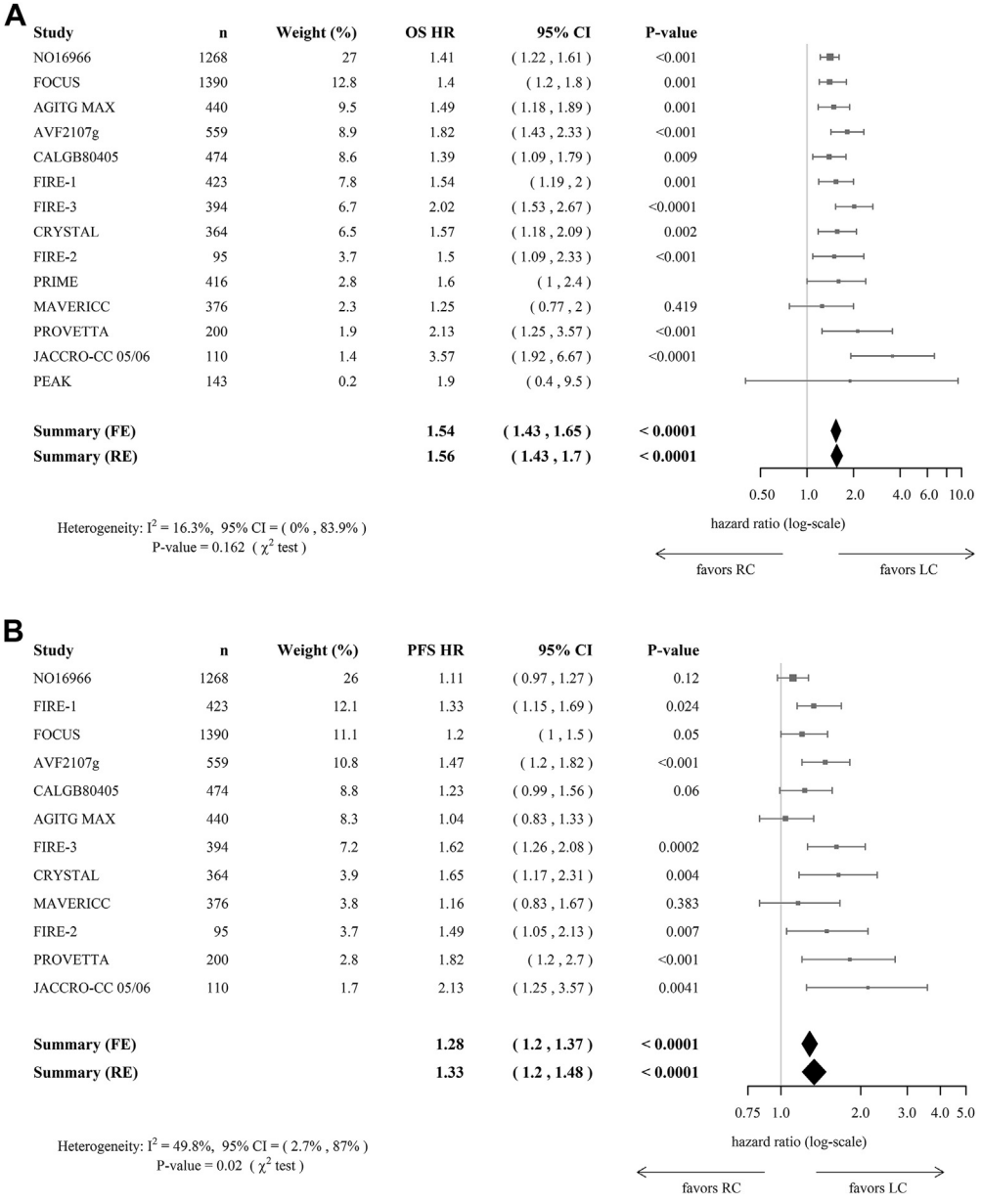

Fig. 1. Forest plots showing hazard ratio (HR) for overall survival (OS; A) and progression-free survival (PFS; B) comparing subgroups defined by primary tumour location (PTL). **Caption**: n = number of patients; CI = confidence interval; RC = right-sided colorectal cancer; LC = left-sided colorectal cancer; n.r. = not reported; FE = fixed-effects model; RE = random-effects model.

results of patients with RAS- and BRAF-wild-type tumours, no significant changes compared with the RAS wild-type selected population was evident for the single evaluated trials (Supplementary Table S2) [32,33].

4. Discussion

Previous reports have suggested that PTL has prognostic implications and impacts on response to targeted therapy in patients with mCRC. Nevertheless, these analyses are limited by sample size and heterogeneity of molecular subgroups and treatments. The presented meta-analysis summarises the available evidence from clinical studies and investigates the prognostic and predictive relevance of PTL.

The data clearly indicate that RC is associated with an inferior prognosis compared to LC. In the RE model for OS, this is reflected by a clinically relevant HR of 1.56 (95% CI: 1.43–1.70; $P < 0.0001$). The clear prognostic effect was evident for first-line chemotherapy alone and chemotherapy plus targeted therapy.

To evaluate the predictive relevance of PTL with regard to efficacy of anti-EGFR targeted therapy, a meta-analysis of studies (PRIME and CRYSTAL) comparing

Table 2
Treatment effects within subgroups defined by primary tumour location (PTL) in patients with RAS wild-type metastatic colorectal cancer.

Study	Treatment arms	Number of patients	OS (months)	HR OS	95% CI	P-Value	PFS (months)	HR PFS	95% CI	P-Value	ORR (%)	OR	95% CI	P-Value
Left-sided colorectal cancer														
CRYSTAL [21]	FOLFIRI	138	21.7	0.65	0.50–0.86	0.02	8.9	0.50	0.34–0.72	<0.001	40.6	3.99	2.40–6.62	<0.001
	FOLFIRI + cet	142	28.7				12.0				72.5			
PRIME [29,31]	FOLFOX	159	23.6	0.73	0.57–0.93	n.r.	9.2	0.72	0.57–0.90	n.r.	53	1.9	1.3–2.7	n.r.
	FOLFOX + pani	169	30.3				12.9				68			
CALGB/SWOG	FOLFOX/FOLFIRI + bev	152	32.6	0.77	0.59–0.99	0.04	11.2	0.84	0.66–1.06	0.15	–	1.6	1.2–2.3	n.r.
80405 [19,31]	FOLFOX/FOLFIRI + cet	173	39.3				12.7				–			
FIRE-3 [21]	FOLFIRI + bev	149	28.0	0.63	0.48–0.85	0.002	10.7	0.90	0.71–1.14	0.38	61.7	1.37	0.85–2.19	0.23
	FOLFIRI + cet	157	38.3				10.7				68.8			
PEAK [29,31]	FOLFOX + pani	53	43.4	0.84	0.22–3.27	n.r.	14.6	0.65	0.21–2.0	n.r.	64	1.3	0.7–2.5	n.r.
	FOLFOX + bev	54	32.0				11.5				57			
Right-sided colorectal cancer														
CRYSTAL [21]	FOLFIRI	51	15.0	1.08	0.65–1.81	0.76	7.1	0.87	0.47–1.62	0.66	33.3	1.45	0.58–3.46	0.43
	FOLFIRI + cet	33	18.5				8.1				42.4			
PRIME [29,31]	FOLFOX	49	15.4	0.87	0.55–1.37	n.r.	7.0	0.80	0.50–1.26	n.r.	35	1.4	0.6–3.1	n.r.
	FOLFOX + pani	39	11.1				7.5				42			
CALGB/SWOG	FOLFOX/FOLFIRI + bev	78	29.2	1.36	0.93–1.99	0.10	10.2	1.64	1.15–2.36	0.006	n.r.	1.1	0.6–2.0	n.r.
80405 [19,31]	FOLFOX/FOLFIRI + cet	71	13.7				7.5				n.r.			
FIRE-3 [21]	FOLFIRI + bev	50	23.0	1.31	0.81–2.11	0.28	9.0	1.44	0.92–2.26	0.11	50.0	1.11	0.48–2.59	0.83
	FOLFIRI + cet	38	18.3				7.6				52.6			
PEAK [29,31]	FOLFOX + pani	22	17.5	0.45	0.08–2.49	n.r.	8.7	0.84	0.18–3.79	n.r.	63	1.8	0.6–5.4	n.r.
	FOLFOX + bev	14	21.0				12.6				50			

Abbreviations: OS, overall survival; PFS, progression-free survival; HR, hazard ratio; ORR, overall response rate; OR, odds ratio; CI, confidence interval; WT, wild-type; FOL, folinic acid; F, fluorouracil; IRI, irinotecan; OX, oxaliplatin; bev, bevacizumab; cet, cetuximab; pani, panitumumab; n.r., not reported.
All patients were RAS wild-type and unselected with regard to BRAF mutation status.

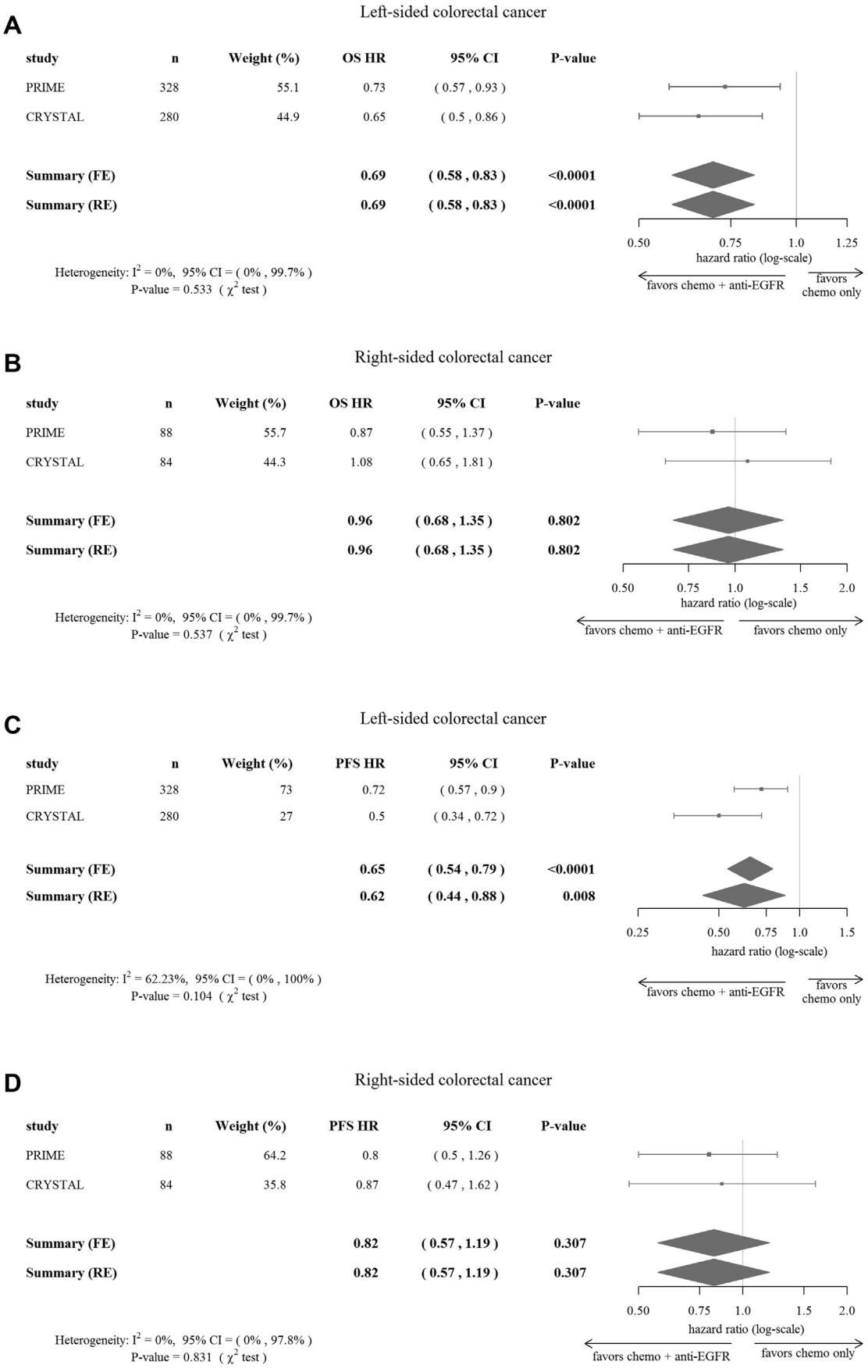

Fig. 2. Forest plots showing hazard ratio (HR) for overall survival (OS; A–B), progression-free survival (PFS; C–D) and overall response rate (ORR; E–F) comparing standard chemotherapy plus anti-EGFR antibody with chemotherapy only for the subgroups of left-sided and right-sided colorectal cancer. **Caption**: FE = fixed-effects model; RE = random-effects model.

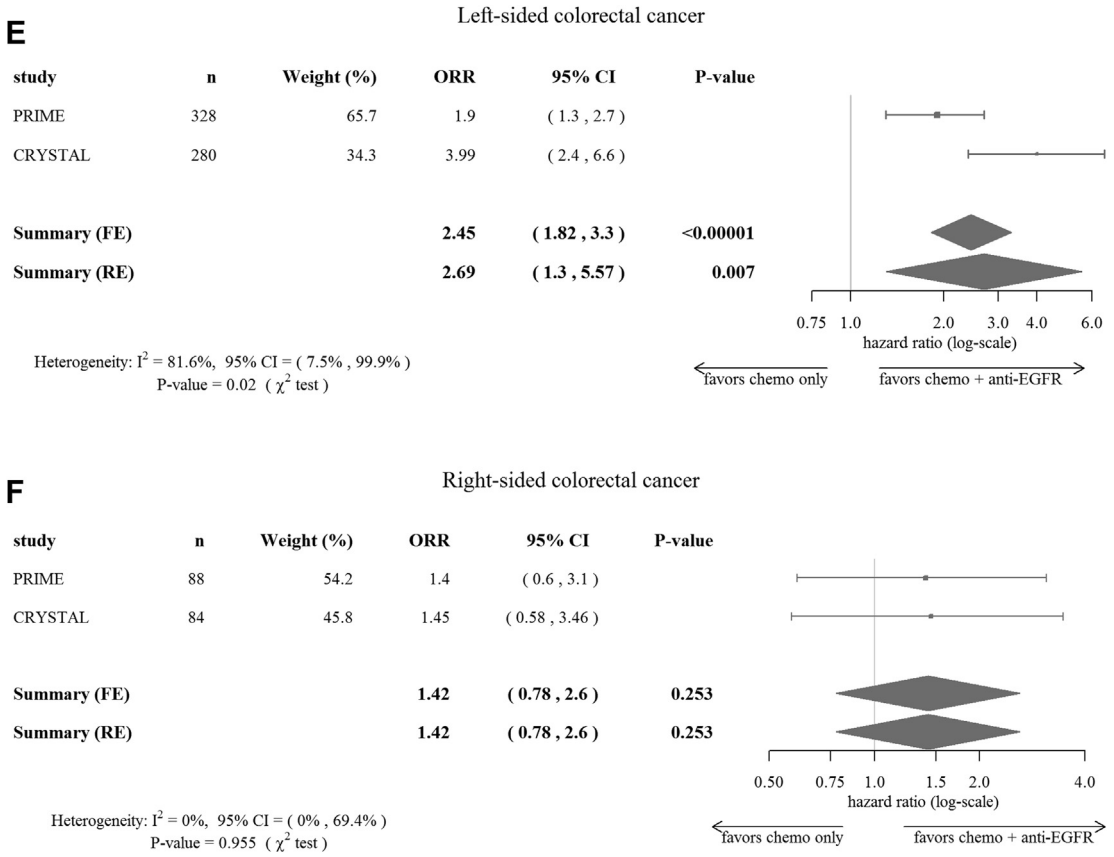

Fig. 2. (*continued*).

chemotherapy plus anti-EGFR agents to chemotherapy alone was performed. The evidence clearly demonstrates that the benefit from anti-EGFR–based therapy was markedly greater in RAS wild-type LC compared to RC. Most likely due to the limited sample size, a significant interaction between PTL and treatment benefit from anti-EGFR therapy could not be observed.

In the head-to-head comparison of anti-EGFR and anti-VEGF therapy, patients with RAS wild-type LC had a markedly greater benefit from anti-EGFR–based therapy. A significant interaction between PTL and treatment effect could be observed for OS and PFS, but not for ORR. While BRAF mutant tumours expectedly occurred more frequently in RC, results from patients with RAS- and BRAF-wild-type tumours did not differ significantly compared with those obtained from patients selected for RAS wild-type only. We therefore limited our analysis to patients with RAS wild-type tumours without additionally considering BRAF mutation status. In summary, LC appears to be a positive predictive factor for survival benefit from anti-EGFR treatment in patients with RAS wild-type tumours.

By contrast, in RC response to standard chemotherapy and targeted therapy was generally poor. In the head-to-head comparisons, anti-VEGF-based therapy was associated with a more favourable outcome with regard to PFS and OS. Interestingly enough, the reverse was found for ORR, where, at least numerically, the overall odds ratio favoured anti-EGFR–based treatment. Due to the limited sample size, the findings in regard of RC are less strong and require further investigation. While an interaction of PTL with efficacy of bevacizumab has not been demonstrated, the additive effect of anti-VEGF therapy on survival time in RC has not been shown in quantitative terms [28].

A prognostic relevance of PTL has also been shown in the study 20050181 comparing second-line treatment with either FOLFIRI alone or in combination with panitumumab [29]. It was of interest to note that two studies investigating PTL in later-line treatment (PICCOLO and NCIC CO.17) did not indicate a prognostic relevance of sidedness for OS and PFS [15,23]. PICCOLO investigated second-line and third-line treatment with Irinotecan either alone or plus panitumumab and NCIC CO.17 evaluated cetuximab versus best supportive care in chemotherapy refractory mCRC patients. These observations are likely attributable to patient selection in later-line studies, where patients with initially poor prognosis are naturally excluded.

Regarding the predictive relevance of PTL in the study 20050181, the limited number for patients with RC hampered an evaluation [29]. In the setting of later-line treatment, the predictive relevance of PTL for efficacy of anti-EGFR antibodies is controversial. Data from the PICCOLO study suggest that patients with RC and LC

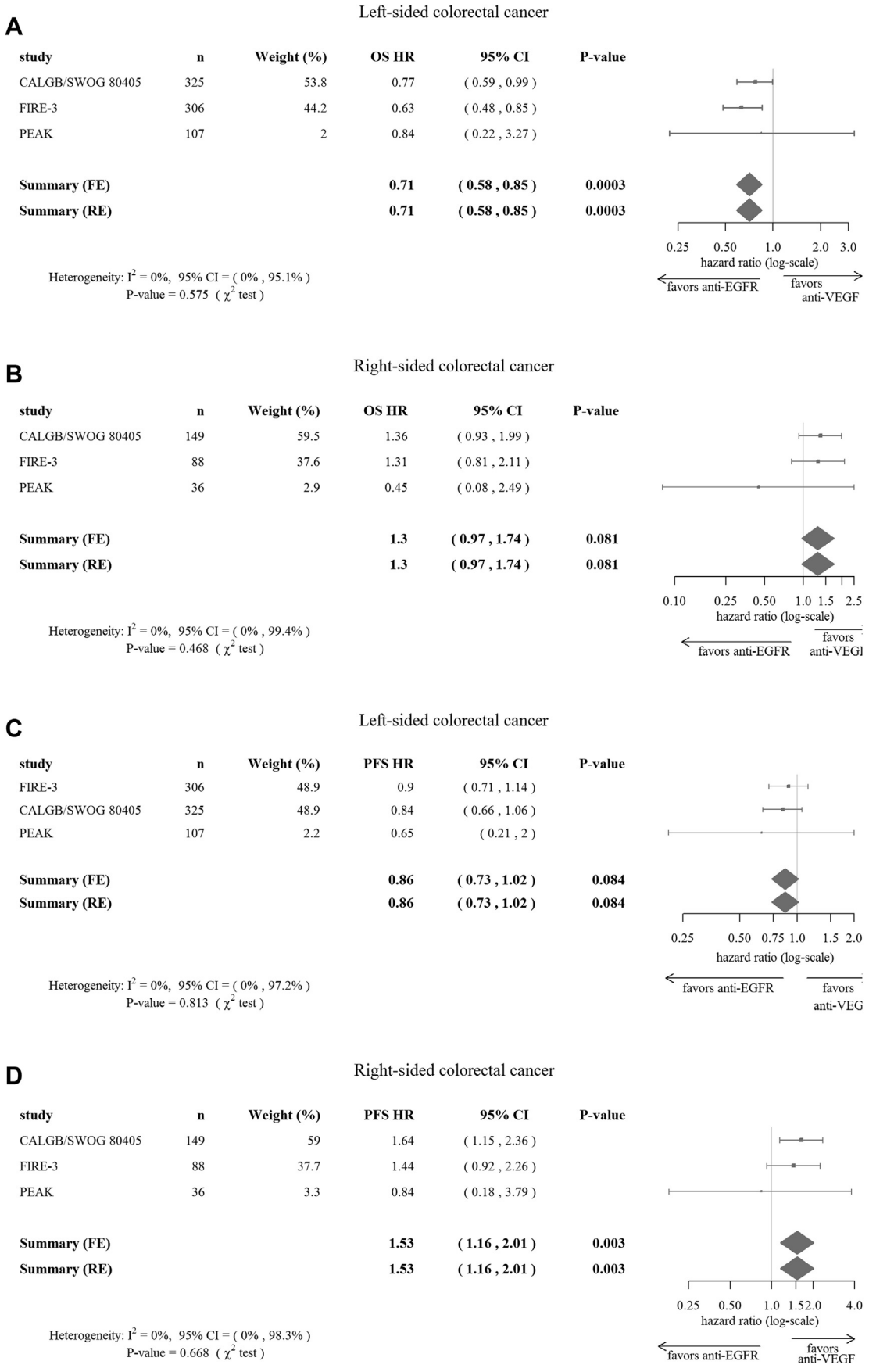

Fig. 3. Forest plots showing hazard ratio (HR) for overall survival (OS; A–B), progression-free survival (PFS; C–D) and overall response rate (ORR; E–F) comparing standard chemotherapy plus either anti-EGFR antibody or anti-VEGF antibody for the subgroup of left-sided and right-sided colorectal cancer. **Caption:** FE = fixed-effects model; RE = random-effects model.

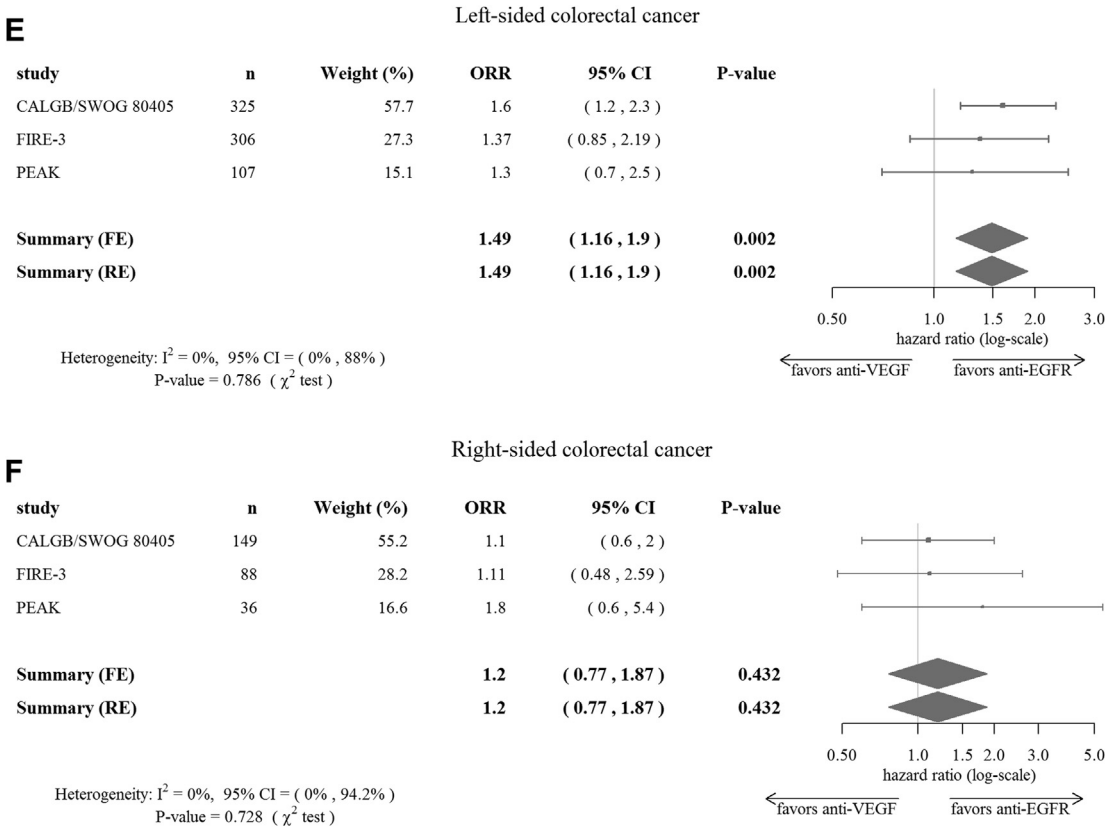

Fig. 3. (*continued*).

equally benefit from addition of panitumumab to second or third-line irinotecan regarding PFS [15]. Three other analyses, however, conclude that adding cetuximab to second and third-line chemotherapy principally benefits patients with LC regarding OS and PFS [22,24,26].

Regarding the predictive implications of PTL for first-line anti-VEGF treatment, data from the AGITG MAX trial suggest that the benefit from bevacizumab regarding PFS is independent of PTL [14]. This statement is supported by data from the NO16966 and AVF2107g trials suggesting that treatment effects of bevacizumab (OS, PFS and ORR) are independent of PTL as interaction tests were not significant [16]. However, it should be noted in this context that treatment effects of bevacizumab were not shown separately for RC and LC [28]. Taken together, the currently available evidence does not support PTL as a relevant predictor of first-line anti-VEGF treatment efficacy.

We acknowledge several limitations of the present investigation: the trials included into the meta-analysis were heterogeneous with regard to study phase (phase II versus phase III), (K)RAS testing, treatment and outcome assessment. Furthermore, the demarcation line for the definition of RC and LC was not consistent or consistently reported for all trials. Also, no data were available to evaluate the relevance of PTL in the context of triplet chemotherapy with FOLFOXIRI. Data regarding the impact of PTL for RAS mutated patients were not available, as well. Taken together, more substudies of RCTs are urgently needed to evaluate the predictive implications of PTL, whereas patient-level rather than study-level data should be utilised.

At present time, for patients with RAS wild-type LC it can be advised to initiate first-line chemotherapy in combination with an anti-EGFR antibody. For patients with RC, poor outcome has been reported. When prolongation of survival end-points is a goal, there is presently no support for initial use of anti-EGFR agents in RAS wild-type RC. In these patients, chemotherapy plus bevacizumab is a treatment option, but new treatment strategies need to be explored to improve outcome. By contrast, when ORR is considered a primary goal, the data indicate a numerically greater effect from anti-EGFR–based therapy also in RC thereby providing a rationale also for this treatment option in selected cases.

As a word of caution, it should be pointed out that there is a substantial heterogeneity within the molecular biology of RC and LC, which may impact on the efficacy of various treatment strategies [1,8]. With more insight into these heterogeneous subgroups, it can be assumed that treatment recommendations need to be adapted in the future.

Conflict of interest statement

Julian Walter Holch: None declared. Ingrid Ricard: None declared. Sebastian Stintzing has received honoraria from Merck, Roche, Amgen, Bayer, Sanofi-aventis and has served on advisory boards for Merck Serono, Roche
Travel support: Roche, Merck Serono, Sanofi-aventis. Dominik Paul Modest has received honoraria from Merck, Roche, Amgen, Bayer and has received research grant from Amgen (inst), Merck (inst), Roche (inst) and has received travel support from Amgen, Merck, Sanofi, Bayer and has served on advisory boards for Merck, Bayer, Amgen.
Volker Heinemann has received honoraria from Merck KgaA, Roche AG, Amgen, Sanofi, SIRTEX, BAXALTA and has received travel support from Merck KgaA, Roche AG, Amgen, SIRTEX, Baxalta and has served on advisory boards for Merck KgaA, Roche AG, Amgen, Sanofi, Lilly, SIRTEX, Böhringer Ingelheim, Baxalta, Taiho, Merrimack.

Acknowledgements

The authors thank all patients and families for participation in the studies, as well as all involved study centres, colleagues and nurses.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2016.10.007.

References

[1] Missiaglia E, Jacobs B, D'Ario G, Di Narzo AF, Soneson C, Budinska E, et al. Distal and proximal colon cancers differ in terms of molecular, pathological, and clinical features. Ann Oncol 2014;25(10):1995–2001.
[2] Yamauchi M, Lochhead P, Morikawa T, Huttenhower C, Chan AT, Giovannucci E, et al. Colorectal cancer: a tale of two sides or a continuum? Gut 2012;61(6):794–7.
[3] Yamauchi M, Morikawa T, Kuchiba A, Imamura Y, Qian ZR, Nishihara R, et al. Assessment of colorectal cancer molecular features along bowel subsites challenges the conception of distinct dichotomy of proximal versus distal colorectum. Gut 2012;61(6):847–54.
[4] Carethers JM. One colon lumen but two organs. Gastroenterology 2011;141(2):411–2.
[5] Bufill JA. Colorectal cancer: evidence for distinct genetic categories based on proximal or distal tumor location. Ann Intern Med 1990;113(10):779–88.
[6] LaPointe LC, Dunne R, Brown GS, Worthley DL, Molloy PL, Wattchow D, et al. Map of differential transcript expression in the normal human large intestine. Physiol Genomics 2008;33(1):50–64. Epub 2007 Dec 4.
[7] Iacopetta B. Are there two sides to colorectal cancer? Int J Cancer 2002;101(5):403–8.
[8] Guinney J, Dienstmann R, Wang X, de Reynies A, Schlicker A, Soneson C, et al. The consensus molecular subtypes of colorectal cancer. Nat Med 2015;21(11):1350–6.
[9] Bendardaf R, Buhmeida A, Hilska M, Laato M, Syrjanen S, Syrjanen K, et al. VEGF-1 expression in colorectal cancer is associated with disease localization, stage, and long-term disease-specific survival. Anticancer Res 2008;28(6B):3865–70.
[10] Benedix F, Kube R, Meyer F, Schmidt U, Gastinger I, Lippert H. Comparison of 17,641 patients with right- and left-sided colon cancer: differences in epidemiology, perioperative course, histology, and survival. Dis Colon Rectum 2010;53(1):57–64.
[11] Boisen MK, Johansen JS, Dehlendorff C, Larsen JS, Osterlind K, Hansen J, et al. Primary tumor location and bevacizumab effectiveness in patients with metastatic colorectal cancer. Ann Oncol 2013;24(10):2554–9.
[12] Modest DP, Schulz C, von Weikersthal LF, Quietzsch D, von Einem JC, Schalhorn A, et al. Outcome of patients with metastatic colorectal cancer depends on the primary tumor site (midgut vs. hindgut): analysis of the FIRE1-trial (FuFIRI or mIROX as first-line treatment). Anticancer Drugs 2014;25(2):212–8.
[13] von Einem JC, Heinemann V, von Weikersthal LF, Vehling-Kaiser U, Stauch M, Hass HG, et al. Left-sided primary tumors are associated with favorable prognosis in patients with KRAS codon 12/13 wild-type metastatic colorectal cancer treated with cetuximab plus chemotherapy: an analysis of the AIO KRK-0104 trial. J Cancer Res Clin Oncol 2014;140(9):1607–14.
[14] Price T, Buizen L, Hardingham J, Lee C, Townsend A. Molecular subgroups from the AGITG MAX trial; right or left primary site of colorectal cancer and outcomes for metastatic colorectal cancer (mCRC). Ann Oncol 2014;25(suppl 4):iv167–209. EMSO 2014. Abstract 511P 2014. http://dx.doi.org/10.1093/annonc/mdu333.
[15] Seligmann J, Elliott F, Richman S, Southward K, Barrett J, Quirke P, et al. Primary tumour location (PTL) as a prognostic and predictive factor in advanced colorectal cancer: data from 2075 patients in randomised trials. Ann Oncol 2014;25(Suppl. 4):iv167–209.
[16] Loupakis F, Yang D, Yau L, Feng S, Cremolini C, Zhang W, et al. Primary tumor location as a prognostic factor in metastatic colorectal cancer. J Natl Cancer Inst 2015;107(3) (pii):dju427.
[17] Zhang Y, Ma J, Zhang S, Deng G, Wu X, He J, et al. A prognostic analysis of 895 cases of stage III colon cancer in different colon subsites. Int J Colorectal Dis 2015;30(9):1173–83.
[18] Sunakawa Y, Ichikawa W, Tsuji A, Denda T, Segawa Y, Negoro Y. Prognostic impact of primary tumor location on survival time in patients (pts) with metastatic colorectal cancer (mCRC) treated with cetuximab plus oxaliplatin-based chemotherapy: a subgroup analysis of the JACCRO CC-05/06. ASCO-GI 2016 Abstr 613. 2016.
[19] Outcome in CALGB 80405. Presenter: H. Lenz https://cslide.ctimeetingtech.com/library/esmo/browse/search/p#2z95y02nD [Special session, ESMO 2016 Congress, 10/10/2016].
[20] Schrag D, Weng S, Brooks G, Meyerhardt J, Venook A. The relationship between primary tumor sidedness and prognosis in colorectal cancer. J Clin Oncol 2016;34 (Suppl; abstr 3505) 2016.
[21] Tejpar S, Stintzing S, Ciardiello F, Tabernero J, Van Cutsem E, Beier F, et al. Prognostic and predictive relevance of primary tumor location in patients with RAS wild-type metastatic colorectal cancer: retrospective analyses of the CRYSTAL and FIRE-3 trials. JAMA Oncol 2016. http://dx.doi.org/10.1001/jamaoncol.2016.3797.
[22] Wang F, Bai L, Liu TS, Yu YY, He MM, Liu KY, et al. Right-sided colon cancer and left-sided colorectal cancers respond differently to cetuximab. Chin J Cancer 2015;34(9):384–93. http://dx.doi.org/10.1186/s40880-015-0022-x.
[23] Brule SY, Jonker DJ, Karapetis CS, O'Callaghan CJ, Moore MJ, Wong R, et al. Location of colon cancer (right-sided versus left-sided) as a prognostic factor and a predictor of benefit from cetuximab in NCIC CO.17. Eur J Cancer 2015;51(11):1405–14.
[24] Chen KH, Shao YY, Chen HM, Lin YL, Lin ZZ, Lai MS, et al. Primary tumor site is a useful predictor of cetuximab efficacy in

the third-line or salvage treatment of KRAS wild-type (exon 2 non-mutant) metastatic colorectal cancer: a nationwide cohort study. BMC Cancer 2016;16(1):327.

[25] He W-Z, Yang Q, Jiang C, Liao F-X, Liu S-S, Xia L-P. Bevacizumab effectiveness and primary tumor location in metastatic colorectal cancer patients. J Clin Oncol 2016;34 (Suppl. 4S; abstr 683) 2016.

[26] Moretto R, Cremolini C, Rossini D, Pietrantonio F, Battaglin F, Mennitto A, et al. Location of primary tumor and benefit from anti-epidermal growth factor receptor monoclonal antibodies in patients with RAS and BRAF wild-type metastatic colorectal cancer. Oncologist 2016;21(8):988–94. http://dx.doi.org/10.1634/theoncologist.2016-0084. [Epub 2016 Jul 5].

[27] Wong H-L, Field K, Lomax A, Tacey M, Shapiro J, McKendrick J, et al. Impact of tumor site on bevacizumab (BEV) efficacy in metastatic colorectal cancer (mCRC). J Clin Oncol 2014;32 (Suppl; abstr e14558) 2014.

[28] He WZ, Xia LP. RE: primary tumor location as a prognostic factor in metastatic colorectal cancer. J Natl Cancer Inst 2015; 107(9).

[29] Outcome according to Left vs. Right side in the panitumumab studies. Presenter: M. Peeters https://cslide.ctimeetingtech.com/library/esmo/browse/search/p#2z95y02nA [Special session, ESMO 2016 Congress, 10/10/2016].

[30] Lenz H-J, Lee F-C, Yau L, Koh H, Knost J, Mitchell E, et al. MAVERICC, a phase 2 study of mFOLFOX6-bevacizumab (BV) vs FOLFIRI-BV with biomarker stratification as first-line (1L) chemotherapy (CT) in patients (pts) with metastatic colorectal cancer (mCRC). J Clin Oncol 2016;34 (Suppl. 4S; abstr 493) 2016.

[31] Pro Discussion. Presenter: D. Arnold https://cslide.ctimeetingtech.com/library/esmo/browse/search/p#2z95y02nE [Special session, ESMO 2016 Congress, 10/10/2016].

[32] Boeckx N, Toler A, Op de Beeck K, Kafatos G, Deschoolmeester V, Rolfo C, et al. Primary tumor sidedness impacts on prognosis and treatment outcome: results from three randomized studies of panitumumab plus chemotherapy versus chemotherapy or chemotherapy plus bevacizumab in 1 and 2 line RAS/BRAF WT mCRC. Ann Oncol 2016;27(Suppl 6). Abstr 89P, ESMO 2016.

[33] Outcome according to Left vs. Right side in the FOLFIRI cetuximab and FIRE 3 study. Presenter: V. Heinemann. https://cslide.ctimeetingtech.com/library/esmo/browse/search/bcc#2z95y02nB [Special session, ESMO 2016 Congress, 10/10/2016].