Panitumumab in the management of patients with KRAS wild-type metastatic colorectal cancer

Christopher M. Hocking and Timothy J. Price

Ther Adv Gastroenterol

2014, Vol 7(1) 20–37

DOI: 10.1177/

1756283X13498660

© The Author(s), 2013.

Reprints and permissions:

[http://www.sagepub.co.uk/](http://www.sagepub.co.uk/journalsPermissions.nav)

[journalsPermissions.nav](http://www.sagepub.co.uk/journalsPermissions.nav)

Abstract: The past 15 years has seen a marked increase in available therapeutic options for patients with metastatic colorectal cancer resulting in improvements in median survival from 12 to 24 months. One of these new options is panitumumab, which is a fully humanized monoclonal antibody that binds to the epidermal growth factor receptor of tumor cells and inhibits downstream cell signaling with antitumor effects of inhibition of tumor growth, induction of apoptosis and inhibition of angiogenesis. Large randomized clinical trials have demonstrated significant improvements in tumor response rates and progression-free survival when panitumumab is combined with chemotherapy and as monotherapy in chemorefractory metastatic colorectal cancer. Clinical benefit with panitumumab is limited to patients with nonmutated KRAS tumors. Rash is a common toxicity of panitumumab treatment but can potentially be ameliorated with the use of prophylactic strategies. The role of panitumumab in the overall treatment of metastatic colorectal cancer is evolving and future clinical trials will focus on improved patient selection through use of novel predictive biomarkers, and the optimal timing of treatment.

Keywords: colorectal, EGFR, KRAS, panitumumab, review

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide, and the second leading cause of cancer mortality (behind lung cancer) in the developed world [Jemal *et al.* 2011]. While the incidence of CRC is reducing or stabilizing in historically high incident areas such as North America, Europe and Australia, there has been an increase in incidence rates in Spain, Eastern Europe and Eastern Asia, due to dietary changes and higher rates of obesity and smoking [Center *et al.* 2009a, 2009b]. Outcomes in patients with metastatic CRC (mCRC) have improved significantly over the last 15 years largely due to increased adoption of surgical resection of liver-limited metastasis and improved systemic therapeutic options [Kopetz *et al.* 2009]. In the late 1990s 5-fluorouracil (5-FU) was the only available systemic therapy for mCRC, a contrast to today where nine drugs with significant antitumor activity are approved by the US Food and Drug Administration (FDA) for use in mCRC (Table 1). The availability of these agents

has seen median overall survival (OS) in patients with mCRC improve from 8–12 months in 1998 to 18–21 months with the availability of capecitabine, oxaliplatin and irinotecan [Grothey *et al.* 2004]. The addition of targeted therapies has further improved reported OS in mCRC to 21–24 months [Douillard *et al.* 2010; Saltz *et al.* 2008; Van Cutsem *et al.* 2009].

Despite these improvements, long-term survival of patients with unresectable mCRC remains poor with 5-year survival of approximately 10% [Kopetz *et al.* 2009; Peeters and Price, 2012].

Approximately 60–70% of patients with mCRC receive a biological agent during their treatment course targeting one of two main pathways; vascular endothelial growth factor (VEGF) and epidermal growth factor receptor (EGFR) [Peeters and Price, 2012].

Bevacizumab (Avastin®, F. Hoffmann-La Roche Ltd, Basel, Switzerland), a monoclonal antibody

Correspondence to:

Timothy J. Price,

MBBS, FRACP

Department of Medical

Oncology, TQEH,

Woodville, Woodville

Road, Woodville, SA 5011,

Australia

[timothy.price@health.](mailto:timothy.price@health.sa.gov.au)

[sa.gov.au](mailto:timothy.price@health.sa.gov.au)

Christopher M. Hocking,
MBBS

Department of Medical

Oncology, The Queen

Elizabeth Hospital,

Woodville, SA, Australia

Table 1. US Food and Drug Administration approved agents for metastatic colorectal cancer.

Chemotherapy
Fluoropyrimidines [5-fluorouracil, capecitabine]
Oxaliplatin
Irinotecan
Targeted Agents
Vascular endothelial growth factor
Bevacizumab
Aflibercept
Regorafenib
Epidermal growth factor receptor
Cetuximab
Panitumumab

(MoAb) targeting VEGF, prolongs progression-free survival (PFS) and OS when used in the first and second lines of treatment in combination with chemotherapy [Peeters and Price, 2012]. A median OS benefit of 1.4 months (21.3 *versus* 19.9 months) was demonstrated in the NO16966 trial with the addition of bevacizumab to first-line infusional 5-FU/folinic acid/oxaliplatin (FOLFOX) chemotherapy [Saltz *et al.* 2008]. Aflibercept (Zaltrap, Sanofi U.S., Inc.), also targeting VEGF, was approved by the FDA in August 2012 for second-line treatment of mCRC in combination with infusional 5-FU/folinic acid/irinotecan (FOLFIRI) chemotherapy after demonstrating improved PFS and OS (13.5 *versus* 12.1 months) in this setting [Van Cutsem *et al.* 2012]. Regorafenib, an oral kinase inhibitor of angiogenic signaling (including VEGF) has demonstrated improved OS (6.4 *versus* 5.0 months) and PFS as monotherapy in treatment refractory mCRC [Grothey *et al.* 2013]. FDA approval of Regorafenib in September 2012 provides a further treatment option for patients with mCRC.

Two EGFR inhibitors are available for treatment of mCRC: cetuximab (Erbix®, Merck KGaA, Darmstadt, Germany) and panitumumab (Vectibix®, Amgen Inc., CA, USA). The efficacy of these drugs is limited to patients with wild-type (nonmutated) Kirsten Rat Sarcoma (*KRAS* WT) tumors. Evidence supports use of these agents as monotherapy in chemotherapy refractory mCRC and in first and second lines of treatment in combination with chemotherapy.

The markedly increased number of active agents and plethora of recent clinical trial data have

made the overall treatment algorithm for mCRC more complex. There is a lack of randomized trial data evaluating the optimal sequencing and combinations of available agents, and apart from *KRAS* mutation status there is a lack of predictive biomarkers available to support drug selection for individual patients. Until such data are available the clinician relies on an understanding of data relating to each class of agent with the goal of exposing a patient to all available active agents to achieve improved survival and optimal disease control [Kopetz *et al.* 2009].

The following paper examines the clinical trial data relating to panitumumab in the treatment of *KRAS* WT mCRC and provides a commentary for clinicians on how panitumumab may be best used in the clinic until further data becomes available.

Pharmacology of panitumumab

The EGFR is a transmembrane cell surface glycoprotein and a member of the human epithelial growth factor receptor (HER) family of tyrosine kinases [El Zouhairi *et al.* 2011]. Binding of ligands to the EGFR leads to homodimerization or heterodimerization of HER family members and results in autophosphorylation of intracellular tyrosine residues, initiating several key cell-signaling pathways including Ras/Raf/MAPK and PI3K/AKT pathways [El Zouhairi *et al.* 2011; Jean and Shah, 2008; Yang *et al.* 2010]. Binding to EGFR enhances processes critical to tumor growth and progression such as angiogenesis, apoptosis inhibition, tumor invasiveness and metastatic spread, making EGFR inhibition an important therapeutic target in cancer [Toffoli *et al.* 2007; Yang *et al.* 2010].

Panitumumab is a fully humanized IgG2 monoclonal antibody that binds to the extracellular domain of the EGFR of both tumor and normal cells with high affinity. By competing with endogenous ligand binding panitumumab inhibits receptor phosphorylation and activation of EGFR associated cell signaling (see figure 1) [Yang *et al.* 2010]. This also results in downregulation of EGF receptors through receptor internalization, induction of apoptosis, autophagy and inhibition of angiogenesis [Giannopoulou *et al.* 2009; Keating, 2010; Yang *et al.* 1999].

Panitumumab is administered intravenously at a recommended dosing schedule of 6 mg/kg once every 2 weeks [Doi *et al.* 2009; Stephenson *et al.*

Figure 1. Panitumumab and epidermal growth factor receptor (EGFR) signaling pathway. (Illustration courtesy of Alessandro Balani. Copyright © 2013.)

2009]. This schedule results in steady-state concentrations by the third infusion [Jean and Shah, 2008]. The elimination half-life of panitumumab is approximately 7 days, longer than cetuximab where the half-life (following 400 mg/kg infusion) is 4 days, providing the rationale for the weekly

schedule of cetuximab *versus* the alternate weekly administration schedule for panitumumab [Jean and Shah, 2008].

Panitumumab has dual clearance mechanisms. Specific clearance of panitumumab involves

binding to EGFR, internalization into the cell and degradation in lysosomes. This mechanism of clearance plays an important role of panitumumab clearance but is capacity limited resulting in nonlinear clearance. At doses above 2 mg/kg clearance is dependent on nonspecific mechanisms mediated by the reticuloendothelial system (RES) [Yang *et al.* 2010].

Predictive markers of response to panitumumab

KRAS exon 2 mutations

Tumor *KRAS* gene mutation predicts for resistance to anti-EGFR antibodies and remains the only prospectively validated predictive biomarker to assist choice of systemic treatment in mCRC.

KRAS is a small serine-threonine kinase activated just downstream of activation of the EGFR (or other tyrosine kinase receptors) and propagates further signaling events. Gain of function mutations in *KRAS* result in a constitutively active protein, regardless of EGFR activation, resulting in increased proliferation, tumor angiogenesis, metastasis, and inhibition of apoptosis, which support continued cancer cell survival [Peeters *et al.* 2009a]. This provides the biological rationale for the finding that *KRAS* mutations predict for resistance to anti-EGFR antibody therapy [Yang *et al.* 2010].

KRAS mutations are found in 30–45% of CRC tumors, with high concordance between primary and metastatic lesions [Maughan *et al.* 2011; Peeters *et al.* 2012b; Price *et al.* 2011; Van Cutsem *et al.* 2011]. Mutations are most common in exon 2 (codon 12 and 13) but also occur in exon 3 (codon 61) and exon 4 (codon 117 and 146) [De Roock *et al.* 2010b; Oliner *et al.* 2013; Peeters *et al.* 2012b].

Clinical evidence for the predictive role of *KRAS* exon 2 mutation first came from retrospective analysis of phase III trials evaluating anti-EGFR antibodies as monotherapy in the chemorefractory setting [Amado *et al.* 2008; Karapetis *et al.* 2008]. Subsequently trials of anti-EGFR antibodies in combination with chemotherapy have confirmed, prospectively, the negative predictive role of *KRAS* exon 2 mutation on clinical outcomes [Peeters *et al.* 2010].

Evidence from retrospective analysis of patients treated with cetuximab suggests patients with

G13D *KRAS* mutations may benefit from cetuximab therapy to a similar degree as *KRAS* WT patients [De Roock *et al.* 2010b; Tejpar *et al.* 2012]. This effect, however, was not seen in a retrospective pooled analysis of the three phase III trials of panitumumab therapy [Douillard *et al.* 2010; Peeters *et al.* 2010; Van Cutsem *et al.* 2007]. In 1053 *KRAS* MT patients treated with panitumumab, no specific exon 2 *KRAS* MT allele demonstrated predictive value for outcome [Peeters *et al.* 2012b]. Whether there is a difference between the mechanism of action of the drugs remains unclear and these results highlight the difficulties of retrospective analysis.

Ultimately analysis of *KRAS* mutation status is required prior to treatment with an anti-EGFR antibody in mCRC with regulating bodies restricting use of panitumumab to patients with confirmed *KRAS* WT mCRC, and this is unlikely to change unless there is prospective data relating to G13D.

Predictive markers beyond KRAS exon 2

Importantly, not all *KRAS* WT patients respond to anti-EGFR antibodies, highlighting the need to identify additional predictive biomarkers to better assist patient selection for treatment with this class of drug. Mutations in *KRAS* exon 3 and 4 have since been analyzed retrospectively in phase III randomized trials of panitumumab [Oliner *et al.* 2013; Peeters *et al.* 2013]. While the incidence of *KRAS* mutations beyond exon 2 is relatively small, exon 3 MT (2–4%) and exon 4 MT (5–6%) appear to confirm resistance to panitumumab and exclusion of these patients improves the relative benefit of panitumumab therapy [Oliner *et al.* 2013; Peeters *et al.* 2013; Seymour *et al.* 2013].

Other downstream effector genes, *BRAF*, *NRAS* and *PIK3CA*, and reduced PTEN protein expression have been postulated as conferring resistance to anti-EGFR antibodies though results, largely based on retrospective subgroup analysis have been conflicting [De Roock *et al.* 2010a; Di Nicolantonio *et al.* 2008; Oliner *et al.* 2013; Peeters *et al.* 2013; Tol *et al.* 2010; Van Cutsem *et al.* 2011].

NRAS mutation, found in 5–7% of CRC specimens, is emerging as a consistent negative predictive biomarker for panitumumab therapy with supporting evidence from both retrospective and now prospective large phase III panitumumab

trials [Oliner *et al.* 2013; Peeters *et al.* 2013; Seymour *et al.* 2013]. Mutation in tumor *BRAF* gene occurs in approximately 10% of mCRC, is mutually exclusive of *KRAS* mutation and an independent poor prognostic marker in mCRC [Price *et al.* 2011]. *BRAF* mutation may provide an explanation for an additional population of patients resistant to anti-EGFR antibodies, although conflicting trial results have failed to establish *BRAF* firmly as a predictive biomarker. *BRAF* requires further validation in large cohorts of mCRC patients [Bardelli and Siena, 2010; Tie *et al.* 2011].

The relatively low incidence of these mutations has reduced the power of retrospective analysis to draw conclusions about the predictive role of individual mutations. Some authors have suggested selection of 'triple wild-type' patients (*KRAS/NRAS/BRAF*) for anti-EGFR antibody treatments may improve patient selection, response rates and outcome, although given the low prevalence of *BRAF* and *NRAS* mutations, further validation, probably by way of meta-analysis, is required [Bardelli and Siena, 2010; De Roock *et al.* 2010a].

Preclinical trials have classified CRC into subgroups based on extended gene expression profiles [De Sousa *et al.* 2013; Sadanandam *et al.* 2013]. *In vitro* resistance to anti-EGFR antibodies has been demonstrated in specific subgroups and the development of a clinically useful assay may allow improved patient selection for these therapies.

Inferior outcome in RAS MT patients treated with panitumumab

The predictive biomarkers discussed above identify subgroups of patients who do not benefit from anti-EGFR antibody therapy. Of concern is the emerging evidence regarding the potential harm of these subgroups of patients when receiving such therapy.

The first-line PRIME trial of FOLFOX chemotherapy with or without panitumumab was the first trial to demonstrate an inferior outcome in *KRAS* MT patients treated with panitumumab (PFS 7.3 *versus* 8.8 months, hazard ratio [HR] 1.29, $p = 0.02$; and OS 15.5 *versus* 19.3 month, HR 1.24, $p = 0.068$). Inferior PFS and OS were also seen in *KRAS* MT patients in the first-line

OPUS trial, evaluating cetuximab and FOLFOX in mCRC [Bokemeyer *et al.* 2011]. A prespecified retrospective analysis of the PRIME trial assessing *RAS* mutations beyond *KRAS* exon 2 was recently presented [Oliner *et al.* 2013]. With exon 3 and 4 *KRAS* MT and *NRAS* MT included in the analysis, a further 17% of patients were identified as *RAS* MT. This group had a numerically inferior OS when treated with panitumumab. When included in the updated analysis, patients with any *RAS* MT had inferior PFS (HR 1.31, 95% confidence interval [CI] 1.07–1.60) and OS (HR 1.25, CI 1.02–1.55) when treated with panitumumab in combination with FOLFOX compared with FOLFOX alone. The finding of inferior outcome in *RAS* MT patients with panitumumab was also demonstrated in the second-line phase III PICCOLO trial randomizing patients to irinotecan *versus* irinotecan and panitumumab [Seymour *et al.* 2013]. In the analysis of patients with any mutation (*KRAS/NRAS/BRAF/PIK3CA*) a statistically inferior OS was seen in the panitumumab-treated patients *versus* irinotecan alone (HR 1.64, 95% CI 1.14–2.34). Given the low prevalence of each individual mutation statistical significance of inferiority was not demonstrated individually, except for *BRAF* MT which predicted for inferior OS with panitumumab (HR 1.84, 95% CI 1.10–3.08). Interestingly inferior outcomes were not observed in *KRAS* MT patients in the other phase III trials of panitumumab [Amado *et al.* 2008; Peeters *et al.* 2010]. The evidence of a potentially harmful effect in *RAS* MT patients treated with oxaliplatin in combination has led to a recommendation that *RAS* testing beyond exon 2 should occur in clinical practice.

The mechanism for the observed adverse outcome in *KRAS* MT patients treated with anti-EGFR antibodies remains unclear. A recent hypothesis suggests nonmutant isoforms of *RAS* may play a role in suppressing the mutant *RAS* isoform. For example, in the setting of mutant *KRAS*, wild-type *NRAS* and *HRAS* have been shown to continue to play an important role in modulating downstream signaling. Furthermore wild-type *RAS* isoforms have an inhibitory effect on oncogenic mutant *KRAS* [Young *et al.* 2013]. Inhibition of EGFR (i.e. with panitumumab) inhibits the function of wild-type *RAS* isoforms and may remove its inhibitory effect on mutant *RAS*, paradoxically leading to increase in MAPK signaling and cell proliferation.

Table 2. Progression-free survival and overall survival in first-line trials of panitumumab.

Trials	KRAS status	Treatment regimen (Control)	PFS (months)	HR (<i>p</i> values)	Median OS (months)	HR (<i>p</i> values)	ORR
Phase III trials							
PRIME (<i>n</i> = 1183)	KRAS WT	FOLFOX4 + P	9.6	0.8 (<i>p</i> =0.02)	23.9	0.83 (<i>p</i> =0.072)	55%
		(FOLFOX4)	8		19.7		48%
	KRAS MT	FOLFOX4 + P	7.3	1.29 (<i>p</i> =0.02)	15.5	1.24 (<i>p</i> =0.068)	40%
		(FOLFOX4)	8.8		19.3		40%
Phase II trials							
PEAK	KRAS WT	FOLFOX + P	10.9	HR 0.87 [CI 0.65–1.17]	Not Reached	HR 0.72 [CI 0.47–1.11]	58%
(<i>n</i> =285)		FOLFOX + Bev	10.1		25.4		54%
[Kohne <i>et al.</i> 2012]	Unselected	FOLFIRI + P	7.6		NR		48%
(<i>n</i> =154)	KRAS WT	FOLFIRI + P	8.9		NR		56%
	KRAS MT	FOLFIRI + P	7.2		NR		38%
[Berlin <i>et al.</i> 2007]	Unselected	IFL + P	5.6		17		46%
(<i>n</i> =43)	Unselected	FOLFIRI + P	10.9		22.5		42%
Bev, bevacizumab; CI, 95% confidence interval; FOLFIRI, infusional 5-fluorouracil/folinic acid/irinotecan; FOLFOX, infusional 5-fluorouracil/folinic acid/oxaliplatin; HR, hazard ratio; IFL, bolus 5-fluorouracil/folinic acid/irinotecan; KRAS, Kirsten rat sarcoma gene; MT, mutated; <i>n</i> , number of patients; NR, not reported; ORR, objective response rate; OS, overall survival; P, panitumumab; PFS, progression-free survival; WT, wild-type (nonmutated).							

Evidence for clinical efficacy of panitumumab

First-line trials

The evidence to support the use of panitumumab in the first-line treatment setting comes from the phase III PRIME trial [Douillard *et al.* 2010] and two single-arm phase II trials [Berlin *et al.* 2007; Kohne *et al.* 2012] (Table 2).

The PRIME (Panitumumab Randomized Trial in Combination with Chemotherapy for Metastatic Colorectal Cancer to Determine Efficacy) trial randomized 1183 untreated patients with mCRC to FOLFOX chemotherapy (the control arm) *versus* FOLFOX chemotherapy and panitumumab. PFS in KRAS WT patients (the primary endpoint) was significantly improved in the panitumumab/FOLFOX arm *versus* FOLFOX alone (9.6 *versus* 8.0 months; *p* = 0.02). There was a trend to improvement in OS (23.9 *versus* 19.7 months; *p* = 0.072) and objective response rate (ORR) (55% *versus* 48%; *p* = 0.068) in the panitumumab arm although these did not reach statistical significance. Unexpectedly inferior outcomes were seen in KRAS MT patients treated with panitumumab is

discussed in detail above (see the section on 'Inferior outcome in RAS MT patients treated with panitumumab').

Further evidence for the use of panitumumab in the first-line setting comes from three phase II trials (Table 2). The recently completed PEAK study, a randomized trial presented in abstract form, is the first head-to-head analysis of FOLFOX combined with either panitumumab or bevacizumab in KRAS WT mCRC [Schwartzberg *et al.* 2013a]. PFS was 10.9 *versus* 10.1 months (HR 0.87, 95% CI 0.65–1.17), OS not reached *versus* 25.4 months (HR 0.72, 95% CI 0.47–1.11) and RR 58% *versus* 54%, respectively. Extended RAS mutation analysis (KRAS exon 3 and 4 and NRAS MT) was also undertaken. In a finding similar to the PRIME trial, patients with WT KRAS exon 2 but MT in other RAS locus demonstrated inferior PFS with panitumumab therapy [Schwartzberg *et al.* 2013b]. These early results suggest that either biological agent may be considered in first-line therapy of RAS WT patients although larger phase III trials are awaited to confirm these results.

Table 3. Progression-free survival and overall survival in second-line trials of panitumumab.

Trials	KRAS status	Treatment regimen (Control)	PFS (months)	HR (<i>p</i> values)	Median OS (months)	HR (<i>p</i> values)	ORR	HR (<i>p</i> values)
Phase III trials								
[Peeters <i>et al.</i> 2010] (<i>n</i> =1186)	KRAS WT	FOLFIRI + P	5.9	0.73 (<i>p</i> =0.004)	14.0	0.85 (<i>p</i> =0.12)	35%	<i>p</i> <0.001
		FOLFIRI	3.9		12.5		10%	
	KRAS MT	FOLFIRI + P	5.0	0.85 (<i>p</i> =0.14)	11.8	0.94	13%	
		FOLFIRI	4.9		11.1		14%	
PICCOLO (<i>n</i> =460)	KRAS WT	IrPan	NR	0.78 (<i>p</i> =0.015)	10.4	1.01 (<i>p</i> =0.91)	34%	<i>p</i> =0.0001
		Irinotecan	NR		10.9		12%	
Phase II trials								
SPIRITT (<i>n</i> =182)	KRAS WT	FOLFIRI + P	7.7	HR 1.01 [CI 0.68–1.50]	18	HR 1.06 [CI 0.75–1.49]	32%	(KRAS WT <i>versus</i> KRAS MT) OR 1.6 [CI 0.6–4.3]
[Cohn <i>et al.</i> 2011]	KRAS WT	FOLFIRI + Bev	9.2		21.4		19%	
	KRAS WT	FOLFIRI + P	6.0	(KRAS WT <i>versus</i> KRAS MT)	11.5	(KRAS WT <i>versus</i> KRAS MT)	23%	
(<i>n</i> =109)	KRAS MT	FOLFIRI + P	4.3	HR 0.8 [CI 0.5–1.1]	7.1	HR 0.6 [CI 0.4–0.9]	16%	
STEPP								
(<i>n</i> =87)	KRAS WT	I/FOLFIRI + P	5.5		13.7		16%	
	KRAS MT	I/FOLFIRI + P	3.3		13.3		8%	
CI, 95% confidence interval; FOLFIRI, infusional 5-fluorouracil/folinic acid/irinotecan; HR, hazard ratio; I, irinotecan; IrPan, irinotecan and panitumumab; KRAS, Kirsten rat sarcoma gene; MT, mutated; P, panitumumab; PFS, progression-free survival; NR, not reported; ORR, objective response rate; OS, overall survival; WT, wild-type.								

CI, 95% confidence interval; FOLFIRI, infusional 5-fluorouracil/folinic acid/irinotecan; HR, hazard ratio; I, irinotecan; IrPan, irinotecan and panitumumab; KRAS, Kirsten rat sarcoma gene; MT, mutated; P, panitumumab; PFS, progression-free survival; NR, not reported; ORR, objective response rate; OS, overall survival; WT, wild-type.

Kohne and colleagues evaluated FOLFIRI chemotherapy with panitumumab in 154 patients with ORR as the primary endpoint [Kohne *et al.* 2012]. When assessed by *KRAS* status there was improved ORR (56% *versus* 38%) and PFS (8.9 *versus* 7.2 months) in the *KRAS* WT compared with *KRAS* MT group with the degree of benefit consistent with the findings of the PRIME trial. Berlin and colleagues assessed panitumumab in combination with irinotecan-based chemotherapy in 43 patients with mCRC [Berlin *et al.* 2007]. *KRAS* status was not determined.

Summary. The PRIME study supports the use of first-line panitumumab in combination with FOLFOX for *KRAS* WT patients, with significant improvement in PFS and ORR demonstrated with the addition of panitumumab. The inferior outcome seen in the *KRAS* MT patients emphasizes the need to determine *KRAS* status prior to treatment with an anti-EGFR antibody, as treatment in an unselected population has the potential for inferior outcomes.

Second-line trials

The evidence supporting the use of panitumumab in second-line treatment of mCRC comes from two large phase III randomized trials, and two single-arm phase II trials. All of these trials assessed panitumumab in combination with irinotecan-based chemotherapy (Table 3).

The large phase III trial conducted by Peeters and colleagues randomized 1345 patients to FOLFIRI chemotherapy alone or in combination with panitumumab for second-line treatment of mCRC [Peeters *et al.* 2010]. Statistically significant improvement in PFS was seen in *KRAS* WT patients treated with panitumumab compared with FOLFIRI alone (5.9 *versus* 3.9 months, HR 0.73, *p* = 0.004). A trend to improved OS was observed in *KRAS* WT patients (14.5 *versus* 12.5 months, HR 0.85, *p* = 0.12). No difference in PFS or OS was seen in *KRAS* MT patients. There was an imbalance in subsequent anti-EGFR use in the *KRAS* WT patients (9% in panitumumab group *versus* 31% control), which

may have attenuated the treatment effect of panitumumab on OS. The reported ORR of 35% in panitumumab-treated *KRAS* WT patients is impressive and the highest reported in a second-line mCRC trial. No detrimental effect was observed in the *KRAS* MT patients treated with panitumumab and FOLFIRI. The results of this trial are consistent with findings of the second-line EPIC trial evaluating the addition of cetuximab to irinotecan, where a PFS improvement of 1.2 months was reported in the *KRAS* WT population (4.0 *versus* 2.8 months; HR 0.77; $p = 0.095$) [Sobrero *et al.* 2008]. The EPIC trial did not have the same methodological rigor, however, with the *KRAS* status analyzed retrospectively and in only 23% of patients.

Seymour and colleagues conducted a randomized phase III trial of irinotecan with or without panitumumab (IrPan) in mCRC patients progressing after fluoropyrimidine therapy [Seymour *et al.* 2013]. Panitumumab was administered at a schedule of 9 mg/kg 3-weekly. Of the 460 randomized exon 2 and 3 *KRAS* WT patients no difference was seen in the primary endpoint median OS in the IrPan-treated patients (10.4 *versus* 10.9 months, HR 1.01, 95% CI 0.83–1.23). IrPan did lead to prolonged PFS (HR 0.78, 95% CI 0.64–0.95) and improved ORR (34% *versus* 12%, $p < 0.0001$).

Cohn and colleagues evaluated FOLFIRI and panitumumab in 116 patients who had progressed following an oxaliplatin and bevacizumab containing first-line treatment for mCRC [Cohn *et al.* 2011]. *KRAS* mutation analysis was available in 109 patients with *KRAS* MT found in 41%. PFS was improved in *KRAS* WT patients compared with *KRAS* MT patients (6.0 *versus* 4.9 months), as were OS (11.5 *versus* 7.1 months) and ORR (23% *versus* 16%).

The STEPP trial specifically evaluated optimal management of skin toxicity with panitumumab treatment, but provides further evidence for use in combination with irinotecan-based chemotherapy in the second-line setting. A total of 98 patients treated with panitumumab plus either irinotecan or FOLFIRI (at investigators choice) were randomized to pre-emptive *versus* reactive treatment of skin toxicity [Lacouture *et al.* 2010; Mitchell *et al.* 2011]. *KRAS* MT were found in 44%. ORR (16% *versus* 8%), PFS (5.5 *versus* 3.3 months) and OS (13.7 *versus* 13.3 months) were higher in *KRAS* WT patients compared with *KRAS* MT. The

results skin toxicity management is discussed below (see the section on ‘Tolerability’).

As is the case in first-line therapy, head-to-head trials of chemotherapy with either panitumumab or bevacizumab in *KRAS* WT mCRC are awaited. The recently reported randomized phase II SPIRITT trial randomized patients with *KRAS* WT mCRC who had received first-line FOLFOX and bevacizumab to second-line FOLFIRI with either panitumumab or bevacizumab [Hecht *et al.* 2013]. PFS (7.7 *versus* 9.2 months, HR 1.01, 95% CI 0.68–1.50) and OS (18 *versus* 21.4 months, HR 1.06, 95% CI 0.75–1.49) were not significantly different between treatment groups. ORR was higher with panitumumab (32% *versus* 19%) [Cohn *et al.* 2013].

Summary. Panitumumab in combination with FOLFIRI is associated with an improved PFS compared with FOLFIRI alone in second-line treatment of *KRAS* WT mCRC. Any difference in outcome between second-line/continuation bevacizumab *versus* panitumumab is awaited in phase III trials.

Third-line trials

The first phase III evidence of clinical efficacy of panitumumab in mCRC came from trials of panitumumab monotherapy in patients with chemorefractory disease. Van Cutsem and colleagues conducted a phase III trial, randomizing 463 patients to panitumumab plus best supportive care (BSC) *versus* BSC alone [Van Cutsem *et al.* 2007]. Panitumumab improved PFS (8.0 *versus* 7.3 weeks, HR 0.54, $p < 0.0001$) and ORR (10% *versus* 0%, $p \leq 0.0001$) compared with BSC alone. No difference in OS was seen (Table 4). Retrospective analysis by tumor *KRAS* status helped define the role of *KRAS* as a predictor of response [Amado *et al.* 2008]. Exon 2 *KRAS* mutations were identified in 43% and the benefit of panitumumab was restricted to patients with *KRAS* WT tumors (PFS 12.3 *versus* 7.3 weeks, HR 0.45, 95% CI 0.34–0.59). No benefit was observed in *KRAS* MT patients treated with panitumumab (PFS 7.4 *versus* 7.3 weeks, HR 0.99, 95% CI 0.73–1.36). No improvement in OS was demonstrated irrespective of *KRAS* status. It is likely any panitumumab-related OS survival benefit was attenuated by the high crossover rate (76%) of BSC patients to panitumumab as part of a prespecified crossover extension study [Van Cutsem *et al.* 2008]. These results are consistent with the CO.17 trial of cetuximab

Table 4. Progression-free survival and overall survival in third-line trials of panitumumab.

Trials	KRAS status	Treatment regimen (Control)	PFS (weeks)	HR (<i>p</i> values)	Median OS (months)	HR (<i>p</i> values)	ORR	HR (<i>p</i> values)
Phase III trials								
[Van Cutsem <i>et al.</i> 2007] (<i>n</i> =463)	Unselected	P + BSC	8	HR 0.54 (<i>p</i> <0.0001)	NR	HR 1.0	10%	<i>p</i> =0.0001
		BSC	7.3		NR		0%	
	KRAS WT	P + BSC	12.3	HR 0.34	8.1	HR 0.99	17%	
		BSC	7.3		7.6		0%	
	KRAS MT	P + BSC	7.4	HR 0.99	4.9	HR 1.02	0%	
		BSC	7.3		4.4		0%	
Phase II trials								
[Hecht <i>et al.</i> 2007] (<i>n</i> =148)	Unselected	P	14		9		9%	
[Muro <i>et al.</i> 2009] (<i>n</i> =52)	Unselected	P	8		9.3		14%	
BSC, best supportive care; HR, hazard ratio; KRAS, Kirsten rat sarcoma gene; P, panitumumab; PFS, progression-free survival; NR, not reported; ORR, objective response rate; OS, overall survival.								

monotherapy where efficacy was also limited to *KRAS* WT patients. In this trial crossover was not permitted and only 7% of patients randomized to BSC subsequently received cetuximab. OS was improved in cetuximab-treated *KRAS* WT patients compared with BSC [Jonker *et al.* 2007; Karapetis *et al.* 2008].

An interesting subgroup analysis was reported from the original phase III panitumumab trial, evaluating the association between skin toxicity and efficacy outcomes [Peeters *et al.* 2009b]. In patients randomized to the panitumumab arm, PFS was improved in those who experienced grade 2–4 compared with grade 1 skin toxicity (HR 0.63, 95% CI 0.45–0.88). This benefit was limited to patients with *KRAS* WT tumors. Severe (grade 2–4) skin toxicity was also associated with improved OS (HR 0.60, 95% CI 0.43–0.85). This association has also been demonstrated retrospectively with cetuximab treatment [Cunningham *et al.* 2004; Saltz *et al.* 2004; Stintzing *et al.* 2013].

Two single-arm phase II trials have reported activity with panitumumab monotherapy although effect by *KRAS* status was not reported (Table 4) [Hecht *et al.* 2007; Muro *et al.* 2009]. The use of panitumumab following progression on cetuximab was evaluated in two small trials with conflicting results. A small number of responses were reported in one trial, with the other demonstrating no activity [Metges *et al.*

2010; Wadlow *et al.* 2012]. An EGFR mutation (S492R) arising following treatment with cetuximab and resulting in acquired resistance has been identified *in vitro*. This mutation was found in 2 out of 10 patients with cetuximab resistance and the 1 patient who then received panitumumab achieved a partial tumor response. This provides an explanation for a group of patients who remain sensitive to panitumumab despite progression with cetuximab [Montagut *et al.* 2012]. At present the use of an alternate anti-EGFR antibody following progression is not recommended.

Summary. Panitumumab significantly prolongs PFS when used as monotherapy in chemotherapy refractory mCRC. The benefit is restricted to *KRAS* WT patients. An overall survival benefit has not been demonstrated although it is likely the crossover in the pivotal panitumumab trial may have obscured the OS gain seen in the cetuximab trial. The severity of skin rash with panitumumab may predict likelihood of clinical benefit.

Meta-analysis

A recent meta-analysis provides further evidence for panitumumab and cetuximab in *KRAS* WT mCRC. Data was pooled from randomized trials where standard treatment was compared with standard treatment plus an anti-EGFR antibody [Petrelli *et al.* 2011]. Overall the relative risk

(RR) of an objective response (OR) was 1.69 ($p = 0.003$), indicating patients with *KRAS* WT mCRC are 69% more likely to obtain a response with the addition of anti-EGFR antibody. HR for PFS and OS were 0.65 ($p = 0.0006$) and 0.84 ($p = 0.03$), respectively. When analyzed for each drug, only panitumumab resulted in a statistically improved PFS and OS compared with control. The addition of an anti-EGFR antibody in all lines of treatment led to a statistically significant improved likelihood of achieving an OR. This is particularly true when used as monotherapy where the RR of an OR is 33.84 ($p = 0.0005$). Significant HRs for PFS were seen in both first and subsequent lines of treatment, while OS difference was not significant in either first or subsequent lines of treatment.

In combination with bevacizumab

The large phase III Panitumumab Advanced Colorectal Cancer Evaluation (PACCE) trial investigated first-line dual VEGF and EGFR inhibition in combination with chemotherapy for mCRC [Hecht *et al.* 2009]. A total of 1043 patients were assigned to oxaliplatin-based (Ox-CT; $n = 823$) or irinotecan-based (Iri-CT; $n = 230$) chemotherapy cohorts by investigator choice in combination with bevacizumab (the control). Patients were then randomized to panitumumab *versus* no other treatment. The primary endpoint was PFS in the oxaliplatin chemotherapy cohort. Panitumumab was discontinued following a planned interim analysis demonstrating decreased PFS in the investigational arm. In an updated analysis a statistically significant inferior median PFS (the primary endpoint) was demonstrated in those treated with Ox-CT, bevacizumab and panitumumab *versus* Ox-CT and bevacizumab alone (10 *versus* 11.4 months, HR 1.27, 95% CI 1.06–1.52). There was a significantly inferior OS in the panitumumab-treated Ox-CT cohort.

Inferior outcomes with dual antibody inhibition were seen across all treatment cohorts irrespective of *KRAS* status. Severe (grade 3 and higher) toxicity was greater in the panitumumab arm compared with controls in both Ox-CT (90% *versus* 77%) and Iri-CT (90% *versus* 63%) cohorts. Mechanistic explanations for the inferior outcomes in this study are not known. Pharmacokinetic interactions between dual antibodies, reduced drug exposure due to higher toxicity or a pharmacodynamic interaction between dual antibodies and chemotherapy have been postulated.

The results of PACCE while unexpected and largely unexplained are consistent with other trials investigating dual EGFR/VEGF inhibition in mCRC in first line. The CAIRO2 study randomized 755 patients to capecitabine, oxaliplatin and bevacizumab with or without cetuximab [Tol *et al.* 2009]. In the *KRAS* unselected population PFS was lower in the cetuximab arm (10.7 *versus* 9.4 months; $p = 0.01$). No differences were seen in OS and RR. Toxicity with dual antibody treatment was significantly higher. Treatment with combined anti-EGFR and anti-VEGF antibodies in first-line therapy is not recommended outside of a clinical trial, noting that there may still be a role in late stage disease based on the BOND 2 data for cetuximab [Saltz *et al.* 2008]. The CALGB 80405 (first line) and SWOG S0600 trials (second line) are assessing combination of cetuximab and bevacizumab in *KRAS* WT mCRC and may provide further insight.

Summary. The PACCE trial demonstrates significant inferior outcomes with dual EGFR/VEGF inhibition and this strategy should be avoided outside a clinical trial. Further analysis of additional predictive markers may further enhance the individualization of panitumumab (and cetuximab) in the future.

Tolerability

While the rate of severe (grade 3 or higher) toxicity with panitumumab is low, mild to moderate toxicity, particularly dermatological, is common. This has significant quality of life (QOL) implications and close monitoring, early intervention and routine preventative measures are important.

Rash

The most common clinical manifestations are erythema, acneiform dermatitis and pruritus, but can include skin desquamation, paronychia, skin fissures, pustular rash and skin infection. The distribution of rash typically involves the face and upper body [Lenz, 2006]. Exposure to sunlight can exacerbate skin toxicity [Amgen Inc., 2009].

In the large phase III trial of panitumumab monotherapy the rate of skin toxicity was 90% but severe in only 16% of patients [Amgen Inc., 2009; Van Cutsem *et al.* 2007]. Skin toxicity from trials of panitumumab in combination with chemotherapy is also high, with reported rates of any grade skin toxicity of 95% with severe skin

toxicity occurring in 35–37% of patients [Douillard *et al.* 2010; Hecht *et al.* 2009; Peeters *et al.* 2010].

The STEPP trial, described above, examined the benefit of pre-emptive skin treatment in 98 patients receiving panitumumab in combination with irinotecan based chemotherapy [Lacouture *et al.* 2010]. Pre-emptive skin treatment included use of skin moisturizers, sunscreen, topical corticosteroid and oral doxycycline. Pre-emptive skin treatment was associated with a significantly reduced rate of grade 2 or higher skin toxicity compared to reactive skin treatment (29% *versus* 62%, OR 0.3, 95% CI 0.1–0.6).

Pre-emptive supportive measures are advised for all patients commencing anti-EGFR antibodies and includes advice on sun-protective measures and avoidance of activities and products likely to contribute to skin dryness (long, hot showers and alcohol-based perfumed products) [Fakih and Vincent, 2010]. Canadian guidelines on the management of anti-EGFR antibody induced rash represent sound recommendations [Melosky *et al.* 2009]. Mild (grade 1) toxicity should be managed with a topical antibiotic and corticosteroid cream, moderate toxicity with an oral tetracycline in addition to topical therapy and severe toxicity necessitates an interruption to anti-EGFR treatment.

Hypomagnesemia

Hypomagnesemia occurred in 36% of patients receiving panitumumab monotherapy, which was severe in 3% of cases [Van Cutsem *et al.* 2007]. High EGFR expression at the ascending loop of Henle, the site of 70% of filtered magnesium resorption, is thought to result in damage to the renal tubule from anti-EGFR antibodies [Fakih and Vincent, 2010].

Serum magnesium levels should be closely monitored during treatment with panitumumab and continue for 8 weeks following discontinuation of treatment [Amgen Inc., 2009]. Patients with mild hypomagnesemia (lower level of normal (LLN) 1.2 mg/dl) are generally asymptomatic and do not require routine replacement therapy. Options for treatment of moderate hypomagnesemia (1.2–0.9 mg/dl) include close surveillance, oral supplementation or weekly intravenous magnesium infusion [Fakih, 2008]. Severe hypomagnesemia often leads to fatigue, muscle cramps and

somnolence, which can be under-recognized [Tejpar *et al.* 2007]. All grade 3 or higher hypomagnesemia (Mg <0.9 mg/dl) should be corrected with intravenous magnesium and may be required several times per week and necessitate treatment interruption.

Diarrhea

Diarrhea can be problematic particularly when panitumumab is used in combination with chemotherapy. In trials of panitumumab monotherapy the rate of diarrhea has been reported at 21% but as high as 69–79% in combination with chemotherapy [Berlin *et al.* 2007; Cohn *et al.* 2011; Mitchell *et al.* 2011; Van Cutsem *et al.* 2007]. The rate of severe diarrhea with panitumumab monotherapy is very low (1%). Patient education, ensuring adequate oral fluid intake and the use of loperamide can prevent more significant complications and the need for intravenous fluid replacement.

Infusion reactions

The rate infusion reaction with panitumumab monotherapy is 3% with severe infusion reactions (anaphylaxis, bronchospasm, and hypotension) occurring in 1% of patients [Amgen Inc., 2009; Keating, 2010]. The rate of infusion reaction is significantly lower than with cetuximab, consistent with the fully human nature of panitumumab.

Pulmonary fibrosis

Pulmonary fibrosis has occurred in 2 of 1467 patients treated with panitumumab monotherapy in clinical trials. While the rate of pulmonary fibrosis appears low, prescribing information contains warnings of pulmonary fibrosis and interstitial lung disease (ILD) and suggests caution in patients with pre-existing ILD [Australian Government, 2013; Amgen Inc., 2009].

Regulating affairs

Approval of panitumumab and the indications for its use have been inconsistent between world regulating agencies. Panitumumab was first approved by the US FDA in September 2006 as monotherapy in patients with mCRC with disease progression following fluoropyrimidine, irinotecan and oxaliplatin chemotherapy [Amgen Inc., 2009]. In July 2009, following identification of the predictive value of *KRAS*, the product labeling was

amended such that treatment with panitumumab was restricted to *KRAS* WT patients [Trotta *et al.* 2011].

The European Medicines Agency's (EMA) Committee for Medicinal Products for Human Use (CMPH) initially rejected the application for panitumumab given the small absolute difference in median PFS (5 days) when used in *KRAS* unselected patients. When retrospective analysis demonstrated the benefit was restricted to patients with *KRAS* WT tumors approval was granted in December 2007 [Amado *et al.* 2008; Trotta *et al.* 2011].

The EMA and Australian Therapeutic Goods Association (TGA) have recently extended approval of panitumumab to include treatment of patients with *KRAS* WT mCRC as first-line therapy in combination with FOLFOX and as second-line therapy in combination with FOLFIRI [Australian Government, 2013; European Medicines Agency, 2013]. The US FDA does not carry this indication.

Role of panitumumab in the overall treatment of mCRC

The role of panitumumab in the treatment algorithm of patients with mCRC continues to evolve. While randomized clinical trial data, as described in this paper, demonstrates the activity of panitumumab in *KRAS* WT mCRC many important questions remain unanswered. The optimal timing of use of anti-EGFR antibodies, choice of first-line biological agent, optimal chemotherapy backbone, further predictive biomarkers and the clinical differences between panitumumab and cetuximab are all areas which require further study.

The data presented within this review suggests efficacy for anti-EGFR antibody treatment is best established in chemorefractory *KRAS* WT patients, and represents the standard of care in this group. Single agent panitumumab, single-agent cetuximab and combination cetuximab and irinotecan are all supported by phase III trials demonstrating improved outcomes in this setting [Amado *et al.* 2008; Cunningham *et al.* 2004; Karapetis *et al.* 2008].

The use of anti-EGFR antibody treatment in combination with chemotherapy in earlier lines of treatment is a less common and more complex issue. For *KRAS* WT patients the optimal targeted

agent in first line therapy remains undefined with the addition of either bevacizumab or an anti-EGFR antibody supported by multiple phase III trials. Several factors may lead the clinician to prefer an anti-EGFR antibody to bevacizumab. In patients with a contraindication to bevacizumab, such as refractory hypertension, proteinuria, recent surgery, major thrombosis or hemorrhage risk, the addition of anti-EGFR antibody to chemotherapy improves PFS and ORR compared with chemotherapy alone.

The use of first-line anti-EGFR inhibitor may be of particular relevance in the subset of patients with borderline resectable liver metastasis. The concept of preoperative 'conversion therapy' to allow borderline resectable patients to undergo curative intent resection has received increasing interest in the literature. At present the optimal conversion chemotherapy or biological agent is undefined, although given the importance of tumor response in this setting the ORR of 55% in *KRAS* WT patients treated with panitumumab/FOLFOX in the PRIME trial is comparable or better to any first-line phase III trial in mCRC and represents a reasonable approach in this subset of patients. Retrospective subset analysis from first line trials of bevacizumab, cetuximab and panitumumab in combination with chemotherapy have reported numerically improved attempted curative resection rates and rates of successful complete resection compared to chemotherapy alone [Douillard *et al.* 2010; Okines *et al.* 2009; Van Cutsem *et al.* 2011]. That said, the recently reported 'new EPOC' trial which reported inferior outcomes for *KRAS* WT 'resectable' patients, including those defined as borderline, who received oxaliplatin-based chemotherapy and cetuximab when compared with chemotherapy alone [Primrose *et al.* 2013]. As this was an abstract presentation we await the full data set and manuscript to fully understand the implications.

Head-to-head comparisons of biological agents in the first-line setting, assessing survival outcomes and rates of successful metastatic resection are needed. The German FIRE-3 trial, a phase III trial comparing first-line cetuximab with bevacizumab in combination with FOLFIRI in *KRAS* WT patients, was recently reported. The primary endpoint of ORR was improved in the cetuximab arm (ORR 72% *versus* 63%; $p = 0.017$) in those patients receiving at least three cycles of treatment

[Heinemann *et al.* 2013]. While no difference was demonstrated in PFS, a significant OS benefit (median OS 28.7 *versus* 25.0 months, HR 0.77, 95% CI 0.62–0.96) was seen in cetuximab-treated patients. Information on subsequent anticancer therapy and differences in liver resection rates are awaited. Further insight will hopefully come from the CALGB 80405 trial also comparing first-line cetuximab with bevacizumab. As discussed earlier, the phase II PEAK trial also demonstrates a trend to improved OS with anti-EGFR antibody (panitumumab) compared with bevacizumab in the first-line setting in *KRAS* WT mCRC [Schwartzberg *et al.* 2013a].

Factors against first-line panitumumab include the potential treatment delay to obtain tumor *KRAS* mutation status and toxicity concerns (particularly dermatological). Access to panitumumab in the first-line setting may be problematic in some regions, with the US FDA currently restricting the use of panitumumab to the chemorefractory setting.

It is important to highlight a degree of uncertainty exists regarding the evidence for cetuximab in combination with chemotherapy. The MRC COIN and NORDIC VII trials were large first-line studies of cetuximab- and oxaliplatin-based chemotherapy which did not demonstrate a benefit of cetuximab irrespective of *KRAS* status [Maughan *et al.* 2011; Tveit *et al.* 2012]. The OPUS and CRYSTAL trials demonstrated a significant benefit [Bokemeyer *et al.* 2011; Van Cutsem *et al.* 2011]. Whether these conflicting results relate to an interaction between cetuximab and the chemotherapy backbone or whether improved biomarkers would allow better patient selection is unknown. The implications for panitumumab–chemotherapy combination is also unclear.

Future developments

Several upcoming clinical trials will hopefully provide answers regarding the optimal use of panitumumab for mCRC. The head-to-head phase III comparison trial, ASPECCT, of cetuximab *versus* panitumumab monotherapy may identify differences in efficacy or toxicity profile that have not been evident to date. The role of panitumumab in cetuximab refractory mCRC, the benefit of panitumumab in combination with irinotecan in irinotecan refractory mCRC, and tumor response with panitumumab

in combination with 5-FU, folinic acid, oxaliplatin and irinotecan (FOLFOXIRI) are all being evaluated in current single-arm phase II clinical trials [Peeters *et al.* 2012a]. Panitumumab is also being assessed in combination with FOLFOX in the neoadjuvant setting prior to resection of high-risk primary CRC (T3/4). A phase II trial has reported the safety of this strategy and the extension phase III FOXTROT trial is currently recruiting [Foxtrot Collaborative Group, 2012].

Predictive biomarkers, beyond *KRAS*, to guide patient selection for anti-EGFR antibody treatment is crucial to optimize outcomes and minimize toxicity in patients with mCRC. The role of other implicated biomarkers such as *BRAF*, *NRAS* and *PIK3CA* mutations and loss of *PTEN* expression will hopefully be clarified in coming years. Given the relatively low frequency of these mutations a carefully conducted meta-analysis of *RAS* mutations in panitumumab-treated patients is likely to be required. These identified markers and newly discovered ones are likely to be the focus of research over the next 5 years to further define the patient population best treated with this class of drugs.

Conclusion

The efficacy of panitumumab in *KRAS* WT mCRC has been demonstrated in multiple randomized phase III clinical trials [Douillard *et al.* 2010; Peeters *et al.* 2010; Seymour *et al.* 2013; Van Cutsem *et al.* 2007]. Panitumumab results in improved ORR and PFS the first- and second-line treatment settings in combination with chemotherapy and in chemorefractory patients as monotherapy. A statistically significant overall survival benefit has not been demonstrated in a phase III trial in any line of treatment. Defining optimal biomarker selection prior to panitumumab therapy is the immediate research priority, particularly given the possibility of adverse outcomes in subgroups of patients with mutations beyond *KRAS*, most notably *NRAS* [Oliner *et al.* 2013].

Funding

No financial support was received for the preparation and writing of this manuscript.

Conflict of interest statement

A/Prof Price has been an uncompensated member of an AMGEN advisory board.

References

- Amado, R., Wolf, M., Peeters, M., Van Cutsem, E., Siena, S., Freeman, D. *et al.* (2008) Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. *J Clin Oncol* 26: 1626–1634.
- Amgen Inc. (2009) Vectibix (panitumumab) Prescribing Information. Available at: <http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm165410.htm>.
- Australian Government (2013) Australian Public Assessment Report for Panitumumab. <http://www.tga.gov.au/pdf/auspar/auspar-panitumumab-120507.pdf>
- Bardelli, A. and Siena, S. (2010) Molecular mechanisms of resistance to cetuximab and panitumumab in colorectal cancer. *J Clin Oncol* 28: 1254–1261.
- Berlin, J., Posey, J., Tchekmedyian, S., Hu, E., Chan, D., Malik, I. *et al.* (2007) Panitumumab with irinotecan/leucovorin/5-fluorouracil for first-line treatment of metastatic colorectal cancer. *Clin Colorectal Cancer* 6: 427–432.
- Bokemeyer, C., Bondarenko, I., Hartmann, J., de Braud, F., Schuch, G., Zubel, A. *et al.* (2011) Efficacy according to biomarker status of cetuximab plus FOLFOX-4 as first-line treatment for metastatic colorectal cancer: the OPUS study. *Ann Oncol* 22: 1535–1546.
- Center, M., Jemal, A., Smith, R. and Ward, E. (2009a) Worldwide variations in colorectal cancer. *CA Cancer J Clin* 59: 366–378.
- Center, M., Jemal, A. and Ward, E. (2009b) International trends in colorectal cancer incidence rates. *Cancer Epidemiol Biomarkers Prev* 18: 1688–1694.
- Cohn, A., Hecht, J., Dakhil, S., Saleh, M., Piperdi, B., Cline-Burkhardt, M. *et al.* (2013) SPIRITT (study 20060141): A randomized phase II study of FOLFIRI with either panitumumab (pmb) or bevacizumab (bev) as second-line treatment (tx) in patients (pts) with wild-type (WT) KRAS metastatic colorectal cancer (mCRC). In *2013 ASCO Annual Meeting*, Abstract 3616.
- Cohn, A., Shumaker, G., Khandelwal, P., Smith, D., Neubauer, M., Mehta, N. *et al.* (2011) An open-label, single-arm, phase 2 trial of panitumumab plus FOLFIRI as second-line therapy in patients with metastatic colorectal cancer. *Clin Colorectal Cancer* 10: 171–177.
- Cunningham, D., Humblet, Y., Siena, S., Khayat, D., Bleiberg, H., Santoro, A. *et al.* (2004) Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 351: 337–345.
- De Roock, W., Claes, B., Bernasconi, D., De Schutter, J., Biesmans, B., Fountzilas, G. *et al.* (2010a) Effects of KRAS, BRAF, NRAS, and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal cancer: a retrospective consortium analysis. *Lancet Oncol* 11: 753–762.
- De Roock, W., Jonker, D., Di Nicolantonio, F., Sartore-Bianchi, A., Tu, D., Siena, S. *et al.* (2010b) Association of KRAS p.G13D mutation with outcome in patients with chemotherapy-refractory metastatic colorectal cancer treated with cetuximab. *JAMA* 304: 1812–1820.
- De Sousa, E., Wang, X., Jansen, M., Fessler, E., Trinh, A., de Rooij, L. *et al.* (2013) Poor-prognosis colon cancer is defined by a molecularly distinct subtype and develops from serrated precursor lesions. *Nat Med*, in press.
- Di Nicolantonio, F., Martini, M., Molinari, F., Sartore-Bianchi, A., Arena, S., Saletti, P. *et al.* (2008) Wild-type BRAF is required for response to panitumumab or cetuximab in metastatic colorectal cancer. *J Clin Oncol* 26: 5705–5712.
- Doi, T., Ohtsu, A., Tahara, M., Tamura, T., Shirao, K., Yamada, Y. *et al.* (2009) Safety and pharmacokinetics of panitumumab in Japanese patients with advanced solid tumors. *Int J Clin Oncol* 14: 307–314.
- Douillard, J., Siena, S., Cassidy, J., Tabernero, J., Burkes, R., Barugel, M. *et al.* (2010) 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* 28: 4697–4705.
- El Zouhairi, M., Charabaty, A. and Pishvaian, M. (2011) Molecularly targeted therapy for metastatic colon cancer: proven treatments and promising new agents. *Gastrointest Cancer Res* 4: 15–21.
- European Medicines Agency (2013) European public assessment report (EPAR) for Vectibix. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000741/human_med_001128.jsp&mid=WC0b01ac058001d124
- Fakih, M. (2008) Management of anti-EGFR-targeting monoclonal antibody-induced hypomagnesemia. *Oncology (Williston Park)* 22: 74–76, <http://www.ncbi.nlm.nih.gov/pubmed/18251285>.
- Fakih, M. and Vincent, M. (2010) Adverse events associated with anti-EGFR therapies for the treatment of metastatic colorectal cancer. *Curr Oncol* 17(Suppl. 1): S18–S30.

- Foxtrot Collaborative Group (2012) Feasibility of preoperative chemotherapy for locally advanced, operable colon cancer: the pilot phase of a randomised controlled trial. *Lancet Oncol* 13: 1152–1160.
- Giannopoulou, E., Antonacopoulou, A., Matsouka, P. and Kalofonos, H. (2009) Autophagy: novel action of panitumumab in colon cancer. *Anticancer Res* 29: 5077–5082.
- Grothey, A., Cutsem, E., Sobrero, A., Siena, S., Falcone, A., Ychou, M. *et al.* (2013) Regorafenib monotherapy for previously treated metastatic colorectal cancer (CORRECT): an international, multicentre, randomised, placebo-controlled, phase 3 trial. *Lancet* 381(9863): 303–312.
- Grothey, A., Sargent, D., Goldberg, R. and Schmoll, H. (2004) Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. *J Clin Oncol* 22: 1209–1214.
- Hecht, J., Cohn, A. and Dakhil, S. (2013) SPIRITT (study 2006014): A randomized phase II study of FOLFIRI with either panitumumab or bevacizumab as second-line treatment in patients with wild-type KRAS metastatic colorectal cancer. In *2013 Gastrointestinal Cancers Symposium*, Abstract 454.
- Hecht, J., Mitchell, E., Chidiac, T., Scroggin, C., Hagenstad, C., Spigel, D. *et al.* (2009) A randomized phase IIIB trial of chemotherapy, bevacizumab, and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. *J Clin Oncol* 27: 672–680.
- Hecht, J., Patnaik, A., Berlin, J., Venook, A., Malik, I., Tchekmedyan, S. *et al.* (2007) Panitumumab monotherapy in patients with previously treated metastatic colorectal cancer. *Cancer* 110: 980–988.
- Heinemann, V., Fischer von Weikersthal, L., Decker, T., Kiani, A., Vehling-Kaiser, U., Al-Batran, S. *et al.* (2013) Randomized comparison of FOLFIRI plus cetuximab versus FOLFIRI plus bevacizumab as first-line treatment of KRAS wild-type metastatic colorectal cancer: German AIO study KRK-0306 (FIRE-3). In *2013 ASCO Annual Meeting*, Abstract LBA3506.
- Jean, G. and Shah, S. (2008) Epidermal growth factor receptor monoclonal antibodies for the treatment of metastatic colorectal cancer. *Pharmacotherapy* 28: 742–754.
- Jemal, A., Bray, F., Center, M., Ferlay, J., Ward, E. and Forman, D. (2011) Global cancer statistics. *CA Cancer J Clin* 61(2): 69–90.
- Jonker, D., O’Callaghan, C., Karapetis, C., Zalberg, J., Tu, D., Au, H. *et al.* (2007) Cetuximab for the treatment of colorectal cancer. *N Engl J Med* 357: 2040–2048.
- Karapetis, C., Khambata-Ford, S., Jonker, D., O’Callaghan, C., Tu, D., Tebbutt, N. *et al.* (2008) K-ras mutations and benefit from cetuximab in advanced colorectal cancer. *N Engl J Med* 359: 1757–1765.
- Keating, G. (2010) Panitumumab: a review of its use in metastatic colorectal cancer. *Drugs* 70: 1059–1078.
- Kohne, C., Hofheinz, R., Mineur, L., Letocha, H., Greil, R., Thaler, J. *et al.* (2012) First-line panitumumab plus irinotecan/5-fluorouracil/leucovorin treatment in patients with metastatic colorectal cancer. *J Cancer Res Clin Oncol* 138: 65–72.
- Kopetz, S., Chang, G., Overman, M., Eng, C., Sargent, D., Larson, D. *et al.* (2009) Improved survival in metastatic colorectal cancer is associated with adoption of hepatic resection and improved chemotherapy. *J Clin Oncol* 27: 3677–3683.
- Lacouture, M., Mitchell, E., Piperdi, B., Pillai, M., Shearer, H., Iannotti, N. *et al.* (2010) Skin toxicity evaluation protocol with panitumumab (STEPP), a phase II, open-label, randomized trial evaluating the impact of a pre-emptive skin treatment regimen on skin toxicities and quality of life in patients with metastatic colorectal cancer. *J Clin Oncol* 28: 1351–1357.
- Lenz, H. (2006) Anti-EGFR mechanism of action: antitumor effect and underlying cause of adverse events. *Oncology (Williston Park)* 20(5 Suppl. 2): 5–13.
- Maughan, T., Adams, R., Smith, C., Meade, A., Seymour, M., Wilson, R. *et al.* (2011) Addition of cetuximab to oxaliplatin-based first-line combination chemotherapy for treatment of advanced colorectal cancer: results of the randomised phase 3 MRC COIN trial. *Lancet* 377(9783): 2103–2114.
- Melosky, B., Burkes, R., Rayson, D., Alcindor, T., Shear, N. and Lacouture, M. (2009) Management of skin rash during EGFR-targeted monoclonal antibody treatment for gastrointestinal malignancies: Canadian recommendations. *Curr Oncol* 16: 16–26.
- Metges, J., Raoul, J., Achour, N., Capitain, O., Gourlaouen, A., Ramée, J. *et al.* (2010) PANERB study: Panitumumab after cetuximab-based regimen failure. *J Clin Oncol* 28(Suppl.): abstract e14000.
- Mitchell, E., Piperdi, B., Lacouture, M., Shearer, H., Iannotti, N., Pillai, M. *et al.* (2011) The efficacy and safety of panitumumab administered concomitantly with FOLFIRI or Irinotecan in second-line therapy for metastatic colorectal cancer: the secondary analysis from STEPP (Skin Toxicity Evaluation Protocol With Panitumumab) by KRAS status. *Clin Colorectal Cancer* 10: 333–339.

- Montagut, C., Dalmases, A., Bellosillo, B., Crespo, M., Pairet, S., Iglesias, M. *et al.* (2012) Identification of a mutation in the extracellular domain of the Epidermal Growth Factor Receptor conferring cetuximab resistance in colorectal cancer. *Nat Med* 18: 221–223.
- Muro, K., Yoshino, T., Doi, T., Shirao, K., Takiuchi, H., Hamamoto, Y. *et al.* (2009) A phase 2 clinical trial of panitumumab monotherapy in Japanese patients with metastatic colorectal cancer. *Jpn J Clin Oncol* 39: 321–326.
- Okines, A., Puerto, O., Cunningham, D., Chau, I., Van Cutsem, E., Saltz, L. *et al.* (2009) Surgery with curative-intent in patients treated with first-line chemotherapy plus bevacizumab for metastatic colorectal cancer First BEAT and the randomised phase-III NO16966 trial. *Br J Cancer* 101: 1033–1038.
- Oliner, K., Douillard, J., Siena, S., Tabernero, J., Burkes, R., Barugel, M. *et al.* (2013) Analysis of KRAS/NRAS and BRAF mutations in the phase III PRIME study of panitumumab and FOLFOX vs FOLFOX as first line treatment for metastatic colorectal cancer. In: *2013 ASCO Annual Meeting*, Abstract 3511.
- Peeters, M., Cohn, A., Kohne, C. and Douillard, J. (2012a) Panitumumab in combination with cytotoxic chemotherapy for the treatment of metastatic colorectal carcinoma. *Clin Colorectal Cancer* 11: 14–23.
- Peeters, M., Douillard, J., Van Cutsem, E., Siena, S., Zhang, K., Williams, R. *et al.* (2012b) Mutant KRAS codon 12 and 13 alleles in patients with metastatic colorectal cancer: assessment as prognostic and predictive biomarkers of response to panitumumab. *J Clin Oncol*, in press.
- Peeters, M., Oliner, K., Parker, A., Siena, S., Van Cutsem, E., Huang, J. *et al.* (2013) Massively parallel tumor multigene sequencing to evaluate response to panitumumab in a randomized phase III study of metastatic colorectal cancer. *Clin Cancer Res*, in press.
- Peeters, M. and Price, T. (2012) Biologic therapies in the metastatic colorectal cancer treatment continuum – applying current evidence to clinical practice. *Cancer Treat Rev* 38: 397–406.
- Peeters, M., Price, T. and Van Laethem, J. (2009a) Anti-epidermal growth factor receptor monotherapy in the treatment of metastatic colorectal cancer: where are we today? *Oncologist* 14: 29–39.
- Peeters, M., Price, T., Cervantes, A., Sobrero, A., Ducreux, M., Hotko, Y. *et al.* (2010) Randomized phase III study of panitumumab with fluorouracil, leucovorin, and irinotecan (FOLFIRI) compared with FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer. *J Clin Oncol* 28: 4706–4713.
- Peeters, M., Siena, S., Van Cutsem, E., Sobrero, A., Hendlisch, A., Cascinu, S. *et al.* (2009b) Association of progression-free survival, overall survival, and patient-reported outcomes by skin toxicity and KRAS status in patients receiving panitumumab monotherapy. *Cancer* 115: 1544–1554.
- Petrelli, F., Borgonovo, K., Cabiddu, M., Ghilardi, M. and Barni, S. (2011) Cetuximab and panitumumab in KRAS wild-type colorectal cancer: a meta-analysis. *Int J Colorectal Dis* 26: 823–833.
- Price, T., Hardingham, J., Lee, C., Weickhardt, A., Townsend, A., Wrin, J. *et al.* (2011) Impact of KRAS and BRAF gene mutation status on outcomes from the phase III AGITG MAX trial of capecitabine alone or in combination with bevacizumab and mitomycin in advanced colorectal cancer. *J Clin Oncol* 29: 2675–2682.
- Primrose, J., Falk, S., Finch-Jones, M., Valle, J., Sherlock, D., Hornbuckle, J. *et al.* (2013) A randomized clinical trial of chemotherapy compared to chemotherapy in combination with cetuximab in k-RAS wild-type patients with operable metastases from colorectal cancer: The new EPOC study. *J Clin Oncol* 31: Abstract 3504.
- Sadanandam, A., Lyssiotis, C., Homicsko, K., Collisson, E., Gibb, W., Wulschleger, S. *et al.* (2013) A colorectal cancer classification system that associates cellular phenotype and responses to therapy. *Nat Med*, in press.
- Saltz, L., Clarke, S., Diaz-Rubio, E., Scheithauer, W., Figer, A., Wong, R. *et al.* (2008) Bevacizumab in combination with oxaliplatin-based chemotherapy as first-line therapy in metastatic colorectal cancer: a randomized phase III study. *J Clin Oncol* 26: 2013–2019.
- Saltz, L., Meropol, N., Loehrer, P., Sr, Needle, M., Kopit, J. and Mayer, R. (2004) Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. *J Clin Oncol* 22: 1201–1208.
- Schwartzberg, L., Rivera, F. and Karthaus, M. (2013a) PEAK (study 20070509): A randomized phase II study of mFOLFOX6 with either panitumumab or bevacizumab as first-line treatment in patients with unresectable wild-type KRAS metastatic colorectal cancer. In *2013 Gastrointestinal Cancers Symposium*, Abstract 446.
- Schwartzberg, L., Rivera, F., Karthaus, M., Fasola, G., Canon, J., Yu, H. *et al.* (2013b) Analysis of KRAS/NRAS mutations in PEAK: a randomised phase 2 study of FOLFOX6 + panitumumab or bevacizumab as 1st line treatment for wild-type KRAS

- (exon 2) metastatic colorectal cancer. In *2013 ASCO Annual Meeting*, Abstract 3631.
- Seymour, M., Brown, S., Middleton, G., Maughan, T., Richman, S., Gwyther, S. *et al.* (2013) Panitumumab and irinotecan versus irinotecan alone for patients with KRAS wild-type, fluorouracil-resistant advanced colorectal cancer (PICCOLO): a prospectively stratified randomised trial. *Lancet Oncol*, in press.
- Sobrero, A., Maurel, J., Fehrenbacher, L., Scheithauer, W., Abubakr, Y., Lutz, M. *et al.* (2008) EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. *J Clin Oncol* 26: 2311–2319.
- Stephenson, J., Gregory, C., Burris, H., Larson, T., Verma, U., Cohn, A. *et al.* (2009) An open-label clinical trial evaluating safety and pharmacokinetics of two dosing schedules of panitumumab in patients with solid tumors. *Clin Colorectal Cancer* 8: 29–37.
- Stintzing, S., Kapaun, C., Laubender, R., Jung, A., Neumann, J., Modest, D. *et al.* (2013) Prognostic value of cetuximab-related skin toxicity in metastatic colorectal cancer patients and its correlation with parameters of the epidermal growth factor receptor signal transduction pathway: results from a randomized trial of the GERMAN AIO CRC Study Group. *Int J Cancer* 132: 236–245.
- Tejpar, S., Celik, I., Schlichting, M., Sartorius, U., Bokemeyer, C. and Van Cutsem, E. (2012) Association of KRAS G13D tumor mutations with outcome in patients with metastatic colorectal cancer treated with first-line chemotherapy with or without cetuximab. *J Clin Oncol* 30: 3570–3577.
- Tejpar, S., Piessevaux, H., Claes, K., Piront, P., Hoenderop, J., Verslype, C. *et al.* (2007) Magnesium wasting associated with epidermal-growth-factor receptor-targeting antibodies in colorectal cancer: a prospective study. *Lancet Oncol* 8: 387–394.
- Tie, J., Gibbs, P., Lipton, L., Christie, M., Jorissen, R., Burgess, A. *et al.* (2011) Optimizing targeted therapeutic development: analysis of a colorectal cancer patient population with the BRAF(V600E) mutation. *Int J Cancer* 128: 2075–2084.
- Toffoli, G., De Mattia, E., Cecchin, E., Biason, P., Masier, S. and Corona, G. (2007) Pharmacology of epidermal growth factor inhibitors. *Int J Biol Markers* 22(1 Suppl. 4): S24–S39.
- Tol, J., Dijkstra, J., Klomp, M., Teerenstra, S., Dommerholt, M., Vink-Borger, M. *et al.* (2010) Markers for EGFR pathway activation as predictor of outcome in metastatic colorectal cancer patients treated with or without cetuximab. *Eur J Cancer* 46: 1997–2009.
- Tol, J., Koopman, M., Cats, A., Rodenburg, C., Creemers, G., Schrama, J. *et al.* (2009) Chemotherapy, bevacizumab, and cetuximab in metastatic colorectal cancer. *N Engl J Med* 360: 563–572.
- Trotta, F., Leufkens, H., Schellens, J., Laing, R. and Tafuri, G. (2011) Evaluation of oncology drugs at the European Medicines Agency and US Food and Drug Administration: when differences have an impact on clinical practice. *J Clin Oncol* 29: 2266–2272.
- Tveit, K., Guren, T., Glimelius, B., Pfeiffer, P., Sorbye, H., Pyrhonen, S. *et al.* (2012) Phase III trial of cetuximab with continuous or intermittent fluorouracil, leucovorin, and oxaliplatin (Nordic FLOX) versus FLOX alone in first-line treatment of metastatic colorectal cancer: the NORDIC-VII study. *J Clin Oncol* 30: 1755–1762.
- Van Cutsem, E., Kohne, C., Hitre, E., Zaluski, J., Chang Chien, C., Makhson, A. *et al.* (2009) Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. *N Engl J Med* 360: 1408–1417.
- Van Cutsem, E., Kohne, C., Lang, I., Folprecht, G., Nowacki, M., Cascinu, S. *et al.* (2011) 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* 29: 2011–2019.
- Van Cutsem, E., Peeters, M., Siena, S., Humblet, Y., Hendlisz, A., Neyns, B. *et al.* (2007) Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol* 25: 1658–1664.
- Van Cutsem, E., Siena, S., Humblet, Y., Canon, J., Maurel, J., Bajetta, E. *et al.* (2008) An open-label, single-arm study assessing safety and efficacy of panitumumab in patients with metastatic colorectal cancer refractory to standard chemotherapy. *Ann Oncol* 19: 92–98.
- Van Cutsem, E., Tabernero, J., Lakomy, R., Prenen, H., Prausova, J., Macarulla, T. *et al.* (2012) Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. *J Clin Oncol* 30: 3499–3506.
- Wadlow, R., Hezel, A., Abrams, T., Blaszkowsky, L., Fuchs, C., Kulke, M. *et al.* (2012) Panitumumab in patients with KRAS wild-type colorectal cancer after progression on cetuximab. *Oncologist* 17: 14.
- Yang, B., Lum, P., Chen, A., Arends, R., Roskos, L., Smith, B. *et al.* (2010) Pharmacokinetic and

pharmacodynamic perspectives on the clinical drug development of panitumumab. *Clin Pharmacokinet* 49: 729–740.

Yang, X., Jia, X., Corvalan, J., Wang, P., Davis, C. and Jakobovits, A. (1999) Eradication of established tumors by a fully human monoclonal antibody to the

epidermal growth factor receptor without concomitant chemotherapy. *Cancer Res* 59: 1236–1243.

Young, A., Lou, D. and McCormick, F. (2013) Oncogenic and wild-type RAS play divergent roles in the regulation of mitogen-activated protein kinase signaling. *Cancer Discov* 3: 112–123.

Visit SAGE journals online
<http://tag.sagepub.com>

SAGE journals