CURRENT ONCOLOGY
A Canadian Cancer Research Journal

PRACTICE GUIDELINE

The predictive effect of primary tumour location in the treatment of metastatic colorectal cancer: a Canadian consensus statement

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ABSTRACT

In recently published data, the predictive value of primary tumour location for the treatment of metastatic colorectal cancer with available biologic therapies has been explored. Recognizing the potential effect of those data on clinical practice, we convened a meeting of Canadian experts who treat metastatic colorectal cancer to develop a set of national, evidence-based treatment guidelines based on primary tumour location. This report summarizes the relevant evidence and presents the consensus recommendations of those experts.

Key Words Metastatic colorectal cancer, primary tumour location, tumour side, prognostic value, predictive value, EGFR monoclonal antibodies, *RAS* wild-type, consensus statements

Curr Oncol. 2017 Dec;24(6):390-400 www.current-oncology.com

INTRODUCTION

Purpose

The purpose of the national meeting reported here was to develop a set of national, evidence-based guidelines for the treatment of metastatic colorectal cancer (MCRC) based on primary tumour location (PTL). Here, we summarize the evidence with respect to this topic and present the consensus recommendations of the Canadian MCRC experts who attended the meeting.

Participants

A representative group of gastrointestinal medical oncology experts from across Canada was invited to attend. A group of 12 medical oncologists formed the consensus expert panel, which also received input from 10 additional experts (Table I).

Target Audience

The target audience for this report includes

- medical oncologists involved in the treatment of MCRC,
- patient advocacy and education groups such as Colorectal Cancer Canada, and
- provincial or jurisdictional cancer agencies and funding bodies.

SUMMARY OF THE EVIDENCE

Colorectal cancer is the second leading cause of cancer death in the Western world[1]. Despite improvements in screening and diagnosis, approximately 10%–15% of patients present with synchronous metastatic disease, and 25%–40% of patients originally diagnosed with potentially curable disease will develop metastases[2]. In recent years, several clinical and molecular markers that influence outcomes and guide treatment decisions have been identified. Of those markers, PTL has regained considerable attention.

The hypothesis that proximal and distal colorectal cancers represent distinct entities originated in the late 1980s[3–5]. Anatomically, the right and left colon arise from different embryonic origins: The proximal colon arises from the midgut and receives its main blood supply by way of the superior mesenteric artery. The distal colon arises from the hindgut and is supplied by way of the inferior mesenteric artery. A variety of histologic[6,7], genetic[8–11], and clinical[12–14] differences between the left and the right colon have been described. Several recent studies, including two meta-analyses, have shown that prognosis is worse for patients with metastatic right-sided colon cancer (RCC) than for those with left-sided disease (LCC)[12–14].

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Earlier work has shown that PTL might influence response to various targeted treatments. That hypothesis is based on evidence that RCC and LCC have different molecular characteristics that could affect sensitivity to given targeted agents[15,16]. Recently, several retrospective analyses of pivotal clinical trials involving the anti–epidermal growth factor receptor (EGFR) monoclonal antibodies (mAbs) cetuximab and panitumumab and the anti–vascular endothelial growth factor (VEGF) inhibitor bevacizumab have evaluated the predictive value of PTL.

Here, we summarize the available evidence for the predictive value of PTL for treatment with EGFR mAbs and bevacizumab in patients with MCRC.

TABLE I Participants at the National Colorectal Cancer Sidedness Consensus Meeting, 28 April 2017, Toronto, Ontario

Participant	Affiliation
Chairs	
Scott Berry	Medical oncologist, Sunnybrook Health Sciences Centre, Odette Cancer Centre, Toronto, ON
Jim Biagi	Medical oncologist, Queen's University, Kingston, ON
Bruce Colwell	Medical oncologist, Dalhousie University, Halifax, NS
Consensus expert panel	
Sharlene Gill	Medical oncologist, BC Cancer Agency, Vancouver, BC
Dan Renouf	Medical oncologist, BC Cancer Agency, Vancouver, BC
Patricia Tang	Medical oncologist, Tom Baker Cancer Centre, Calgary, AB
Winson Cheung	Medical oncologist, Tom Baker Cancer Centre, Calgary, AB
Shaheed Ahmed	Medical oncologist, Saskatchewan Cancer Agency, Saskatoon, SK
Ralph Wong	Medical oncologist, CancerCare Manitoba, Winnipeg, MB
Scott Berry	Medical oncologist, Sunnybrook Health Sciences Centre, Odette Cancer Centre, Toronto, ON
Jim Biagi	Medical oncologist, Queen's University, Kingston, ON
Bruce Colwell	Medical oncologist, Dalhousie University, Halifax, NS
Samantha Gray	Medical oncologist, Horizon Health Network, Saint John, NB
Mahmoud Abdelsalam	Medical oncologist, Moncton City Hospital, Moncton, NS
Mustapha Tehfe	Medical oncologist, Centre hospitalier de l'université de Montréal, Montreal, QC
Additional experts	
Brandon Meyers	Medical oncologist, Juravinski Cancer Centre, Hamilton, ON
Stephen Welch	Medical oncologist, London Health Sciences Centre, London, ON
Mohammed Harb	Medical oncologist, Moncton City Hospital, Moncton, NS
Tim Asmis	Medical oncologist, The Ottawa Hospital, Ottawa, ON
Rachel Goodwin	Medical oncologist, The Ottawa Hospital, Ottawa, ON
Michael Vickers	Medical oncologist, The Ottawa Hospital, Ottawa, ON
Chris Booth	Medical oncologist, Kingston General Hospital, Kingston, ON
Mark Rother	Medical oncologist, Credit Valley Hospital, Mississauga, ON
Observers	
Michele Caveen	Amgen
Manny Chohan	Amgen
Denis Gaudreault	Amgen
Brad Gillesby	Amgen
Diana Mak	Amgen
Barry Stein	Colorectal Cancer Canada
Lauren Lazowski	Eli Lilly Canada Inc.
Amy Lee Chong	Eli Lilly Canada Inc.
Christopher Thomson	Eli Lilly Canada Inc.
Laura Thorpe	Eli Lilly Canada Inc.
Brett Hogan	Roche Canada
Mark Moroz	Roche Canada
David Merritt	Roche Canada
Editors	
Ana B.K. Abrahao	Medical oncology fellow, Sunnybrook Health Sciences Centre, Odette Cancer Centre, Toronto, ON
Safiya Karim	Medical oncology fellow, Queen's University, Kingston, ON

Effect of PTL on Therapy with EGFR mAbs

The trials of EGFR mAbs in *RAS* wild-type tumours are summarized in Table II.

First Line

The EGFR mAbs cetuximab and panitumumab have been shown to improve outcomes in mCRC. The randomized phase III CRYSTAL trial studied the combination of cetuximab and FOLFIRI (folinic acid–5-fluorouracil–irinotecan) compared with FOLFIRI alone in the first-line treatment of patients with *RAS* wild-type mCRC. With the addition of cetuximab, improvements were observed in overall survival (OS), progression-free survival (PFS), and the overall response rate (ORR)[17,25].

A study looking at the influence of PTL in the population of the CRYSTAL trial was recently published[18]. Baseline characteristics in the patients with LCC were relatively balanced; however, in patients with RCC, several differences between the treatment groups appeared to favour the FOLFIRI arm. Those differences in the FOLFIRI-only group included more patients having an Eastern Cooperative Oncology Group performance status of 0, measurements of the index metastatic lesion that were shorter, fewer patients having received prior adjuvant therapy, and patients receiving more subsequent lines of cancer treatment—factors that were neither adjusted nor controlled for in the analysis.

Patients with LCC receiving cetuximab experienced significant benefits in ORR [72.5% vs. 40.6%; odds ratio (OR): 3.99; 95% CI: 2.40 to 6.62; $p < 0.001$], PFS [12.0 months vs. 8.9 months; hazard ratio (HR): 0.50; 95% CI: 0.34 to 0.72; $p < 0.001$], and OS duration (28.7 months vs. 21.7 months; HR: 0.65; 95% CI: 0.50 to 0.86; $p = 0.002$). Although the analysis was limited by a small sample size, the same benefit was not observed for patients in the cetuximab arm with RCC, with the differences in ORR (42.4% vs. 33.3%; OR: 1.45; 95% CI: 0.58 to 3.64; $p = 0.43$), PFS (8.1 months vs. 7.1 months; HR: 0.87; 95% CI: 0.47 to 1.62; $p = 0.66$), and OS duration (18.5 months vs. 15 months; HR: 1.08; 95% CI: 0.65 to 1.81; $p = 0.76$) being nonsignificant. The authors reported a significant interaction with respect to PFS and OS, but not ORR, between PTL and treatment.

The randomized phase III PRIME trial showed that the combination of FOLFOX (folinic acid–5-fluorouracil–oxaliplatin) and panitumumab given as first-line treatment was associated with improved OS duration and PFS in patients with *RAS* wild-type mCRC[20]. A retrospective analysis of the PRIME study based on PTL was recently published by Boeckx and colleagues[26,27]. Hazard ratios were adjusted for *BRAF* status, prior adjuvant treatment, and baseline Eastern Cooperative Oncology Group performance status. The addition of panitumumab was associated with an improved median OS duration in patients with LCC (30.3 months vs. 23.6 months; HR: 0.73; 95% CI: 0.57 to 0.93). However, in patients with RCC, no benefit in OS duration was associated with combination treatment (11.1 months vs. 15.4 months; HR: 0.87; 95% CI: 0.55 to 1.37). Similarly, the addition of panitumumab was associated with improved PFS in patients with LCC (12.9 months vs. 9.2 months; HR: 0.72; 95% CI: 0.57 to 0.9), but not in those with RCC (7.5 months vs. 7.0 months; HR: 0.8; 95% CI: 0.50 to 1.26). Similar results for OS duration and for PFS were seen when *BRAF*-mutant tumours were excluded.

Second Line

In the second-line setting, the combination of chemotherapy and panitumumab was studied in the 20050181 trial[21,22]. The combination of FOLFIRI and the EGFR mAb was associated with improved ORR and PFS (OS duration was not significantly different). The analysis by tumour location did not uncover a significant difference in OS duration between treatments for either LCC or RCC (LCC HR: 0.96; 95% CI: 0.74 to 1.23; RCC HR: 1.14; 95% CI: 0.68 to 1.89). Similar results were observed for PFS[28]. Exclusion of patients with *BRAF*-mutant tumours did not significantly affect those results. Moreover, an analysis of PTL in the PICCOLO trial (irinotecan plus panitumumab as second- or third-line treatment) did not demonstrate an interaction between panitumumab treatment effect and PTL[23,29].

Third Line

The randomized phase III NCIC CO.17 trial demonstrated an improvement in OS duration by 4.7 months with the use of single-agent cetuximab compared with best supportive care in patients with *KRAS* wild-type, chemotherapy-refractory disease[24]. Brulé *et al.*[14] undertook a retrospective analysis of that study to examine outcomes according PTL. They showed that, compared with best supportive care in patients with LCC, treatment with cetuximab was associated with significantly improved OS duration (10.1 months vs. 4.8 months; HR: 0.49; 95% CI: 0.31 to 0.77; $p = 0.002$) and PFS (5.4 months vs. 1.8 months; HR: 0.28; 95% CI: 0.18 to 0.45; $p < 0.0001$). However, no statistical difference in either OS duration or PFS was observed in patients with RCC (OS: 6.2 months vs. 3.5 months; HR: 0.66; 95% CI: 0.36 to 1.21; $p = 0.18$; PFS: 1.9 months vs. 1.9 months; HR: 0.73; 95% CI: 0.42 to 1.27; $p = 0.26$).

Table III summarizes the analyses of PTL in trials with EGFR mAbs.

Effect of PTL on Therapy with Bevacizumab

The randomized phase III MAX trial from the Australasian Gastrointestinal Trials Group (Table IV) evaluated capecitabine as a single agent or in combination with bevacizumab, with a third arm adding mitomycin C in the first-line treatment of mCRC. In the overall population, the combination of capecitabine and bevacizumab was associated with significantly prolonged PFS and a trend toward improved OS and ORR[30,31]. A subgroup analysis of the trial presented at the European Society for Medical Oncology meeting in 2014 showed HRs for PFS of 0.82 in RCC (95% CI: 0.54 to 1.22) and 0.51 in LCC (95% CI: 0.4 to 0.63), with $p = 0.10$ for interaction. Similarly, interaction tests for tumour location and bevacizumab treatment were nonsignificant for OS duration, PFS, and ORR in the first-line NO16966 trial (capecitabine–oxaliplatin or FOLFOX ± bevacizumab) and the AVF2107g trial (FOLFIRI ± bevacizumab)[32].

Impact of PTL on Therapy with Either EGFR mAbs or Bevacizumab

Three prospective randomized trials have examined the benefit of an EGFR mAb or bevacizumab combined with chemotherapy in the first-line setting (Table V). Results from the combined Cancer and Leukemia Group B (CALGB) and Southwest Oncology Group (SWOG) 80405 trial showed

TABLE II Trials with EGFR monoclonal antibodies

Reference	Treatment	Pts (*n*)	*RAS* analysis (%)	*RAS* wild-type population											
				Overall response rate				Progression-free survival				Overall survival			
				(%)	HR/OR	95% CI	*p* Value	(months)	HR/OR	95% CI	*p* Value	(months)	HR/OR	95% CI	*p* Value
First line															
CRYSTAL, 2009[17]	FOLFIRI–Cmab	599	45	46.9	1.4	1.12 to 1.17	0.004	8.9	0.85	0.72 to 0.99	0.048	19.9	0.93	0.81 to 1.07	0.31
	FOLFIRI	599	(*KRAS*)	38.7				8.0				18.6			
CRYSTAL, 2015 (update)[18]	FOLFIRI–Cmab	316	64	66.3	3.11	2.03 to 4.78	<0.001	11.4	0.56	0.41 to 0.76	<0.001	28.4	0.69	0.54 to 0.89	0.002
	FOLFIRI	350	(*KRAS, NRAS*)	38.6				8.4				20.2			
PRIME, 2010[19]	FOLFOX–Pmab	593	93	55.0	1.55		0.68	9.6	0.80	0.66 to 0.97	0.02	23.7	0.83	0.67 to 1.02	0.072
	FOLFOX	590	(*KRAS*)	48.0				8.0				19.7			
PRIME, 2013 (update)[20]	FOLFOX–Pmab	546	90	Data not available				10.1	0.72	0.58 to 0.90	0.004	26.0	0.78	0.62 to 0.99	0.04
	FOLFOX	550	(*KRAS, NRAS*)					7.9				20.2			
Second line															
20050181, 2010[21]	FOLFIRI–Pmab	591	91	35.0			<0.0001	5.9	0.73	0.59 to 0.90	0.004	14.5	0.85	0.70 to 1.04	0.12
	FOLFIRI	595	(*KRAS*)	10.0				3.9				12.5			
20050181, 2014 (update)[22]	FOLFIRI–Pmab	591	91	36.0	5.50	3.32 to 8.87	<0.0001	6.7	0.82	0.69 to 0.97	0.023	11.8	0.93	0.77 to 1.13	0.48
	FOLFIRI	595	(*KRAS*)	10.0				4.9				11.1			
PICCOLO, 2013[23]	Irinotecan–Pmab	230	100	34			<0.0001	Favours	0·78	0·64 to 0·95	0·015	10.4	1.01	0.83 to 1.23	0.91
	Irinotecan	230	(*KRAS*)	12				Irinotecan–Pmab				10.9			
	(2nd and 3rd line)														
Third line															
CO.17, 2008[24]	Cetuximab	287	69	12.8		Not reported		3.7	0.40	0.3 to 0.54	<0.001	9.5	0.55	0.41 to 0.74	<0.001
	BSC	285		0				1.9				4.8			

Pts = patients; HR = hazard ratio; OR = odds ratio; CI = confidence interval; FOLFIRI = folinic acid–5-fluorouracil–irinotecan; Cmab = cetuximab; FOLFOX = folinic acid–5-fluorouracil–oxaliplatin; Pmab = panitumumab.

TABLE III Analysis of primary tumour location in trials with EGFR monoclonal antibodies

Variable	Results of monoclonal antibody studies by tumour location															
	CRYSTAL[17] (FOLFIRI±cetuximab, first line)				PRIME[19] (FOLFOX±panitumumab, first line)				20050181[21] (FOLFIRI±panitumumab, second line)				CO.17[24] (cetuximab vs. BSC, third line)			
	Cetuximab use				Panitumumab use				Panitumumab use				Cetuximab use			
	Left-sided		Right-sided		Left-sided		Right-sided		Left-sided		Right-sided		Left-sided		Right-sided	
	Yes (*n*=142)	No (*n*=138)	Yes (*n*=33)	No (*n*=51)	Yes (*n*=81)	No (*n*=76)	Yes (*n*=19)	No (*n*=24)	Yes (*n*=83)	No (*n*=79)	Yes (*n*=17)	No (*n*=21)	Yes (*n*=105)	No (*n*=105)	Yes (*n*=56)	No (*n*=56)
ORR (%)	72.5	40.6	42.4	33.3	68.0	53.0	42.0	35.0	50.0	13.0	13.3	2.6	Data not available			
OR	3.99		1.45		1.9		1.36		6.49		5.69					
95% CI	2.40 to 6.62		0.58 to 3.64		1.30 to 2.27		0.6 to 3.1		3.73 to 11.3		0.60 to 53.6					
p Value	<0.001		0.43		<0.001		0.46		<0.001		0.13					
PFS (months)	12.0	8.9	8.1	7.1	12.9	9.2	7.5	7.0	8.0	5.8	4.8	2.4	5.4	1.8	1.9	1.9
HR	0.50		0.87		0.72		0.8		0.88		0.75		0.28		0.73	
95% CI	0.34 to 0.72		0.47 to 1.62		0.57 to 0.90		0.50 to 1.26		0.69 to 1.12		0.45 to 1.27		0.18 to 0.45		0.42 to 1.27	
p Value	<0.001		0.66		0.005		0.33						<0.0001		0.26	
OS (months)	28.7	21.7	18.5	15.0	30.3	23.6	11.1	15.4	20.1	16.6	10.3	8.1	10.1	4.8	6.2	3.5
HR	0.65		1.08		0.73		0.87		0.96		1.14		0.49		0.66	
95% CI	0.50 to 0.86		0.65 to 1.81		0.57 to 0.93		0.55 to 1.37		0.74 to 1.23		0.68 to 1.89		0.31 to 0.77		0.36 to 1.21	
p Value	0.002		0.76		0.012		0.55						0.002		0.18	

FOLFIRI = folinic acid–5-fluorouracil–irinotecan; FOLFOX = folinic acid–5-fluorouracil–oxaliplatin; BSC = best supportive care; ORR = overall response rate; OR = odds ratio; CI = confidence interval; PFS = progression-free survival; HR = hazard ratio; OS = overall survival.

TABLE IV Trials with bevacizumab

Study	Treatment	Pts (*n*)	*RAS* analysis (%)	*RAS* wild-type population											
				Overall response rate				Progression-free survival				Overall survival			
				(%)	HR/OR	95% CI	*p* Value	(months)	HR/OR	95% CI	*p* Value	(months)	HR/OR	95% CI	*p* Value
AGITG MAX, 2010[30]	Capecitabine	578	NA	30.0			0.16	5.7	0.63	0.50 to 0.79	<0.001	18.9	0.87	0.67 to 1.3510.31	
	Capecitabine–Bev	559		38.1				8.5				18.9			

Pts = patients; HR = hazard ratio; OR = odds ratio; CI = confidence interval; AGITG = Australasian Gastrointestinal Trials Group; Bev = bevacizumab; NA = not available.

TABLE V Trials with bevacizumab and EGFR monoclonal antibodies

Study	Treatment	Pts (*n*)	*RAS* analysis (%)	*RAS* wild-type population									
				Overall response rate			Progression-free survival			Overall survival			
				(%)	HR/OR	95% CI	*p* Value	(months)	HR/OR	95% CI	*p* Value	(months)	HR/OR	95% CI	*p* Value
First line															
CALGB/SWOG 80405, 2014[12]	FOLFOX or FOLFIRI-Cmab	578	100	Data not available				10.4	1.04	0.91 to 1.17	0.55	29.9	0.92	0.78 to 1.09	0.34
	FOLFOX or FOLFIRI–Bev	559	(*KRAS*)					10.8				29.0			
FIRE-3, 2015[33]	FOLFIRI–Cmab	297	69	62.0	1.18	0.85 to 1.64	0.18	10.4	1.06	0.88 to 1.26	0.55	33.1	0.77	0.62 to 0.96	0.02
	FOLFIRI–Bev	295	(*KRAS*)	58.0				10.2				25.6			
PEAK, 2014[34]	FOLFOX-Pmab	142	100	57.8				10.9	0.87	0.85 to 1.17	0.35	34.2	0.62	0.44 to 0.89	0.009
(phase II)	FOLFOX-Bev	143	(*KRAS*)	53.3				10.1				24.3			

Pts = patients; HR = hazard ratio; OR = odds ratio; CI = confidence interval; FOLFOX = folinic acid–5-fluorouracil–oxaliplatin; FOLFIRI = folinic acid–5-fluorouracil–irinotecan; Cmab = cetuximab; Bev = bevacizumab; Pmab = panitumumab.

no difference in OS duration or PFS with chemotherapy (FOLFIRI or FOLFOX) plus cetuximab or bevacizumab as first-line therapy[35]. A retrospective analysis of PTL in that trial was first presented at the 2016 American Society of Clinical Oncology annual meeting[36] and updated in a recently published meta-analysis[28]. Those analyses showed that, in patients with LCC, treatment with cetuximab was associated with a median OS duration of 39.3 months; treatment with bevacizumab was associated with a median OS duration of 32.6 months (HR: 0.77; $p = 0.04$). However, in patients with RCC, treatment with cetuximab was associated with a median OS duration of only 13.9 months; treatment with bevacizumab was associated with an OS duration of 29.2 months (HR: 1.36; $p = 0.10$). The PTL was observed to be similarly associated with PFS: patients with LCC experienced a nonsignificant improvement in PFS (HR: 0.84; $p < 0.15$) with cetuximab, and patients with RCC experienced worse PFS (HR: 1.64; $p = 0.006$) with cetuximab.

The FIRE-3 trial demonstrated that, in the first-line setting, compared with FOLFIRI plus bevacizumab, FOLFIRI plus cetuximab was associated with improved OS[33]. A retrospective analysis looking at the effect of PTL in that trial was recently published in *JAMA Oncology*[18]. Among patients with LCC, the median OS duration was significantly longer for those treated with FOLFIRI plus cetuximab than for those treated with FOLFIRI plus bevacizumab (38.3 months vs. 28.0 months; HR: 0.63; $p = 0.002$). Conversely, the median OS duration was shorter (although not statistically significantly so) in patients with RCC treated with first-line cetuximab than in those treated with bevacizumab (18.3 months vs. 23.0 months; HR: 1.31; $p = 0.28$). The ORR and PFS did not appear to differ between the treatments in either LCC or RCC.

Finally, in the PEAK trial, panitumumab was compared with bevacizumab, both in combination with FOLFOX; an improvement in PFS was observed in patients treated with panitumumab[34]. In addition, chemotherapy plus panitumumab yielded a statistically nonsignificant improvement in OS duration.

The effect of PTL in that trial was recently published[27]. After the HRS were adjusted for *BRAF* status, prior adjuvant treatment, and baseline Eastern Cooperative Oncology Group performance status, the investigators showed that, in patients with LCC, a statistically nonsignificant improvement in median OS duration was associated with panitumumab (43.4 months vs. 32.0 months with bevacizumab; HR: 0.77; 95% CI: 0.46 to 1.28; $p = 0.31$). In patients with RCC, no clear signal of median OS duration benefit was evident (17.5 months vs. 21.0 months; HR: 0.67; 95% CI: 0.30 to 1.50; $p = 0.32$). A nonsignificant trend toward improvement in PFS was observed for patients with LCC treated with panitumumab (14.6 months vs. 11.5 months; HR: 0.68; 95% CI: 0.45 to 1.04; $p = 0.07$). In patients with RCC, the PFS associated with the two treatments did not differ (8.7 months with panitumumab vs. 12.6 months with bevacizumab; HR: 1.04; 95% CI: 0.50 to 2.18; $p = 0.90$). The foregoing results did not change significantly when patients with *BRAF*-mutant disease were excluded from the analysis. The small number of patients with RCC in the trial ($n = 36$) likely limited the analysis by PTL.

Table VI summarizes the effect of PTL in trials with bevacizumab and EGFR mAbs.

TABLE VI Analysis of primary tumour location in first-line trials comparing EGFR monoclonal antibodies with bevacizumab

Variable	CALGB/SWOG 80405[12] (FOLFOX or FOLFIRI with cetuximab vs. FOLFOX or FOLFIRI with bevacizumab)				FIRE-3[33] (FOLFIRI with cetuximab vs. FOLFIRI with bevacizumab)				PEAK[34] (FOLFOX with panitumumab vs. FOLFOX with bevacizumab)			
	Left-sided		Right-sided		Left-sided		Right-sided		Left-sided		Right-sided	
	Cmab (*n*=173)	Bev (*n*=152)	Cmab (*n*=71)	Bev (*n*=78)	Cmab (*n*=157)	Bev (*n*=149)	Cmab (*n*=38)	Bev (*n*=50)	Pmab (*n*=53)	Bev (*n*=54)	Pmab (*n*=22)	Bev (*n*=14)
ORR (%)	69.4	57.9	42.3	39.7	69.0	62.0	52.6	50.0	64.2	57.4	63.6	50.0
OR	1.65		1.11		1.37		1.11		1.33		1.75	
95% CI	1.16 to 2.34		0.61 to 2.01		0.85 to 2.19		0.48 to 2.59		0.57 to 3.11		0.36 to 8.39	
p Value	0.005		0.73		0.23		0.83					
PFS (months)	12.7	11.2	7.5	10.5	10.7	10.7	7.6	9.0	14.6	11.5	8.7	12.6
HR	0.84		1.64		0.90		1.44		0.68		1.04	
95% CI	0.66 to 1.06		1.15 to 2.36		0.71 to 1.14		0.92 to 2.26		045 to 1.04		0.50 to 2.18	
p Value	0.15		0.006		0.38		0.11		0.07		0.90	
OS (months)	39.3	32.6	13.9	29.2	38.3	28.0	18.3	23.0	43.4	32.0	17.5	21.0
HR	0.77		1.36		0.63		1.31		0.77		0.67	
95% CI	0.59 to 0.99		0.93 to 1.99		0.48 to 0.75		0.81 to 2.11		0.46 to 1.28		0.30 to 1.50	
p Value	0.04		0.10		0.002		0.28		0.31		0.32	

FOLFOX = folinic acid–5-fluorouracil–oxaliplatin; FOLFIRI = folinic acid–5-fluorouracil–irinotecan; Cmab = cetuximab; Bev = bevacizumab; Pmab = panitumumab; ORR = overall response rate; OR = odds ratio; CI = confidence interval; PFS = progression-free survival; HR = hazard ratio; OS = overall survival.

Meta-Analyses of the Effect of PTL

Several recently published meta-analyses have evaluated the predictive effect of PTL (Table VII). Arnold and colleagues[28] recently published the results of summary data from six randomized trials of tumour sidedness and EGFR mAb treatment in patients with advanced CRC. They used a standard fixed-effects model to calculate the HRS for OS duration and PFS, and the OR for ORR. The six trials included in the pooled analysis were CRYSTAL, FIRE-3, PEAK, PRIME, 20050181, and CALGB/SWOG 80405. The HRS were adjusted for covariates, but the covariates adjusted for were different in each study. The results showed that chemotherapy (either FOLFOX or FOLFIRI) plus an EGFR mAb (cetuximab or panitumumab) was associated with improved OS duration (HR: 0.75; 95% CI: 0.67 to 0.84) in patients with LCC, but not in patients with RCC (HR: 1.14; 95% CI: 0.88 to 1.47). The HR for interaction between PTL and OS duration was 1.53 ($p < 0.001$). In terms of ORR, LCC had an OR of 2.12 (95% CI: 1.77 to 2.55) with EGFR mAb treatment. Interestingly, an improved ORR was also seen for RCC, although it was not statistically significant (OR: 1.47; 95% CI: 0.94 to 2.29). A trend toward a greater benefit of chemotherapy plus EGFR mAb was observed in patients with LCC (p value for interaction: 0.07).

Holch *et al.*[12] performed a meta-analysis of the relevant first-line trials. It included an analysis of the two trials that compared chemotherapy with or without an EGFR mAb, CRYSTAL and PRIME, to examine the predictive implications of PTL. A significant benefit of first-line EGFR mAb treatment for OS duration, PFS, and ORR was observed only in patients with *RAS* wild-type LCC (OS HR: 0.69; $p < 0.0001$; PFS HR: 0.65; $p < 0.0001$; ORR OR: 2.45; $p < 0.00001$). The Holch meta-analysis[12] also included a separate examination of the three trials comparing chemotherapy plus bevacizumab with chemotherapy plus EGFR mAbs: CALGB/SWOG 80405, FIRE-3, and PEAK. In patients with *RAS* wild-type LCC, the analysis revealed a significant benefit associated with EGFR mAb treatment with respect to OS duration and ORR, but not PFS. In RCC, improved PFS and OS duration were associated with bevacizumab treatment, but only the PFS benefit was statistically significant (PFS HR: 1.53; 95% CI: 1.16 to 2.01; $p = 0.003$; OS HR: 1.3; 95% CI: 0.97 to 1.74; $p = 0.081$). The OR for ORR favoured EGFR mAb treatment in RCC (OR: 1.2; 95% CI: 0.77 to 1.22; $p = 0.432$). In addition, a significant interaction between PTL and treatment was observed for OS duration and PFS, but not for ORR.

Li *et al.*[37] published a meta-analysis of primary tumour site and anti-EGFR mAb benefit in MCRC. The analysis of the prognostic value of PTL included eleven studies, but the analysis of the predictive effect was limited to just two randomized controlled trials (CRYSTAL and NCIC CO.17). The results showed that, with respect to OS duration, the addition of an anti-EGFR mAb was associated with a significant improvement in LCC (HR: 0.60; 95% CI: 0.47 to 0.77; $p < 0.0001$), but not in RCC (HR: 0.87; 95% CI: 0.54 to 1.40; $p = 0.56$). Similarly, PFS was improved with the addition of cetuximab in LCC (HR: 0.38; 95% CI: 0.22 to 0.67; $p = 0.0008$), but not in RCC (HR: 0.79; 95% CI: 0.52 to 1.19; $p = 0.26$). Significant interaction between tumour location and treatment was observed for OS duration and PFS ($p = 0.0002$ for OS and PFS alike).

Limitations

Several limitations apply to the interpretation of the analyses presented in this review. First, the analyses of PTL from

TABLE VII Analysis of primary tumour location in meta-analyses of trials with EGFR monoclonal antibodies (mAbs)

Variable	Arnold *et al.*, 2017[28] (CRYSTAL, FIRE-3, PEAK, PRIME, 20050181, CALGB/SWOG 80405)				Li *et al.*, 2017[37] (CRYSTAL, NCIC CO.17)				Holch *et al.*, 2017[12] (CRYSTAL, PRIME)				Holch *et al.*, 2017[12] (FIRE-3, PEAK, CALGB/SWOG 80405)			
	Use of *EGFR* mAb				Use of *EGFR* mAb				Use of *EGFR* mAb				Use of *EGFR* mAb			
	Left-sided		Right-sided		Left-sided		Right-sided		Left-sided		Right-sided		Left-sided		Right-sided	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No, Bev
ORR (%)	Favours *EGFR* mAb		No difference		Favours *EGFR* mAb		No difference		Favours *EGFR* mAb		No difference		Favours *EGFR* mAb		No difference	
OR	2.12		1.47		1.37		1.11		2.45		1.42		1.49		1.2	
95% CI	1.77 to 2.55		0.94 to 2.29		0.85 to 2.19		0.48 to 2.59		1.82 to 3.3		0.78 to 2.6		1.19 to 1.9		0.77 to 1.87	
p Value					0.23		0.83		<0.00001		0.25		0.002		0.43	
PFS (months)	Data not available		Data not available		Favours *EGFR* mAb		No difference		Favours *EGFR* mAb		No difference		No difference		Favours bevacizumab	
HR					0.38		0.79		0.65		0.82		0.86		1.53	
95% CI					0.22 to 0.67		0.52 to 1.19		0.54 to 0.79		0.57 to 1.19		0.73 to 1.02		1.16 to 2.01	
p Value					0.0008		0.26		<0.0001		0.30		0.08		0.003	
OS (months)	Favours *EGFR* mAb		No difference		Favours *EGFR* mAb		No difference		Favours *EGFR* mAb		No difference		Favours *EGFR* mAb		No difference	
HR	0.75		1.14		0.60		0.87		0.69		0.96		0.71		1.3	
95% CI	0.67 to 0.84		0.88 to 1.47		0.47 to 0.77		0.54 to 1.40		0.58 to 0.83		0.68 to 1.35		0.58 to 0.85		0.97 to 1.74	
p Value					<0.0001		0.56		<0.0001		0.80		0.0003		0.08	

ORR = overall response rate; OR = odds ratio; CI = confidence interval; PFS = progression-free survival; HR = hazard ratio; OS = overall survival.

the randomized trials are retrospective in nature, potentially resulting in selection, systematic, and random bias. Second, the trials included in the meta-analyses are heterogeneous with respect to study phase, type of *RAS* testing performed, line of treatment, and treatment arms. Third, the meta-analyses did not analyze individual patient data. In addition, although most trials defined LCC as beginning at the splenic flexure, the CALGB 80405 and Australasian Gastrointestinal Trials Group MAX trials excluded the transverse colon in their analysis. Furthermore, there is evidence to show that, even within RCC and LCC, significant heterogeneity is evident with respect to molecular characteristics[34,37], such that classification by side could be oversimplifying a more complex interaction between tumour and treatment. Finally, to date, no data are available about the effect of PTL in the context of triplet therapy (that is, FOLFOXIRI) combined with either bevacizumab or an EFGR mAb.

DATA SUMMARY AND IMPLICATIONS FOR PRACTICE

The foregoing section has summarized the evidence for the predictive value of PTL with respect to treatment with anti-EGFR mAbs and bevacizumab in patients with *RAS* wild-type MCRC. Despite the limitations already noted, it is important that current guidelines reflect the best available evidence.

For patients with *RAS*-mutant MCRC, there is no benefit of EGFR mAb treatment as a single agent or combined with standard chemotherapy in either LCC or RCC. In patients with *RAS* wild-type MCRC, treatment should take into account the location of the primary tumour.

Basis of Recommendations

A draft of the evidence summary was provided to participants before the consensus meeting. All recommendations are based on a structured presentation and discussion of the best available evidence.

Preamble

The recommendations that follow are intended for patients who are fit and eligible for the doublet chemotherapy and biologic combinations being proposed. The recommendations provide a basis for discussion with patients about the management options for their MCRC and informed decision-making by patients about their care. Individual treatment plans will depend on appropriate patient selection and a complete discussion of the risks and benefits of proposed therapies with individual patients. Although improving OS duration is an important goal of treatment, efforts to maximize quality of life by effective management of regimen-related toxicities and provision of appropriate supportive measures are essential.

Heterogeneity with respect to *KRAS* or *RAS* testing was observed in the evidentiary studies, but the recommendations provided here have been extrapolated to include only patients with wild-type tumours on extended *RAS* testing (*KRAS* or *NRAS* exons 2–4). In addition, although heterogeneity in the definition of right-sided and left-sided tumours was also observed, most studies defined RCC as arising from the cecum up to, but not including, the splenic flexure;

and LCC as arising from the splenic flexure to the rectum. That definition is therefore the one that we propose in the implementation of the recommendations presented here.

Consensus Statements

First-Line Treatment

In the first-line setting, retrospective analyses of four of five trials show, for *RAS* wild-type LCC tumours, a statistically significant benefit in OS duration associated with chemotherapy plus an EGFR inhibitor compared with chemotherapy plus bevacizumab or chemotherapy alone. Furthermore, the results of two meta-analyses (including one focused on first-line studies) confirmed that association. In the analyses, the benefit of EGFR mAb treatment in LCC is consistent, regardless of the EGFR mAb or the chemotherapy backbone used. Conversely, in patients with *RAS* wild-type RCC tumours, the addition of EGFR mAb to chemotherapy alone was not associated with an OS duration benefit. In the meta-analysis of first-line trials comparing chemotherapy plus EGFR mAb with chemotherapy plus bevacizumab for patients with RCC tumours, chemotherapy plus bevacizumab was associated with a statistically significant benefit in PFS and a statistically nonsignificant trend toward improved OS duration.

The consensus meeting therefore made these recommendations:

1. (a) In patients with *RAS* wild-type LCC, standard chemotherapy (FOLFOX or FOLFIRI) in combination with an EGFR mAb (cetuximab or panitumumab) is recommended in the first-line setting.
   (b) In patients with *RAS* wild-type RCC, first-line EGFR mAbs are not recommended. The combination of bevacizumab plus standard chemotherapy remains the standard of care for these patients.
   (c) Extended *RAS* testing should be available in a timely manner to allow for the appropriate selection of a biologic for first-line treatment decisions.

Second-Line Treatment

Data with respect to the use of EGFR mAb in the second-line setting did not clearly demonstrate outcome improvements based on PTL. In the PICCOLO trial, tumour side was not a predictive factor for benefit with panitumumab. Moreover, the 20050181 trial did not demonstrate statistically significant differences between the FOLFIRI plus panitumumab arm and the FOLFIRI arm in right- or left-sided tumours.

The consensus meeting therefore made these recommendations:

2. (a) At this time, there is no evidence to recommend the selective use of EGFR mAbs in the second-line setting based on PTL.
   (b) In the second-line setting, patients who were treated with EGFR mAbs instead of bevacizumab in the first line can be considered for bevacizumab in combination with standard chemotherapy.

Third-Line Treatment

In the third-line setting, the only analysis of PTL comes from the CO.17 trial. That analysis clearly showed that, in LCC, a benefit was associated with cetuximab compared with best supportive care. However, patients with RCC did achieve a 3-month improvement in OS duration with cetuximab (although that gain was not statistically significant), with no difference in PFS.

The consensus meeting therefore made this recommendation:

3. All patients with *RAS* wild-type disease who have not previously been treated with an EGFR mAb should be offered one.

Tumour Response

In contrast to the differential benefits associated with EGFR mAbs by sidedness for OS duration, EGFR mAbs appear to produce a superior ORR in both LCC and RCC, as shown in the Holch *et al.*[12] meta-analysis and the Arnold *et al.*[28] pooled analysis. That observation could suggest that, if tumour shrinkage is the primary initial goal of treatment (for example, in patients with high-bulk, symptomatic, unresectable disease), an EGFR mAb combined with chemotherapy might be more effective than bevacizumab combined with doublet chemotherapy. However, the use of an EGFR mAb with such a goal in RCC would have to be balanced with the effect on long-term outcomes (PFS and OS duration). Given the conflicting data concerning the use of EGFR mAb–based therapy in conjunction with surgical resection, the ORR evidence is also insufficient for a recommendation favouring EGFR mAbs in patients for whom conversion therapy for resection is the primary goal[38–40]. The selective use of biologics based on PTL for patients requiring maximal response based on the observed ORR data requires further prospective study.

The consensus meeting therefore made this recommendation:

4. At this time, in cases in which tumour response is the primary goal of therapy, the evidence is insufficient for the selective use of EGFR mAbs based on PTL.

Future Research

The consensus meeting made these recommendations with respect to future research in this area:

5 (a) Primary tumour location should be factored into the design of future clinical trials in the treatment of *RAS* wild-type MCRC.
   (b) Given that PTL is a surrogate for more complex biologic mechanisms, ongoing research should seek to understand the patient- and tumour-related factors that underlie the observed differential benefits of biologics based on PTL.

Table VIII summarizes all of the foregoing recommendations.

CONCLUSIONS AND PRACTICAL CONSIDERATIONS

In view of the opinions of the expert panel members, the results of the retrospective analyses discussed earlier in this article indicate that, although tumour sidedness might

TABLE VIII Recommendations in *RAS* wild-type metastatic colorectal cancer (mCRC)

Scenario	Recommendation
First line	■ For patients with left-sided disease, standard chemotherapy (FOLFOX or FOLFIRI) in combination with an EGFR mAb (cetuximab or panitumumab) is recommended in the first-line setting.
	■ For patients with right-sided disease, first-line EGFR monoclonal antibodies are not recommended. The combination of bevacizumab with standard chemotherapy remains the standard of care for these patients.
	■ Extended *RAS* testing should be available in a timely manner to allow for the appropriate selection of a biologic for first-line treatment decisions.
Second line	■ There is no evidence to recommend the selective use of EGFR monoclonal antibodies in the second-line setting based on the location of the primary tumour.
	■ Patients who have not been treated with bevacizumab in the first line should be offered bevacizumab in combination with standard chemotherapy.
Third line	■ All *RAS* wild-type patients who have not previously been treated with an EGFR monoclonal antibody should be offered one.
Tumour response	■ At this time, there is insufficient evidence for the selective use of EGFR monoclonal antibodies based on primary tumour location if tumour response is the primary goal of therapy.
Future research	■ Primary tumour location should be factored into the design of future clinical trials in the treatment of *RAS* wild-type mCRC.
	■ Given that primary tumour location is a surrogate for more complex biologic mechanisms, ongoing research should try to understand the patient- and tumour-related factors that underlie the differential benefit of biologics that have been observed based on primary tumour location.

FOLFOX = folinic acid–5-fluorouracil–oxaliplatin; FOLFIRI = folinic acid–5-fluorouracil–irinotecan.

be a surrogate for more complex molecular mechanisms, it currently represents a practical predictive and prognostic biomarker that should guide treatment in patients with *RAS* wild-type mCRC.

Finally, the panel acknowledged that some practical considerations would accompany the consensus statements. The most important consideration is that implementation of the recommendations would necessitate a change in the current drug funding model for most provinces. Specifically, patients would require access to funded EGFR mAbs in combination with chemotherapy in the first-line setting and to funded bevacizumab in the second-line setting (if they have not previously been treated with bevacizumab).

ACKNOWLEDGMENTS

The authors thank the Canadian Association of Medical Oncologists, Colorectal Cancer Canada, and Oncology Education for logistics support for the consensus meeting.

CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: SB and BC have received speaker fees from Amgen. SB has received fees as an advisory board member for Amgen and Lilly. BC has received fees as an advisory board member for Amgen, Celgene, and Pfizer.

The cost of the consensus meeting was covered by participation fees paid by employees of Amgen, Lilly, and Roche to attend the meeting as observers. No panel members or gastrointestinal experts received any compensation or reimbursements for attending the meeting.

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