ANTICANCER RESEARCH *39*: 5645-5652 (2019)
doi:10.21873/anticanres.13761

The Predictive Role of Primary Tumour Sidedness in Metastatic Colorectal Cancer Treated With Targeted Agents

ONDREJ FIALA[1,2], PAVEL OSTASOV[2], PETR HOSEK[2], ONDREJ SOREJS[1,2], VACLAV LISKA[2,3], TOMAS BUCHLER[4], ALEXANDR POPRACH[5], RADEK KUCERA[6], ONDREJ TOPOLCAN[6], JAN SUSTR[1], MONIKA SEDIVCOVA[7] and JINDRICH FINEK[1]

[1]*Department of Oncology and Radiotherapy, Medical School and University Hospital in Pilsen, Charles University, Pilsen, Czech Republic;*
[2]*Biomedical Center, Faculty of Medicine in Pilsen, Charles University, Pilsen, Czech Czech Republic;*
[3]*Department of Surgery, Medical School and University Hospital in Pilsen, Charles University, Pilsen, Czech Republic;*
[4]*Department of Oncology, First Faculty of Medicine, Charles University and Thomayer Hospital, Prague, Czech Republic;*
[5]*Department of Comprehensive Cancer Care and Faculty of Medicine, Masaryk Memorial Cancer Institute and Masaryk University, Brno, Czech Republic;*
[6]*Department of Immunochemistry Diagnostics, Medical School and University Hospital in Pilsen, Charles University, Pilsen, Czech Republic;*
[7]*Molecular Pathology Laboratory, Bioptic Laboratory, Ltd., Pilsen, Czech Republic*

Abstract. *Background/Aim: The aim of our study was to assess the predictive role of primary tumour sidedness (PTS) in patients with metastatic colorectal cancer (mCRC) harbouring wild-type RAS and treated with targeted agents. Patients and Methods: The cohort included 178 patients treated with first-line chemotherapy plus cetuximab, panitumumab or bevacizumab. Results: We observed longer progression-free survival (PFS) and overall survival (OS) in patients with left-sided (L-CRC) compared to right-sided tumours (R-CRC) treated with anti-EGFR mAbs (p=0.0033 and p=0.0037), while there was no difference in patients treated with bevacizumab (p=0.076 and p=0.56). Finally, we observed longer PFS and OS in patients with L-CRC treated with anti-EGFR mAbs and those with R-CRC treated with bevacizumab compared to the reverse combination (p=0.0002 and p=0.011). Conclusion: PTS is a predictive factor for anti-EGFR mAbs, not for bevacizumab. Superior survival was observed when anti-EGFR mAbs were used for L-CRC and bevacizumab for R-CRC.*

Correspondence to: Ondrej Fiala, MD, Ph.D., Department of Oncology and Radiotherapy, Medical School and University Hospital Pilsen, Charles University Prague, alej Svobody 80, CZ-304 60 Pilsen, Czech Republic. Tel: +42 0728655488, e-mail: fiala.o@centrum.cz

Key Words: Primary tumour sidedness, colorectal cancer, cetuximab, panitumumab, bevacizumab.

Colorectal cancer (CRC) is the second most commonly diagnosed malignancy and the leading cause of cancer-related death in Europe (1). Considerable progress in the treatment of metastatic CRC (mCRC) has been reached in recent years and several novel active agents have been approved for the systemic therapy of mCRC patients. The monoclonal antibody (mAb) against vascular endothelial growth factor (VEGF) bevacizumab and mAbs cetuximab and panitumumab against epidermal growth factor receptor (EGFR) are widely used in the treatment of metastatic CRC (mCRC). Anti-EGFR mAbs are used for patients with tumours harbouring the wild-type *RAS* gene, which is a well-established predictive biomarker (2-11). However, optimal selection of targeted agents for use in the first-line treatment of wild-type *RAS* mCRC patients is still not fully resolved. Recently, several retrospective analyses have shown an association between the primary tumour location and the efficacy of different targeted agents (12-19).

The aim of our study was to assess the predictive role of primary tumour sidedness (PTS) in patients with wild-type *RAS* mCRC treated with first-line anti-EGFR mAbs or bevacizumab in combination with standard chemotherapy, and to compare two different therapy approaches: anti-EGFR mAbs for left-sided CRC (L-CRC) with bevacizumab for right-sided CRC (R-CRC) *vs.* anti-EGFR mAbs for R-CRC with bevacizumab for L-CRC.

Patients and Methods

Patients and treatment. Clinical data of 178 adult patients with histologically confirmed mCRC harbouring the wild-type *RAS* gene (*KRAS* and *NRAS*) who underwent a first-line treatment consisting of a combination of standard chemotherapy with cetuximab, panitumumab or bevacizumab between the years 2009 and 2018 at the Department of Oncology and Radiotherapy, Medical School and University Hospital Pilsen, Czech Republic were analyzed retrospectively. Baseline characteristics of patient group are described in Table I.

Cetuximab (Erbitux, Merck & Co., Kenilworth, NJ, USA) was used in combination with chemotherapy or as a single agent in a standard approved dose (initial dose 400 mg/m^2 and next doses 250 mg/m^2 every 7 days). Panitumumab (Vectibix, Amgen Inc., Thousand Oaks, CA, USA) was used in combination with chemotherapy or as a single agent in a standard approved dose (6.0 mg/kg every 14 days). Bevacizumab (Avastin, F. Hoffman-La Roche Ltd., Basel, Switzerland) was used in combination with chemotherapy or as a single agent in standard approved doses (5.0 mg/kg every 14 days or 7.5 mg every 21 days). The chemotherapy consisted of the following schedules: fluorouracil and leucovorin in combination with irinotecan (FOLFIRI) or with oxaliplatin (FOLFOX). The participating patients had not received targeted therapies in the past.

The genetic assessment including *KRAS* and *NRAS* gene status was done at the time of diagnosis of metastatic disease. The sample analysis was performed using direct sequencing, real-time PCR (2008-2010) and reverse hybridization (StripAssay) (since 2010) as it is standard practice in the Czech Republic. To assure long-term quality, the methods were certified by the Czech Accreditation Institute (ČIA) or intended for use in clinical laboratories (CE-IVD).

The protocol of the study and the form of Informed consent for participants were approved by the Ethical Committee of the Medical School and University Hospital in Pilsen on 12th May 2016 and complied with the International Ethical Guidelines for Biomedical Research, the Declaration of Helsinki, and local laws. The Informed consent with subsequent analysis of the follow-up data was obtained from all the participants.

Study design. R-CRC was defined as tumour localized in the caecum or in the colon ascending up to the flexura hepatica. L-CRC was defined as tumour localized in the flexura splenica and distal parts including rectum. Patients with CRC localized in the transverse colon were not included. The outcome of patients including progression-free survival (PFS) and overall survival (OS) was compared between groups with L-CRC and with R-CRC treated with either bevacizumab or anti-EGFR mAbs. Finally, PFS and OS were compared for two different therapy approaches: anti-EGFR mAbs for L-CRC with bevacizumab for R-CRC *vs*. anti-EGFR mAbs for R-CRC with bevacizumab for L-CRC. The results were tested in a Cox multivariate model.

Clinical monitoring. The follow-up controls including a physical examination and routine laboratory tests were performed every two weeks and restaging using radiological imaging techniques including computed tomography (CT) or positron emission tomography - (PET)-CT was performed every three months during the time of treatment or in case of clinical suspicion of progression. The objective tumour response was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST) (20). The clinical data were obtained retrospectively from the hospital information system.

Table I. *Baseline patient's characteristics according to the first-line targeted treatment*.

Characteristic	n (%)	
	Anti-EGFR mAbs	Bevacizumab
Gender		
Male	72 (66.06)	45 (65.22)
Female	37 (33.94)	24 (34.78)
Age		
<70 years	88 (80.73)	60 (86.96)
≥70 years	21 (19.27)	9 (13.04)
Median, years (range)	64.09 (36.42-77.57)	61.93 (32.65-74.46)
ECOG PS		
0	18 (16.51)	7 (10.14)
1	88 (80.74)	60 (86.96)
2	3 (2.75)	2 (2.90)
Location of primary tumour		
Rectum	37 (33.94)	29 (42.03)
Colon	72 (66.06)	40 (57.97)
Location L/R		
Left	90 (82.57)	56 (81.16)
Right	19 (17.43)	13 (18.84)
Type of first-line chemotherapy		
FOLFOX	90 (82.57)	60 (86.95)
FOLFIRI	19 (17.43)	9 (13.05)
Type of first-line targeted therapy		
Cetuximab	56 (51.38)	x
Panitumumab	53 (48.62)	x
Bevacizumab	x	69 (100.0)
Type of second-line targeted therapy		
Cetuximab	x	26 (37.68)
Panitumumab	x	11 (15.94)
Bevacizumab	42 (38.53)	x
Aflibercept	8 (7.34)	3 (4.35)
Grading		
G1	14 (12.84)	9 (13.04)
G2	72 (66.06)	41 (59.42)
G3	16 (14.68)	12 (17.39)
Unknown	7 (6.42)	7 (10.14)
Synchronous/metachronous		
Synchronous	58 (53.21)	45 (65.22)
Metachronous	51 (46.79)	24 (34.78)
Liver-limited metastases		
Yes	40 (36.70)	29 (42.03)
No	69 (63.30)	40 (57.97)

Statistical analysis. Descriptive statistics and standard frequency tables were used to characterize the sample data set. PFS was determined from the date of treatment initiation until the date of first documented progression or death. OS was determined from the date of treatment initiation until the date of death. PFS and OS were estimated using the Kaplan–Meier method and all point estimates were accompanied by two-sided 95% confidence intervals. The statistical analysis was performed using R (version 3.5.1) (Foundation for Statistical Computing, Vienna, Austria) and packages survival

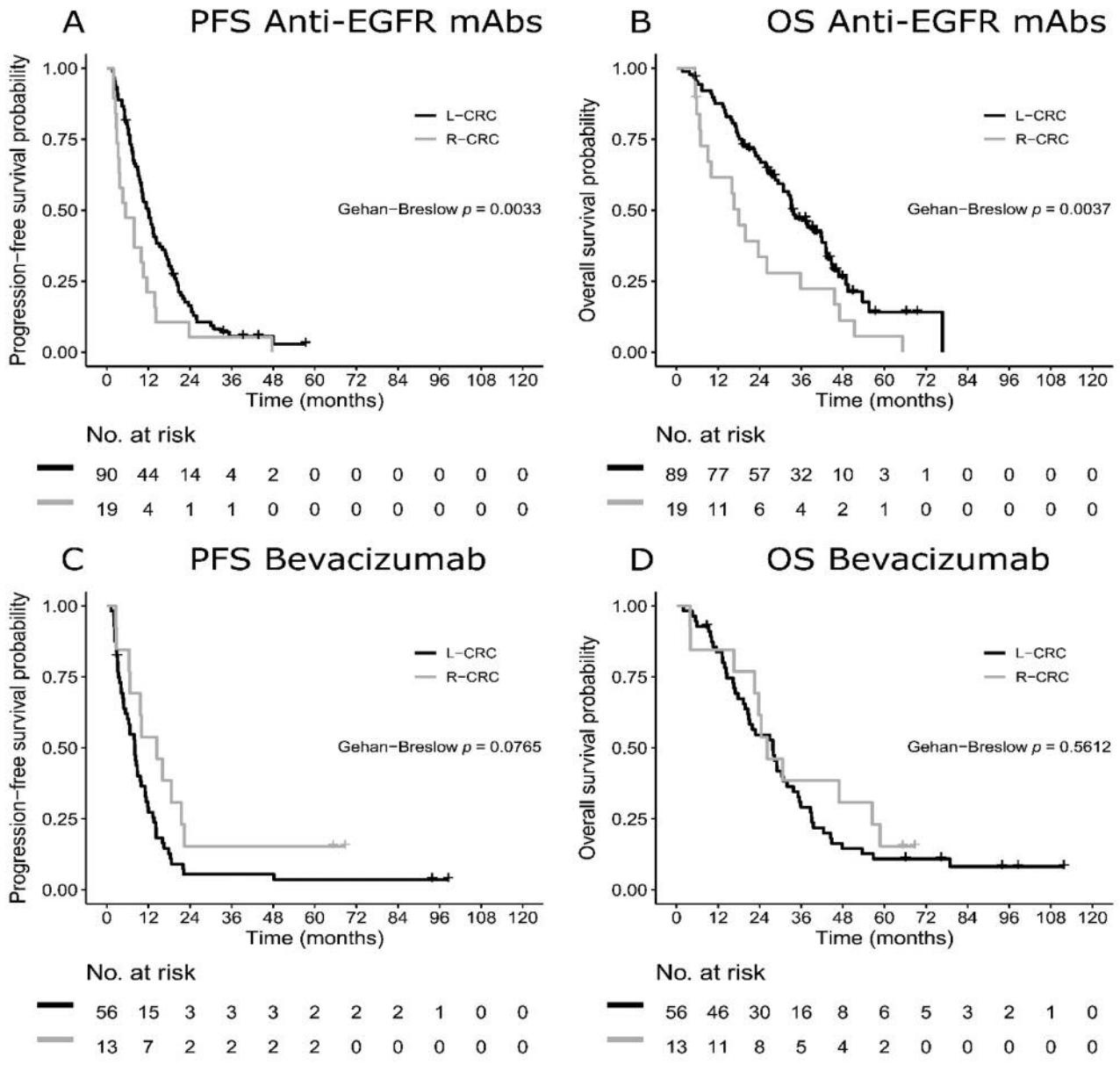

Figure 1. *Comparison of progression-free (PFS) and overall survival (OS) between patients with L-CRC and R-CRC treated with bevacizumab (A, B) and between patients with L-CRC and R-CRC treated with anti-EGFR mAbs (A, B). Our data clearly demonstrate that patients with L-CRC had significantly greater survival benefit from anti-EGFR treatment (A, B). This effect was not visible for R-CRC when isolated results of bevacizumab are presented (C, D).*

(version 2.46) and survminer (0.4.3) for survival analysis and visualisation (21, 22). The Gehan-Breslow-Wilcoxon test was used for assessment of statistical significance of the differences in survival according to treatment and the primary tumour sidedness. A multivariable Cox proportional hazards model was used to evaluate the effect of all potential prognostic factors on the survival indicators. The Wald test was used for assessment of statistical significance of hazard ratios. The level of statistical significance was set at α=0.05 and all reported *p*-values are two-tailed.

Results

The median PFS and OS for patients with L-CRC treated with anti-EGFR mAbs was 11.93 and 33.22 months compared to 5.45 and 17.97 months for those with R-CRC treated with anti-EGFR mAbs (p=0.0033 and p=0.0037, respectively) (Figure 1). The median PFS and OS for patients with L-CRC treated with bevacizumab was 8.05 and

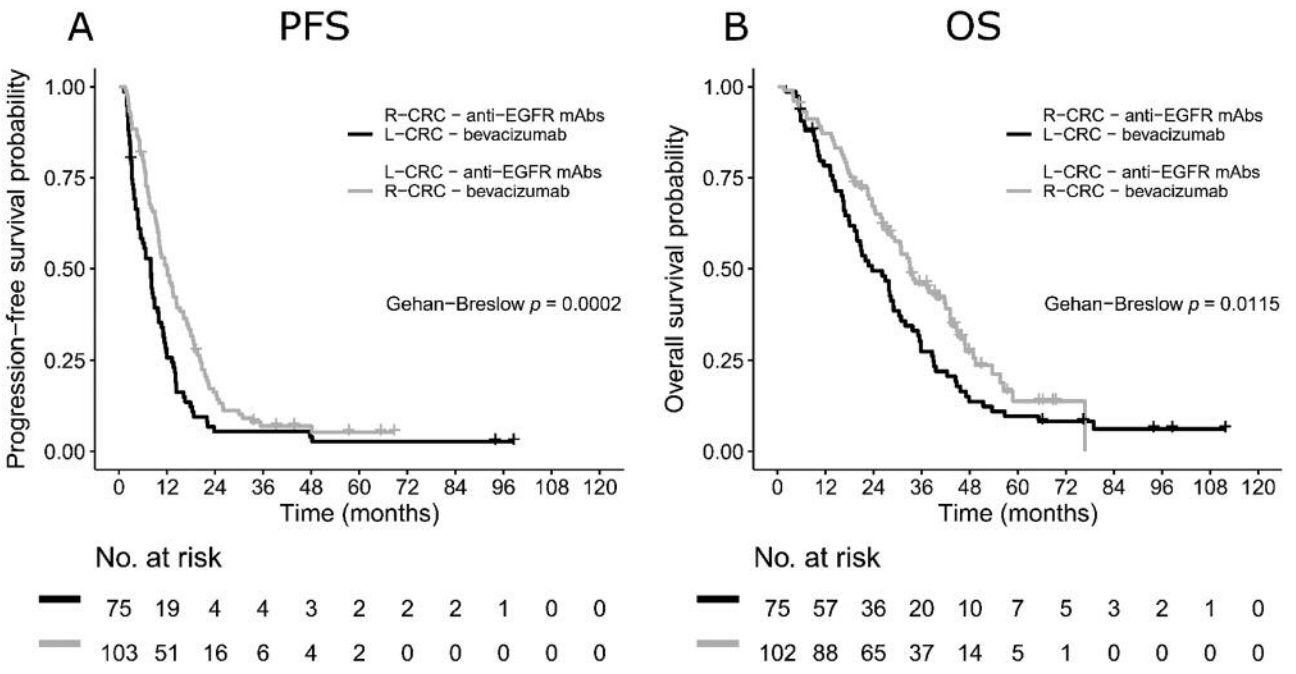

Figure 2. *Comparison of progression-free (PFS) and overall survival (OS) between anti-EGFR mAbs for L-CRC and bevacizumab for R-CRC vs. anti-EGFR mAbs for R-CRC and bevacizumab for L-CRC. Our results suggest anti-EGFR mAbs for L-CRC and bevacizumab for R-CRC as an optimal treatment strategy. We found significantly longer PFS and OS for patients with L-CRC treated with anti-EGFR mAbs and with R-CRC treated with bevacizumab. The multivariate Cox proportional hazards model confirmed that anti-EGFR mAbs for L-CRC and bevacizumab for R-CRC approach is significantly associated with longer PFS.*

27.83 months compared to 14.46 and 26.15 months for those with R-CRC treated with bevacizumab (p=0.076 and p=0.56, respectively) (Figure 1). The median PFS and OS for patients with L-CRC treated with anti-EGFR mAbs and those with R-CRC treated with bevacizumab was 12.16 and 33.15 months compared to 7.92 and 23.59 months for patients with R-CRC treated with anti-EGFR mAbs and those with L-CRC treated with bevacizumab (p=0.0002 and p=0.011, respectively) (Figure 2). Survival data are summarized in Table II. In the Cox multivariable analysis, anti-EGFR mAbs for L-CRC and bevacizumab for R-CRC remains a significant factor for PFS (HR=0.6286, p=0.0096), but not for OS (HR=0.6973, p=0.0612) (Table III).

Discussion

The results of our study suggest that PTS is a predictive factor feasible for the selection of the optimal first-line targeted therapy for mCRC patients with tumours harbouring wild-type *RAS* gene and that the use of anti-EGFR mAbs for L-CRC and bevacizumab for R-CRC is a promising treatment approach.

CRC is a heterogeneous disease with differing outcomes and clinical responses to systemic therapies. Proximal and distal parts of the colon differ in embryologic origins; R-CRC arises from midgut and L-CRC from hindgut. According to PTS, CRCs can be grouped into R-CRCs and L-CRCs. R-CRCs are located within the caecum and colon ascendens through the transverse colon, excluding the appendix. L-CRCs are located within the flexura splenica, colon descendens, colon sigmoideum and rectum (23). For clarity, we excluded patients with primary tumour in the transverse colon from our study. There has been growing evidence showing that R-CRCs and L-CRCs are distinct biological and clinical entities. Various characteristics associated with primary tumour location have been described including epidemiology, pathogenesis, morphology, pathophysiology, and genetic and epigenetic alterations (24-35). The prognostic and possible predictive role of location of the primary tumour, in terms of right and left sided origin, has been recently investigated. R-CRCs are frequently characterized by several adverse prognostic factors, including mucinous histology, hypermutation, microsatellite instability and *BRAF* gene mutation positivity (36-38). Different molecular characteristics translate into different clinical outcomes. In general, R-CRCs are associated with a markedly worse prognosis (39). Moreover, several retrospective analyses have suggested that PTS may also be

Table II. *Comparison of progression-free survival (PFS) and overall survival (OS) in selected groups in months.*

Patient group	Median PFS (95%CI)	*p*-Value (Gehan-Breslow)	Median OS (95% CI)	*p*-Value (Gehan-Breslow)
L-CRC - anti-EGFR mAbs	11.93 (9.95-14.29)	0.0033	33.22 (29.31-43.04)	0.0037
R-CRC - anti-EGFR mAbs	5.45 (3.52-13.86)		17.97 (9.10-45.60)	
L-CRC - bevacizumab	8.05 (5.95-11.04)	0.076	27.83 (20.86-33.71)	0.56
R-CRC - bevacizumab	14.46 (6.60-NA)		26.15 (22.54-NA)	
L-CRC - anti-EGFR mAbs and R-CRC - bevacizumab	12.16 (9.99-15.24)	0.0002	33.15 (28.52-43.04)	0.011
L-CRC - bevacizumab and R-CRC - anti-EGFR mAbs	7.92 (5.42-9.92)		23.59 (19.78-30.82)	

mAbs: Monoclonal antibodies; L-CRC: left-sided colorectal cancer; R-CRC: right-sided colorectal cancer.

Table III. *Multivariable Cox-proportional hazards model for progression-free survival (PFS) and overall survival (OS).*

Parameter	Progression-free survival (PFS)		Overall survival (OS)	
	HR (95%CI)	*p*-Value	HR (95%CI)	*p*-Value
Gender				
Female	1	0.2288	1	0.1211
Male	1.2471 (0.8704–1.7868)		1.368 (0.921-2.034)	
Age				
<70 years	1	0.4158	1	0.3130
≥70 years	0.9918 (0.9723–1.0117)		0.989 (0.9889-0.9679)	
ECOG PS				
0	1	0.8147	1	0.8936
1-2	0.9473 (0.6025-1.4895)		0.9630 (0.5546-1.6724)	
Grade				
1	1	0.6573	1	0.1214
2-3	1.1064 (0.7077-1.7299)		1.489 (0.8997-2.4635)	
Location of primary tumour				
Colon	1	0.4578	1	0.9825
Rectum	0.8703 (0.6032–1.2558)		1.004 (0.6775-1.4890)	
Synchronous/metachronous metastases				
Synchronous	1	0.6937	1	0.3341
Metachronous	0.9264 (0.6333–1.3552)		1.2437 (0.7989-1.9362)	
Liver-limited metastases				
Yes	1	0.1013	1	0.0179
No	1.3543 (0.9422-1.9466)		1.6692 (1.0924-2.5508)	
Type of chemotherapy				
FOLFOX	1	0.5581	1	0.5476
FOLFIRI	1.1827 (0.6744-2.0742)		0.8260 (0.4432-1.5398)	
Therapy and primary tumour sidedness				
L-CRC - bevacizumab or R-CRC - anti-EGFR mAbs	1	0.0096	1	0.0612
R-CRC - bevacizumab or L-CRC - anti-EGFR mAbs	0.6286 (0.4425–0.8931)		0.6973 (0.4781-1.0171)	

mAbs: Monoclonal antibodies; L-CRC: left-sided colorectal cancer; R-CRC: right-sided colorectal cancer.

a predictive marker of the efficacy of targeted therapies with anti-VEGF and anti-EGFR mAbs directed agents (12-19).

To evaluate the predictive role of PTS with regard to the efficacy of anti-EGFR mAbs, data from randomised clinical trials evaluating anti-EGFR mAbs were studied. These retrospectively analysed clinical trials include CRYSTAL, PRIME, NCIC CO.17 and study 20050181. It has been reported that for *RAS* wild-type cases, the efficacy of anti-EGFR mAbs was greater in L-CRC compared to R-CRC (12-15). On the other hand, the response to either of the standard chemotherapy targeted agents is generally poor in R-CRC. The data from the randomised clinical trials

including AGITG MAX, NO16966, AVF2107g, as well as the data from the Australian registry evaluating the predictive role of PTS for anti-VEGF treatment suggest that treatment effects of bevacizumab are independent of the primary tumour location (17-19). Thus, PTS seems to be to be a predictive factor for the efficacy of anti-EGFR mAbs in the first- or second-line setting. By contrast, it seems that it has no predictive role for bevacizumab. This is in agreement with our study. In patients treated with anti-EGFR mAbs we found significantly longer PFS and OS for those with L-CRC compared to R-CRC. On the other hand, in patients treated with bevacizumab we did not find any significant difference in PFS or OS between the PTS groups.

Currently, data on direct comparisons of the first-line anti-EGFR mAbs and bevacizumab with regard to PTS are limited to retrospective analyses of several randomised clinical trials and meta-analyses of their results. These include data from two randomised phase III trials (FIRE-3/AIO KRK0306 and CALGB/SWOG 80405) and one phase II trial (PEAK) directly comparing anti-EGFR mAbs and bevacizumab in combination with standard chemotherapy (FOLFOX, FOLFIRI) in the first-line treatment of wild-type *RAS* mCRC patients (12, 13, 16). The relevance of PTS has recently been investigated in a meta-analysis of first-line clinical trials by Holch *et al*. (40). A meta-analysis of FIRE-3/AIO KRK0306, CALGB/SWOG 80405 and PEAK trials showed that patients with L-CRC had greater survival benefit from anti-EGFR mAbs compared to bevacizumab in combination with standard chemotherapy regimens (HR=0.71; 95%CI=0.58-0.85; p=0.0003). On the other hand, in patients with R-CRC, the benefit from standard chemotherapy was poor and a combination with bevacizumab was associated with significantly longer survival (HR=1.3; 95%CI=0.97-1.74; p=0.081) (40). Overall, these results suggest anti-EGFR mAbs for L-CRC and bevacizumab for R-CRC as an optimal treatment strategy. In our study, we compared PFS and OS of patients treated with two different treatment approaches, anti-EGFR mAbs for L-CRC with bevacizumab for R-CRC *vs*. anti-EGFR mAbs for R-CRC with bevacizumab for L-CRC. We found significantly longer PFS and OS for patients with L-CRC treated with anti-EGFR mAbs and with R-CRC treated with bevacizumab. The multivariate Cox proportional hazards model confirmed that the anti-EGFR mAbs for L-CRC and bevacizumab for R-CRC approach is significantly associated with longer PFS, but not OS. Even though the OS results from the multivariate Cox model were not significant, there was a visible trend and the results could have been influenced by the subsequent cross-over use of targeted agents in the second or third-line settings. In conclusion, the results of the presented retrospective study suggest that PTS is a predictive factor for anti-EGFR mAbs, but not for bevacizumab in the first-line treatment of patients with wild-type *RAS* mCRC. Moreover, the results show superior PFS and OS for anti-EGFR mAbs for L-CRC and bevacizumab for R-CRC as compared to anti-EGFR mAbs for R-CRC and bevacizumab for L-CRC. The treatment approach was revealed to be an independent factor for PFS. Prospective studies on the predictive role of PTS and also providing elucidation of the molecular background responsible for such effects are urgently needed.

Conflicts of Interest

OF received honoraria from Roche, GSK and Pfizer for consultations and lectures unrelated to this project. TB and AP received lecture honoraria from Novartis, Pfizer, Bayer-Schering and Roche. TB also received research support from Roche and Novartis. JF has received honoraria from Astra Zeneca, Roche and Novartis for consultations and lectures unrelated to this project. PO, PH, OS, VL, RK, OT, JS and MS declare that they have no actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations that could inappropriately influence this work.

Authors' Contributions

OF designed the study and wrote the manuscript with support from VL, TB, AP, RK, OT and JF. OS, JS and MS collected clinical data. PO and PH performed statistical analyses.

Acknowledgements

The Authors would like to thank all patients voluntarily taking part in the study. This study was supported by the project "Centrum of clinical and experimental liver surgery", UNCE/MED/006, by the National Sustainability Program I (NPU I) Nr. LO1503 provided by the Ministry of Education Youth and Sports of the Czech Republic and by the Charles University Research Fund (Progres Q39) and by the European Regional Development Fund-Project "Application of Modern Technologies in Medicine and Industry" (No.CZ.02.1.01/0.0/0.0/17_048/0007280) and by Ministry of Health, Czech Republic - conceptual development of research organization (University Hospital in Pilsen - FNPl, 00669806).

References

1 Jemal A, Bray F, Center MM, Ferlay J, Ward E and Forman D: Global cancer statistics. CA Cancer J Clin *61(2)*: 69-90, 2011. PMID: 21296855. DOI: 10.3322/caac.20107

2 Vaughn CP, Zobell SD, Furtado LV, Baker CL and Samowitz WS: Frequency of KRAS, BRAF, and NRAS mutations in colorectal cancer. Genes Chromosomes Cancer *50(5)*: 307-312, 2011. PMID: 21305640. DOI: 10.1002/gcc.20854

3 Lièvre A, Bachet JB, Le Corre D, Boige V, Landi B, Emile JF, Côté JF, Tomasic G, Penna C, Ducreux M, Rougier P, Penault-Llorca F and Laurent-Puig P: KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. Cancer Res *66(8)*: 3992-3995, 2006. PMID: 16618717.

4 Lièvre A, Bachet JB, Boige V, Cayre A, Le Corre D, Buc E, Ychou M, Bouché O, Landi B, Louvet C, André T, Bibeau F, Diebold MD, Rougier P, Ducreux M, Tomasic G, Emile JF,

Penault-Llorca F and Laurent-Puig P: KRAS mutations as an independent prognostic factor in patients with advanced colorectal cancer treated with cetuximab. J Clin Oncol *26(3)*: 374-379, 2008. PMID: 18202412. DOI: 10.1200/JCO.2007.12.5906

5 Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC, Simes RJ, Chalchal H, Shapiro JD, Robitaille S, Price TJ, Shepherd L, Au HJ, Langer C, Moore MJ and Zalcberg JR: K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med *359(17)*: 1757-1765, 2008. PMID: 18946061. DOI: 10.1056/NEJMoa0804385

6 Amado RG, Wolf M, Peeters M, Van Cutsem E, Siena S, Freeman DJ, Juan T, Sikorski R, Suggs S, Radinsky R, Patterson SD and Chang DD: Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol *26(10)*: 1626-1634, 2008. PMID: 18316791. DOI: 10.1200/JCO.2007.14.7116

7 Douillard JY, Oliner KS, Siena S, Tabernero J, Burkes R, Barugel M, Humblet Y, Bodoky G, Cunningham D, Jassem J, Rivera F, Kocákova I, Ruff P, Błasińska-Morawiec M, Šmakal M, Canon JL, Rother M, Williams R, Rong A, Wiezorek J, Sidhu R and Patterson SD: Panitumumab-FOLFOX4 treatment and RAS mutations in colorectal cancer. N Engl J Med *369(11)*: 1023-1034, 2013. PMID: 24024839. DOI: 10.1056/NEJMoa1305275

8 Ciardiello F, Normanno N, Martinelli E, Troiani T, Pisconti S, Cardone C, Nappi A, Bordonaro AR, Rachiglio M, Lambiase M, Latiano TP, Modoni G, Cordio S, Giuliani F, Biglietto M, Montesarchio V, Barone C, Tonini G, Cinieri S, Febbraro A, Rizzi D, De Vita F, Orditura M, Colucci G and Maiello E: Cetuximab continuation after first progression in metastatic colorectal cancer (CAPRI-GOIM): a randomized phase II trial of FOLFOX plus cetuximab versus FOLFOX. Ann Oncol *27(6)*: 1055-1061, 2016. PMID: 27002107. DOI: 10.1093/annonc/mdw136

9 Bokemeyer C, Köhne CH, Ciardiello F, Lenz HJ, Heinemann V, Klinkhardt U, Beier F, Duecker K, van Krieken JH and Tejpar S: FOLFOX4 plus cetuximab treatment and RAS mutations in colorectal cancer. Eur J Cancer *51(10)*: 1243-1252, 2015. PMID: 25937522. DOI: 10.1016/j.ejca.2015.04.007

10 Sorich MJ, Wiese MD, Rowland A, Kichenadasse G, McKinnon RA and Karapetis CS: Extended RAS mutations and anti-EGFR monoclonal antibody survival benefit in metastatic colorectal cancer: a meta-analysis of randomized, controlled trials. Ann Oncol *26(1)*: 13-21, 2015. PMID: 25115304. DOI: 10.1093/annonc/mdu378

11 Irahara N, Baba Y, Nosho K, Shima K, Yan L, Dias-Santagata D, Iafrate AJ, Fuchs CS, Haigis KM and Ogino S: NRAS mutations are rare in colorectal cancer. Diagn Mol Pathol *19(3)*: 157-163, 2010. PMID: 20736745. DOI: 10.1097/PDM.0b013e3181c93fd

12 Tejpar S, Stintzing S, Ciardiello F, Tabernero J, Van Cutsem E, Beier F, Esser R, Lenz HJ and Heinemann V: 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 *3(2)*: 194-201, 2017. PMID: 27722750. DOI: 10.1001/jamaoncol.2016.3797

13 Boeckx N, Koukakis R, Op de Beeck K, Rolfo C, Van Camp G, Siena S, Tabernero J, Douillard JY, André T and Peeters M: Primary tumor sidedness has an impact on prognosis and treatment outcome in metastatic colorectal cancer: results from two randomized first-line panitumumab studies. Ann Oncol *28(8)*: 1862-1868, 2017. PMID: 28449055. DOI: 10.1093/ annonc/mdx119

14 Brulé SY, Jonker DJ, Karapetis CS, O'Callaghan CJ, Moore MJ, Wong R, Tebbutt NC, Underhill C, Yip D, Zalcberg JR, Tu D and Goodwin RA: 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 *51(11)*: 1405-1414, 2015. PMID: 25979833. DOI: 10.1016/j.ejca.2015.03.015

15 Modest DP, Stintzing S, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, Heintges T, Kahl C, Seipelt G, Kullmann F, Scheithauer W, Moehler M, Holch JW, von Einem JC, Held S and Heinemann V: Exploring the effect of primary tumor sidedness on therapeutic efficacy across treatment lines in patients with metastatic colorectal cancer: analysis of FIRE-3 (AIOKRK0306). Oncotarget *8(62)*: 105749-105760, 2017. PMID: 29285289. DOI: 10.18632/oncotarget.22396

16 Venook AP, Niedzwiecki D, Lenz HJ, Innocenti F, Fruth B, Meyerhardt JA, Schrag D, Greene C, O'Neil BH, Atkins JN, Berry S, Polite BN, O'Reilly EM, Goldberg RM, Hochster HS, Schilsky RL, Bertagnolli MM, El-Khoueiry AB, Watson P, Benson AB 3rd, Mulkerin DL, Mayer RJ and Blanke C: Effect of first-line chemotherapy combined with cetuximab or bevacizumab on overall survival in patients with KRAS wild-type advanced or metastatic colorectal cancer: A randomized clinical trial. JAMA *317(23)*: 2392-2401, 2017. PMID: 28632865. DOI: 10.1001/jama.2017.7105

17 Tapia Rico G, Price T, Tebbutt N, Hardingham J, Lee C, Buizen L, Wilson K, Gebski V and Townsend A: Right or left primary site of colorectal cancer: outcomes from the molecular analysis of the AGITG MAX Trial. Clin Colorectal Cancer *18(2)*: 141-148, 2019. PMID: 30713134. DOI: 10.1016/j.clcc.2018.12.002

18 Loupakis F, Yang D, Yau L, Feng S, Cremolini C, Zhang W, Maus MK, Antoniotti C, Langer C, Scherer SJ, Müller T, Hurwitz HI, Saltz L, Falcone A and Lenz HJ: Primary tumor location as a prognostic factor in metastatic colorectal cancer. J Natl Cancer Inst *107(3)*: dju427, 2015. PMID: 25713148. DOI: 10.1093/jnci/dju427

19 Wong HL, Lee B, Field K, Lomax A, Tacey M, Shapiro J, McKendrick J, Zimet A, Yip D, Nott L, Jennens R, Richardson G, Tie J, Kosmider S, Parente P, Lim L, Cooray P, Tran B, Desai J, Wong R and Gibbs P: Impact of primary tumor site on bevacizumab efficacy in metastatic colorectal cancer. Clin Colorectal Cancer *15(2)*: e9-e15, 2016. PMID: 26968236. DOI: 10.1016/j.clcc.2016.02.007

20 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, Verweij J, Van Glabbeke M, van Oosterom AT, Christian MC and Gwyther SG: New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst *92(3)*: 205-216, 2000. PMID: 10655437.

21 Therneau TM and Grambsch PM: Modeling Survival Data: Extending the Cox Model. New York, USA: Springer; 2000.

22 Kassambara A, Kosinski and Survminer M: Drawing Survival Curves using 'ggplot2' R-package version0.4.3. (2018). https://CRAN.R-project.org/package=survminer

23 Iacopetta B: Are there two sides to colorectal cancer? Int J Cancer *101(5)*: 403-408, 2002. PMID: 12216066.

24 Bufill JA: Colorectal cancer: evidence for distinct genetic categories based on proximal or distal tumor location. Ann Intern Med *113(10)*: 779-788, 1990. PMID: 2240880.

25 Beart RW, Melton LJ 3rd, Maruta M, Dockerty MB, Frydenberg HB and O'Fallon WM: Trends in right and left-sided colon cancer. Dis Colon Rectum *26(6)*: 393-398, 1983. PMID: 6851801.

26 Delattre O, Olschwang S, Law DJ, Melot T, Remvikos Y, Salmon RJ, Sastre X, Validire P, Feinberg AP and Thomas G: Multiple genetic alterations in distal and proximal colorectal cancer. Lancet *2(8659)*: 353-361, 1989. PMID: 2569552.

27 Pocard M, Salmon RJ, Muleris M, Remvikos Y, Bara J, Dutrillaux B and Poupon MF: Two colons--two cancers? Proximal or distal denocarcinoma: arguments for a different carcinogenesis. Bull Cancer *82(1)*: 10-21, 1995. PMID: 7742609.

28 Distler P and Holt PR: Are right- and left-sided colon neoplasms distinct tumors? Dig Dis *15(4-5)*: 302-311, 1997. PMID: 9359 018.

29 Lindblom A: Different mechanisms in the tumorigenesis of proximal and distal colon cancers. Curr Opin Oncol *13(1)*: 63-69, 2001. PMID: 11148689.

30 Gervaz P, Bouzourene H, Cerottini JP, Chaubert P, Benhattar J, Secic M, Wexner S, Givel JC and Belin B: Dukes B colorectal cancer: distinct genetic categories and clinical outcome based on proximal or distal tumor location. Dis Colon Rectum *44(3)*: 364-372, 2001. PMID: 11289282.

31 Snaebjornsson P, Jonasson L, Jonsson T, Möller PH, Theodors A and Jonasson JG: Colon cancer in Iceland--a nationwide comparative study on various pathology parameters with respect to right and left tumor location and patients age. Int J Cancer *127(11)*: 2645-2653, 2010. PMID: 20162576. DOI: 10.1002/ijc.25258

32 Slattery ML, Pellatt DF, Mullany LE, Wolff RK and Herrick JS: Gene expression in colon cancer: A focus on tumor site and molecular phenotype. Genes Chromosomes Cancer *54(9)*: 527-541, 2015. PMID: 26171582. DOI: 10.1002/gcc.22265

33 Maus MK, Hanna DL, Stephens CL, Astrow SH, Yang D, Grimminger PP, Loupakis F, Hsiang JH, Zeger G, Wakatsuki T, Barzi A and Lenz HJ: Distinct gene expression profiles of proximal and distal colorectal cancer: implications for cytotoxic and targeted therapy. Pharmacogenomics J *15(4)*: 354-362, 2015. PMID: 25532759. DOI: 10.1038/tpj.2014.73

34 Yamauchi M, Morikawa T, Kuchiba A, Imamura Y, Qian ZR, Nishihara R, Liao X, Waldron L, Hoshida Y, Huttenhower C, Chan AT, Giovannucci E, Fuchs C and Ogino S: Assessment of colorectal cancer molecular features along bowel subsites challenges the conception of distinct dichotomy of proximal versus distal colorectum. Gut *61(6)*: 847-854, 2012. PMID: 22427238. DOI: 10.1136/gutjnl-2011-300865

35 Glebov OK, Rodriguez LM, Nakahara K, Jenkins J, Cliatt J, Humbyrd CJ, DeNobile J, Soballe P, Simon R, Wright G, Lynch P, Patterson S, Lynch H, Gallinger S, Buchbinder A, Gordon G, Hawk E and Kirsch IR: Distinguishing right from left colon by the pattern of gene expression. Cancer Epidemiol Biomarkers Prev *12(8)*: 755-762, 2003. PMID: 12917207.

36 Missiaglia E, Jacobs B, D'Ario G, Di Narzo AF, Soneson C, Budinska E, Popovici V, Vecchione L, Gerster S, Yan P, Roth AD, Klingbiel D, Bosman FT, Delorenzi M and Tejpar S: Distal and proximal colon cancers differ in terms of molecular, pathological, and clinical features. Ann Oncol *25(10)*: 1995-2001, 2014. PMID: 25057166. DOI: 10.1093/annonc/mdu275

37 LaPointe LC, Dunne R, Brown GS, Worthley DL, Molloy PL, Wattchow D and Young GP: Map of differential transcript expression in the normal human large intestine. Physiol Genomics *33(1)*: 50-64, 2008. PMID: 18056783.

38 Guinney J, Dienstmann R, Wang X, de Reyniès A, Schlicker A, Soneson C, Marisa L, Roepman P, Nyamundanda G, Angelino P, Bot BM, Morris JS, Simon IM, Gerster S, Fessler E, De Sousa E Melo F, Missiaglia E, Ramay H, Barras D, Homicsko K, Maru D, Manyam GC, Broom B, Boige V, Perez-Villamil B, Laderas T, Salazar R, Gray JW, Hanahan D, Tabernero J, Bernards R, Friend SH, Laurent-Puig P, Medema JP, Sadanandam A, Wessels L, Delorenzi M, Kopetz S, Vermeulen L and Tejpar S: The consensus molecular subtypes of colorectal cancer. Nat Med *21(11)*: 1350-1356, 2015. PMID: 26457759. DOI: 10.1038/ nm.3967

39 Yahagi M, Okabayashi K, Hasegawa H, Tsuruta M and Kitagawa Y: The worse prognosis of right-sided compared with left-sided colon cancers: A systematic review and meta-analysis. J Gastrointest Surg *20(3)*: 648-655, 2016. PMID: 26573851. DOI: 10.1007/s11605-015-3026-6

40 Holch JW, Ricard I, Stintzing S, Modest DP and Heinemann V: The relevance of primary tumour location in patients with metastatic colorectal cancer: A meta-analysis of first-line clinical trials. Eur J Cancer *70*: 87-98, 2017. PMID: 27907852. DOI: 10.1016/j.ejca.2016.10.007

Received August 1, 2019
Revised August 11, 2019
Accepted August 14, 2019