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SYSTEMIC THERAPIES IN COLORECTAL CANCER (RD KIM, SECTION EDITOR)

What Is the Best Systemic Therapy for Left-sided *RAS* Wild-type Metastatic Colorectal Cancer?

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Abstract

Purpose of Review There is a significant difference in embryological origin, gene expression, gene mutation profile, and microbiome between the right-sided and left-sided colon. It has been shown that the sidedness of primary colorectal cancer is a significant prognostic factor and predictive to the clinical benefit of anti-epidermal growth factor receptor (EGFR) antibody-containing chemotherapy in patients with metastatic CRC. Herein, current clinical recommendations for the treatment of patients with left-sided *RAS* wild-type mCRC are reviewed.

Recent Findings Retrospective analyses of prior randomized trials (CRYSTAL, PRIME, FIRE-3, CALGB 80405, and PEAK trials) showed that primary tumor sidedness is predictive to anti-EGFR antibody therapy in the first-line treatment of patients with *RAS* wild-type mCRC, and patients with left-sided *RAS* wild-type mCRC had a significantly better survival benefit with anti-EGFR antibody plus chemotherapy when compared with anti-VEGF treatment plus chemotherapy.

Summary The primary tumor sidedness is a significant prognostic factor and predictive to anti-EGFR antibody-containing chemotherapy in patients with metastatic CRC. Based on the currently available data, chemotherapy plus anti-EGFR antibody is recommended for the first-line treatment of patients with left-sided *RAS* wild-type mCRC. Chemotherapy plus bevacizumab or anti-EGFR antibody is recommended for the second-line therapy of *RAS* wild-type mCRC regardless of sidedness. However, these recommendations are based on the limited data from the retrospective analyses of prior trials, warranting further prospective randomized trials.

Keywords Colorectal cancer · Sidedness · EGFR · VEGF · FOLFOX · FOLFIRI · RAS · Left-sided · Metastatic · Chemotherapy

Introduction

Colorectal cancer (CRC) is a major public health problem in the USA and globally. In the USA, 140,000 new cases of CRC will be diagnosed in 2018, and nearly 50,000 deaths will be attributed to this disease [1]. Metastatic CRC (mCRC) is usually associated with poor prognosis, with 5-year survival rates in the 5–8% range. Systemic chemotherapy has been the main treatment modality for patients with mCRC. Considerable advances have been made for the clinical development of systemic chemotherapy options for patients with mCRC. The combinations of a fluoropyrimidine (5-FU or capecitabine) with either oxaliplatin (FOLFOX/XELOX) or irinotecan (FOLFIRI/XELIRI) have been widely accepted as standard cytotoxic chemotherapeutic regimens in combination with either anti-epidermal growth factor receptor (EGFR) antibody or anti-vascular endothelial growth factor (VEGF) antibody for the first- and second-line treatment of patients with mCRC [2–4].

The primary tumor sidedness is a significant prognostic marker and predictive to anti-EGFR antibody-containing chemotherapy in patients with metastatic CRC [5–10, 11••, 12–14]. A meta-analysis of 66 clinical trials showed that left-sided CRC is associated with a significantly reduced risk of death (hazard ratio [HR], 0.82; 95% confidence interval [95% CI], 0.79–0.84; $P < 0.001$), independent of tumor stage,

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and adjuvant chemotherapy [15]. Several phase 3 randomized clinical trials have shown that there is a clear difference in survival benefit by the primary tumor sidedness, especially with anti-EGFR antibody-containing chemotherapy [5–10, 11••]. Herein, current recommendations for the treatment of patients with left-sided *RAS* wild-type mCRC are reviewed.

Primary Tumor Sidedness

The colon has unique embryological development with the proximal part of the colon originated from the midgut and the remaining distal part from the hindgut with different blood circulation by superior mesenteric artery (SMA) and inferior mesenteric artery (IMA). There are also significant differences in gene mutation profiles, gene expression patterns, chromosomal aberration, and microbiome between the proximal and distal part of the colon [16••]. There is gradual difference in the distribution of intraluminal microbiome from proximal part to distal part of the colon with higher prevalence of *Fusobacterium*, *Escherichiae-Shigella* and *Leptotrichia* in left-side colon compared with right-side colon [17, 18].

There are several evidences showing that CRCs have different unique biological characteristics depending on the location of the primary tumors between right-sided and left-sided colon [19–21]. In general, primary CRCs distal to the splenic flexure are classified as left-sided tumors. Left-sided tumors harbor numerous large chromosomal alterations, including gain of 20q and loss of 18q, and the amplification of *EGFR* or *HER-2*, and more frequent overexpression of epiregulin [22••]. *EGFR* and *HER-2* amplification were observed in 12% of distal CRC. High expression of *EREG* and *AREG* in tumor tissues is associated with better clinical outcome with anti-EGFR antibody therapy in patients with *RAS* wild-type metastatic CRC [23–25]. Left-sided CRCs are associated with the activation of WNT and MYC pathways, and the presence of intestinal stem cells [22••]. Left-sided CRCs carry lower rates of microsatellite instability, less frequent aberrant activation of the EGFR pathway including lower *BRAF* and *PIK3CA* mutation rates, and decreased mutational burden when compared with right-sided tumors [26]. The mutation rates of *TP53*, *KRAS*, *BRAFV600*, *PIK3CA*, *SMAD4*, *CTNNB1*, *GNAS*, and *PTEN* differ by sidedness and location within the colon [27]. There are substantial variations in mutation rates within left-sided tumors, with more *TP53* mutations, but less *PIK3CA*, *BRAF*, and *CTNNB1* mutations in the sigmoid and rectal region [27]. Rectal cancers have higher rates of *TOPO1* expression and *HER-2* amplification compared to both left- and right-sided tumors [26].

First-line Treatment of Patients with Left-sided *RAS* Wild-type mCRC

Several prior randomized phase 3 trials have been analyzed retrospectively to investigate the predictive effect of primary tumor sidedness on the clinical outcome of the first-line treatment of patients with mCRC [5–10, 11••]. These analyses showed that primary tumor sidedness is predictive to the clinical benefit of anti-EGFR antibody-containing systemic chemotherapy in the first-line treatment of patients with *RAS* wild-type mCRC.

CRYSTAL Study

The CRYSTAL study was a randomized phase 3 trial to evaluate the efficacy and safety of cetuximab in combination with FOLFIRI chemotherapy in the first-line treatment of patients with mCRC. This study demonstrated that the addition of cetuximab to FOLFIRI chemotherapy significantly improved progression-free survival (PFS), OS, and overall response rate (ORR) in the first-line treatment of patients with *KRAS* wild-type mCRC [28–30]. A total of 280 patients in the CRYSTAL study population had left-sided *RAS* wild-type tumor (142 patients in FOLFIRI/cetuximab arm; 138 patients in FOLFIRI arm).

Retrospective analysis of the primary tumor sidedness in the CRYSTAL study population showed that the addition of cetuximab to FOLFIRI significantly improved PFS in the first-line treatment of patients with left-sided *RAS* wild-type mCRC in comparison with FOLFIRI alone (median PFS [mPFS], 8.9 months in FOLFIRI arm and 12.0 months in FOLFIRI/cetuximab arm; HR, 0.50; 95% CI, 0.34–0.72; $P < 0.001$) [31••]. OS was also significantly improved with the addition of cetuximab to FOLFIRI (median OS [mOS], 21.7 versus 28.7 months; HR, 0.65; 95% CI, 0.50–0.86; $P = 0.002$) [31••]. ORR was 40.6% in FOLFIRI arm and 72.5% in FOLFIRI/cetuximab arm [31••]. This retrospective analysis of the CRYSTAL study showed that the addition of cetuximab to FOLFIRI chemotherapy significantly improved PFS and OS in the first-line treatment of patients with left-sided *RAS* wild-type mCRC.

PRIME Study

The PRIME study was a phase 3 trial of panitumumab plus FOLFOX4 versus FOLFOX4 alone in the first-line treatment of patients with wild-type *KRAS* exon 2 mCRC [32]. Retrospective analysis of the PRIME study patients with left-sided *RAS* wild-type mCRC showed the addition of panitumumab to FOLFOX4 ($N = 169$) was associated with significant improvement in PFS (median PFS [mPFS], 12.9 versus 9.2 months; adjusted HR, 0.72; $P = 0.0048$) and OS (median OS [mOS], 30.3 versus 23.6 months; adjusted HR,

0.73; $P = 0.0112$) when compared with FOLFOX treatment alone ($N = 159$) [33••]. This retrospective analysis of the PRIME study showed that the addition of panitumumab to FOLFOX4 chemotherapy significantly improved both PFS and OS in the first-line treatment of patients with left-sided *RAS* wild-type mCRC.

These retrospective analyses of the PRIME and CRYSTAL studies showed that the addition of anti-EGFR antibody (either cetuximab or panitumumab) to doublet chemotherapy backbone (FOLFOX4 or FOLFIRI) improved PFS and OS in the first-line treatment of patients with left-sided *RAS* wild-type mCRC. The improved survival benefit with the addition of anti-EGFR antibody to cytotoxic chemotherapy backbone is not agent-specific but rather a class effect of anti-EGFR antibody therapy. And chemotherapy backbone of either oxaliplatin- or irinotecan-containing doublets seems to be equally active in combination with anti-EGFR antibody in the first-line treatment of patients with left-sided *RAS* wild-type mCRC.

PEAK Study

The PEAK trial was a phase 2 randomized study to investigate the clinical benefit of panitumumab plus mFOLFOX6 when compared with bevacizumab plus mFOLFOX6 in the first-line treatment of patients with wild-type *KRAS* exon 2 mCRC [34]. Subgroup analysis of patients with *RAS* wild-type tumor (wild-type exons 2, 3, and 4 of *KRAS* and *NRAS*) showed a significant improvement in PFS in the mFOLFOX6/panitumumab arm ($N = 88$) when compared with mFOLFOX6/bevacizumab arm ($N = 82$) (mPFS, 13.9 versus 9.5 months; HR, 0.65; 95% CI, 0.44–0.96; $P = 0.029$). However, there was no significant improvement in OS (mOS, 41.3 versus 28.9 months; HR, 0.63; 95% CI, 0.39–1.02; $P = 0.058$).

Retrospective analysis of patients with left-sided *RAS* wild-type mCRC did not show significant survival difference between mFOLFOX6 plus panitumumab and mFOLFOX6 plus bevacizumab in the first-line treatment of patients with left-sided *RAS* wild-type mCRC, with similar OS (mOS, 43.4 versus 32.0 months; adjusted HR, 0.77; $P = 0.3125$) and PFS (mPFS, 14.6 versus 11.5 months; adjuvant HR, 0.68; $P = 0.0732$) in mFOLFOX6 plus panitumumab and mFOLFOX6 plus bevacizumab, respectively [33••]. This analysis showed that mFOLFOX6 in combination with either anti-EGFR or anti-VEGF antibody have similar anti-tumor efficacy in the first-line treatment of patients with left-sided *RAS* wild-type mCRC.

CALGB/SWOG 80405 Study

CALGB/SWOG 80405 study was a phase 3 trial, which randomized 1074 patients with mCRC to bevacizumab plus chemotherapy (either mFOLFOX6 or FOLFIRI) or cetuximab plus chemotherapy (either mFOLFOX6 or FOLFIRI) in the first-line setting. Among patients with wild-type *KRAS* codons 12/13, there was no significant difference in OS and PFS between the addition of cetuximab versus bevacizumab to chemotherapy in the first-line treatment of mCRC [35].

Among 732 study patients with left-sided wild-type *KRAS* codons 12/13 mCRC, 356 patients received bevacizumab plus chemotherapy, and 376 patients received cetuximab plus chemotherapy [36••]. Retrospective analysis of the study patients with left-sided wild-type *KRAS* codons 12/13 mCRC showed that cetuximab plus chemotherapy was associated with improved PFS (mPFS, 12.4 versus 11.2 months; HR, 0.84; 95% CI, 0.72–0.98) and OS (mOS, 36.0 versus 31.4 months; HR, 0.817; 95% CI, 0.69–0.96; $P = 0.018$) when compared with bevacizumab plus chemotherapy [36••, 37]. This result has a limitation as it did not address the outcome of patients with left-sided *RAS* wild-type mCRC rather than wild-type *KRAS* codons 12/13 alone. Even with this limitation, it showed that anti-EGFR antibody-containing chemotherapy is more favorable than anti-VEGF-containing chemotherapy in the first-line treatment of patients with left-sided *KRAS* codons 12/13 wild-type mCRC.

FIRE-3 Study

The FIRE-3 trial was a randomized phase 3 trial to compare FOLFIRI plus cetuximab with FOLFIRI plus bevacizumab in the first-line treatment of patients with *KRAS* wild-type mCRC [38]. PFS was similar in both arms (mPFS, 10.0 months in FOLFIRI/cetuximab arm versus 10.3 months in FOLFIRI/bevacizumab arm; HR, 1.06; 95% CI, 0.88–1.26; $P = 0.55$), but OS was significantly improved in FOLFIRI/cetuximab arm (mOS, 28.7 months in FOLFIRI/cetuximab arm versus 25.0 months in FOLFIRI/bevacizumab arm; HR, 0.77; 95% CI, 0.62–0.96; $P = 0.017$) [38].

Retrospective analysis of the patients with left-sided *RAS* wild-type mCRC ($N = 306$) in the FIRE-3 trial, who were randomized to either FOLFIRI/cetuximab arm ($N = 157$) or FOLFIRI/bevacizumab arm ($N = 149$), showed that patients in the FOLFIRI/cetuximab arm had significantly improved OS when compared with those in the FOLFIRI/bevacizumab (mOS, 38.3 versus 28.0 months; HR, 0.63; 95% CI, 0.48–0.85; $P = 0.002$) [8, 11••, 39••]. However, there was no significant difference in ORR and PFS between these two arms, consistent with the data from the overall study population [8, 11••, 39••]. This retrospective data indicates that FOLFIRI plus cetuximab is a better choice of the first-line treatment for patients with left-sided *RAS* wild-type mCRC. This is somewhat consistent with the result of the CALGB/SWOG 80405 study in patients with wild-type *KRAS* codons 12/13, showing that anti-EGFR antibody plus doublet chemotherapy is preferred combination regimen for the first-line treatment of patients with left-sided *RAS* wild-type mCRC.

Meta-analysis

A meta-analysis of the PRIME and CRYSTAL trials showed that tumor sidedness was predictive of improved OS with the addition of anti-EGFR antibody to chemotherapy in patients with *RAS* wild-type mCRC (HR, 0.69; 95% CI, 0.58–0.83; $P < 0.0001$). A meta-analysis of FIRE-3/AIO KRK0306, CALGB/SWOG 80405 and PEAK trials indicated that patients with left-sided *RAS* wild-type mCRC had a significantly better survival benefit with anti-EGFR antibody plus chemotherapy when compared with anti-VEGF treatment plus chemotherapy (HR, 0.71; 95% CI, 0.58–0.85; $P = 0.0003$) [8].

Retrospective analysis of the prognostic and predictive influence of the sidedness in patients with *RAS* wild-type mCRC enrolled in six randomized trials (CRYSTAL, FIRE-3, CALGB 80405, PRIME, PEAK, and 20050181) showed that patients with left-sided *RAS* wild-type mCRC had significant improvement in OS (HR, 0.75; 95% CI, 0.67–0.84) and PFS (HR, 0.78; 95% CI, 0.70–0.87) with the addition of anti-EGFR antibody to the standard chemotherapy [11••].

These phase 3 trials evaluated different chemotherapy backbones, including oxaliplatin-based (FOLFOR or XELOX) and irinotecan-based (FOLFIRI) systemic chemotherapy, in the first-line setting. The role of chemotherapy backbone in relation to the primary tumor sidedness has not been fully evaluated with limited available data and warrants further study. The MAVERICC trial was a randomized phase 2 trial to assess the efficacy and safety of mFOLFOX6 plus bevacizumab versus FOLFIRI plus bevacizumab in the first-line treatment of patients with mCRC [40]. A total of 376 patients were randomized. In the overall study population, there was no significant difference in PFS and OS in either mFOLFOX6 plus bevacizumab arm or FOLFIRI plus bevacizumab arm. Among 222 randomized patients with left-sided tumor, 113 patients were randomized to mFOLFOX6 plus bevacizumab arm and 109 patients to FOLFIRI plus bevacizumab arm. There was significant improvement in PFS with FOLFIRI plus bevacizumab combination in the first-line treatment of patients with left-sided tumor when compared with mFOLFOX6 plus bevacizumab combination (mPFS, 13.8 in FOLFIRI/bevacizumab arm versus 10.2 in mFOLFOX6 plus bevacizumab arm; HR, 0.71; 95% CI, 0.51–0.98; $P = 0.040$) [40].

The retrospective analyses of prior phase II/III trials, especially FIRE-3 and CALGB/SWOG 80405, have shown that anti-EGFR antibody-containing systemic chemotherapy is associated with significantly better survival benefit in the first-line treatment of patients with left-sided *RAS* wild-type mCRC than anti-VEGF antibody plus systemic chemotherapy (Table 1). However, these data have limitations due to the nature of retrospective analysis with the possibility of imbalances in baseline characteristics and a small number of patients. The ESMO panel recommends chemotherapy doublet plus anti-EGFR antibody as preferred choice for the first-line treatment of patients with left-sided *RAS* wild-type mCRC [41••]. The NCCN guidelines recommend that only patients with left-sided mCRC (splenic flexure to rectum) should be offered cetuximab or panitumumab in the first-line treatment of mCRC [42••].

Second- or Later-line Treatments of Patients with Left-sided *RAS* Wild-type mCRC

There are limited data on the clinical outcome of the second-line or later treatment of patients with left-sided *RAS* wild-type CRC (Table 2). The 20050181 trial was a phase 3 trial in the second-line treatment of patients with *KRAS* wild-type mCRC to evaluate the effect of panitumumab plus FOLFIRI when compared with FOLFIRI alone [43, 44]. Panitumumab plus FOLFIRI had significant activity in the second-line treatment of patients with *RAS* wild-type mCRC. Retrospective analysis of patients with left-sided *RAS* wild-type mCRC in the 20050181 trial showed that the addition of panitumumab to FOLFIRI ($N = 150$) in the second-line treatment was associated with numerically better but statistically not significant improvement in PFS (mPFS, 8.0 versus 5.8 months; adjusted HR, 0.88; 95% CI, 0.69–1.12; $P = 0.3086$) and OS (mOS, 20.1 versus 16.6 months; adjusted HR, 0.96; 95% CI, 0.75–1.23; $P = 0.7388$) when compared with FOLFIRI alone ($N = 148$) [45••]. Further analysis of patients with left-sided *RAS* wild-type/*BRAF* wild-type mCRC did not show any significant improvement with the addition of panitumumab to FOLFIRI ($N = 143$) in PFS and OS when compared with FOLFIRI alone ($N = 144$) [45••].

In the FIRE-3 study, 33.7% of the patients with *KRAS* exon 2 wild-type tumors on the FOLFIRI/cetuximab arm received anti-VEGF-containing second-line therapy at the time of tumor progression, and 30.3% of the patients with *KRAS* exon 2 wild-type tumors in the FOLFIRI/cetuximab arm received anti-EGFR antibody-containing second-line therapy [39••]. Among patients with left-sided *KRAS* exon 2 wild-type tumors, FOLFIRI/cetuximab in the first-line followed by FOLFIRI/bevacizumab in the second-line was associated with significant improvement in the PFS of the second-line therapy (PFS2nd) when compared with the reverse sequence (FOLFIRI/bevacizumab in the first-line followed by FOLFIRI/cetuximab in the second-line), with median PFS2nd of 7.3 versus 5.8 months (HR = 0.59; 95% CI, 0.40–0.88; $P = 0.01$) [39••]. The OS of the second-line therapy (OS2nd) was also significantly better with FOLFIRI/cetuximab in the first-line followed by FOLFIRI/bevacizumab in the second-line when compared with the reverse sequence, with median OS2nd of 15.9 months versus 9.3 months. This result showed that FOLFIRI plus cetuximab is a preferred choice for the

Table 1 The first-line treatment of patients with left-sided *RAS* wild-type mCRC [11••, 31••, 33••]

Efficacy	CRYSTAL		PRIME		FIRE-3		CALGB 80405		PEAK	
	RAS WT left-sided tumors (*N* = 280)		*RAS* WT left-sided tumors (*N* = 328)		*RAS* WT left-sided tumors (*N* = 306)		*RAS* WT left-sided tumors (*N* = 325)		*RAS* WT left-sided tumors (*N* = 107)	
	FOLFIRI	FOLFIRI + Cet	FOLFOX4	FOLFOX4 + Pan	FOLFIRI + Bev	FOLFIRI + Cet	Chemo + Bev	Chemo + Cet	mFOLFOX6 + Bev	mFOLFOX6 + Pan
Number of patients	138	142	159	169	149	157	152	173	54	53
OS										
Median (months)	21.7	28.7	23.6	30.3	28.0	38.3	32.6	39.3	32.0	43.4
HR (95% CI)	0.65 (0.50–0.86)	0.73 (0.57–0.90)	0.63 (0.48–0.85)	0.77 (0.59–0.99)	0.77 (0.46–1.28)					
P value	0.002	0.011	0.002	0.05	0.31					
PFS										
Median (months)	8.9	12.0	9.2	12.9	10.7	10.7	11.2	12.7	11.5	14.6
HR (95% CI)	0.50 (0.34–0.72)	0.72 (0.57–0.90)	0.90 (0.71–1.14)	0.84 (0.66–1.06)	0.68 (0.45–1.04)					
P value	< 0.001	0.005	0.38	0.15	0.07					
ORR										
Rate (%)	40.6	72.5	52.6	67.9	61.7	68.8	57.9	69.4	57.4	64.2
Odds ratio (95% CI)	3.99 (2.40–6.62)	1.91 (1.33–2.72)	1.37 (0.85–2.19)	1.65 (1.16–2.34)	1.33 (0.57–3.11)					
P value	< 0.001	< 0.001	0.19	0.005	–					

RAS WT RAS wild-type, *Chemo* chemotherapy, *Cet* cetuximab, *Pan* panitumumab, Bev bevacizumab

Table 2 The second- or later-line treatment of patients with left-sided *RAS* or *KRAS* wild-type mCRC [45••]

Efficacy	20050181[45••]		FIRE-3 [39••]		NCIC CTG CO.17 [6]		20020408 [45••]	
	RAS WT left-sided tumors		*KRAS* exon 2 WT left-sided tumors		*KRAS* WT left-sided tumors		*RAS* WT left-sided tumors	
	FOLFIRI	FOLFIRI + Panitumumab	FOLFIRI + Bevacizumab	FOLFIRI + Cetuximab	BSC	BSC + Cetuximab	BSC	BSC + Panitumumab
Number of patients	148	150	84	60	45	60	43	42
OS								
Median (months)	16.6	20.1	9.7	15.9	4.8	10.1	8.8	9.4
HR (95% CI)	0.96 (0.75–1.23)		0.49 (0.31–0.77)	1.02 (0.64–1.63)				
P value	0.7388	0.007	0.002	0.9326				
PFS								
Median (months)	5.8	8.0	5.8	7.3	1.8	5.4	1.6	5.5
HR (95% CI)	0.88 (0.69–1.12)	0.59 (0.40–0.88)	0.28 (0.18–0.45)	0.31 (0.19–0.50)				
P value	0.3086	0.01	< 0.0001	< 0.0001				
ORR			–	–	–	–		
Rate (%)	13.2	49.7	–	–	–	–	0	23.8
Odds ratio (95% CI)	6.49 (3.52–12.26)	–	–	–	–	Infinity (3.51–infinity)		
P value	–	–	–	–	–	–		

RAS WT RAS wild-type, *KRAS WT KRAS* wild-type, *BSC* best supportive care

first-line treatment of patients with left-sided *KRAS* wild-type mCRC than FOLFIRI plus bevacizumab [39••, 41••]. This finding has a limitation as it did not include information about other *RAS* mutations.

The NCIC CTG CO.17 was a phase 3 trial of cetuximab versus best supportive care (BSC) in patients ($N = 572$) who had previously been treated with, or had contraindications to treatment with, a fluoropyrimidine, irinotecan, and oxaliplatin [46]. The addition of cetuximab to BSC improved OS and PFS in patients with *KRAS* wild-type chemo-refractory mCRC [47]. Retrospective analysis of patients with left-sided tumor ($N = 249$) enrolled in the NCIC CTG CO.17 trial showed that cetuximab treatment of patients with left-sided *KRAS* wild-type mCRC ($N = 60$) was associated with improved OS (mOS, 10.1 versus 4.8 months; HR, 0.49; 95% CI, 0.31–0.77; $P = 0.002$) and PFS (mPFS, 5.4 versus 1.8 months; HR, 0.28; 95% CI, 0.18–0.45; $P < 0.0001$) when compared with BSC alone ($N = 45$) [6]. Of note, patients with right-sided *KRAS* wild-type mCRC ($N = 56$) did not get any significant survival benefit with cetuximab when compared with BSC alone without any significant difference in mPFS (1.9 months in both groups) and mOS (6.2 versus 3.5 months; HR, 0.66; 95% CI, 0.36–1.21; $P = 0.18$) [6].

The 20020408 trial was a phase 3 trial to evaluate the benefit of panitumumab plus best supportive care (BSC) ($N = 231$) versus BSC alone ($N = 232$) in mCRC patients ($N = 463$) with disease progression during or within 6 months following the last administration of fluoropyrimidine, irinotecan, and oxaliplatin. Retrospective analysis of patients with left-sided *RAS* wild-type mCRC showed that panitumumab plus BSC ($N = 42$) in the third-line treatment of patients with left-sided *RAS* wild-type mCRC was associated with significant improvement in PFS (mPFS, 5.5 versus 1.6 months; HR, 0.31; 95% CI, 0.19–0.50; $P < 0.0001$) when compared with supportive care (BSC) alone [45••]. However, there was no significant difference in OS (mOS, 9.4 versus 8.8 months; HR, 1.02; 95% CI, 0.64–1.63; $P = 0.9326$), mainly due to a high cross-over rate (77%) of the BSC patients to panitumumab arm at tumor progression [45••]. Of note, patients with right-sided *RAS* wild-type mCRC did not get any significant survival benefit with the addition of panitumumab with no significant difference in mPFS (1.7 versus 1.5 months; HR, 0.50; 95% CI, 0.22–1.15; $P = 0.1029$) and mOS (3.1 versus 4.6 months; HR, 0.72; 95% CI, 0.31–1.66; $P = 0.4349$) [45••]. This result is consistent with improved survival with the addition of cetuximab in the NCIC CTG CO.17 trial, confirming that anti-EGFR antibody therapy improves survival in the third-line or later treatment of patients with left-sided *RAS* wild-type mCRC.

The results of retrospective analyses of prior randomized phase 3 trials in the second- or later-line treatment of patients with left-sided RAS wild-type mCRC are not

conclusive, requiring further research. The ESMO panel recommends that chemotherapy doublet plus bevacizumab or chemotherapy doublet plus anti-EGFR antibody are recommended as preferred choice for the second-line therapy of *RAS* wild-type mCRC regardless of sidedness [41••]. And chemotherapy doublet plus anti-EGFR antibody or irinotecan plus cetuximab is recommended as preferred choice for the third-line treatment of *RAS* wild-type mCRC regardless of sidedness [41••]. The NCCN guideline recommends that all patients with *RAS* wild-type mCRC can be considered for panitumumab or cetuximab in the second- or later-line of therapy if neither was previously given [42••].

Conclusion

The primary tumor sidedness is a significant prognostic marker and predictive to anti-EGFR antibody-containing chemotherapy in patients with metastatic CRC. Retrospective analyses of prior randomized trials (CRYSTAL, PRIME, FIRE-3, CALGB 80405, and PEAK trials) showed that primary tumor sidedness is predictive to anti-EGFR antibody therapy in the first-line treatment of patients with *RAS* wild-type mCRC [8, 11••]. Based on the currently available data, chemotherapy plus anti-EGFR antibody is recommended for the first-line treatment of patients with left-sided *RAS* wild-type mCRC (splenic flexure to rectum) [41••, 42••]. Chemotherapy plus bevacizumab or anti-EGFR antibody is recommended for the second-line therapy of *RAS* wild-type mCRC regardless of sidedness [41••, 42••]. However, the results of these retrospective analyses have limitations due to potential imbalance in the baseline characteristics and small sample size, warranting further prospective randomized trials. It has not been fully investigated whether cytotoxic chemotherapy backbones play a significant role in the clinical outcome based on primary tumor sidedness, warranting further study. Further research is necessary to elucidate the role of biologics in the second- and later-line treatment of patients with left-sided *RAS* wild-type mCRC.

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Compliance with Ethical Standards

Conflict of Interest The author declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
•• Of major importance

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. CA Cancer J Clin. 2018;68(1):7–30. https://doi.org/10.3322/caac.21442.
2. Lee JJ, Chu E. First-line use of anti-epidermal growth factor receptor monoclonal antibodies in metastatic colorectal cancer. Clin Colorectal Cancer. 2007;6(Suppl 2):S42–6. https://doi.org/10.3816/CCC.2007.s.001.
3. Lee JJ, Chu E. An update on treatment advances for the first-line therapy of metastatic colorectal cancer. Cancer J. 2007;13(5):276–81. https://doi.org/10.1097/PPO.0b013e3181570062.
4. Lee JJ, Sun W. Options for second-line treatment in metastatic colorectal cancer. Clin Adv Hematol Oncol. 2016;14(1):46–54.
5. O'Dwyer PJ, Manola J, Valone FH, Ryan LM, Hines JD, Wadler S, et al. Fluorouracil modulation in colorectal cancer: lack of improvement with N -phosphonoacetyl- l -aspartic acid or oral leucovorin or interferon, but enhanced therapeutic index with weekly 24-hour infusion schedule–an Eastern Cooperative Oncology Group/Cancer and Leukemia Group B Study. J Clin Oncol. 2001;19(9):2413–21.
6. 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. https://doi.org/10.1016/j.ejca.2015.03.015.
7. Loupakis F, Yang D, Yau L, Feng S, Cremolini C, Zhang W, Maus MKH, Antoniotti C, Langer C, Scherer SJ, Müller T, Hurwitz HI, Saltz L, Falcone A, Lenz HJ Primary tumor location as a prognostic factor in metastatic colorectal cancer. J Natl Cancer Inst 2015;107(3). doi:https://doi.org/10.1093/jnci/dju427.
8. Holch JW, Ricard I, Stintzing S, Modest DP, 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. 2017;70:87–98. https://doi.org/10.1016/j.ejca.2016.10.007.
9. 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). Anti-Cancer Drugs. 2014;25(2):212–8. https://doi.org/10.1097/CAD.0000000000000041.
10. 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. https://doi.org/10.1007/s00432-014-1678-3.
11.•• Arnold D, Lueza B, Douillard JY, Peeters M, Lenz HJ, Venook A, et al. Prognostic and predictive value of primary tumour side in patients with RAS wild-type metastatic colorectal cancer treated with chemotherapy and EGFR directed antibodies in six randomized trials. Ann Oncol. 2017;28(8):1713–29. https://doi.org/10.1093/annonc/mdx175 **This retrospective analysis of 6 randomized trials (CRYSTAL, FIRE-3, CALGB 80405, PRIME, PEAK, and 20050181) showed that patients with left-sided RAS wild-type mCRC had significant improvement in OS and PFS with the addition of anti-EGFR antibody to the standard chemotherapy**.

12. 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. https://doi.org/10.1634/theoncologist.2016-0084.
13. 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;16:327. https://doi.org/10.1186/s12885-016-2358-2.
14. Warschkow R, Sulz MC, Marti L, Tarantino I, Schmied BM, Cerny T, et al. Better survival in right-sided versus left-sided stage I - III colon cancer patients. BMC Cancer. 2016;16:554. https://doi.org/10.1186/s12885-016-2412-0.
15. Petrelli F, Tomasello G, Borgonovo K, Ghidini M, Turati L, Dallera P, et al. Prognostic survival associated with left-sided vs right-sided colon cancer: a systematic review and meta-analysis. JAMA Oncol. 2016. https://doi.org/10.1001/jamaoncol.2016.4227.
16.•• Stintzing S, Tejpar S, Gibbs P, Thiebach L, Lenz HJ. Understanding the role of primary tumour localisation in colorectal cancer treatment and outcomes. Eur J Cancer. 2017;84:69–80. https://doi.org/10.1016/j.ejca.2017.07.016 **This paper reviewed differences in the microbiome, chromosomal and molecular characteristics between the right and left side of the colon**.
17. Gao Z, Guo B, Gao R, Zhu Q, Qin H. Microbiota disbiosis is associated with colorectal cancer. Front Microbiol. 2015;6:20. https://doi.org/10.3389/fmicb.2015.00020.
18. Raskov H, Burcharth J, Pommergaard HC. Linking gut microbiota to colorectal cancer. J Cancer. 2017;8(17):3378–95. https://doi.org/10.7150/jca.20497.
19. Lee MS, Menter DG, Kopetz S. Right versus left colon cancer biology: integrating the consensus molecular subtypes. J Natl Compr Cancer Netw. 2017;15(3):411–9.
20. Weiss JM, Pfau PR, O'Connor ES, King J, LoConte N, Kennedy G, et al. Mortality by stage for right- versus left-sided colon cancer: analysis of surveillance, epidemiology, and end results–Medicare data. J Clin Oncol. 2011;29(33):4401–9. https://doi.org/10.1200/JCO.2011.36.4414.
21. Benedix F, Kube R, Meyer F, Schmidt U, Gastinger I, Lippert H, et al. 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. https://doi.org/10.1007/DCR.0b013e3181c703a4.
22.•• 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. https://doi.org/10.1093/annonc/mdu275 **This paper reviewed differences in key molecular features between the right-sided and left-sided colon**.
23. Khambata-Ford S, Garrett CR, Meropol NJ, Basik M, Harbison CT, Wu S, et al. Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. J Clin Oncol. 2007;25(22):3230–7. https://doi.org/10.1200/JCO.2006.10.5437.
24. Jacobs B, De Roock W, Piessevaux H, Van Oirbeek R, Biesmans B, De Schutter J, et al. Amphiregulin and epiregulin mRNA expression in primary tumors predicts outcome in metastatic colorectal cancer treated with cetuximab. J Clin Oncol. 2009;27(30):5068–74. https://doi.org/10.1200/JCO.2008.21.3744.
25. Seligmann JF, Elliott F, Richman SD, Jacobs B, Hemmings G, Brown S, et al. Combined Epiregulin and amphiregulin expression levels as a predictive biomarker for panitumumab therapy benefit or lack of benefit in patients with RAS wild-type advanced colorectal cancer. JAMA Oncol. 2016;2:633. https://doi.org/10.1001/jamaoncol.2015.6065.
26. Salem ME, Weinberg BA, Xiu J, El-Deiry WS, Hwang JJ, Gatalica Z, et al. Comparative molecular analyses of left-sided colon, right-sided colon, and rectal cancers. Oncotarget. 2017;8(49):86356–68. https://doi.org/10.18632/oncotarget.21169.
27. Loree JM, Pereira AAL, Lam M, Willauer AN, Raghav K, Dasari A, et al. Classifying colorectal cancer by tumor location rather than sidedness highlights a continuum in mutation profiles and consensus molecular subtypes. Clin Cancer Res. 2018;24(5):1062–72. https://doi.org/10.1158/1078-0432.CCR-17-2484.
28. Van Cutsem E, Kohne CH, Hitre E, Zaluski J, Chang Chien CR, Makhson A, et al. Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med. 2009;360(14):1408–17. https://doi.org/10.1056/NEJMoa0805019.
29. Van Cutsem E, Kohne CH, Lang I, Folprecht G, Nowacki MP, Cascinu S, et al. Cetuximab plus irinotecan, fluorouracil, and leucovorin as first-line treatment for metastatic colorectal cancer: updated analysis of overall survival according to tumor KRAS and BRAF mutation status. J Clin Oncol. 2011;29(15):2011–9. https://doi.org/10.1200/JCO.2010.33.5091.
30. Van Cutsem E, Lenz HJ, Kohne CH, Heinemann V, Tejpar S, Melezinek I, et al. Fluorouracil, leucovorin, and irinotecan plus cetuximab treatment and RAS mutations in colorectal cancer. J Clin Oncol. 2015;33(7):692–700. https://doi.org/10.1200/JCO.2014.59.4812.
31.•• 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. https://doi.org/10.1001/jamaoncol.2016.3797 **This retrospective analysis of the CRYSTAL and FIRE-3 trials showed that the addition of cetuximab to FOLFIRI chemotherapy significantly improved PFS and OS in the first-line treatment of patients with left-sided RAS wild-type mCRC**.
32. Douillard JY, Siena S, Cassidy J, Tabernero J, Burkes R, Barugel M, et al. Randomized, phase III trial of panitumumab with infusional fluorouracil, leucovorin, and oxaliplatin (FOLFOX4) versus FOLFOX4 alone as first-line treatment in patients with previously untreated metastatic colorectal cancer: the PRIME study. J Clin Oncol. 2010;28(31):4697–705. https://doi.org/10.1200/JCO.2009.27.4860.
33.•• Boeckx N, Koukakis R, Op de Beeck K, Rolfo C, Van Camp G, Siena S, et al. 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. 2017;28(8):1862–8. https://doi.org/10.1093/annonc/mdx119 **This retrospective analysis of the PRIME and PEAK trials showed that the addition of panitumumab to FOLFOX chemotherapy significantly improved both PFS and OS in the first-line treatment of patients with left-sided RAS wild-type mCRC**.
34. Schwartzberg LS, Rivera F, Karthaus M, Fasola G, Canon JL, Hecht JR, et al. PEAK: a randomized, multicenter phase II study of panitumumab plus modified fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) or bevacizumab plus mFOLFOX6 in patients with previously untreated, unresectable, wild-type KRAS exon 2 metastatic colorectal cancer. J Clin Oncol. 2014;32:2240–7. https://doi.org/10.1200/JCO.2013.53.2473.
35. Venook AP, Niedzwiecki D, Lenz HJ, Innocenti F, Fruth B, Meyerhardt JA, et al. 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. 2017;317(23):2392–401. https://doi.org/10.1001/jama.2017.7105.
36.•• Venook AP, Ou F-S, Lenz H-J, Kabbarah O, Qu X, Niedzwiecki D, et al. Primary (1°) tumor location as an independent prognostic

marker from molecular features for overall survival (OS) in patients (pts) with metastatic colorectal cancer (mCRC): Analysis of CALGB / SWOG 80405 (Alliance). J Clin Oncol. 2017;35(15_suppl):3503. https://doi.org/10.1200/JCO.2017.35.15_suppl.3503 **This analysis of CALGB/SWOG 80405 showed that anti-EGFR antibody-containing chemotherapy is more favorable than anti-VEGF-containing chemotherapy in the first-line treatment of patients with left-sided KRAS codons 12/13 wild-type mCRC**.

37. Innocenti F, Ou F-S, Zemla T, Niedzwiecki D, Qu X, Tam R, et al. Somatic DNA mutations, MSI status, mutational load (ML): association with overall survival (OS) in patients (pts) with metastatic colorectal cancer (mCRC) of CALGB/SWOG 80405 (Alliance). J Clin Oncol. 2017;35(15_suppl):3504. https://doi.org/10.1200/JCO.2017.35.15_suppl.3504.
38. Heinemann V, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, Al-Batran SE, et al. FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment for patients with metastatic colorectal cancer (FIRE-3): a randomised, open-label, phase 3 trial. Lancet Oncol. 2014;15(10):1065–75. https://doi.org/10.1016/S1470-2045(14)70330-4.
39.•• Modest DP, Stintzing S, von Weikersthal LF, Decker T, Kiani A, Vehling-Kaiser U, et al. 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. 2017;8(62):105749–60. https://doi.org/10.18632/oncotarget.22396 **This retrospective analysis of patients with left-sided KRAS exon 2 wild-type tumors in the FIRE-3 study population showed that FOLFIRI/cetuximab in the first-line followed by FOLFIRI/bevacizumab in the second-line is a preferred choice for the treatment of patients with left-sided KRAS wild-type mCRC than FOLFIRI/bevacizumab in the first-line followed by FOLFIRI/cetuximab in the second-line**.
40. Lenz H-J, Lee F-C, Yau L, Koh HA, Knost JA, Mitchell EP, 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(4_suppl):493. https://doi.org/10.1200/jco.2016.34.4_suppl.493.
41.•• Yoshino T, Arnold D, Taniguchi H, Pentheroudakis G, Yamazaki K, Xu RH, et al. Pan-Asian adapted ESMO consensus guidelines for the management of patients with metastatic colorectal cancer: a JSMO-ESMO initiative endorsed by CSCO, KACO, MOS, SSO and TOS. Ann Oncol. 2018;29(1):44–70. https://doi.org/10.1093/annonc/mdx738 **This is an update ESMO recommendation with specific recommendations of preferred treatment options for the first-, second-, and later-line treatments of patients with left-sided RAS wild-type mCRC**.
42.•• Benson AB, Venook AP, Cederquist L, Chan E, Chen Y-J, Cooper HS, et al. Colon cancer, version 1.2017, NCCN clinical practice guidelines in oncology. J Natl Compr Cancer Netw. 2017;15(3):370–98. https://doi.org/10.6004/jnccn.2017.0036 **This is an update NCCN recommendation with specific recommendations of preferred treatment options for mCRC based on sidedness**.
43. Peeters M, Price TJ, Cervantes A, Sobrero AF, Ducreux M, Hotko Y, et al. Randomized phase III study of panitumumab with fluoro-uracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. J Clin Oncol. 2010;28(31):4706–13. https://doi.org/10.1200/JCO.2009.27.6055.
44. Peeters M, Oliner KS, Price TJ, Cervantes A, Sobrero AF, Ducreux M, et al. Analysis of KRAS/NRAS mutations in a phase III study of panitumumab with FOLFIRI compared with FOLFIRI alone as second-line treatment for metastatic colorectal cancer. Clin Cancer Res. 2015;21(24):5469–79. https://doi.org/10.1158/1078-0432.CCR-15-0526.
45.•• Boeckx N, Koukakis R, Op de Beeck K, Rolfo C, Van Camp G, Siena S, et al. Effect of primary tumor location on second- or later-line treatment outcomes in patients with RAS wild-type metastatic colorectal cancer and all treatment lines in patients with RAS mutations in four randomized panitumumab studies. Clin Colorectal Cancer. 2018. https://doi.org/10.1016/j.clcc.2018.03.005 **This is a retrospective analysis of two phase 3 trials in the second- or later-line treatment of patients with mCRC (20050181 and 20020408 trials), showing that anti-EGFR antibody therapy improves survival in the third-line or later treatment of patients with left-sided RAS wild-type mCRC**.
46. Jonker DJ, O'Callaghan CJ, Karapetis CS, Zalcberg JR, Tu D, Au HJ, et al. Cetuximab for the treatment of colorectal cancer. N Engl J Med. 2007;357(20):2040–8. https://doi.org/10.1056/NEJMoa071834.
47. Karapetis CS, Khambata-Ford S, Jonker DJ, O'Callaghan CJ, Tu D, Tebbutt NC, et al. K-ras mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med. 2008;359(17):1757–65. https://doi.org/10.1056/NEJMoa0804385.