

modes of action of these two inhibitor classes, as well as their differing specificity for the EGFR, may contribute to the differences seen in their efficacy and toxicity profiles [12]. EGFR-targeted mAbs have been extensively researched in mCRC, whereas the tyrosine kinase inhibitors appear to have little activity in

this setting [8]. Other novel chemotherapy-free regimens such as EGFR-targeted mAbs combined with insulin-like growth factor (IGF) receptor, VEGF, mTOR, COX-2 or MET inhibitors are also currently under investigation in a variety of tumours; results of these studies are awaited with interest.

Potential markers of response and resistance to anti-EGFR therapies

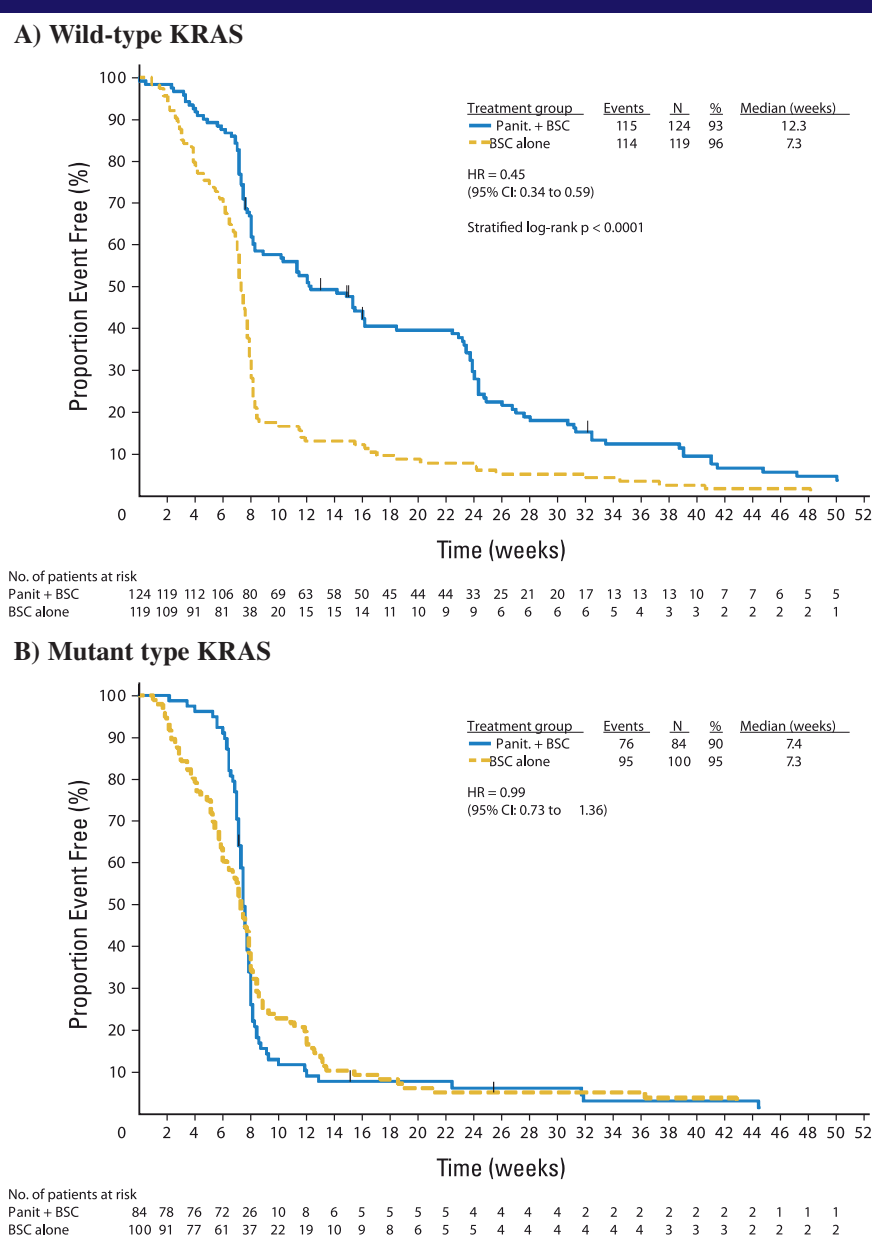
Understanding the mechanisms of resistance and sensitivity to anti-EGFR therapies may result in better patient selection and improved outcomes. Resistance can develop via many processes including the activation of alternative tyrosine kinase receptors that bypass the EGFR pathway, e.g. c-Met and IGF-1 receptors, or via increased angiogenesis [13].

EGFR expression, as detected by immunohistochemistry, is not a reliable marker for the activity of anti-EGFR therapies and this led to a search for other more effective markers. KRAS is a protein involved in the signalling pathways downstream of the EGFR and so is similarly important in cell growth and division. Activating mutations within the KRAS gene can result in constitutive activation of EGFR-independent RAS signalling, and such mutations are found in approximately 35–40% of patients with mCRC [14]. Mutations in KRAS have been shown to be predictive of resistance to anti-EGFR therapies [15, 16], therefore mutational analysis is essential before prescribing any anti-EGFR therapy.

Wild-type KRAS does not, however, guarantee a response to anti-EGFR therapies and the status of genes encoding other proteins involved in the signalling pathways downstream of the EGFR may also be important. BRAF is a serine-threonine kinase and is the principal effector of KRAS activity. Mutations in BRAF account for approximately 10% of the patients who are non-responsive to anti-EGFR therapy [17]. Recently it has been shown that activating mutations of BRAF may be associated with a lack of response to cetuximab or panitumumab and shorter PFS [18].

Mutation or loss of tumour suppressor genes downstream of the EGFR may also promote growth and invasion of cancer cells [8]. PTEN is a lipid phosphatase and tumour suppressor that acts as a negative regulator of PI3K. Loss of PTEN function/expression and/or mutations in PI3K, e.g. PIK3CA, have been associated with non-responsiveness to cetuximab [17, 19]. Screening of CRC tumours for PTEN

Figure 2: Progression-free survival (PFS) with panitumumab or best supportive care by KRAS status



BSC: best supportive care; CI: confidence interval; HR: hazard ratio; Panit: panitumumab
The treatment effect on PFS was significantly greater in the wild-type KRAS group ($p < 0.0001$; Panel A) than in the mutant group (Panel B) [15].
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Table 1: Most common adverse events occurring during panitumumab treatment [4]

Affected body system	Very common side effects (≥10% of patients)	Common side effects (≥1% but <10% of patients)
Skin and subcutaneous tissue disorders	Rash; erythema; skin exfoliation	Stomatitis; mucosal inflammation; onycholysis; hypertrichosis; alopecia; nasal dryness; dry mouth
Gastrointestinal disorders	Diarrhoea	Nausea; vomiting
General disorders	Fatigue	
Administrative site conditions		Infusion reactions (pyrexia; chills)
Metabolism and nutrition disorders		Hypomagnesaemia; hypocalcaemia; hypokalaemia; dehydration
Respiratory, thoracic and mediastinal disorders		Dyspnoea; cough
Nervous system disorders		Headache
Eye disorders		Conjunctivitis; growth of eyelashes; increased lacrimation; ocular hyperaemia; dry eye; eye pruritus

expression status and PI3K/BRAF mutation status could, therefore, further help in the selection of those patients most likely to benefit from anti-EGFR therapy.

Panitumumab – the first fully human anti-EGFR mAb

Although the incidence varies between treatments, all chimeric human: murine mAbs, e.g. cetuximab, trastuzumab (Herceptin) and infliximab (Remicade), are associated with cytokine-induced infusion reactions [20, 21]. Approximately 5% of patients undergoing cetuximab therapy experience severe infusion reactions [20]. Symptoms of these reactions can be life-threatening and include rapid onset of airway obstruction, urticaria, hypotension and/or cardiac arrest [3, 20]. Consequently, prophylaxis with systemic antihistamines and corticosteroids is mandatory prior to the first cetuximab infusion and is generally recommended prior to all subsequent infusions [3]. The aetiology of infusion reactions is not completely understood, but may be due to the immunogenicity of mouse sequences in humans. Among the approaches developed to overcome this problem were transgenic mice, possessing a ‘humanised’ humoral immune system, such as the Xenomouse. This system was used to generate the first fully human mAb for mCRC, panitumumab [22]. Because of its fully human structure, panitu-

mumab has the potential for enhanced efficacy and low immunogenicity [23]. Panitumumab is also associated with a low risk of severe infusion reactions (<1%) and, therefore, has no requirement for prophylactic premedication [4].

Panitumumab – an individualised therapy for patients with tumours expressing wild-type KRAS

The efficacy of panitumumab monotherapy has been demonstrated in a randomised, open label, phase III trial in patients with mCRC [24]. Panitumumab treatment was found to significantly prolong PFS in the overall, non-selected population compared with best supportive care (BSC) alone (hazard ratio 0.54; 95% confidence interval 0.44–0.66; $p < 0.0001$) [24]. Similarly, disease control occurred in 36% of patients receiving panitumumab versus 10% of those receiving BSC alone [24].

A subsequent retrospective analysis of data from this trial carried out to assess the predictive role of KRAS status demonstrated that the efficacy of panitumumab was confined to those patients whose tumours expressed wild-type KRAS [15]. Median PFS was 12.3 weeks for panitumumab versus 7.3 weeks for BSC alone in patients

whose tumours expressed wild-type KRAS, see Figure 2 [15]. In contrast, in the KRAS mutant group, median PFS was 7.4 weeks for panitumumab versus 7.3 weeks for BSC alone. Over 50% of patients whose tumours expressed wild-type KRAS achieved disease control during panitumumab treatment [15], with a median PFS of 6 months [8].

As treatments are now beginning to be tailored to be patients, mutational analysis of KRAS (and perhaps other biomarkers such as BRAF and PI3K [25]) should avoid unnecessary side effects and costs in patients who are unlikely to benefit from panitumumab treatment. Patients whose tumours have a mutated KRAS gene should be directed to alternative treatment.

Panitumumab dosing and administration

Early pharmacokinetic studies indicated that the optimal panitumumab dose was 2.5 mg/kg/week; however, more convenient 6 mg/kg every 2 weeks or 9 mg/kg every 3 weeks schedules were found to yield similar pharmacokinetic profiles [26]. The recommended dose of panitumumab is 6 mg/kg every 2 weeks via IV infusion [4]. Evaluation of the 9 mg/kg every 3 weeks panitumumab dose is ongoing with further data expected in 2010.

Panitumumab is available in 100 mg vials (5 mL solution), which should be diluted using 0.9% sodium chloride to a final volume of 100 or 150 mL (final concentration ≤10 mg/mL), mixed by gentle inversion and should not be shaken. Total volumes of 100 mL should be infused over approximately 60 minutes through a peripheral line or indwelling catheter [4]. Doses in excess of 1,000 mg, i.e. a total volume of 150 mL, should be infused over approximately 90 minutes. Because of the low incidence of infusion reactions, no premedication or post treatment observation is required during panitumumab treatment. Vials containing panitumumab should be refrigerated at 2–8°C (not frozen) and protected from light [4]. Panitumumab should be used within 24 hours of dilution and any unused drug should be discarded.

Safety and tolerability of panitumumab

Panitumumab is generally well tolerated and, like all other EGFR inhibitors, the most common treatment-related side effects are skin and subcutaneous tissue disorders, such as acneiform-like rash, erythema, skin exfoliation, dry skin and pruritus [4], see Table 1. Skin reactions are related to the pharmacological effects of panitumumab and occur in up to 90% of patients receiving monotherapy [24]. Reactions are mostly mild to moderate in nature [24] and can generally be managed with antibiotics and topical steroid treatment [27]. Recent evidence suggests that prophylactic management of skin toxicities may be beneficial [28], although further data are required to confirm any benefit. Consistent with its fully human structure, infusion reactions and antibody formation are rare during panitumumab treatment [4]. Overall, infusion reactions occurred in approximately 4% of patients receiving panitumumab monotherapy in clinical trials, of which <1% were severe.

Summary

The introduction of new, targeted therapies has already improved outcomes for patients with mCRC and with further characterisation of markers of response and resistance to anti-EGFR therapies, additional improvements should occur due to better patient selection. Although generally well tolerated, mAb therapies targeting the EGFR can be associated with severe infusion reactions that add to the burden of treatment for patients and healthcare providers. Panitumumab is the first fully human mAb licensed for the treatment of patients with mCRC and offers an effective and well-tolerated mAb therapy for patients whose tumours express wild-type KRAS. The biweekly dosing schedule, low incidence of infusion reactions and shorter treatment time of panitumumab may reduce the burden of treatment for both patients and healthcare providers.

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