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**Title:**

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**Date:**

2015-06-24

**Citation:**

Tay, R. Y., Wong, R. & Hawkes, E. A. (2015). Treatment of metastatic colorectal cancer: Focus on panitumumab. *Cancer Management and Research*, 7 (0), pp.189-198. <https://doi.org/10.2147/CMAR.S71821>.

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# Treatment of metastatic colorectal cancer: focus on panitumumab

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**Abstract:** Targeted agents are an important therapeutic option in the treatment of metastatic colorectal cancer (mCRC). Panitumumab is a recombinant, fully humanized, immunoglobulin G2 monoclonal antibody that targets the epidermal growth factor receptor (EGFR) with efficacy in mCRC as monotherapy and in combination with chemotherapy. *Kirsten rat sarcoma (KRAS)* mutation status has emerged as an important biomarker to predict response to anti-EGFR therapy. Optimal timing for panitumumab use in the mCRC treatment algorithm has not been established. This review discusses the mechanism of action, predictive biomarkers, and role of panitumumab in the treatment of mCRC.

**Keywords:** panitumumab, metastatic colorectal cancer, *KRAS*, *RAS*, EGFR, monoclonal antibody

## Introduction

Colorectal cancer (CRC) is the third leading cause of cancer worldwide and accounts for 10% of all new cancer diagnoses.<sup>1,2</sup> Twenty percent of patients will have metastatic disease at presentation and a further 30% of those diagnosed with early stage CRC will develop metastatic disease.<sup>3,4</sup>

The introduction of combination chemotherapy and biological agents over the past decade has led to an improvement in median overall survival (OS) from 9 months to more than 30 months for metastatic colorectal cancer (mCRC). Furthermore, surgical resection of oligometastatic disease in selected patients may lead to long-term cure.<sup>5,6</sup> Despite these advances, 5-year OS remains at 5%–15%, indicating that further refinement of our current treatment strategies for mCRC, alongside the development of new therapeutics, remains a priority.<sup>7</sup>

Targeted therapy has now been incorporated into routine clinical care for mCRC. The vascular endothelial growth factor (VEGF) and epidermal growth factor (EGF) pathways are two signaling pathways central to growth and proliferation in mCRC for which there are well-established therapeutic targeted agents available. Up to 60%–70% of patients with mCRC receive a biological agent during their treatment course.<sup>8</sup>

Anti-VEGF agents such as bevacizumab, ziv-aflibercept, regorafenib, and ramucirumab all have efficacy in mCRC; however, a predictive biomarker has not yet been identified.<sup>9–12</sup> Bevacizumab, ziv-aflibercept, and regorafenib have been US Food and Drug Administration (FDA) approved for use in mCRC. Bevacizumab in combination with chemotherapy is an established standard of care in the first- and second-line settings.

Inhibition of the EGF pathway with epidermal growth factor receptor (EGFR) antibodies is also an important therapeutic strategy. Importantly, efficacy is restricted to patients

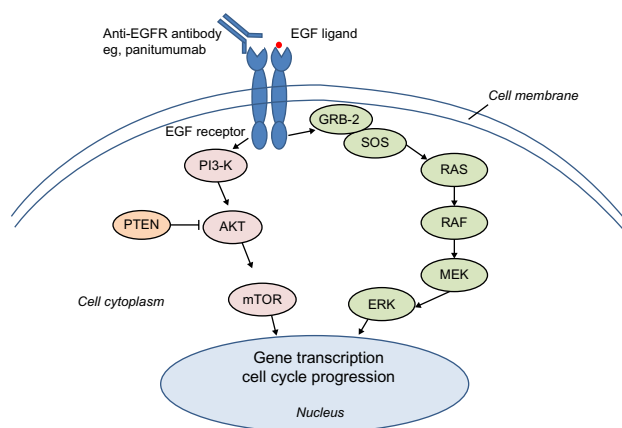
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whose tumors do not harbor *Kirsten rat sarcoma* (*KRAS*) mutations, although *rat sarcoma* wild-type (WT) (*RAS*-WT) status does not guarantee response. Two monoclonal agents, cetuximab, a immunoglobulin G1 (IgG1) mouse–human chimeric monoclonal antibody, and panitumumab, a recombinant, fully humanized, IgG2 monoclonal anti-EGFR antibody specifically target the EGFR pathway and have proven activity in selected mCRC patients as monotherapy and in combination with chemotherapy.<sup>13,14</sup> Both are FDA approved for use in mCRC. This paper discusses the mechanism of action of panitumumab, current evidence for panitumumab use in CRC, and future directions in the management of mCRC.

## Pharmacology of panitumumab

EGFR is a member of the human epidermal growth factor receptor (HER)-erbB family of receptor tyrosine kinases. This family also includes three other receptor tyrosine kinases; HER2/C-neu (ErbB2), HER3 (ErbB3), and HER4 (ErbB4).<sup>15</sup>

In malignant cells, activation of the EGFR initiates a downstream signaling cascade through two main axes (Figure 1). The first axis, the *KRAS*-RAF-mitogen-activated protein kinase (MAPK) pathway, promotes gene transcription, cell cycle progression, and proliferation. The second axis, the phosphatidylinositol 3-kinase (PI3K) pathway, results in AKT-mammalian target of rapamycin (mTOR) activation that initiates anti-apoptosis signals. These two axes remain interconnected through the p110 subunits of PI3K. Further activation of these pathways also occurs via *RAS* protein interactions.<sup>15</sup> The EGFR pathway plays a critical role in CRC tumorigenesis; hence, blockade of this pathway is an attractive therapeutic strategy.<sup>16</sup>



**Figure 1** Simplified EGFR pathway.

**Abbreviations:** EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol 3-kinase.

Panitumumab binds to the extracellular domain of the EGFR, inhibiting receptor phosphorylation and subsequent activation of downstream cell signaling pathways.<sup>17</sup> Evidence suggests panitumumab may further inhibit tumor proliferation by EGFR downregulation through receptor internalization, induction of apoptosis, autophagy, and angiogenesis inhibition.<sup>17,18</sup>

Panitumumab is administered intravenously at a recommended dose of 6 mg/kg once every 2 weeks. An acceptable alternative dosing schedule is 9 mg/kg once every 3 weeks.<sup>19</sup> Panitumumab exhibits nonlinear pharmacokinetics involving saturable binding to EGFR and subsequent intracellular degradation. EGFR membrane expression, gender, age, race, or renal or hepatic dysfunction does not meaningfully affect panitumumab pharmacokinetics.<sup>20</sup> Concurrent administration of irinotecan, folinic acid/infusional 5-fluorouracil/irinotecan (FOLFIRI), or paclitaxel/carboplatin also does not alter panitumumab pharmacokinetics.<sup>17</sup> Panitumumab is cleared via the reticuloendothelial system.<sup>20</sup>

## Predicting response to panitumumab

It is now well established that not all patients with mCRC will respond to anti-EGFR therapy. Presence in the tumor tissue of activating mutations of the *KRAS* protein, specifically in exon 2 (codons 12 and 13) are predictive for intrinsic resistance to anti-EGFR therapy.<sup>21</sup> Mutations of *KRAS* occur in 35%–45% of mCRC, with proven concordance between primary and metastatic sites.<sup>22</sup> Despite the landmark discovery of the relationship between *KRAS* mutation status and response to anti-EGFR antibodies, the response rate in *KRAS* wild-type (*KRAS*-WT) chemo-refractory patients remains in the order of 20%.<sup>21</sup>

Expanding biomarker testing beyond *KRAS* exon 2 has offered greater insight into predicting response to anti-EGFR antibody therapy. Activating mutations in *KRAS* exon 3 (codons 59 and 61) and exon 4 (codons 117 and 146); and *neuroblastoma rat sarcoma* (*NRAS*) exon 2 (codons 12 and 13), exon 3 (codons 59 and 61), and exon 4 (codons 117 and 146) have all been demonstrated as negative predictors of response to panitumumab.<sup>23</sup> *NRAS* mutations occur in only 3%–5% of CRCs and are mutually exclusive of mutations in *KRAS*.<sup>24</sup> In patients who are WT for *KRAS* exon 2 mutations, a further 17% will exhibit a mutation in another *RAS* exon.<sup>25</sup>

Given the predictive significance of *RAS* mutations, determination of *RAS* mutation status from tumor samples is now a prerequisite prior to considering treatment with anti-EGFR

inhibitors.<sup>26</sup> Use of these agents in *KRAS*-mutated (*KRAS*-MT) tumors has been associated with worse survival outcomes.<sup>27</sup>

Other biomarkers have been less conclusive. There is a distinct lack of correlation between tumor EGFR expression measured by immunohistochemistry and response to cetuximab or panitumumab.<sup>28,29</sup> *BRAF* exon V600E mutation is a known negative prognostic marker; however, while no objective response to panitumumab monotherapy has been reported in *BRAF*-mutated mCRC, its role as a predictive marker is yet to be established.<sup>30</sup> EGFR gene copy number, *PIK3CA* mutations, or loss of *PTEN* expression all have been identified as potential predictive biomarkers.<sup>24</sup> Further work is clearly warranted to improve patient selection.

## Evidence for clinical efficacy of panitumumab in mCRC Monotherapy in the chemotherapy refractory setting

Panitumumab efficacy was initially demonstrated as monotherapy in chemotherapy-refractory mCRC. A summary of these trials is presented in Table 1. The phase III open label trial by Van Cutsem et al demonstrated a limited progression-free survival (PFS) benefit with single agent panitumumab compared to best supportive care (BSC) alone (8 vs 7.3 weeks, hazard ratio [HR] 0.54,  $P < 0.0001$ ) in an unselected *KRAS* population.<sup>31</sup> No OS benefit was observed; however, any demonstrable survival benefit may have been attenuated with 76% of patients in the BSC arm crossing over to panitumumab on progression. Overall response rate (ORR) was 10%, similar to that described in an earlier cetuximab study in a comparable population.<sup>32</sup> From this study

population, Amado et al further clarified the predictive role of *KRAS*.<sup>21</sup> *KRAS* status was available in 427/463 patients (92%), with *KRAS* exon 2 mutation detected in 43% of samples analyzed. In the *KRAS*-WT exon 2 population, panitumumab significantly improved median PFS compared to BSC (12.3 vs 7.3 weeks, HR 0.45, 95% CI 0.34–0.59,  $P < 0.0001$ ). In the *KRAS*-MT population, no PFS benefit was detected (7.4 vs 7.3 weeks, HR 0.99, 95% CI 0.73–1.36,  $P$ -value not specified). Response rate was 17% in the *KRAS*-WT group and 0% in *KRAS*-MT group. In a multivariate analysis, *KRAS*-WT status was a predictor for OS in both the panitumumab (HR 0.64,  $P = 0.004$ ) and BSC arms (HR 0.68,  $P = 0.007$ ), the latter result suggesting a possible prognostic role; however, this has not been replicated elsewhere.

The phase III non-inferiority study ASPECCT (A Study of Panitumumab Efficacy and Safety Compared to Cetuximab in Patients with *KRAS* Wild-Type Metastatic Colorectal Cancer) compared panitumumab and cetuximab in 1,010 patients with chemotherapy-refractory *KRAS*-WT exon 2 mCRC with a primary endpoint of OS.<sup>33</sup> Panitumumab was administered at 6 mg/kg once every 2 weeks. Cetuximab was administered at an initial dose of 400 mg/m<sup>2</sup>, then 250 mg/m<sup>2</sup> once a week thereafter. Panitumumab was proven to be non-inferior to cetuximab, with OS reported as 10.4 months and 10 months, respectively (HR 0.97, 95% CI 0.84–1.11,  $P = 0.0007$ ). PFS (4.1 vs 4.4 months, HR 1.0, 95% CI 0.88–1.14) and ORR (panitumumab at 22% vs cetuximab at 19.8%) were also similar. Toxicity profiles differed only slightly between the two arms. Fewer infusion reactions were reported in the panitumumab arm of any grade (3% vs 14%) and particularly of grade 3+ (<0.5% vs 2%). Higher rates of grade 3–4 hypomagnesemia were reported with panitumumab compared to

**Table 1** Summary of panitumumab monotherapy trials

Trial	<i>KRAS</i> status	Treatment regimen	PFS (months)	HR ( $P$ -value)	OS (months)	HR ( $P$ -value)	ORR
<b>Phase III</b>							
Van Cutsem et al <sup>31</sup> (n=463)	Unselected	BSC + Pan	8	0.54 (<0.0001)	NR	1	10%
		BSC	7.3		NR		
	<i>KRAS</i> -WT	BSC + Pan	12.3	0.45 (<0.0001)	8.1	0.99	17%
		BSC	7.3		7.6		
	<i>KRAS</i> -MT	BSC + Pan	7.4	0.99	4.9	1.02	0%
		BSC	7.3		4.4		
ASPECCT <sup>33</sup> (n=1,010)	<i>KRAS</i> -WT exon 2	Pan	4.1	1	10.4	0.97 (0.0007)	22%
		Cetuximab	4.4		10		
<b>Phase II</b>							
Hecht et al <sup>42</sup> (n=148)	Unselected	Pan	14 weeks		9		9%
Muro et al <sup>49</sup> (n=52)	Unselected	Pan	8 weeks		9.3		14%

**Abbreviations:** PFS, progression-free survival; HR, hazard ratio; OS, overall survival; ORR, overall response rate; BSC, best supportive care; Pan, panitumumab; NR, not reported; n, number of patients.

cetuximab (7% vs 3%). Incidence of grade 3–4 skin toxicity was 13% and 10% in the panitumumab and cetuximab arms, respectively.

In summary, as monotherapy in chemotherapy-refractory mCRC, panitumumab has demonstrated PFS benefit in the *KRAS*-WT exon 2 population. No OS benefit was observed; however, this may in part be due to treatment cross over. ASPECCT<sup>33</sup> provides greater insight into use and toxicity profiles of anti-EGFR antibody monotherapy in the chemotherapy-refractory mCRC setting, given the head-to-head nature of the trial design. Given the non-inferior outcomes of panitumumab compared to cetuximab, the clinician's choice of anti-EGFR agent should be considered in the context of previous treatments, cost, toxicity profile, and dosing schedules of the agents.

## Panitumumab in combination with chemotherapy

### First-line therapy

#### Chemotherapy with or without panitumumab

Panitumumab has demonstrated efficacy and acceptable toxicity when paired with both FOLFIRI and folinic acid/infusional 5-fluorouracil/oxaliplatin (FOLFOX) chemotherapy in the first-line setting in both phase II and III trials. A summary of these trials is listed in Table 2.

The phase III PRIME study (Panitumumab Randomized trial In combination with chemotherapy for Metastatic colorectal cancer to determine Efficacy) randomized 1,183 patients to first-line FOLFOX4 with or without panitumumab (6 mg/kg every 2 weeks), with a primary endpoint of PFS.<sup>25</sup> *KRAS* status was available in 1,096/1,183 (93%) patients, with 440 (40%) harboring a *KRAS* mutation. In the

*KRAS*-WT population (n=656), the addition of panitumumab to FOLFOX4 resulted in a 1.4 month improvement in median PFS compared to FOLFOX4 alone (10 vs 8.6 months, HR 0.80, *P*=0.01) and an improved ORR (57% vs 48%). No difference in ORR was detected in the *KRAS*-MT group.

While an initial analysis of OS in the *KRAS*-WT patients yielded no benefit from the addition of panitumumab, after a median follow-up of 30 months, an updated report described a significant survival advantage in *KRAS*-WT tumors with panitumumab + FOLFOX4 compared to FOLFOX4 alone (23.8 vs 19.4 months, HR 0.83, *P*=0.03). *KRAS*-MT patients gained no OS benefit from the addition of panitumumab with chemotherapy, with a trend toward inferior outcomes compared to chemotherapy alone (15.5 vs 19.2 months, HR 1.16, *P*=0.16). These results are consistent with the phase II OPUS study, in which the addition of cetuximab to FOLFOX chemotherapy in the *KRAS*-MT population also resulted in shorter median survival.<sup>27</sup>

#### Chemotherapy with panitumumab vs chemotherapy with bevacizumab

A first-line standard of care is bevacizumab with combination chemotherapy.<sup>9</sup> The improved outcomes seen with first-line EGFR inhibition with chemotherapy have led to a direct comparison of these two targeted agents. Two randomized phase III studies have compared cetuximab to bevacizumab in combination with first-line chemotherapy in *KRAS*-WT mCRC patients, with conflicting results. The open label randomized FIRE-3 study compared FOLFIRI + cetuximab vs FOLFIRI + bevacizumab.<sup>5</sup> In FIRE-3, no difference was seen in the primary endpoint, ORR (62% vs 58%, odds ratio 1.18, 95% CI 0.85–1.64, *P*=0.18) or secondary endpoint,

**Table 2** Summary of first-line panitumumab trials

Trial	<i>KRAS</i> status	Treatment regimen	PFS (months)	HR (P-value)	OS (months)	HR (P-value)	ORR
<b>Phase III</b>							
PRIME <sup>25</sup> (n=1,183)	<i>KRAS</i> -WT	FOLFOX4 + Pan	10	0.8 (0.01)	23.8	0.83 (0.03)	57%
		FOLFOX4	8.6		19.4		48%
	<i>KRAS</i> -MT	FOLFOX4 + Pan	7.4	1.27 (0.02)	15.5	1.17 (0.014)	40%
		FOLFOX4	9.2		19.2		41%
<b>Phase II</b>							
PEAK <sup>35</sup> (n=285)	<i>KRAS</i> -WT exon 2	FOLFOX + Pan	10.9	0.87 (0.35)	34.2	0.62 (0.009)	57.8%
		FOLFOX + Bev	10.1		24.3		53.5%
Kohne et al <sup>50</sup> (n=154)	Unselected	FOLFIRI + Pan	7.6		NR		49%
	<i>KRAS</i> -WT	FOLFIRI + Pan	8.9		NR		56%
		<i>KRAS</i> -MT	FOLFIRI + Pan		7.2		NR
Berlin et al <sup>51</sup> (n=43)	Unselected	FOLFIRI + Pan	10.9		22.5		42%
	Unselected	IFL + Pan	5.6		17		46%

**Abbreviations:** PFS, progression-free survival; HR, hazard ratio; OS, overall survival; ORR, overall response rate; Pan, panitumumab; FOLFOX, folinic acid/infusional 5-fluorouracil/oxaliplatin; Bev, bevacizumab; FOLFIRI, folinic acid/infusional 5-fluorouracil/irinotecan; IRL, folinic acid/bolus 5-fluorouracil/irinotecan; n, number of patients; NR, not reported.

PFS (10 vs 10.3 months, HR 1.06, 95% CI 0.88–1.26,  $P=0.55$ ). A significant OS benefit was seen in the cetuximab group (28.7 vs 25 months, HR 0.77, 95% CI 0.62–0.96,  $P=0.017$ ). In contrast, CALBG/SWOG 80405 compared FOLFIRI or mFOLFOX6 (investigator's choice) with cetuximab or bevacizumab in the *KRAS*-WT population.<sup>34</sup> In the all-*RAS*-WT population, no OS (32 vs 31.2 months, HR 0.9,  $P=0.4$ ) or PFS (11.4 vs 11.3 months, HR 1.1,  $P=0.31$ ) difference was detected between the cetuximab or bevacizumab groups. Higher response rates were observed in patients receiving cetuximab (68.6% vs 53.6%,  $P<0.01$ ).

To date, the optimal first-line targeted agent for *KRAS*-WT patients remains unclear. While no phase III data are available comparing first-line chemotherapy with bevacizumab vs panitumumab, phase II results from PEAK (Panitumumab Efficacy in combination with mFOLFOX6 Against bevacizumab plus mFOLFOX6 in mCRC subjects with wild-type *KRAS* tumors) provides some insight into this question.<sup>35</sup> Similar to FIRE-3; no significant PFS difference in the panitumumab and bevacizumab arms was detected (10.9 vs 10.1 months, HR 0.87,  $P=0.35$ ). Secondary endpoint OS was significantly improved with panitumumab (34.2 vs 24.3 months, HR 0.62,  $P=0.009$ ). A pre-specified extended-*RAS* analysis, including *KRAS* exons 2, 3, and 4 and *NRAS* exons 2, 3, and 4, was undertaken. Of the *KRAS*-WT exon 2 population, 60% were extended-*RAS*-WT. In the extended-*RAS*-WT cohort, a trend toward improved OS was observed with panitumumab vs bevacizumab (41.3 vs 28.9 months, HR 0.63,  $P=0.58$ ). Higher ORR was observed with panitumumab vs bevacizumab (57.8% vs 53.5%). Toxicity relating to the targeted agents was consistent with previous reports, with a higher incidence of skin toxicity and hypomagnesemia in

the panitumumab group, and hypertension more frequently noted in the bevacizumab arm.

### Second-line therapy

The combination of irinotecan-based chemotherapy and panitumumab has been evaluated in the second-line setting. Table 3 summarizes the main trials. The unblinded phase III study by Peeters et al recruited 1,186 mCRC patients who had progressed after first-line fluoropyrimidine-based chemotherapy. Patients were randomized 1:1 to FOLFIRI ± panitumumab.<sup>36</sup> First-line oxaliplatin and bevacizumab had been received by 67% and 19% of the study population, respectively. *KRAS* mutation status was available in 91% of patients, with *KRAS* exon 2 mutation identified in 45% of tumors tested.<sup>8</sup> Co-primary endpoints were PFS and OS. Final analysis in the *KRAS*-WT population ( $n=597$ , or 55%) demonstrated a significantly improved median PFS with the addition of panitumumab to FOLFIRI (6.7 vs 4.9 months, HR 0.82, 95% CI 0.69–0.97,  $P=0.023$ ), improved ORR (36% vs 10%,  $P<0.0001$ ), and a non-significant trend toward improved OS in favor of the panitumumab arm (14.5 vs 12.5 months, HR 0.92,  $P=0.37$ ). There was no OS difference in *KRAS*-MT tumors. Of note, 34% of the *KRAS*-WT population in the FOLFIRI arm received post-progression anti-EGFR therapy.

In the phase III PICCOLO (Panitumumab, Irinotecan and Ciclosporin in COLOrectal cancer therapy) trial, 460 *KRAS*-WT mCRC patients with prior exposure to fluoropyrimidine chemotherapy were randomized to irinotecan alone or in combination with panitumumab.<sup>37</sup> The addition of panitumumab resulted in improved PFS (HR 0.78, 95% CI 0.64–0.95,  $P=0.015$ ) and higher ORR (34% vs 12%).

**Table 3** Summary of second-line panitumumab trials

Trial	<i>KRAS</i> status	Treatment regimen	PFS (months)	HR (P-value)	OS (months)	HR (P-value)	ORR
<b>Phase III</b>							
Peeters et al <sup>36</sup> ( $n=1,186$ )	<i>KRAS</i> -WT	FOLFIRI + Pan	6.7	0.82 (0.023)	14.5	0.92 (0.37)	36%
		FOLFIRI	4.9		12.5		10%
PICCOLO <sup>37</sup> ( $n=460$ )	<i>KRAS</i> -WT	Irinotecan + Pan	NR	0.78 (0.015)	10.4	1.01 (0.91)	34%
		Irinotecan	NR		10.9		12%
<b>Phase II</b>							
SPIRITT <sup>38</sup> $n=182$	<i>KRAS</i> -WT	FOLFIRI + Pan	7.7	1.01 (0.97)	18	1.06 (0.75)	32%
		FOLFIRI + Bev	9.2		21.4		19%
Cohn et al <sup>52</sup> ( $n=116$ )	<i>KRAS</i> -WT	FOLFIRI + Pan	6	KRAS-WT vs KRAS-MT HR 0.8	11.5	KRAS-WT vs KRAS-MT HR 0.6	23%
	<i>KRAS</i> -MT	FOLFIRI + Pan	4.3		7.1		16%
STEPP <sup>41</sup> ( $n=87$ )	<i>KRAS</i> -WT	Iri/FOLFIRI + Pan	5.5		13.7		16%
	<i>KRAS</i> -MT	Iri/FOLFIRI + Pan	3.3		13.3		8%

**Abbreviations:** PFS, progression-free survival; HR, hazard ratio; OS, overall survival; ORR, overall response rate; FOLFIRI, folinic acid/infusional 5-fluorouracil/irinotecan; Pan, panitumumab; Bev, bevacizumab; Iri, Irinotecan; n, number of patients; NR, not reported.

No significant median OS benefit was demonstrated between the panitumumab and control arms (10.4 vs 10.9 months, HR 1.01,  $P=0.91$ ).

These two large randomized phase III studies demonstrate that panitumumab improves PFS and ORR in *KRAS*-WT mCRC in the second-line therapy setting. Failure to observe improved OS may, at least in part, be due the cross over and subsequent use of anti-EGFR agents.

With demonstrated benefit of adding bevacizumab and EGFR therapies to chemotherapy in the first-line and relapsed settings, the optimal targeted therapy in the second-line setting remains an ongoing question. The phase II SPIRITT (Second-line Panitumumab IRInotecan Treatment Trial) study randomized 182 patients with *KRAS*-WT mCRC who progressed on first-line FOLFOX-bevacizumab to receive second-line FOLFIRI with either panitumumab or bevacizumab.<sup>38</sup> Improved ORR was observed in the panitumumab group compared to bevacizumab group (32% vs 19%). No PFS (7.7 vs 9.2 months, HR 1.01, 95% CI 0.68–1.5,  $P=0.97$ ) or OS (18 vs 21.4 months, HR 1.06, 95% CI 0.75–1.49,  $P=0.75$ ) benefit was demonstrated. These phase II data suggest that after progression on first-line FOLFOX-bevacizumab, panitumumab does not translate to improved survival outcomes compared to bevacizumab when combined with FOLFIRI. However, expanding biomarker testing in a phase III setting may better clarify the optimal ordering of targeted agents in the second-line setting.

### Dual-targeted therapy: anti-VEGF plus anti-EGFR agents

Both the VEGF and EGFR pathways are important for CRC tumorigenesis, with virtually no cross talk. Drugs targeting these have minimal overlapping toxicities, yet individually yield benefit over chemotherapy alone, regardless of the line of treatment. Dual-target blockade of both the EGFR and VEGF pathway in combination with chemotherapy was therefore assessed in the phase IIIb PACCE (Panitumumab Advanced Colorectal Cancer Evaluation) trial.<sup>39</sup> The study randomized 1,053 mCRC patients to receive bevacizumab plus oxaliplatin- or irinotecan- containing chemotherapy with or without panitumumab. Chemotherapy was allocated by investigator's choice, with 78% receiving oxaliplatin-based chemotherapy. *KRAS* mutation status (exon location not specified) was determined in 82% of patients, with a mutation found in 40% of tumor samples. In the unselected *KRAS* population, the addition of panitumumab resulted in reduced median PFS (10 vs 11.4 months, HR 1.27, 95% CI 1.06–1.52) and inferior median OS (19.4 vs 24.5 months, HR 1.43, 95%

CI 1.11–1.83) compared to the control arm. Regardless of *KRAS* mutation status, the addition of panitumumab resulted in inferior PFS compared to control. Skin toxicity occurred in 95% of patients exposed to panitumumab. Diarrhea, infection, hypomagnesemia, dehydration, and pulmonary embolism all occurred with higher frequency in the panitumumab group. Higher rates of grade 3+ adverse events were reported in the panitumumab cohort compared to control (mean rate 90% vs 70%). Panitumumab-related death occurred in seven (1%) patients. Similar ORR between *KRAS*-WT and *KRAS*-MT tumors (50% vs 47%) was observed in the group receiving oxaliplatin chemotherapy, whereas a higher ORR to panitumumab was observed in the *KRAS*-WT vs *KRAS*-MT population (54% vs 30%) in the group receiving irinotecan chemotherapy.

Several hypotheses exist that may account these poorer survival outcomes with dual-pathway inhibition. It has been proposed that the therapeutic effects of bevacizumab or chemotherapy may be blunted by EGFR inhibition via alteration to downstream targets or through cell cycle arrest leading to cytotoxic resistance. The similar response rate to panitumumab observed between *KRAS*-WT and *KRAS*-MT tumors in those receiving oxaliplatin chemotherapy suggests a possible interaction between oxaliplatin and panitumumab that has not been fully explored.

Significantly higher rates of toxicity may have also contributed to dose delays, lower dose intensity, and increased mortality in the panitumumab group. As extended *RAS* testing was not specified in this trial, the true number of patients with EGFR antibody-resistant tumors remains unknown. Results of PACCE mirror the inferior outcomes and excess toxicity demonstrated in the randomized phase III CAIRO2 study, in which the addition of cetuximab to first-line capecitabine, oxaliplatin, and bevacizumab resulted in poorer PFS (9.4 vs 10.7 months, HR 1.22, 95% CI 1.04–1.43,  $P=0.01$ ) in the unselected *KRAS* population. In *KRAS*-WT tumors, no significant PFS difference was observed between the two treatment groups.<sup>40</sup> Based on these results, combination treatment using chemotherapy plus dual-targeted agents (anti-EGFR antibody agents and bevacizumab) cannot be recommended for *KRAS*-WT patients.

## Safety and tolerability of panitumumab

### Skin toxicity

Skin toxicity is the most common adverse effect of EGFR inhibitors. Acneiform dermatitis, erythema, pruritus, dry skin, or skin fissures have all been described. Typically, rash

and pruritus develop within the first fortnight of treatment, followed by paronychia, desquamation, and/or infections by the fourth week of treatment.<sup>41</sup> Rash occurs in up to 90% of patients administered panitumumab. Grade 2+ toxicity has been found to correlate with improved PFS and OS.<sup>42</sup> Management of skin toxicity has been evaluated in the randomized phase II STEPP (Skin Toxicity Evaluation Protocol with Panitumumab) study.<sup>41</sup> Use of a pre-emptive strategy including skin moisturizers, sunscreen, topical steroids, and doxycycline for the duration of anti-EGFR therapy was reportedly well tolerated and reduced grade 2+ skin toxicity at 6 weeks by more than 50% compared to standard care. Patients randomized to the pre-emptive strategy reported better quality of life.<sup>41</sup>

As skin toxicity may result in dose modification and discontinuation, optimizing management of skin toxicity is paramount. Withholding the subsequent panitumumab dose is recommended by the manufacturer in the event of the first occurrence of grade 3+ dermatologic reaction, despite full pre-emptive treatment. Re-challenge of panitumumab at the original dose is recommended once the reaction is deemed less than grade 3. Dose reduction is recommended by the manufacturer upon subsequent occurrence of grade 3+ reactions.<sup>14</sup>

## Hypomagnesemia

Hypomagnesemia occurs due to EGFR inhibition in the distal convoluted tubule that usually prevents renal magnesium wasting. Panitumumab-induced hypomagnesemia occurs in up to 28%–36% of patients and is associated with treatment duration.<sup>31,39,43</sup> Most cases of hypomagnesemia can be managed by oral or intravenous magnesium replacement, and rarely should it precipitate dose modification or cessation of therapy. Cardiac arrhythmia and seizure are rare but serious clinical sequelae of inadequate magnesium replacement. Hypomagnesemia is a reversible toxicity with recovery of serum magnesium levels occurring within 4–6 weeks anti-EGFR therapy cessation.<sup>43</sup> Compared to cetuximab, higher rates of hypomagnesemia (all grades) are reported with panitumumab use (27% vs 17%).<sup>33</sup>

## Infusion reactions

Infusion reactions are reported with most monoclonal antibodies. Severe infusion reactions with panitumumab administration occur at a rate of 2%.<sup>33</sup> Use of premedication with panitumumab is not routine. Fewer infusion reactions (all grades) have been reported with panitumumab compared to cetuximab (3% vs 14%), consistent with the

fully humanized nature of panitumumab.<sup>31,33</sup> Grade 1 or 2 infusion reactions should prompt reduction of the infusion rate by 50%. Administration of pre-medications such as antihistamines and/or corticosteroids prior to infusions can prevent further reactions in this scenario. Recurrent or severe infusion reactions, despite maximal pre-medication, should result in cessation of the infusion and in rare cases panitumumab discontinuation.

## Patient-reported quality of life

A number of phase III trials have incorporated patient quality of life reported using assessments such as the Health State Index score and Overall Health Rating.<sup>25</sup> Thus far, the addition of panitumumab to a chemotherapy backbone does not appear to result in poorer quality of life. With regard to the most common adverse event, skin toxicity, there was no detrimental effect on quality of life in patients who experienced grade 2+ skin toxicity compared with patients with no or milder skin toxicity.<sup>25</sup>

## The place of Panitumumab in therapy and future directions

Panitumumab has therapeutic efficacy in *KRAS*-WT mCRC as a first- or second-line agent in combination with chemotherapy and as monotherapy in chemotherapy-refractory disease. Improved outcomes with single agent anti-EGFR therapies in late stage disease are convincing; however, the optimal sequencing of panitumumab, namely the benefit of introduction into earlier lines of treatment, is yet to be established.

Data from the first-line, phase II PEAK study demonstrated an OS benefit with panitumumab/FOLFOX compared to bevacizumab/FOLFOX (32.2 vs 24.3 months) in the selected *KRAS*-WT population. There is a trend toward an even greater OS benefit in the extended *RAS*-WT cohort (41.3 vs 28.9 months). While these results support utilizing *RAS* mutation status to direct choice of first-line targeted agent, further phase III data are required to establish the optimal first-line targeted agent in the all-*RAS*-WT population.<sup>35</sup> Dual-pathway inhibition with both panitumumab and bevacizumab in combination with chemotherapy should be avoided after phase III data demonstrated inferior survival outcomes irrespective of *KRAS* status.<sup>39</sup>

Moving forward, extended *RAS* testing should be mandatory for all mCRC patients prior to considering anti-EGFR therapy. Mutations in *KRAS* exons 3 and 4 and *NRAS* exons 2 and 3 predict lack of response to anti-EGFR therapy, as demonstrated in the chemotherapy-refractory ASPECCT

population, where response rates approached 0% in mutated *RAS* tumors.<sup>33</sup> Despite this significant advance in identification of non-responders, work remains to further define those most likely to derive benefit.

At a preclinical level, resistance to anti-EGFR agents has been demonstrated in tumors with HER2 gene amplification, low EGFR gene copy number, MET oncogene amplification, PIK3CA mutations (exon 9 and 20), or loss of function of key tumor suppressor gene *PTEN*.<sup>24,44,45</sup> Circulating tumor cell status assessed between 2 and 10 weeks after initiating anti-EGFR antibody agents has also been shown to predict treatment failure in advance compared to traditional imaging modalities.<sup>46</sup> However, data are conflicting, and validation is lacking for these potential biomarkers; therefore, they cannot be recommended for use in routine clinical care at present.

Identifiable mutations in mCRC also lend scope to developing new targeted therapies and novel combinations with existing drugs. New combinations are currently being evaluated with established agents such as combination panitumumab, irinotecan, and everolimus (<http://www.clinicaltrials.gov> identifier NCT01139138). Use of MET kinase inhibitors to overcome MET oncogene amplification in patients that acquire resistance to anti-EGFR therapies is a potential new strategy warranting further evaluation.<sup>47</sup>

More efficient and sensitive approaches to identify tumor mutations are also in development. Utilizing circulating tumor DNA from peripheral blood to screen for mutations allows for real-time identification of predictive or prognostic markers using tissue (blood) that is readily available. This approach requires further validation for commercial use but remains a promising approach in improving overall management of mCRC.<sup>48</sup>

## Conclusion

Panitumumab is a recombinant, fully human, IgG2 monoclonal anti-EGFR antibody with an acceptable safety profile. For many years, panitumumab has remained an important agent in the treatment paradigm for *KRAS*-WT mCRC with demonstrated efficacy in the first-, second-line and chemorefractory settings. A recent advance has been the observation that the benefit of EGFR inhibitors is restricted to the all-*RAS*-WT population, although response rates for single agent therapy in chemorefractory patients remain in the order of 20%. The future of mCRC research will involve optimizing the sequence of currently proven therapies while incorporating novel agents, as well as further translational work to build upon current knowledge of prognostic and

predictive biomarkers and to identify additional druggable targets.

## Disclosure

The authors report no conflicts of interest in this work.

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