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Targeting colorectal cancer with anti-epidermal growth factor receptor antibodies: focus on panitumumab

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Abstract: The tumor biology targeted therapies have improved outcomes in colorectal cancer (CRC). The epidermal growth factor receptor (EGFR) inhibitors represent one of these successful strategies. EGFR is frequently overexpressed in CRCs and associated with a malignant phenotype. Two EGFR inhibitors have shown efficacy in metastatic CRC, cetuximab and panitumumab. Cetuximab is a human–mouse chimeric monoclonal antibody that binds to the extracellular domain of the EGF-receptor. Similarly, panitumumab is a fully humanized monoclonal IgG₂ antibody, directed against EGFR. Being fully humanized, panitumumab does not contain mouse protein reducing the risk of hypersensitivity. In a pivotal clinical trial, panitumumab was well tolerated and effective, demonstrating an objective response rate of 10% vs best supportive care (ORR = 0%; $P < 0.0001$). Panitumumab was approved for the treatment of mCRC by the FDA in 2006. Studies combining panitumumab with cytotoxic chemotherapy and other targeted therapies have been completed while others are ongoing to further evaluate the clinical utility of this agent. Recently it has been demonstrated that mutations in *KRAS* predict the efficacy of panitumumab and cetuximab, limiting their use to CRC patients with wild-type *KRAS*, and moving the clinical field towards personalized cancer care.

Keywords: colorectal cancer, epidermal growth factor receptor, panitumumab, cetuximab, *KRAS*

Introduction

World-wide, colorectal cancer is the third most common cancer in both men and women. In 2008, it is estimated that 148,810 cases of colorectal cancer will be diagnosed and 49,960 people will die from this disease.¹ Despite the prevalence of this disease, the overall incidence and death rates have declined over the last 20 years, suggesting improvements in early detection and treatments. Unfortunately, approximately 20% of patients will have metastatic disease at the time of presentation. Chemotherapeutic agents that have been US Food and Drug Administration (FDA) approved for the use in metastatic colorectal cancer (mCRC) include 5-fluorouracil (5-FU), capecitabine, irinotecan and oxaliplatin. In recent clinical trials, the median overall survival for patients treated with irinotecan and oxaliplatin-based regimens approaches 20 months, an improvement in comparison to the 12 month median survival prior to the approval of these agents.^{2,3}

As we learn more about the biology of cancer and its pathways, potential targets for therapy have been identified. These novel biologic agents are well poised to potentially advance the progress of the treatment of mCRC. Bevacizumab, an anti-angiogenic agent, is an example of a targeted agent improving outcomes in mCRC. The addition of bevacizumab to a combination chemotherapy regimen of irinotecan, 5-FU and leucovorin (IFL)

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increased the median duration of survival from 15.6 months (IFL) to 20.3 months (bevacizumab plus IFL; $P < 0.001$).⁴

The epidermal growth factor receptor (EGFR) has been shown to be frequently overexpressed in CRC^{5,6} and has been associated with a malignant phenotype.^{6–9} Multiple clinical trials have been performed and are currently ongoing to evaluate EGFR-targeted agents in CRC. Thus far, two EGFR inhibitors have shown efficacy in mCRC, namely cetuximab (Erbix[®]; ImClone Systems, Brachburg, NJ, USA) and panitumumab (Vectibix[®]; Amgen, Thousand Oaks, CA, USA). Cetuximab, a human–mouse chimeric monoclonal antibody that binds specifically to the extracellular domain of the EGF-receptor results in inhibition of cellular growth, and angiogenesis and promotes apoptosis. Significant improvement in overall response rates were demonstrated in patients with colorectal cancer, refractory to irinotecan, who received cetuximab in combination with irinotecan (overall response rate [ORR] 22.9%) vs cetuximab alone (ORR 10.8%).¹⁰ There was a trend in improved overall survival for the cetuximab in combination with irinotecan arm vs the cetuximab alone arm (8.6 months vs 6.9 months, $P = 0.48$). The results of this study led to the approval of cetuximab for the treatment of patients with mCRC.

Panitumumab is a fully humanized monoclonal antibody to EGFR that has shown encouraging activity and tolerability in heavily pretreated patients with mCRC. It selectively targets the extracellular domain of the EGFR. It was Food and Drug Administration (FDA) approved in September 2006 and is currently indicated for the treatment of mCRC in EGFR-expressing tumors that have progressed following treatment with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. There are also ongoing trials in first- and second-line settings. In this review, we will discuss the EGFR signaling pathway, focusing on panitumumab and its pharmacology and efficacy in colorectal cancer. We will also review the toxicities related to panitumumab as well as provide insight into potential biomarkers of response, including *k-ras* and BRAF.

EGFR signaling and its role in colorectal cancer

EGFR is a transmembrane tyrosine kinase, belonging to a family of human epidermal growth factor receptors (HER1). Other members within this family include HER2 (ERBB2), HER3 (ERBB3) and HER4 (ERBB4). All members within this family, with the exception of HER2, which has no apparent ligand, have an extracellular ligand-binding domain, a transmembrane lipophilic segment and an intracellular domain

with tyrosine kinase activity. In response to ligand binding by the epidermal growth factor and transforming growth factor α (TGF- α), the EGFR homodimerizes and/or forms heterodimers with other members of the ERBB family (especially HER2). This then leads to the activation of EGFR tyrosine kinases through phosphorylation. This phosphorylation results in the activation of several intracellular second-messenger signal transduction pathways, such as the Janus kinase-Signal transducer an activator of transcription signaling, the phosphatidylinositol-3-kinase and the protein-serine/threonine kinase Akt signal, and the Ras-Raf-MAP-kinase signal, which further activates the mitogen-activated phosphorylation protein kinases. Ultimately, the signaling of the pathways leads to increased cell proliferation, division, survival, invasion, adhesion and DNA repair in malignant and nonmalignant cells. If these pathways are dysregulated, such as in the case of EGFR overexpression, alterations in cellular growth, survival, angiogenesis and metastases may occur.^{11–18}

The proposed development of colorectal cancer evolves from the progressive accumulation of genetic and epigenetic alterations resulting in the transformation of normal colonic mucosa to invasive adenocarcinoma.¹⁹ EGFR has been implicated in the initiation of colorectal tumors and has also been noted to be frequently overexpressed in CRC.^{5,20} The prognostic significance of EGFR in CRC remains unclear.^{6,20}

Panitumumab pharmacology and pharmacokinetics

Panitumumab (ABX-EGF, E.7.6.3, Vectibix[®]), is a high-affinity, fully humanized monoclonal IgG₂ antibody, directed against EGFR, generated in XenoMouse[®] (Abjenix, Fremont, CA; transgenic mouse capable of producing human antibodies). It is produced by immunizing a XenoMouse strain of mice with human cervical epidermal carcinoma cell line A431, a cell line known for its abundance of EGFR on the cell surface.^{21,22} Unlike chimeric antibodies, fully humanized monoclonal antibodies do not contain any amount of foreign elements (ie, mouse protein) and thus do not generate human antimouse antibodies. This reduces this risk of hypersensitivity reactions and thus, represents a theoretical clinical advantage over previously developed chimeric antibodies.

The mechanism of action of panitumumab involves binding of panitumumab to the EGFR with inhibition of ligand binding of EGFR. It is rapidly internalized but not degraded internally. The binding of panitumumab to EGFR results in downregulation of cell-surface EGFR by internalization of the receptor, interruption of the intracellular signaling EGFR resulting in apoptosis and initiation of cell-cycle arrest, inhibition of

angiogenesis and possible inhibition of differentiation of the tumor cells. With panitumumab being an IgG₂ isotype, it is unlikely to produce an immunologic-mediated response. Thus, antibody-dependant cellular cytotoxicity (ADCC) is not implicated in panitumumab's mechanism of action.^{23,24}

The recommended dose of panitumumab is 6 mg/kg given over 60 minutes as an intravenous infusion once every 2 weeks (package insert Vectibix: Thousand Oaks, CA: Amgen Inc, Sept 2006). According to the manufacturer, available pharmacokinetic data do not indicate that sex, age, ethnicity, mild-to-moderate renal or hepatic dysfunction or EGFR membrane-staining intensity in tumor cells affect the pharmacokinetic properties of panitumumab. Use of the drug has not been evaluated in pediatric and pregnant patients. There have also not been any formal pharmacokinetic studies performed in patients with hepatic and/or renal dysfunction.

Phase I studies

Panitumumab was initially evaluated in a multicenter, open-label, dose-escalating phase I trial, where 43 patients with various solid tumor types; renal (n = 10), prostate (n = 13), non-small-cell lung cancer (n = 7), pancreatic (n = 3), esophageal (n = 3) and CRC (n = 7), received 4 intravenous infusions of panitumumab once weekly for up to 1 hour, at doses ranging from 0.01 mg/kg to 2.5 mg/kg. In all the patients receiving the 2.0 to 2.5 mg/kg dose, a transient dose-dependent skin rash was noted. No allergic reactions, infusion reactions or serious adverse events were noted and no human anti-human antibodies (HAHA) were found.²⁵ Those patients with evidence of response or stable disease were eligible to continue to receive treatment every other week for 6 additional months or until disease progression. Biologic activity was noted in patients even at the lowest doses. One patient with esophageal cancer treated with the lowest dose had stable disease (SD) for 7 months. A partial response (PR) of 10 months duration was noted in one patient with colorectal cancer treated with the 2.5 mg/kg dose.

An additional 50 patients were treated on the above study and the updated results were presented by Weiner et al at the ASCO 2005 meeting and has been subsequently published.²⁶ Sequential cohorts were enrolled to receive four infusions of panitumumab as a single-agent. There were different dose levels ranging from 0.01 mg/kg to 5.0 mg/kg once per week, 6.0 mg/kg every 2 weeks and 9.0 mg/kg every 3 weeks. A total of 96 patients were enrolled and treated (CRC, n = 39, lung, n = 14, pancreatic, n = 21, renal, n = 15, esophageal, n = 3 and anal cancer, n = 1). 10% of the patients experienced Grade 3 or 4 toxicities, with Grade 3 skin rash

being the most common adverse event noted (7%). Dose escalation to 9.0 mg/kg every 3 weeks was achieved and no maximal tolerated dose was reached. Pharmacokinetics were consistent and predictable over the range of dosing, with low intra-patient and inter-patient variability. The minimal serum panitumumab concentrations (C_{trough}) were similar among all the dose levels, with steady-state reached after approximately 6 weeks for all dosing schedules. Thus, even though the maximum tolerated dose was not reached, the authors decided that increasing the dose beyond those tested, would unlikely result in increased panitumumab activity. Five of the 39 CRC patients (13%) achieved a partial response (PR) with 9 of 39 CRC patients (23%) had stable disease.

Rowinsky et al²⁷ performed a phase I study of panitumumab in previously treated patients with metastatic renal cell carcinoma. The primary objectives of the study were to evaluate toxicity, immunogenicity, pharmacokinetics as well as pharmacodynamics. A total of 88 patients were enrolled and treated with panitumumab. They were treated with panitumumab doses of 1.0, 1.5, 2.0 or 2.5 mg/kg weekly with no loading dose. Major responses were seen in three patients and two patients had minor responses. Forty four patients had stable disease (50%) at their first assessment at 8 weeks. The median progression-free survival was 100 days [95% confidence interval (CI), 58 to 140 days]. The main toxicity noted was an acneiform rash which was dose dependant, with 68, 95, 87 and 100% of patients who received at least 3 doses of panitumumab at 1.0, 1.5, 2.0, and 2.5 mg/kg/week respectively. The rash reached maximal intensity at weeks 3 and 5, and then continued to dissipate despite ongoing treatment. Other frequent toxicities noted were asthenia, unspecified pain and back pain.

Phase II studies

Panitumumab as single-agent in treatment of metastatic colorectal cancer

A number of phase II studies have confirmed the clinical activity of panitumumab as well as the safety as reported in earlier clinical trials. In the pivotal phase II trial by Malik et al 148 heavily pretreated patients with metastatic CRC were treated with panitumumab administered at 2.5 mg/kg/week over 1 hour with no loading dose or premedications.²⁸ Patients were enrolled into two cohorts, depending on levels of EGFR protein expression (as determined by immunohistochemistry). All the enrolled patients had received prior treatment with fluoropyrimidines, 96% had received irinotecan therapy and 49% had received prior oxaliplatin therapy. Patients were

allowed to continue on panitumumab as long as it was tolerated and there was clinical benefit.

The most common toxicities noted were rash and fatigue. The rash typically appeared within 1 to 3 weeks of initiating therapy and persisted, without worsening throughout therapy. Only 4 patients discontinued therapy due to rash. It was classically described as a maculopapular acneiform rash, appearing on the face and trunk. Only 1 patient had a grade 3 infusion reaction and no HAHA antibodies were detected in the 107 patients tested.

Nine per cent (13) patients were found to have responded after 8 weeks of therapy, with 29% of patients with SD. The median duration of response was 5.2 months and median OS of 9.4 months. No significant difference was noted when the results were analyzed according to the two cohorts based on EGFR protein expression.

As with other EGFR inhibitors, there was a trend in the correlation between the severity of the rash and response. At least 62% of the patients who developed a rash of grade 2 or more had either PR or SD.

Another phase II trial was undertaken to evaluate the efficacy of panitumumab in patients with mCRC, having received more than 2 lines of previous therapy and whose tumors expressed EGFR in 10% or more of the cells. Panitumumab was given at 6 mg/kg every 2 weeks until disease progression. By 16 weeks, 8% of patients had a PR, with 21% having SD. The most common toxicities noted were rash (96%), nail (30%) and eye (8%) reactions, diarrhea (27%) and hypomagnesemia (12%). One patient developed a grade 3 hypersensitivity reaction but continued on with therapy without further reactions. No HAHA were detected.²⁹

Patients with metastatic CRC with low (1% to 9%) or no (<1%) expression of EGFR were evaluated in another phase II trial.³⁰ In the 89 patients available for efficacy analysis, partial responses and tumor control rates ranged from 7% to 9% and 37% to 42% respectively. This is comparable with the responses seen in patients with EGFR-expressing tumors. Among the 118 patients evaluable for toxicity analysis, 72% developed rash, 69% with erythema, pruritus in 65% and hypomagnesemia in 53%. Three patients developed infusion reactions, with only one being a grade 3 reaction.

Panitumumab in combination with cytotoxic chemotherapy or biologic agents

With other EGFR inhibitors, there has been a suggestion of synergy or an additive effect with chemotherapy.¹⁰

Preclinical studies have also demonstrated that panitumumab may also have an additive antitumor effect when used in combination with cytotoxic chemotherapy.

Panitumumab (given at 2.5 mg/kg/week) in combination with IFL (Saltz regimen: irinotecan 125 mg/m², leucovorin 20 mg/m² and 5-FU 500 mg/m² on days 1, 8, 15 and 22) was evaluated in patients with metastatic colorectal cancer as first-line therapy.^{31,32} The primary objectives of the study were to evaluate both safety and efficacy. All patients were required to have EGFR expression of 2+ or 3+ in $\geq 10\%$ of tumor cells by immunohistochemistry. The first 19 patients received panitumumab in combination with IFL weekly for 4 weeks of each 6-week treatment cycle. The protocol was amended to include another regimen (based on data from the first few patients and changing practice from bolus to infusional 5-FU), FOLFIRI (irinotecan 180 mg/m², leucovorin 400 mg/m² and 5-FU as a 400 mg/m² bolus followed by 2.4 to 3 g/m² over 46 hours).

Diarrhea was the most common noncutaneous toxicity noted in the 19 patients that received panitumumab and IFL. Skin toxicity was found in 100% of patients. Sixteen per cent experienced a grade 3 skin reaction with no grade 4 events. Forty-seven per cent experienced grade 3 diarrhea with only 1 patient having grade 4 diarrhea.

The overall response rate was 47% with an additional 5 patients (26%) with stable disease. The disease control rate (DCR = OR + SD) was noted to be 74%. The median PFS and OS were 5.6 months and 17 months respectively.

Twenty-four patients were enrolled into the expanded portion of the study, evaluating panitumumab in combination with FOLFIRI. As previously noted in earlier trial, FOLFIRI was better tolerated with fewer patients experiencing grade 3 and grade 4 diarrhea (25% and 0%, respectively). 100% of the patients experienced skin-related toxicity with grade 3 reactions in 17% and no grade 4 reactions.

The response rates were very similar to the earlier portion of the study, with the DCR of 79% and median PFS of 10.9 months. OS data have not been reported yet. This has ultimately led to a randomized trial of FOLFIRI with or without panitumumab, which is currently underway.

Phase III studies

Van Cutsem et al's multicenter, randomized phase III registration trial for panitumumab included a population of heavily pretreated patients with metastatic CRC.³³ A total of 463 patients with $\geq 1\%$ EGFR-expressing tumors, measurable disease with radiological evidence of disease progression during or within 6 months of their most recent chemotherapy

were enrolled. They were randomized to receive either 6 mg/kg of panitumumab every 2 weeks plus best supportive care (n = 231) or best supportive care (BSC) alone (n = 232). Assessment of treatment response was performed at 8 week intervals and patients continued on treatment until disease progression or intolerable toxicity was noted. The primary endpoint was progression-free survival. Secondary endpoints included objective response, overall survival and safety. Patients randomized to BSC alone were allowed to crossover to receive BSC with panitumumab if they were noted to have disease progression. Panitumumab was found to significantly prolong PFS ($P < 0.0001$). At 8 weeks, 49% and 30% of patients in the panitumumab and BSC groups, respectively, has no evidence of progression.

Objective response rates also favored panitumumab plus BSC arm (10%) over BSC alone (0%; $p < 0.0001$). The median time to response was 7.9 weeks and median duration of response was 17.0 weeks. Stable disease was noted in 64 (28%) and 24 (10%) of patients in the panitumumab and the BSC arms, respectively (results summarized in Table 1). No difference in overall survival was noted, however this was most likely due to the large number of patients in the BSC arm that were allowed to crossover to receive panitumumab on disease progression. In a subgroup analysis, there was a correlation with skin reactions (grade 2 and 3 skin toxicity) and prolonged PFS and OS. Other common toxicities included hypomagnesemia, paronychia, fatigue, abdominal pain, nausea and diarrhea. The most severe toxicities included pulmonary fibrosis, severe dermatologic toxicity complicated by sepsis and death and infusion reactions.

Thus, panitumumab in combination with BSC was found to have antitumor activity in patients who had received multiple previous chemotherapy agents. Results are comparable to those reported with single-agent cetuximab in the same setting.¹⁰ Although response rates are only 10%, more than a third of the patients had significant clinical benefit

with minimal toxicity. The trial design also allowed for crossover to include addition of panitumumab to BSC. This likely explains the lack of statistical difference in overall survival between the two arms. Thus, panitumumab was granted FDA approval in September 2006 for the treatment of patients with EGFR-expressing, metastatic CRC with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens.

More recently, the role of panitumumab was investigated in combination with both cytotoxic chemotherapy and biologic agent, bevacizumab. The PACCE trial (Panitumumab Advanced Colorectal Cancer Evaluation) was a randomized, open-label, multicenter phase IIIB trial originally intended to assess the efficacy and safety of bevacizumab plus FOLFOX4 or FOLFIRI (doses and schedules determined by investigators), with or without panitumumab, in the first-line setting.³⁴ In March 2007, a pre-planned interim analysis of the first 231 events revealed that there was a statistically significant difference in progression-free survival (PFS) in favor of the control arm (without panitumumab). PFS was significantly worse in the panitumumab arm of the oxaliplatin-based chemotherapy (HR, 1.44; 95% CI, 1.13 to 1.85; $P = 0.004$). Median PFS time was 8.8 months (95% CI, 8.3 to 9.5 months) for panitumumab and 10.5 months (95% CI, 9.4 to 12.0 months) for the control arm.

For the irinotecan-based chemotherapy cohort, median PFS was 10.1 months for panitumumab and 11.9 months for the control arm (HR, 1.57; 95% CI, 0.71 to 3.46). Toxicities, notably diarrhea, infections and pulmonary embolism were also increased in the panitumumab arm. Thus, Amgen decided to discontinue the panitumumab treatment arm in the PACCE trial.^{34,35} The exact mechanism is currently unknown but a few hypotheses suggested by the authors included pharmacokinetic interactions as well as increase in toxicity due to dual-pathway inhibition in combination with chemotherapy. Increased toxicity may have lead to more dose reductions,

Table 1 Summary of phase III registration trial results comparing best supportive care with panitumumab monotherapy in patients with previously treated metastatic colorectal cancer, having failed irinotecan- and oxaliplatin-based therapy

	Panitumumab arm (n = 232)	Best supportive care (n = 231)
PFS at 24 weeks (%)	18%	5%
PFS at 32 weeks (%)	10%	4%
RR (%)	8%	0%
Stable disease (%)	28%	10%
Disease control rate (%)	36%	10%
Median duration of response (weeks)	17 weeks	N/A

Abbreviations: PFS, progression-free survival; RR, response rate.

treatment delays, decreases in dose intensity resulting in the inferior results in the panitumumab arms.

A potential pharmacodynamic interaction induced by EGFR inhibition may have also led to a blunting of the therapeutic effects of bevacizumab and/or chemotherapy.³⁴

Ongoing studies

Currently, a number of phase I–III trials are evaluating panitumumab in combination with cytotoxic chemotherapy and/or biologic agents. For current trials, refer to Table 2.

Toxicity profile

The toxicity profile of panitumumab has been found to be both favorable as well as highly predictable when evaluated with pooled data in two safety analyses.^{36,37} Most common toxicities included acneiform rash (all grades 53% to 4%; Grade 3 and 4, 2% to 6%), pruritus (all grades 52% to 53%), erythema (all grades 52% to 54%), paronychia (all grades 20%), fatigue (all grades 33% to 34%, grade 3 and 4, 6%), nausea (all grades 29% to 30%, grade 3 and 4, 2%), diarrhea (all grades 26% to 27%, grade 3 and 4, 3%), abdominal pain (all grades 21%, grade 3 and 4, 5%), hypomagnesemia with clinical symptoms (all grades 5% to 6%, grade 3 and 4, 1% to 2%), hypomagnesemia without clinical symptoms (all grades 38% to 44%, grade 3 and 4, 5% to 6%). The general incidence of treatment-related adverse events experienced with panitumumab included 93% to 94% any grade, 18% grade 3 and 1% grade 4. No deaths have been reported that have been attributed to panitumumab. Three per cent to 4% of patients did discontinue therapy due to adverse toxicities.

Biomarkers of response

Even though EGFR inhibitors do demonstrate antitumor activity in CRC and are well tolerated, there are still a significant portion of patients who do not respond to these therapies or have intolerable toxicities. With the ongoing interest in personalizing cancer care, the shift has been to identify markers of response as well as toxicity.

Skin toxicity with grade 3 or grade 4 rash has been demonstrated to be a clinical marker of response. The underlying rationale for this has yet to be determined. It does not appear to correlate with EGFR expression in tumor cells (evaluated by immunohistochemistry). In a subset analysis of Van Cutsem et al's phase III trial of panitumumab vs best supportive care, correlation was noted with severity of rash and longer OS and PFS as well as improved quality-of-life measures.^{38,39} There has also been some suggestion that skin

toxicity may be a proposed surrogate marker for response to cetuximab therapy^{10,40} and that dose escalation of cetuximab aimed at increasing severity of skin rash may indeed increase response rate. However, the overall effect was modest with no statistically significant impact on disease control rates.⁴¹

Expression of EGFR itself has previously been demonstrated to have no impact on response or clinical benefit.^{10,40,42–45} Other markers of response to anti-EGFR therapy have been investigated including EGFR gene amplification and/or expression, EGFR mutations as well as *KRAS* mutations. Most of the studies were performed in non-small cell lung cancer; however, *KRAS* mutations have been reported to be relatively common in sporadic CRC (30% to 50% incidence).^{46–51} Several previous studies have identified the presence of mutated *KRAS* in lung and CRC tumors, correlating with poorer prognosis^{50–54} and is also associated with lack of response to anti-EGFR therapy.^{48,49,55–58} Up to 90% of activating mutations of the *RAS* gene are detected on codons 12 and 13, but less frequently also in codon 61 and 63. In CRC, majority of the mutations (70%) occur in codon 12, with 30% occurring in codon 13.⁵⁹ Mutations of the *KRAS* gene may activate downstream signal transduction leading to resistance to upstream inhibition of the EGFR by monoclonal antibodies.

Amado et al evaluated *KRAS* mutational status on patients treated in a randomized, trial evaluating panitumumab vs best supportive care.⁶⁰ *KRAS* mutational status was obtained on 427 (92%) of 463 patients (208 panitumumab arm, 219 BSC). *KRAS* mutations were detected by polymerase chain reaction on DNA from tumor sections. *KRAS* mutations were identified in 43% of patients. The results of the analysis identified that the treatment effect on PFS on the wild-type (WT) *KRAS* group (HR, 0.45; 95% CI, 0.34 to 0.59) was significantly greater ($P < 0.0001$) than in the mutant group (HR, 0.99; 95% CI, 0.73 to 1.36). The median PFS in the WT *KRAS* group was 12.3 weeks for panitumumab and 7.3 weeks for BSC. Response rates to panitumumab were 17% and 0% for the WT and mutant groups respectively. WT *KRAS* patients also had longer overall survival (HR, 0.67; 95% CI, 0.55 to 0.82). No significant differences in toxicity were noted between the two groups.

The same effect of *KRAS* mutational status has also been reported with cetuximab therapy.^{56,61} On the basis of these results, the European Union drug regulatory body, the European Medicines Agency, has approved panitumumab only for metastatic CRC patients whose tumors display only wild-type *KRAS* (Table 3). Currently, ASCO (American Society of Clinical Oncology) also recommends following

Table 2 Summary of ongoing clinical trials with panitumumab worldwide

Study title	Study design	Target accrual	Primary objectives	Start date	Locations/ countries
Phase I Panitumumab combination study with AMG 102 or AMG 479 in WT KRAS mCRC	Randomized Phase Ib/2	132	Phase I – safety Phase 2 – objective response	November 2008	United States Belgium, Spain
Panitumumab DDI irinotecan	Open label	23	cMax and AUC of irinotecan with and without concomitant panitumumab administration	January 2008	United States Canada
Safety of AMG 706 plus panitumumab plus chemotherapy in the treatment of subjects with mCRC	Open-label, dose-finding, phase Ib [AMG 706 plus panitumumab + FOLFIRI or FOLFOX4 chemotherapy]	148	Part I – evaluating for DLTs Part 2 – Overall objective tumor response rate	December 2004	United States Australia
Phase II Panitumumab and Irinotecan as third-line therapy in treating patients with mCRC [with WT KRAS in third line chemotherapy] – patients previously treated with FOLFOX or XELOX with or without bevacizumab and irinotecan alone or FOLFIRI or CAPIRI with or without bevacizumab	Open-label	68	Objective response rate	January 2008	France
Phase III SPIRITT – q2w FOLFIRI regimen plus panitumumab or a q2w FOLFIRI regimen plus bevacizumab for 2nd-line mCRC	Multi-center; randomized, open label, parallel assignment	200	Objective response rate	November 2006	United States
Irinotecan and panitumumab as 3rd line treatment for mCRC without KRAS mutations	Non-randomized	39	Response rate	November 2008	Denmark
Phase III Irinotecan with or without panitumumab or cyclosporine in treating patients with advanced or mCRC that did not respond to fluorouracil	Randomized, open-label, active control	1269	Proportion of patients treated with irinotecan hydrochloride (Ir) alone vs Ir and cyclosporine (IrC) who are progression-free at 12 weeks. Overall survival of patients treated with Ir vs Ir and panitumumab (IrP) and no prior cetuximab	December 2006	United Kingdom

Abbreviations: WT, wild-type; AUC, area under curve; mCRC, metastatic colorectal cancer; FOLFIRI, 5-fluorouracil, leucovorin, irinotecan; FOLFOX, 5-fluorouracil, leucovorin, oxaliplatin; DLT, dose limiting toxicity; XELOX, capecitabine, oxaliplatin; CAPIRI, capecitabine, irinotecan; q2w, every 2 weeks.

these guidelines; however, the FDA has held off on making similar recommendations.

Santini et al recently reported high level of concordance in the *KRAS* status of metastatic lesions and primary tumors. In the metastatic setting, selecting therapy based on *KRAS* mutational status is becoming more widely accepted.⁶² However, in the adjuvant setting, this is still under clinical investigation. If both the primary tumor and metastatic lesions share common characteristics such as *KRAS* mutational status, we could propose selecting therapies in the adjuvant setting based on primary tumor characteristics, may ultimately improve outcomes and reduce toxicity and cost.

Although this has changed the face of EGFR-inhibitor therapy in CRC, only 30% to 50% of patient have *KRAS* mutations, thus leaving a large proportion of patients that do not respond to EGFR inhibitors despite having WT *KRAS*. Di Nicolantonio et al proposed that in the absence of *KRAS* mutations, resistance to EGFR inhibitors may be mediated by alterations in the RAS-RAF-MAPK pathway.⁶³ *BRAF* mutations occur in CRC in approximately 10%.⁶⁴ *BRAF* mutations have been linked to microsatellite instability, a condition generally associated with better prognosis and resistance to standard chemotherapy.⁶⁵ Thus, *KRAS* mutational status as well as microsatellite instability were evaluated in this trial. Patients were selected based on evidence that treatment outcome could be attributed only to administration of cetuximab or panitumumab. All patients had $\geq 1\%$ tumor cells expressing EGFR assessed by immunohistochemistry. Once again, *KRAS* was noted in approximately 30% of patients and was associated with resistance to cetuximab or panitumumab ($P = 0.011$). The *BRAF* V600E mutation was detected in 11 of 79 patients with WT *KRAS*. None of the *BRAF*-mutated patients responded to treatment. None of the responders carried *BRAF* mutations ($P = 0.029$). *BRAF* mutations in patients led to a significantly shorter PFS ($P = 0.011$) and OS ($P < 0.0001$) than patients with WT *BRAF*. Thus, patients whose tumors bear the *BRAF* V600E allele are unlikely to benefit from EGFR inhibitor therapy. This could be an additional tool for the selection of mCRC patients who may benefit from EGFR-targeted therapies.

The PI3K/Akt signaling pathway is involved in cell growth, resistance to apoptosis, invasion and migration. PTEN (the lipid phosphatase and tensin homolog) is a key tumor suppressor that normally regulates the activation of PI3K.⁶⁶ The loss of PTEN and mutations in PI3K have been proposed to predict resistance to EGFR inhibitors, however, this is preliminary and no definite conclusions can be derived.⁶⁴

Table 3 Summary of pivotal randomized clinical trials evaluating *KRAS* mutational status and impact on ORR and PFS in patients with mCRC treated with epidermal growth factor receptor inhibitors

Author	Accrual (# tumor assessed)	<i>KRAS</i> status (%)		Treatment	ORR (%)		PFS (months)			
		WT, n (%)	Mutant, n (%)		WT	Mutant	WT	Mutant		
First-line setting in mCRC										
van Cutsem	1198 (540)	348/540 (64.4)	192/540 (35.6)	FOLFIRI + C FOLFIRI	59.43 ($p = 0.0025$)	36.40	9.9	8.7 ($p = 0.017$)	7.6	8.1
[CRYSTAL trial] ⁶⁸										
Bokemeyer	337 (233)	134/233 (58)	99/233 (42)	FOLFOX + C FOLFOX	61.37 ($p = 0.011$)	33.49	7.7	7.2 ($p = 0.016$)	5.5	8.6 ($p = 0.019$)
[OPUS trial] ⁶⁹										
Punt	775 (520)	314/520 (60.3%)	206/520 (39.6%)	Cap/Oxal/B + C Cap/Oxal/B	61.4	45.9	10.5	10.6 ($p = 0.30$)	8.1	12.5 ($p = 0.003$)
[CAIRO2 trial] ⁷⁰										
Second-line or salvage setting in mCRC										
Amado ⁶⁰	427 (463)	243/427 (56.9%)	184/427 (43%)	Panitumumab BSC	17.0	0.0	12.3	wks 7.3 wks	7.4	wks 7.3 wks
Karapetis ⁶¹	394 (572)	230/394 (58.3%)	164/394 (41.6%)	Cetuximab BSC	12.8	1.2	3.7	1.9	1.8	1.8

Abbreviations: WT, wild-type; ORR, overall response rate; PFS, progression-free survival; mCRC, metastatic colorectal cancer; FOLFIRI, fluorouracil, leucovorin, irinotecan; C, cetuximab; FOLFOX, fluorouracil, leucovorin, oxaliplatin; Cap, capecitabine; Oxal, oxaliplatin; B, bevacizumab; BSC, best supportive care; wks, weeks.

Conclusions

We are entering an exciting era in the treatment of colorectal cancer. Many advances have been made in the last few years, specifically the addition of targeted therapies in the treatment of mCRC. However, as we learn more about the agents as well as their mechanism of action, we are able to better target our treatment population. With the focus on developing personalized cancer care, the shift has been to tailor the treatment not only to the patient but also to tumor biology. It has become imperative to identify molecular and genetic mechanisms underlying responsiveness to monoclonal antibodies. This would allow us to select drugs for patients based on the tumor's molecular signature, improving responses and outcomes, and avoiding unnecessary toxicities. By selecting drugs for responsive patients, we would also minimize the financial burden on the current healthcare system.⁶⁴ In targeting the EGFR pathway, panitumumab has been shown to be well tolerated and effective in the treatment of metastatic colorectal cancer. However, panitumumab only be considered should in patients with wild-type *KRAS*.⁶⁷

Disclosures

The authors disclose no conflicts of interest.

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