

Cetuximab in the management of colorectal cancer

Heinz-Josef Lenz

Division of Medical Oncology,
University of Southern California/
Norris, Comprehensive Cancer
Center, Keck School of Medicine,
Los Angeles, CA, USA

Abstract: Cetuximab, a chimeric IgG1 monoclonal antibody that targets the ligand-binding domain of the epidermal growth factor receptor (EGFR), is active in metastatic colorectal cancer (mCRC). As an IgG1 antibody, cetuximab may exert its antitumor efficacy through both EGFR antagonism and antibody-dependent cell-mediated cytotoxicity. Clinical trials established the role of cetuximab, particularly with irinotecan, in irinotecan-refractory/heavily pretreated patients. More recent studies show promising activity in second-line treatment after oxaliplatin-based therapy failure, and with first-line chemotherapy, where increased response rates seen with adding cetuximab to first-line therapy for mCRC may increase chances for curative surgery in a population for whom the therapy goal would otherwise be palliative. Cetuximab is generally well tolerated; common toxicities are acne-form rash and hypomagnesemia. Rash intensity is associated with clinical efficacy, and in the future, may be used as a marker for optimal drug exposure. Cetuximab activity in mCRC is not correlated with EGFR expression, and consequently other markers will be needed to identify the most likely responders. Cetuximab has clinically emerged as a core agent, along with 5-fluorouracil, irinotecan, oxaliplatin, and bevacizumab, for overall mCRC management to optimize survival. Ongoing studies are exploring best combinations of cetuximab with these other agents to maximize patient outcome.

Keywords: cetuximab, epidermal growth factor receptor, colorectal cancer

Introduction

The introduction of irinotecan (Camptosar[®], Pharmacia and Upjohn Co, New York, NY), oxaliplatin (Eloxatin[®], sanofi-aventis U.S. LLC, Bridgewater, NJ), and biologics over the last decade has yielded incremental improvements in survival of patients with metastatic colorectal cancer (mCRC). Both irinotecan and oxaliplatin improved efficacy when added to 5-fluorouracil (5-FU) in first-line therapy (Douillard et al 2000; Saltz et al 2000) and in pretreated patients (Cunningham et al 1998; Rougier et al 1998; de Gramont et al 2000). It has also been shown that oxaliplatin plus 5-FU-based therapy (FOLFOX) and irinotecan plus 5-FU-based therapy (FOLFIRI) can be used sequentially, regardless of order, resulting in median survival times reaching 21 months (Tournigand et al 2004). A pooled analysis of 11 phase III trials found that median survival was significantly correlated with the percentage of patients who received all 3 cytotoxic agents (5-FU, irinotecan, and oxaliplatin) at some point in the course of treatment ($p = 0.0001$), regardless of the sequence in which they were used (Grothey et al 2004; Grothey and Sargent 2005). These findings form the basis for the current paradigm in mCRC management: 5-FU, irinotecan, and oxaliplatin should be administered at some point during the course of treatment, typically starting with either oxaliplatin or irinotecan in combination with 5-FU.

Clinical outcome has been further improved by incorporating biologics into this treatment paradigm. Bevacizumab (Avastin[®], Genentech, Inc South San Francisco, CA) is an anti-angiogenic monoclonal antibody directed against vascular endothelial

Correspondence: Heinz-Josef Lenz
USC/Norris Comprehensive Cancer
Center, Director Colorectal Center,
Keck School of Medicine, 1441 Eastlake
Avenue, Suite 3456, Los Angeles, CA
90033, USA
Tel +1 323 865 3955
Fax +1 323 856 0061
Email lenz@usc.edu

growth factor (VEGF), which improved response rate, as well as progression-free survival (PFS) and median survival by 4.4 and 4.7 months, respectively, when added to irinotecan plus 5-FU in first-line therapy, (Hurwitz et al 2004) and by 2.4 and 2.1 months, respectively, when added to FOLFOX after irinotecan failure (Giantonio et al 2007). The value of adding bevacizumab to irinotecan following FOLFOX failure, or continuing bevacizumab therapy after failure of a bevacizumab-containing regimen is not fully established. The recent report from the retrospective Bevacizumab Regimens Investigation of Treatment Effects and Safety (BRiTE) study suggests that continued use of bevacizumab may provide a meaningful clinical advantage in terms of long-term survival (Grothey et al 2007); however, this approach is currently under investigation in the prospective SWOG 0600 and BOND 2.5 trials. Bevacizumab has very little activity when used alone or in combination with 5-FU in refractory disease (Chen et al 2006; Giantonio et al 2007).

Biologics targeting the epidermal growth factor receptor (EGFR) have shown consistently activity in mCRC. The EGFR mediates cell proliferation, differentiation, migration, and adhesion, and enhances processes critical to tumor growth and progression, including angiogenesis, apoptosis inhibition, tumor invasiveness, and metastatic spread (Lenz 2006). EGFR is overexpressed in many colorectal tumors; although some studies have shown inconsistent findings, the levels of EGFR expression are related to prognosis, with higher expression levels correlating with shorter survival times and greater metastatic potential (Nicholson et al 2001; Spano et al 2005). The chimeric IgG1 monoclonal antibody cetuximab (ERBITUX, ImClone Systems Incorporated, New York, NY and Bristol-Myers Squibb Company, Princeton, NJ) was the first biologic directed against EGFR to receive approval by the FDA for use in mCRC. This article focuses on the clinical efficacy and tolerability of cetuximab, and discusses its role in the management of mCRC. Another anti-EGFR biologic – the human IgG2 monoclonal antibody panitumumab (Vectibix™, Amgen Inc., Thousand Oaks, CA) has only recently arrived on the market, but comprehensive data with this agent, including a demonstration of survival benefit in mCRC, or feasibility as part of therapeutic combinations, are still lacking (Wainberg and Hecht 2006).

Cetuximab: Mechanism of action and pharmacology

The EGFR is a 170-kD transmembrane glycoprotein, which is a member of the ErbB family of receptors, and is sometimes

referred to as ErbB1 or HER1 (Wells 1999; Vallbohmer and Lenz 2005a). It consists of a ligand-binding extracellular domain, a lipophilic transmembrane region, and an intracellular tyrosine kinase domain. Binding of endogenous ligands, such as epidermal growth factor and transforming growth factor- α , promotes EGFR homo- or hetero-dimerization, leading to activation and autophosphorylation of tyrosine residues in the receptor's intracellular domain. As a result, adapter proteins such as Grb2, Ras-specific GTPase-activating protein (GAP), and phosphatidylinositol-3-kinase (PI-3K), can interact with the phosphotyrosine residues and stimulate downstream signaling, including the Ras-MAPK and PI-3K-Akt pathways. The nature of the EGFR ligand as well as the coreceptor involved in dimerization determines which signaling pathways are activated and the final cellular response (Yarden and Slivkowski 2001).

Target-specific mechanisms

Cetuximab binds specifically to the extracellular domain of EGFR as a competitive antagonist of the endogenous ligands (Harding and Burtneess 2005). Cetuximab binding promotes internalization of the EGFR, effectively leading to downregulation of EGFR on the cell surface. Together, these effects block EGFR-mediated signaling leading to cell cycle arrest in G1, and pro-apoptotic processes (Huang et al 1999; Kiyota et al 2002; Harding and Burtneess 2005). EGFR-dependent transcriptional programs are also affected by cetuximab, which reduces angiogenesis, tumor invasiveness, and metastatic spread (Harding and Burtneess 2005).

Preclinical studies showed that cetuximab acts synergistically with various cytotoxic agents to augment tumor growth inhibition (Huang et al 1999; Overholser et al 2000). Such effects have been observed with topotecan (Hycamtin®, GlaxoSmithKline, Research Triangle Park, NC) (Ciardiello et al 1999), and more importantly, with irinotecan (Prewett et al 2002). Notably, the cetuximab-irinotecan combination also produced growth inhibition of irinotecan-refractory DLD-1 and HT-29 xenografts, whereas tumor growth was not controlled by either agent alone. On histological examination, the combination of cetuximab and irinotecan led to extensive tumor necrosis, reduced tumor cell proliferation, increased tumor cell apoptosis, and decreased tumor vasculature.

Cetuximab also enhances radiosensitivity (Huang et al 1999). The EGFR can be activated in a ligand-independent manner, which results in cell cycle arrest and initiation of DNA repair mechanisms. However, in the presence of cetuximab, EGFR nuclear import and subsequent activation of DNA repair mechanisms after radiation exposure were

inhibited, and radiosensitivity was enhanced (Dittmann et al 2005). Taken together, these preclinical studies illustrate that cetuximab restores chemosensitivity to cytotoxic agents and also enhances sensitivity to radiation therapy.

Immune-mediated mechanisms

As an IgG1 monoclonal antibody, cetuximab also has the potential to kill tumor cells through antibody-dependent cell-mediated cytotoxicity (ADCC). The specificity of cetuximab for the EGFR is determined by its antigen-binding region, whereas its Fc region is characteristic of other IgG1 immunoglobulins. After binding to EGFR, the Fc region of cetuximab remains exposed, and may be recognized by Fcγ receptors (FcγR) on natural killer cells and other immune effectors (Iannello and Ahmad 2005). In general, FcγRs bind effectively to IgG1 and IgG3 antibodies, only moderately to IgG4 antibodies, but poorly to IgG2 antibodies (Goldsby et al 2003). Thus, an IgG1 monoclonal antibody like cetuximab would be more likely to stimulate ADCC as compared to IgG2 antibodies (such as panitumumab). Cetuximab has been shown to promote ADCC against tumor cell lines, with activity tending to increase with higher EGFR expression (Kawaguchi et al 2007; Kurai et al 2007).

ADCC is regulated by several different FcγR isoforms, including FcγRIIIa in natural killer cells and FcγRIIa in macrophages. Studies based on the clinical effect of the genetic polymorphisms identified in both receptor isoforms have helped provide proof of principle of the clinical relevance of ADCC (van Sorge et al 2003). These receptor polymorphisms have different affinities for their target Fc domains, which would be expected to translate into different levels of ADCC activity, and ultimately impact clinical response. Indeed, seminal studies with the IgG1 rituximab in patients with follicular lymphoma showed that certain polymorphisms (FcγRIIIa-158V and FcγRIIa-131H) were independently associated with higher response rates and longer PFS (Weng and Levy 2003; Cartron et al 2004).

Whether ADCC actually contributes to the clinical efficacy of cetuximab, however, remains to be determined. Zhang and colleagues (Zhang et al 2007) recently explored whether FcγRIIa and FcγRIIIa polymorphisms would influence the clinical response to single-agent cetuximab in a cohort of 39 mCRC patients who had previously failed irinotecan and oxaliplatin therapy. Analysis of the rates of clinical benefit (stable disease or partial response) as well as median PFS and overall survival favored patients with the FcγRIIa-131H/H and H/R genotypes relative to those with the R/R genotype, as well as patients with FcγRIIIa-158F/F and

F/V genotypes relative to those with the V/V-genotype. When the 2 polymorphisms were considered together, patients with either FcγRIIIa-158V/V or FcγRIIa-116R/R genotype had significantly shorter PFS than the remaining patients (1.1 vs 3.7 months, $p = 0.004$) and tended to have shorter overall survival as well (2.3 vs 10.7 months, $p = 0.093$) (Figure 1). These findings support the potential contribution of ADCC to the clinical efficacy of cetuximab in mCRC, but they differ from the results obtained with rituximab (Rituxan®, Genentech, Inc., South San Francisco, CA and Biogen Idec Inc., Cambridge, MA) in follicular lymphoma. This raises the possibility that solid tumors respond differently than hematological malignancies to ADCC, particularly when comparing late-stage solid tumors with first-line treatment of lymphoma. Additional studies are needed to better define the clinical significance of ADCC to the efficacy of cetuximab.

As knowledge about the role of EGFR in tumor growth and progression continues to advance, it will provide a better understanding about which mechanisms of cetuximab are important in conveying clinical benefit in mCRC as well as in other solid malignancies.

Clinical efficacy

Following the pattern of activity observed in xenograft models, cetuximab was initially investigated in combination with cytotoxic agents, particularly irinotecan. To date, that combination remains the most effective cetuximab-based therapy for patients with mCRC disease who have received prior therapy. Numerous single-arm and randomized studies recently completed or nearing completion are generating a more complete profile of cetuximab as part of non-irinotecan-based combinations, as well as in untreated patients with mCRC. In parallel, and beyond the scope of this review, cetuximab has also been proven effective in head and neck cancers and non-small cell lung cancers (Rosell et al 2004; Bonner et al 2006; Kelly et al 2006; Vermorken et al 2007).

Early clinical studies in refractory mCRC

The initial clinical evaluation of cetuximab in mCRC was performed in patients who had been previously treated with irinotecan (Table 1). Although these studies were not comparative, they provided an important framework for the clinical development of this agent, and warranted its regulatory approval both in North America and the EU. Cetuximab was administered at an initial dose of 400 mg/m² and then weekly at 250 mg/m². This regimen has remained the standard whether cetuximab is given in monotherapy or in combination with other agents.

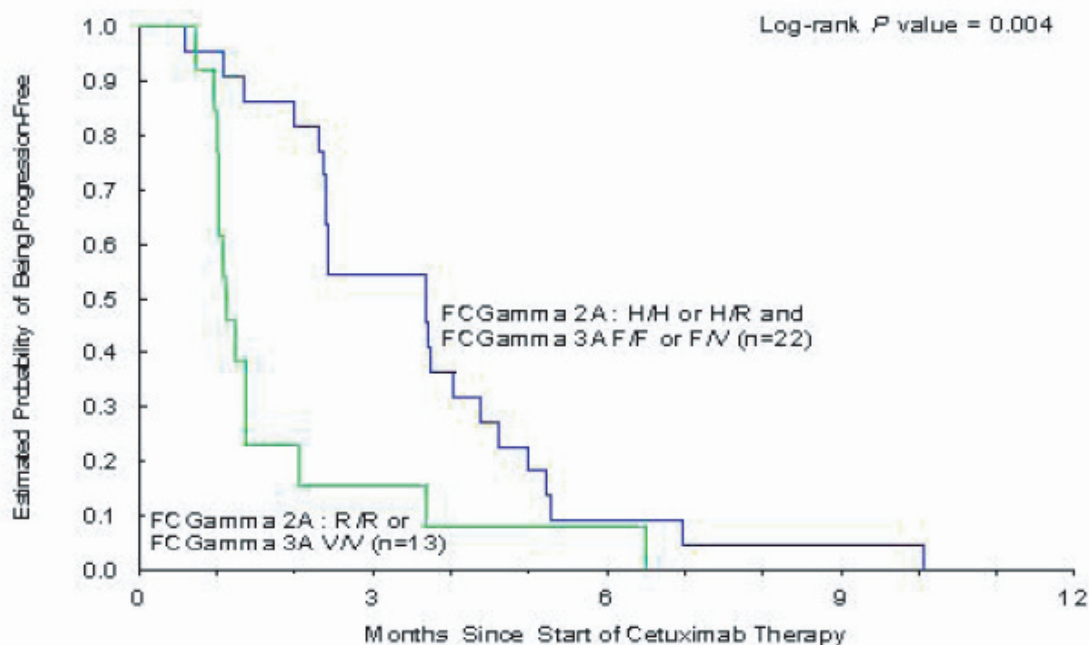


Figure 1 Effect of FcγR polymorphisms on PFS in patients with refractory mCRC treated with single-agent cetuximab. Patients with either the FcγIIa-R/R or FcγIIa-V/V genotypes had significantly shorter PFS than those with other genotypes. Reprinted with permission from Zhang W, Gordon M, Schultheis A, et al 2007. FCGR2A and FCGR3A polymorphisms associated with clinical outcome of epidermal growth factor receptor expressing metastatic colorectal cancer patients treated with single-agent cetuximab. *J Clin Oncol*, 25:3712–18. Copyright © 2006 American Society of Clinical Oncology.

Saltz and colleagues (Saltz et al 2004) evaluated single-agent cetuximab in 57 patients with EGFR-positive mCRC who had failed previous irinotecan-based therapy. Partial responses were achieved in 5 patients (9%), whereas minor responses or stable disease were seen in an additional 20 patients (35%). The median time to tumor progression was 1.4 months, and median survival from the start of cetuximab therapy was 6.4 months. More recently, Lenz and co-workers (Lenz et al 2006) administered single-agent cetuximab to 346 patients with EGFR-positive mCRC refractory to irinotecan, oxaliplatin, and fluoropyrimidines. Forty patients (12%) had partial responses and an additional 110 patients (32%) had stable disease. The median survival was 6.6 months (95% CI: 5.6–7.6 months), with 27.4% of the study cohort surviving at 1 year.

These studies demonstrated the activity of cetuximab as a single agent. The most efficacious modality of cetuximab therapy in refractory mCRC, however, is the combination with irinotecan. Cunningham and colleagues (Cunningham et al 2004) randomly assigned 329 patients with EGFR-expressing mCRC who had failed a previous irinotecan-based regimen in a 2:1 ratio to treatment with cetuximab plus irinotecan or cetuximab alone. Irinotecan was given at the same dose and schedule as in the regimen that the patient had previously failed. Patients receiving the combination of cetuximab and irinotecan had signifi-

cantly higher response rates (23% vs 11%, $p = 0.007$) and disease control rates (56% vs 32%, $p < 0.001$), and a longer median time to progression (4.1 vs 1.5 months, $p < 0.001$) than those who received single-agent cetuximab. Notably, cetuximab showed comparable activity in the subset of 206 patients who had previously failed both irinotecan and oxaliplatin: the response rate was 22% with cetuximab plus irinotecan as compared to 9% with cetuximab alone ($p = 0.01$). Median survival, however, did not differ significantly between treatment groups, although it was numerically longer for those receiving cetuximab and irinotecan (8.6 vs 6.9 months). Consistent results with cetuximab-based combinations have been reported by single-arm studies. Saltz and colleagues (Saltz et al 2001) reported a response rate of 17% with combination cetuximab and irinotecan in a study of 127 patients with irinotecan-refractory mCRC, and Souglakos and coworkers (Souglakos et al 2007) have reported a response rate of 20% with cetuximab added to capecitabine (Xeloda® Roche Laboratories Inc, Nutley, NJ)-oxaliplatin therapy in patients with oxaliplatin- and irinotecan-refractory mCRC.

These results have been obtained mostly in heavily pretreated patients (for instance, although the Cunningham study required only prior irinotecan for eligibility, over 70% of patients had received 2 prior therapies or more), but illustrates several points that have paved the way for the

Table 1 Phase II studies of cetuximab in EGFR-Expressing refractory mCRC (Saltz et al 2001; Saltz et al 2004; Cunningham et al 2004; Lenz et al 2006b; Souglakos et al 2007)

Study	Therapy	Pts (N)	Tumor refractory to	PR (%)	SD (%)	MDR (mo)	Median TTP (mo)	MS (mo)
Saltz et al 2004	Cetuximab	57	Irinotecan	10.5	35.1	4.2	1.4	6.4
Lenz 2006	Cetuximab	346	Irinotecan, oxaliplatin, and 5-FU	11.6	31.8	4.2	1.4 ^a	6.6
Saltz et al 2001	Cetuximab/Irinotecan	121	Irinotecan	17.4	30.6	2.8	NR	NR
Cunningham et al 2004	Cetuximab	111	Irinotecan	10.8	21.6	4.2	1.5	6.9
	Cetuximab/Irinotecan	218		22.9 (p = 0.007)	32.6	5.7	4.1 (p < 0.001)	8.6 (p = 0.48)
Cunningham et al 2004 ^b	Cetuximab	71	Irinotecan and oxaliplatin	8.5	NR	NR	NR	NR
	Cetuximab/Irinotecan	135		22.2 (p = 0.01)				
Souglakos et al 2007	Cetuximab/Capecitabine/Oxaliplatin	40	Irinotecan and oxaliplatin	20 ^c	53	4.9	2.9	10.7

^aMedian progression-free survival.^bSubgroup analysis.^cIncludes 1 patient with complete response (2.5%).**Abbreviations:** PR, partial response; SD, stable disease; MDR, median duration of response; TTP, time to progression; MS, median survival.

current development trajectory of cetuximab in mCRC, and its incorporation in earlier therapy settings (Cunningham et al 2004). First, the cetuximab-irinotecan combination is among the most active regimens in pretreated patients. Second, the greater activity of this combination relative to single-agent cetuximab, even in patients refractory (never responsive) to irinotecan, suggests that chemosensitivity to irinotecan may be restored when it is administered in combination with cetuximab. Third, cetuximab exhibited comparable activity in patients who had received irinotecan as in those treated with both irinotecan and oxaliplatin, suggesting that it maintains its efficacy in mCRC across later lines of therapy. Finally, in these studies, the degree of EGFR expression – whether defined by the percentage of EGFR-expressing cells or by the maximal staining intensity per cell – did not correlate with the clinical activity of cetuximab (Cunningham et al 2004; Lenz et al 2006). Moreover, Chung and co-workers (Chung et al 2005) retrospectively identified 16 irinotecan-refractory mCRC patients with EGFR-negative tumors who received cetuximab within the first 3 months of its commercial availability. Fourteen patients were treated with cetuximab in combination with irinotecan, and the other 2 patients with cetuximab alone. Overall, 4 patients (25%) responded to treatment, consistent with the response rate reported for patients with EGFR-positive tumors in the phase II trials described above. These findings indicate that EGFR expression is not a valid criterion for selecting patients for cetuximab therapy, and underscore the need for selective

biomarkers that can predict which patients are most likely to respond to cetuximab.

Single-agent cetuximab vs BSC in multi-refractory patients

As a confirmation of the role of single-agent cetuximab as standard salvage therapy after multiple treatments, a recently reported phase III has demonstrated the survival benefit associated with cetuximab treatment, over best supportive care (BSC), in multi-refractory patients. The National Cancer Institute of Canada (NCIC) Clinical Trials Group in conjunction with the Australasian Gastro-Intestinal Trials Group conducted a phase III trial (NCIC 017) to compare single-agent cetuximab with BSC in a total of 572 patients with EGFR-expressing mCRC who had previously been treated with 5-FU or another thymidylate synthase inhibitor, and who had failed irinotecan and oxaliplatin (Jonker 2007). Patients were stratified by study center and Eastern Cooperative Oncology Group (ECOG) performance status (0–1 vs 2), and then randomly allocated to cetuximab plus BSC or BSC alone. The primary study endpoint was overall survival. Overall, 82% of the patients had received at least 3 previous chemotherapy regimens. Cetuximab produced a significantly higher objective response rate than BSC alone (6.6% vs 0%; p < 0.0001), and also allowed more patients to achieve stable disease (29.6% vs 10.2%). Importantly, the addition of cetuximab to BSC significantly improved median survival compared with BSC alone (6.1 vs 4.6

months; HR = 0.77; 95% CI: 0.64–0.92; $p = 0.005$), and also significantly improved the time to tumor progression (HR = 0.68; 95% CI: 0.57–0.80; $p < 0.0001$). Notably, these effects of cetuximab remained statistically significant even after adjusting for potential prognostic factors that were specified in the study protocol ($p = 0.014$ and $p = 0.0002$, respectively). Thus, NCIC 017 confirms the efficacy of single-agent cetuximab in multi-refractory mCRC patients, and is the first study to demonstrate a survival benefit associated with an anti-EGFR agent in this setting.

Cetuximab plus irinotecan after FOLFOX failure

As discussed above, by the time of FDA (and EMEA) approval of cetuximab, the combination with irinotecan had been proven to be effective after irinotecan failure; however, bona-fide comparative data documenting the additive contribution of cetuximab to this regimen were lacking. The Erbitux Plus Irinotecan in Colorectal Cancer (EPIC) study was designed to compare cetuximab plus irinotecan versus irinotecan alone in second-line treatment of irinotecan-naïve mCRC patients after failure of previous first-line FOLFOX therapy (Sobrero 2007). Single-agent irinotecan was used as comparator, as it was the standard of care in this setting at the time EPIC was initiated. A total of 1298 patients with EGFR-positive mCRC were stratified by study site and ECOG performance status, and then randomly assigned to receive cetuximab plus irinotecan or irinotecan alone. Irinotecan was administered at a dose of 350 mg/m² every 3 weeks, and cetuximab was given at its standard dose (400 mg/m² initially and then 250 mg/m² weekly). Adding cetuximab to irinotecan was superior to irinotecan alone, as it significantly improved PFS (4.0 vs 2.6 months; HR = 0.69; 95% CI: 0.62–0.78; $p \leq 0.0001$) and produced a higher response rate (16.4% vs 4.2%; $p < 0.0001$). Importantly, adding cetuximab to irinotecan did not exacerbate toxicity, except for acne-form rash.

Despite the positive results for the secondary endpoints, however, the primary study point, overall survival, was not met. Median survival was comparable between treatments (10.7 vs 10.0 months; HR = 0.975; 95.03% CI: 0.85–1.11; $p = 0.71$), tempering, at first glance, the positive conclusions that could be drawn from the secondary endpoint results. This lack of difference, however, is a likely consequence of the imbalances in post-trial therapy. As cetuximab plus irinotecan were adopted as the standard of care after irinotecan failure, nearly half of the patients (approximately 40%) allocated to the comparator arm went on to receive this combination (the

de facto experimental treatment in the study) once they left the protocol after progression (Sobrero 2007).

Beyond the interpretation of these results in terms of cetuximab efficacy, this study also highlights the ongoing challenges of clinical trial design and endpoint selection in a fast evolving area such as mCRC. While prolonging survival is unarguably the most relevant clinical goal, it is debatable whether median survival provides an accurate measure of clinical efficacy, versus PFS, for an agent given in first-line or second-line treatment of mCRC. Depending on the therapeutic setting, the reliability of median survival as an endpoint may be confounded by significant factors beyond the control of a trial design, whereas PFS is more likely to reflect only protocol-controlled variables, and is sufficient for showing the clinical advantage of one regimen over another.

Adding cetuximab to first-line mCRC treatment

Building upon the effectiveness of cetuximab in refractory mCRC, several studies have also been conducted to explore whether adding cetuximab to first-line therapy would improve patient outcome (Table 2). In the CRYSTAL trial, cetuximab was added to the FOLFIRI regimen, one of the possible standards of care for first-line treatment. A total of 1220 patients with untreated EGFR-expressing mCRC were randomly assigned to cetuximab plus FOLFIRI or FOLFIRI alone. A top-line report from the final results of CRYSTAL, recently presented at the 48th annual ASCO meeting, indicated that adding cetuximab to FOLFIRI significantly prolonged PFS (from 8.0 months to 8.9, $p = 0.036$), and increased response rates (from 38.7% to 46.9%, $p = 0.005$) compared to FOLFIRI alone (Van Cutsem 2007). Of particular interest is the benefit derived by patients with liver disease only, whose rates of R0 resectability increased by 3 fold with the addition of cetuximab. These findings infer that cetuximab is active in the first-line setting, and especially valuable for patients with synchronous liver disease, but it is difficult to extrapolate them to current clinical practice in the United States, where practice patterns strongly favor FOLFOX plus bevacizumab as first-line treatment.

Furthermore, several smaller trials in which cetuximab was added to first-line FOLFOX have produced promising results. Andre and colleagues (Andre et al 2007) administered cetuximab in combination with the FOLFOX-4 regimen (oxaliplatin 85 mg/m² on day 1, plus folinic acid 200 mg/m² and 5-FU in a 400 mg/m² bolus followed by a continuous infusion of 600 mg/m² for 22 hours on days 1 and 2 every 2 weeks) to 43 patients with EGFR-positive

Table 2 Clinical studies of cetuximab in first-line treatment of EGFR-expressing mCRC (Folprecht et al 2006; Venook et al 2006b; Van Cutsem 2007; Andre et al 2007)

Study	Treatment	Patients	OR (%)	SD (%)	PFS (mo)	OS (mo)
CRYSTAL	FOLFIRI ^a	609	38.7	NR	8	NR
	FOLFIRI + cetuximab	608	46.9		8.9	
Andre et al 2007	FOLFOX-4 ^b + cetuximab	43	77	18	12.3	30.0 (17.8, 33.8)
CALGB 80203 ^c	FOLFIRI ^a	61	36	38	8.4	NR
	FOLFIRI + cetuximab	59	44	32	10.6	
	FOLFOX ^d	60	40	30	9.8	
	FOLFOX + cetuximab	58	60	26	8.2	
Folprecht et al 2007	Irinotecan/5-FU ^e + cetuximab	21	67	29	9.9	33 (20 to ?)

^aFOLFIRI consisted of irinotecan 180 mg/m², folinic acid 400 mg/m², and 5-FU in a 400 mg/m² bolus followed by a continuous infusion of 2400 mg/m² for 46 hours every 2 weeks (Lang et al 2006; Venook et al 2006b).

^bFOLFOX-4 consisted of oxaliplatin 85 mg/m² on day 1, plus folinic acid 200 mg/m², and 5-FU in a 400 mg/m² bolus followed by a continuous infusion of 600 mg/m² for 22 hours on days 1 and 2 every 2 weeks (Andre et al 2007).

^cPreliminary results.

^dFOLFOX consisted of oxaliplatin 85 mg/m², folinic acid 400 mg/m², and 5-FU in a 400 mg/m² bolus followed by a continuous infusion of 2400 mg/m² for 46 hours every 2 weeks (Venook et al 2006b).

^eIrinotecan 80 mg/m², folinic acid 500 mg/m², and 5-FU as a 1500 mg/m² (n = 6) or 2000 mg/m² (n = 15) continuous infusion for 24 hours weekly for 6 weeks every 50 days (Folprecht et al 2007).

Abbreviations: OR, overall response; SD, stable disease; PFS, progression-free survival; OS, overall survival.

mCRC. Objective responses were confirmed in 33 patients (77%). Median PFS was 12 months, and median survival was 30 months (95% CI: 17.8 to 33.8 months) after a median follow-up of 30.5 months. Notably, 10 patients (23%) with initially unresectable metastases (8 liver, 1 lung, and 1 adrenal) subsequently underwent surgery with curative intent, with complete resections achieved in 9 of these cases. No unexpected toxicities were seen. Initial results from the randomized phase II OPUS trial (Bokemeyer 2007) comparing FOLFOX with or without cetuximab in 337 patients with untreated mCRC, are consistent with these encouraging observations, demonstrating a difference in response rates favoring cetuximab (45.6% vs 35.7%). Folprecht and colleagues (Folprecht et al 2006) reported comparable results in a study of 21 patients with EGFR-expressing mCRC who received cetuximab in combination with weekly irinotecan and low-dose or high-dose infusional 5-FU. Median survival was 33 months, and 4 patients (19%) underwent potentially curative surgery.

The CALGB 80203 study was designed to compare first-line FOLFIRI versus FOLFOX, both with and without cetuximab. Enrollment to this study, however, could not be completed due to the fast adoption of bevacizumab as a component of first-line therapy. The study was closed to accrual after a total of 238 of the planned 2200 patients were enrolled. Preliminary results showed that response rates were higher in the arms with cetuximab, particularly when it was administered with FOLFOX: 60% for FOLFOX plus cetuximab; 40% for FOLFOX alone; 44% for FOLFIRI plus cetuximab; and 36% for FOLFIRI alone. Overall, adding

cetuximab significantly increased response rates compared to treatment without cetuximab (52% vs 38%; $p = 0.029$). At the time of the report, the median follow-up was 16 months, still too early to tell whether adding cetuximab improved PFS (Venook et al 2006b). The ongoing OPUS study is also evaluating whether adding cetuximab to FOLFOX-4 will improve response rates, and secondarily whether it will allow more patients to undergo potentially curative surgery for metastases, and prolong the duration of response, PFS, and overall survival (Bokemeyer 2005).

Combination of biologics

Another promising avenue of therapeutic development for cetuximab in mCRC could bring together the activity of the 2 biologic agents effective in CRC, cetuximab and bevacizumab, based on a strong mechanistic rationale. The EGFR pathway controls the production of VEGF (and other angiogenic factors) in cells, targeting both markers may therefore have a greater antitumor effect. The feasibility of administering these 2 monoclonal antibodies in combination was addressed in the BOND-2 study, focusing on patients otherwise candidates for cetuximab therapy. In this phase II trial, 74 patients with irinotecan-refractory mCRC were randomly assigned to treatment with cetuximab, bevacizumab, and irinotecan, or to cetuximab and bevacizumab (Saltz et al 2005). These patients had not been treated previously with cetuximab or bevacizumab, and were not required to have EGFR-expressing tumors. Bevacizumab was administered at a dose of 5 mg/kg every other week, and irinotecan was given in the same dose and schedule as last given prior to

study entry. Notably, as observed in the initial BOND study by Cunningham et al (2004) (see above), the addition of irinotecan results in greater activity in these patients who had already progressed after one irinotecan-containing regimen. Furthermore, adding bevacizumab increased the response rate and prolonged the time to progression relative to historical controls treated with cetuximab/irinotecan or cetuximab alone in this setting (Table 3) (Saltz et al 2005). The observed toxicities were consistent with those of the individual agents, with no evidence that adding bevacizumab enhanced toxicity. Pharmacogenomic analysis revealed several polymorphisms of genes involved in angiogenesis, the EGFR pathway, and DNA repair that may be potential markers for clinical outcome in mCRC patients receiving both biologics (Lenz et al 2007). Thus, results from BOND-2 are hypothesis-generating and provide preliminary evidence of the clinical benefit of combining cetuximab and bevacizumab in bevacizumab-naïve patients. The BOND2.5 and SWOG 0600 trials are exploring these same combinations in bevacizumab-refractory patients (Saltz et al 2005).

The next step is the investigation of the cetuximab-bevacizumab doublet in untreated patients, for whom bevacizumab is already part of standard treatment. CALGB/SWOG 80405 is designed to determine the optimal combination of these biologics in first-line treatment of mCRC. Patients and their physicians will first choose either the FOLFOX or FOLFIRI chemotherapy regimen and then will be randomized to treatment with cetuximab, bevacizumab, or both. The primary endpoint in this study is overall survival, with response rate, PFS, duration of response, and time to progression as secondary endpoints. Additionally, this study will explore which regimen is most likely to allow patients to undergo potentially curative surgery of metastases following

chemotherapy. Planned accrual is 2,289 patients (Venook et al 2006a). The CAIRO2 trial, sponsored by the Dutch Colorectal Cancer Group, is another randomized phase III trial, which is evaluating whether adding cetuximab to a regimen of capecitabine, oxaliplatin, and bevacizumab will improve PFS relative to the same regimen without cetuximab in previously untreated mCRC patients. Planned accrual is 750 patients (Punt 2005). In the context of the recent results obtained with the IgG2 antibody panitumumab in similar combinations, the outcome from these trials is now crucial to understand the feasibility of simultaneous EGFR and VEGF inhibition in untreated patients. In the phase III Panitumumab Advanced Colorectal Cancer Evaluation (PACCE) trial investigating FOLFOX/bevacizumab with or without panitumumab, an interim analysis revealed no benefit with the addition of this antibody to the bevacizumab/chemotherapy regimen; furthermore, the trial was closed early due to the increased toxicity of the dual targeted combination, with unacceptable rates of pulmonary embolism, diarrhea, dehydration and infections (Amgen press release 2007).

It is likely that some patients may benefit more from FOLFOX plus bevacizumab, others from FOLFIRI plus cetuximab, and still others from different combinations of chemotherapy and biologics. The key will be to identify factors (see below) that predict which patients will respond best to which regimen.

Earlier use of cetuximab in the course of disease: the perioperative setting

The impact of cetuximab improving response rates in patients with metastatic disease may also become extremely important, as it has the potential to dramatically change the therapeutic outlook of certain patients. Preliminary data suggest that use of cetuximab in untreated mCRC may “downstage” unresectable patients and allow potentially curative surgery of metastases. For example, as described previously, R0 resectability rates reached 23% in unselected patients treated with cetuximab and FOLFOX-4, and 25% in patients treated with cetuximab plus 5FU/irinotecan regimens (Folprecht 2006; Andre et al 2007).

Ongoing studies are exploring whether cetuximab may be useful earlier in the course of disease in the adjuvant and neoadjuvant settings. Hofheinz and colleagues (Hofheinz et al 2006) showed that adding cetuximab to neoadjuvant capecitabine, irinotecan, and radiation therapy is feasible in patients with locally advanced rectal cancer. Of 19 patients who underwent resection, nodal downstaging was found in 12 patients and T-stage downstaging in 8 patients. Complete

Table 3 Effect of adding bevacizumab to cetuximab/irinotecan and cetuximab in irinotecan-Refractory mCRC patients: comparison of BOND-2 results with historical controls (Saltz et al 2005)

	Response rate		Time to progression	
	%	p-value	Months	p-value
Cetuximab/irinotecan + bevacizumab	38	0.03	8.5	<0.01
Cetuximab/irinotecan (historical control)	23		4.0	
Cetuximab + bevacizumab	23	0.05	6.9	<0.01
Cetuximab (historical control)	11		1.5	

tumor regression was achieved in 5 patients, with only microfoci within fibrotic tissue found in 6 others. Similarly, Machiels and co-workers (Machiels et al 2007) found down-staging in pathological classification in 14 of 37 patients (38%) with advanced or metastatic rectal cancer following neoadjuvant treatment with cetuximab, capecitabine, and radiation. From a mechanistic as well as safety perspective, cetuximab may be an optimal agent for use in the peri-surgical setting, in that EGFR is not involved in liver regeneration, and cetuximab does not interfere with wound healing.

Alternative dosing schedules

Cetuximab is still given on a weekly basis when used in combination with bi-weekly chemotherapy regimens, such as FOLFIRI and FOLFOX, but additional alternative schedules can be optimized to make cetuximab administration more flexible, and perhaps easier to coordinate with those cytotoxic regimens. The standard regimen of cetuximab is 400 mg/m² initially followed by 250 mg/m² weekly. However, because of its long elimination half-life – 4–5 days at steady-state (ERBITUX PI 2007) – it is possible to administer cetuximab every 2 weeks and thereby improve patient convenience. Tabernero and colleagues (Tabernero et al 2006) reported preliminary results from a phase I study, in which 20 mCRC patients received cetuximab 400 or 500 mg/m² every 2 weeks for 6 weeks in monotherapy and then in combination with FOLFIRI. No dose-limiting toxicities were reported. At steady-state, the pharmacokinetics of cetuximab 500 mg/m² every 2 weeks were comparable to those achieved with the standard once weekly regimen. Preliminary results showed no major differences between the 2 schedules in terms of inhibition of EGFR signaling in skin.

Pfeiffer and colleagues (Pfeiffer et al 2007) subsequently evaluated a biweekly regimen of cetuximab and irinotecan as third-line therapy in 40 consecutive patients with multi-refractory mCRC. Cetuximab was administered at an initial loading dose of 400 mg/m² followed 1 week later by 250 mg/m² and then biweekly by a 500 mg/m² infusion over 100 minutes. Irinotecan 180 mg/m² was also administered biweekly starting 30 minutes after completion of the cetuximab infusion. The bi-weekly cetuximab-irinotecan regimen produced a response rate of 23%, with a median time to progression of 4.7 months. Median survival had not been reached after a median follow-up of 6 months. These results strongly indicate that bi-weekly administration of cetuximab is feasible and does not compromise efficacy. Nonetheless, further evaluation of the bi-weekly cetuximab regimen is needed before it can be routinely used in clinical practice.

Predictive markers

As the clinical trials discussed above have shown, the refinement of patient selection is one area in the clinical development of cetuximab that still requires further study. The initial clinical trials of cetuximab enrolled patients with EGFR-positive mCRC based on immunohistochemical analysis, but results have demonstrated that clinical responses and survival were independent of EGFR expression. Not only there are tumors who respond even without detectable presence of the EGFR, there is a substantial portion of patients who do not respond, even when their tumors express the EGFR at high levels. This underscores the need to identify factors that can predict response or resistance to cetuximab therapy. Recent studies have identified potential predictive factors, although neither has been used to prospectively select patients for a clinical trial. Accordingly, it is too early to determine the value of these factors in clinical practice.

Lievre and coworkers (Lievre et al 2006) recently reported that tumors with mutations in the *K-Ras* gene are associated with resistance to cetuximab therapy. In their study, 11 of 30 patients (37%) responded to cetuximab therapy, which was mostly given in combination with irinotecan alone (75%) and in a multi-refractory setting (80%). None of the patients who responded to cetuximab, but 13 of the 19 nonresponders, had tumors with a mutated *K-Ras* gene ($p = 0.0003$). Similar results have been reported by Di Fiore et al (Di Fiore et al 2007) and De Roock et al (De Roock et al 2007). These studies found *K-Ras* mutations to be predictive of resistance to cetuximab in 59 and 37 patients respectively. All responders to cetuximab harbored wild-type *K-Ras* in their tumors while no responses were observed in patients with tumors bearing mutant versions of the *K-Ras* gene; in addition, Di Fiore et al (Di Fiore et al 2007) were able to document a significant association between *K-ras* mutations and shorter time to progression (3 months vs 5.5 months for wild-type *K-ras*, $p = 0.015$).

Vallböhmer and colleagues (Vallbohmer et al 2005b) evaluated whether mRNA expression of EGFR and 4 other genes involved in EGFR signaling (cyclin D1, cyclooxygenase-2, VEGF, and IL-8) were associated with clinical outcome to single-agent cetuximab in a cohort of 39 patients with mCRC refractory to irinotecan and oxaliplatin. The expression of VEGF was the only factor predictive of response to cetuximab, with higher gene expression predicting progressive disease ($p = 0.038$). None of the factors individually predicted survival in the study cohort, although the combination of low expression of EGFR, cyclooxygenase-2, and IL-8 was associated with significantly longer survival relative to high

levels of expression of any of these genes (13.5 vs 2.3 months; $p = 0.028$). These associations were independent of skin toxicity, which also correlates with response to cetuximab and will be discussed in detail in a later section.

With these data in hand, it is tempting to speculate, for instance, that patients with *K-Ras* mutations should receive a non-cetuximab regimen (ie, with bevacizumab), and those without such mutations should be treated with a cetuximab-based regimen. At the moment, there are no methods to make these decisions reliably.

More comprehensive pharmacogenomic approaches have also been undertaken. A recent report indicated that, in addition to K-RAS mutation being an indicator of resistance, high levels of the EGFR ligands epiregulin and amphiregulin correlated with response (Khambata-Ford 2007). Tools that will allow incorporating these results into the clinic are eagerly awaited, as they may greatly enhance treatment decisions and ultimately patient outcomes.

Tolerability

Dermatologic toxicity

Acne-form rash is associated with all EGFR inhibitors and is the most frequent toxicity associated with cetuximab. The frequency of acne-form rash reported in the large phase III trials of cetuximab in mCRC was 78% to 88%, with most of these events of grade 1 or 2 intensity according to National Cancer Institute Common Toxicity Criteria (Jonker et al 2007; Sobrero et al 2007). Approximately 10% of the cases were severe. The rash is characterized by an erythematous pustular/papular appearance, and has a distribution similar to that of acne vulgaris, in that it typically involves the upper body (face, neck, scalp, chest, and upper back) but rarely the extremities (Lenz 2006; Hu et al 2007). Pruritus, nail disorders, and abnormal hair growth may also be present. The rash typically appears within the first 2–3 weeks of cetuximab therapy, later peaks in intensity, and subsequently fades or resolves during continued treatment (Lenz 2006).

In general, mild rash is easily managed with conventional skin-care measures (such as emollients, mild soaps), and in more moderate cases, by adding topical and/or oral antibiotics, and if pruritus is present, an antihistamine as well (ERBITUX PI 2006; Hu et al 2007). Severe rash may require a reduction in cetuximab dose. Patients who develop dermatological toxicities should be monitored for the development of infectious or inflammatory sequelae, and appropriate treatment provided should they occur (ERBITUX PI 2006). To date, there have been no reports of severe septic complications with cetuximab-related rash.

This particular toxicity seems to be intimately linked to the biologic activity of cetuximab. The EGFR is expressed on epidermal keratinocytes and hair follicles, and is thought to play a role in maintaining skin integrity and follicular homeostasis (Lenz 2006; Hu et al 2007). Accordingly, blocking these effects may be responsible for the acne-form eruptions and its follicular localization. Importantly, the intensity of the acne-form rash has been associated with the clinical efficacy of cetuximab, suggesting that it may be a surrogate marker for its antitumor activity (Perez-Soler and Saltz 2005).

To investigate this possibility, the EVEREST study randomly assigned irinotecan-refractory mCRC patients who had no or mild skin reactions after the first 3 weeks of cetuximab and irinotecan therapy to either continue on the standard cetuximab regimen (ie, 250 mg/m² weekly) or to receive escalating cetuximab doses in combination with irinotecan. In this latter arm, the dose of cetuximab was increased in 50 mg/m² increments every 2 weeks until grade 3 toxicity developed, a tumor response was achieved, or a maximum dose of 500 mg/m² was reached. A total of 166 patients were enrolled; 89 patients were randomized to the study protocol, and the remaining 77 patients who were ineligible for randomization (mostly due to the presence of grade 2 or greater skin toxicity after the first 3 weeks) were followed on the standard regimen (Van Cutsem et al 2007).

In the dose escalation arm, 24 of 44 patients (55%) reached the maximal cetuximab dose of 500 mg/m². Grade 3 skin reactions were more common in the dose escalation group than in those allocated to the standard regimen (9% vs 0%), and similar to the frequency in the group ineligible for randomization (12%). As hypothesized, the response rate was higher in the dose escalation group than in those allocated to standard cetuximab (30% vs 13%), and comparable to the response rate in those ineligible for randomization with grade 2 or greater skin toxicity (34%). Other grade 3/4 toxicities (eg, diarrhea, fatigue, abdominal pain, and hypomagnesemia) were slightly higher in the dose escalation group, possibly reflecting the longer treatment duration rather than the higher cetuximab dose (Van Cutsem et al 2007). EVEREST shows that dose escalation to 500 mg/m² is feasible in patients who do not initially develop intense rash, producing a higher incidence of grade 3 skin reactions, which correlates with an increase in response rates. EVEREST, therefore, provides further evidence of the relationship between skin toxicity and clinical efficacy.

Infusion reactions

Infusion reactions may occur during therapy with monoclonal antibodies and cytotoxics (Lenz 2006). In clinical trials, severe infusion reactions have occurred in 3% of patients treated with

cetuximab, with approximately 90% of these episodes occurring during administration of the first cetuximab dose, (ERBITUX PI 2006) although in the more recent reports, the incidence of severe infusion reactions has dropped to 1.5% (Sobrero 2007). Severe infusion reactions are characterized by a rapid onset of an anaphylactic-like presentation (airway obstruction, urticaria, hypotension, and/or cardiac arrest) and require immediate interruption of the cetuximab infusion and discontinuation from further treatment. Because some patients may experience severe infusion reactions later in the course of treatment, patients should be monitored for at least 1 hour after all cetuximab infusions, and for even longer periods in those with milder reactions (ERBITUX PI 2006). Appropriate medical interventions, including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen, should be kept readily available, and their use considered depending of the severity of the reaction.

The management of infusion reactions is consistent with that for other infusional agents. Premedication with intravenous diphenhydramine 50 mg or an equivalent antihistamine is recommended before cetuximab infusion (ERBITUX PI 2006). Because antihistamines may cause drowsiness, fatigue, bradyarrhythmias, and other side effects, most early clinical trials of cetuximab gave study investigators discretion in use of premedication after the first dose. Chung and colleagues (Chung et al 2007) conducted a retrospective analysis of all patients treated with cetuximab at Memorial Sloan-Kettering Cancer Center (MSKCC) outside of a clinical trial during the first 28 months that the drug was commercially available (February 2004 to June 2006). A total of 453 patients were identified, all of whom received 50 mg of diphenhydramine before the first cetuximab dose and 25 mg before the second dose, consistent with institutional guidelines. Severe infusion reactions occurred in 7 patients (1.5%) – all during the first infusion – and grade 1 or 2 reactions occurred in 17 patients (4%), which were characterized by mild dyspnea, rigors, fever, and/or flushing. Each of these reactions occurred after diphenhydramine premedication. The remaining 429 patients did not experience any infusion reactions during the first 2 cetuximab doses with diphenhydramine premedication nor during a total of 4138 cetuximab infusions administered without diphenhydramine premedication. This study suggests that diphenhydramine premedication can be eliminated after the first 2 cetuximab doses, without negatively affecting patients' safety.

Hypomagnesemia

Hypomagnesemia is a relatively common side effect, which may occur in up to 50% of patients treated with cetuximab (ERBITUX PI 2006). Because serum magnesium is often

not measured, this side effect may be frequently missed, and only become apparent after it becomes severe. Clinical manifestations of hypomagnesemia may occur gradually or suddenly, and include cardiac arrhythmias, seizures, and other electrolyte abnormalities (eg, hypokalemia) (Whang et al 1994; Iannello and Belfiore 2001). Certain patients, such as those with a pre-existing history of cardiac arrhythmias, warrant close monitoring for this toxicity.

The frequency of hypomagnesemia during treatment of mCRC with cetuximab has been evaluated retrospectively at 2 cancer centers. Schrag and colleagues (Schrag et al 2005) reviewed serum chemistry reports from 154 consecutive colorectal cancer patients treated with cetuximab at MSKCC. Only 34 patients had at least 1 serum magnesium measurement during cetuximab treatment, and of these, 6 patients (18%) had grade 3, and 2 patients (6%) had grade 4 hypomagnesemia, characterized by serum magnesium levels <0.9 mg/dL and <0.7 mg/dL, respectively. Similarly, Fakih and co-workers (Fakih et al 2006) reviewed the charts of 114 patients treated with cetuximab at the Roswell Park Cancer Institute. Overall, 48 patients had normal magnesium levels before cetuximab treatment, and a repeat measurement of magnesium during treatment. Of these, 13 patients (27%) developed grade 3 or 4 hypomagnesemia during cetuximab therapy, with the incidence rising from 6% among those treated for <3 months to 47% in those treated >6 months. Accordingly, serum magnesium should be monitored during cetuximab therapy, and electrolyte replacement provided as needed (ERBITUX PI 2006). It is important to note that this effect may persist for 4 weeks or longer after therapy discontinuation.

Development of hypomagnesemia may be related to inhibition of EGFR in the kidneys, although it may also be a consequence of diarrhea (Lenz 2006). Most of the filtered load of magnesium is reabsorbed in the thick ascending loop of Henle, with a smaller percentage reabsorbed in the proximal and distal tubules. Because EGFR is highly expressed in the apical membrane of the loop of Henle, it raises the possibility that blocking EGFR could interfere with magnesium transport in this region of the nephron (Schrag et al 2005). Nevertheless, regulation of serum magnesium also depends on gastrointestinal absorption, and an effect of EGFR inhibition on this process cannot be excluded at the present time.

Practical and patient-related issues

Quality of life

Another important aspect in the practical application of cetuximab therapy in mCRC, where the therapeutic goals

are palliative, is the assessment of its effect on quality of life. That effect may provide a complementary insight on cetuximab's therapeutic profile. The European Organization for Research and Treatment of Cancer (EORTC) QLQ-30 quality of life questionnaire was incorporated into the phase III studies, including NCIC 017 and EPIC (Jonker et al 2007; Sobrero et al 2007). In NCIC 017, cetuximab significantly slowed the deterioration in physical function ($p \leq 0.046$) and global health status ($p \leq 0.008$) relative to BSC when measured after 8 and 16 weeks of treatment. Similarly, in EPIC, cetuximab plus irinotecan was more effective than irinotecan alone in maintaining quality of life, with significant differences between treatments in multiple symptom scales, including fatigue ($p = 0.005$), pain ($p < 0.001$), and nausea and vomiting ($p < 0.001$), as well as in global health status ($p = 0.047$) and in 4 of the 5 functional scales, including physical ($p = 0.002$), role ($p = 0.003$), emotional ($p = 0.002$), and cognitive functioning ($p < 0.001$). Therefore, the improvement in overall activity seen with cetuximab in these studies was accompanied by better maintenance of quality of life.

Adverse event management

The visibility of skin toxicity may impact the patient's acceptance of cetuximab therapy. Some patients may refuse to continue cetuximab therapy for esthetic reasons once severe skin rash appears, particularly when influenced by social or environmental circumstances. This underscores the importance of managing the patient's expectations, and conveying the fact that skin toxicity may subside during continued treatment with cetuximab and eventually resolves without permanent scarring, also, it may be seen in a positive light due to its association with clinical efficacy.

Although cetuximab is generally well tolerated, potential life-threatening events such as infusion reactions may occur. Accordingly, physicians and their staffs should be prepared to handle these emergencies by monitoring patients during and for at least 1 hour after each cetuximab infusion, and by having appropriate interventions readily available should they be needed. In addition, attention should be paid to monitoring patients for electrolyte abnormalities that could evolve into potentially serious adverse events (ERBITUX PI 2006).

Nonetheless, the toxicity profile of cetuximab does not overlap with that of cytotoxic agents, making it an appealing agent for use in combination regimens. As our understanding of cetuximab's profile (and that of other biologics) grows, these toxicity considerations will perhaps play a role in

tailoring long-term individual treatment plans. Because cetuximab enhances the efficacy of chemotherapy, it may be possible to justify a break in chemotherapy for those who respond to treatment while continuing maintenance therapy with cetuximab or another biologic, an approach currently under investigation. This may provide patients with a "toxicity" break while off chemotherapy.

Conclusions

Cetuximab has been used effectively in patients with refractory mCRC, and its role in management of colorectal cancer is growing. Recent clinical studies show that cetuximab has promising activity in second-line, and the adoption of cetuximab plus irinotecan as one of the standard options in that setting has been acknowledged by community guidelines such as the NCCN (Engstrom 2007). Encouraging activity has also been observed in first-line treatment in combination with FOLFIRI and FOLFOX, and when combined with regimens containing bevacizumab in patients with refractory disease. Accordingly, cetuximab – together with 5-FU, irinotecan, oxaliplatin, and bevacizumab – has emerged as one of the basic agents needed in overall mCRC management. Additional clinical research is needed to determine the optimal combination and sequence of these agents for maximizing patient outcome, and the combination with bevacizumab in untreated patients deserves particular attention in light of the negative results obtained with the addition of the IgG2 panitumumab to bevacizumab plus FOLFOX. On the basis of available evidence, the best interactions appear when cetuximab is combined with oxaliplatin in first-line treatment and with irinotecan in refractory disease. The reason for this is unclear, but suggests that interactions between cetuximab and oxaliplatin involve different pathways than those between cetuximab and irinotecan. Ongoing studies, notably CALGB/SWOG 8405, are expected to provide important information regarding the best combinations of biologics with chemotherapy.

It is also particularly encouraging that cetuximab may enhance the curative opportunities in patients with early metastatic disease. Preliminary evidence suggests that adding cetuximab to first-line therapy may downstage disease in some patients, and as a result, allow potentially curative resection of previously unresectable metastases in approximately 20% of mCRC patients (Folprecht et al 2006; Andre et al 2007). Ongoing studies are also exploring whether the benefits of cetuximab extend earlier in the course of colorectal cancer into the adjuvant and neoadjuvant settings. As additional clinical results become available, the role of

cetuximab in management of mCRC as well as in earlier stages of disease should be more clearly understood.

Clearly, the selection of patients based on EGFR expression is no longer sufficient, inasmuch as response rates appear independent of EGFR staining intensity (Cunningham et al 2004; Lenz et al 2006). Moreover, patients whose tumors do not express EGFR have similar response rates as those with EGFR-expressing tumors (Chung et al 2005; Lenz et al 2006). This underscores the need to identify markers that predict response or resistance to cetuximab therapy. The observation that *K-Ras* gene mutation is associated with resistance to cetuximab is a promising first step (Lievre et al 2006).

References

- Amgen Inc. 2007. Amgen discontinues Vectibix(TM) treatment in PACCE trial evaluating Vectibix(TM) as part of triple combination regimen: preliminary pre-planned interim analysis shows negative effect on progression-free survival [online; March 22, 2007 press release]. Accessed June 12, 2007. URL: <http://www.amgen.com>.
- Andre T, Tabernero J, Van Cutsem E, et al. 2007. Phase II study with cetuximab plus FOLFOX-4 in first-line setting for epidermal growth factor (EGFR)-expressing metastatic colorectal cancer (mCRC): final results [abstract]. *J Clin Oncol*, 25(Suppl):334. Abstract 334.
- Bokemeyer C, Bondarenko I, Makhson A, et al. 2007. Cetuximab plus 5-FU/FA/oxaliplatin (FOLFOX-4) versus FOLFOX-4 in the first-line treatment of metastatic colorectal cancer (mCRC): OPUS, a randomized phase II study. [abstract]. *J Clin Oncol*, 25(Suppl):4035. Abstract 4035.
- Bokemeyer C. 2005. OPUS: oxaliplatin and cetuximab in first-line treatment of mCRC [protocol]. Accessed on March 27, 2007. URL: www.medizin.uni-tuebingen.de/extweb/labor/ZGO/Pdf/Kolon_4.pdf.
- Bonner JA, Harari PM, Giralt J, et al. 2006. Radiotherapy plus Erbitux for squamous-cell carcinoma of the head and neck. *New Engl J Med*, 354:567–78.
- Cartron G, Watier H, Golay J, et al. 2004. From the bench to the bedside: ways to improve rituximab efficacy. *Blood*, 104:2635–42.
- Chen HX, Mooney M, Boron M, et al. 2006. Phase II multicenter trial of bevacizumab plus fluorouracil and leucovorin in patients with advanced refractory colorectal cancer: an NCI Treatment Referral Center Trial TRC-0301. *J Clin Oncol*, 24:3354–60.
- Chung KY, Fusco A, Park V, et al. 2007. Evaluation of routine antihistamine premedication after the first 2 doses of cetuximab [abstract]. *Proc Am Soc Clin Oncol GI*, Abstract 357.
- Chung KY, Shia J, Kemeny NE, et al. 2005. Cetuximab shows activity in colorectal cancer patients with tumors that do not express the epidermal growth factor receptor by immunohistochemistry. *J Clin Oncol*, 23:1803–10.
- Ciardiello F, Bianco R, Damiano V, et al. 1999. Antitumor activity of sequential treatment with topotecan and anti-epidermal growth factor receptor monoclonal antibody C225. *Clin Cancer Res*, 5:909–16.
- Cunningham D, Humblet Y, Siena S. 2004. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med*, 351:337–45.
- Cunningham D, Pyrhönen S, James RD, et al. 1998. Randomised trial of irinotecan plus supportive care versus supportive care alone after fluorouracil failure for patients with metastatic colorectal cancer. *Lancet*, 352:1413–8.
- de Gramont A, Figuer A, Seymour M, et al. 2000. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol*, 18:2938–47.
- De Roock W, De Schutter J, De Hertogh G, et al. 2007. KRAS mutations preclude tumor shrinkage of colorectal cancers treated with cetuximab [abstract]. *J Clin Oncol*, 25(18S):4132. Abstract 4132.
- Di Fiore F, Blanchard F, Charbonnier F, et al. 2007. Clinical relevance of *KRAS* mutation detection in metastatic colorectal cancer treated by cetuximab plus chemotherapy. *Br J Cancer*, 96:1166–9.
- Dittmann K, Mayer C, Fehrenbacher B, et al. 2005. Radiation-induced epidermal growth factor receptor nuclear import is linked to activation of DNA-dependent protein kinase. *J Biol Chem*, 280:31182–9.
- Douillard JY, Cunningham D, Roth AD, et al. 2000. Irinotecan combined with fluorouracil compared with fluorouracil alone as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet*, 355:1041–7.
- Engstrom PF, Arnoletti JP, Benson AB, et al. Colon cancer. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology. V.1.2007.
- ERBITUX® (Cetuximab) Package Insert. 2006. ImClone Systems Incorporated, New York, NY 10014 and Bristol-Myers Squibb Company, Princeton, NJ 08543; August 2006.
- Fakih MG, Wilding G, Lombardo J. 2006. Cetuximab-induced hypomagnesemia in patients with colorectal cancer. *Clin Colorectal Cancer*, 6:152–6.
- Folprecht G, Lutz MP, Schöffski P, et al. 2006. Cetuximab and irinotecan/5-fluorouracil/folinic acid is a safe combination for the first-line treatment of patients with epidermal growth factor receptor expressing metastatic colorectal cancer. *Ann Oncol*, 17:450–6.
- Giantonio BJ, Catalano PJ, Meropol NJ, et al. 2007. Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol*, 25:1539–44.
- Goldsby RA, Kindt TJ, Osborne BA, et al. *Immunology*. 5th Edition. New York, NY: WH Freedman and Company; 2003.
- Grothey A, Sargent D. 2005. Overall survival of patients with advanced colorectal cancer correlates with availability of fluorouracil, irinotecan, and oxaliplatin regardless of whether doublet or single-agent therapy is used first line [letter]. *J Clin Oncol*, 23:9441–2.
- Grothey A, Sargent D, Goldberg RM, et al. 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*, 22:1209–14.
- Grothey A, Sugrue M, Hedrick E, et al. 2007. Association between exposure to bevacizumab (BV) beyond first progression (BBP) and overall survival (OS) in patients (pts) with metastatic colorectal cancer (mCRC): results from a large observational study (BRiTE) [abstract]. *J Clin Oncol*, 25(Suppl):4036. Abstract 4036.
- Harding J, Burtneß B. 2005. Cetuximab: an epidermal growth factor receptor chimeric human-murine monoclonal antibody. *Drugs Today*, 41:107–27.
- Hofheinz R-D, Horisberger K, Woernle C, et al. 2006. Phase I trial of cetuximab in combination with capecitabine, weekly irinotecan, and radiotherapy as neoadjuvant therapy for rectal cancer. *Int J Radiat Oncol Biol Phys*, 66:1384–90.
- Hu JC, Sadeghi P, Pinter-Brown LC, et al. 2007. Cutaneous side effects of epidermal growth factor receptor inhibitors: clinical presentation, pathogenesis, and management. *J Am Acad Dermatol*, 56:317–26.
- Huang SM, Bock JM, Harari PM. 1999. Epidermal growth factor receptor blockade with C225 modulates proliferation, apoptosis, and radiosensitivity in squamous cell carcinomas of the head and neck. *Cancer Res*, 59:1935–40.
- Hurwitz H, Fehrenbacher L, Novotny W, et al. 2004. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med*, 350:2335–42.
- Iannello A, Ahmad A. 2005. Role of antibody-dependent cell-mediated cytotoxicity in the efficacy of therapeutic anticancer monoclonal antibodies. *Cancer Met Rev*, 24:487–99.
- Iannello S, Belfiore F. 2001. Hypomagnesemia: a review of pathophysiological, clinical, and therapeutic aspects. *Painminerva Med*, 43:177–209.

- Jonker DJ, Karapetis CS, Moore M, et al. 2007. Randomized phase III trial of cetuximab monotherapy plus best supportive care [BSC] versus BSC Alone in patients with pretreated metastatic epidermal growth factor receptor [EGFR]-positive colorectal carcinoma: a trial of the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) and the Australasian Gastro-Intestinal Trials Group (AGITG) [abstract]. *Proc Am Assoc Cancer Res*, Abstract LB-1.
- Kawaguchi Y, Kono K, Mimura K, et al. 2007. Cetuximab induce antibody-dependent cellular cytotoxicity against EGFR-expressing esophageal squamous cell carcinoma. *Int J Cancer*, 120:781–7.
- Kelly K, Herbst RS, Crowley JJ, et al. 2006. Concurrent chemotherapy plus cetuximab or chemotherapy followed by cetuximab in advanced non-small cell lung cancer (NSCLC): a randomized phase II selection trial SWOG 0342 [abstract]. *J Clin Oncol*, 24(Suppl):7015. Abstract 7015.
- Khambata-Ford S, Garrett CR, Clark EA, et al. 2007. Expression of epiregulin and amphiregulin and K-RAS mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab (Erbix[®]) [abstract]. *Proc Am Assoc Cancer Res*, Abstract 5670.
- Kiyota A, Shintani S, Mihara M, et al. 2002. Anti-epidermal growth factor receptor monoclonal antibody 225 upregulates p27^{KIP1} and p15^{INK4B} and induces G1 arrest in oral squamous carcinoma cell lines. *Oncology*, 63:92–8.
- Kurai J, Chikumi H, Hashimoto K, et al. 2007. Antibody-dependent cellular cytotoxicity mediated by cetuximab against lung cancer cell lines. *Clin Cancer Res*, 13:1552–61.
- Lang I, Zaluski J, Changchien CR, et al. 2006. Cetuximab with irinotecan in first-line treatment of epidermal growth factor receptor (EGFR)-expressing metastatic colorectal cancer (mCRC): preliminary safety results (CRYSTAL) [abstract]. *J Clin Oncol*, 24(Suppl):3555. Abstract 3555.
- Lenz H-J. 2006. Anti-EGFR mechanism of action: antitumor effect and underlying cause and adverse events. *Oncology*, 20(5 Suppl):5–13.
- Lenz H-J, Van Cutsem E, Khambata-Ford S, et al. 2006. Multicenter phase II and translational study of cetuximab in metastatic colorectal carcinoma refractory to irinotecan, oxaliplatin, and fluoropyrimidines. *J Clin Oncol*, 24:4914–21.
- Lenz H, Zhang W, Yang D, et al. 2007. Pharmacogenomic analysis of a randomized phase II trial (BOND 2) of cetuximab/bevacizumab/irinotecan (CBI) versus cetuximab/bevacizumab (CB) in irinotecan-refractory colorectal cancer [abstract]. *Proc Am Soc Clin Oncol GI*, Abstract 401.
- Lievre A, Bachet J-B, Le Corre D, et al. 2006. KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. *Cancer Res*, 66:3992–5.
- Machiels J-P, Sempoux C, Scalliet P, et al. 2007. Phase I/II study of preoperative cetuximab, capecitabine, and external beam radiotherapy in patients with rectal cancer. *Ann Oncol*, 18:738–44.
- Nicholson RI, Gee JM, Harper ME. 2001. EGFR and cancer prognosis. *Eur J Cancer*, 37(Suppl 4):S9–15.
- Overholser JP, Prewett MC, Hooper AT, et al. 2000. Epidermal growth factor receptor blockade by antibody IMC-C225 inhibits growth of a human pancreatic carcinoma xenograft in nude mice. *Cancer*, 89:74–82.
- Perez-Soler R, Saltz L. 2005. Cutaneous adverse effects with HER1/EGFR-targeted agents: is there a silver lining?. *J Clin Oncol*, 23:5235–46.
- Pfeiffer P, Bjerregaard JK, Qvortrup C. 2007. Bi-weekly cetuximab (Cet) and irinotecan (Iri) as third-line therapy in patients with advanced colorectal cancer (ACRC) [abstract]. *Proc Am Soc Clin Oncol GI*, Abstract 305.
- Prewett MC, Hooper AT, Bassi R, et al. 2002. Enhanced antitumor activity of anti-epidermal growth factor receptor monoclonal antibody IMC-C225 in combination with irinotecan (CPT-11) against human colorectal tumor xenografts. *Clin Cancer Res*, 8:994–1003.
- Punt C. JA for the Dutch Colorectal Cancer Group. 2005. Cetuximab, capecitabine, oxaliplatin and bevacizumab in advanced colorectal cancer [protocol identifier: NCT00208546; study ID Number: CAIRO2]. Accessed March 28, 2007. URL: <http://www.clinicaltrials.gov>.
- Rosell R, Daniel C, Ramlau R, et al. 2004. Randomized phase II study of cetuximab in combination with cisplatin (C) and vinorelbine (V) vs. CV alone in the first-line treatment of patients (pts) with epidermal growth factor receptor (EGFR)-expressing advanced non-small-cell lung cancer (NSCLC) [abstract]. *J Clin Oncol*, 22(Suppl):7012. Abstract 7012.
- Rougier P, Van Cutsem E, Bajetta E, et al. 1998. Randomised trial of irinotecan versus fluorouracil by continuous infusion after fluorouracil failure in patients with metastatic colorectal cancer. *Lancet*, 352:1407–12.
- Saltz LB, Cox JV, Blanke C, et al. 2000. Irinotecan plus fluorouracil and leucovorin for metastatic colorectal cancer. *N Engl J Med*, 343:905–14.
- Saltz LB, Lenz H, Kindler H, et al. 2005. Interim report of randomized phase II trial of cetuximab/bevacizumab/irinotecan (CBI) versus cetuximab/bevacizumab (CB) in irinotecan-refractory colorectal cancer [abstract]. *Proc Am Soc Clin Oncol GI*, Abstract 169b.
- Saltz LB, Meropol NJ, Loehrer PJ Sr, et al. 2004. Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. *J Clin Oncol*, 22:1201–8.
- Saltz L, Rubin M, Hochester H, et al. 2001. Cetuximab (IMC-C225) plus irinotecan (CPT-11) is active in CPT-11-refractory colorectal cancer (CRC) that expresses epidermal growth factor receptor (EGFR) [abstract]. *Proc Am Soc Clin Oncol*, 20:Abstract 7.
- Schrag D, Chung KY, Flombaum C, et al. 2005. Cetuximab therapy and symptomatic hypomagnesemia. *J Natl Cancer Inst*, 97:1221–4.
- Sobrero AF, Fehrenbacher L, Rivera F, et al. 2007. Randomized phase III trial of cetuximab plus irinotecan versus irinotecan alone for metastatic colorectal cancer in 1298 patients who have failed prior oxaliplatin-based therapy: the EPIC trial. 2007 [abstract]. *Proc Am Assoc Cancer Res*, Abstract LB-2.
- Souglakos J, Kalykaki A, Vamvakas L, et al. 2007. Phase II trial of capecitabine and oxaliplatin (CAPOX) plus cetuximab in patients with metastatic colorectal cancer who progressed after oxaliplatin-based chemotherapy. *Ann Oncol*, 18:305–10.
- Spano J-P, Lagorce C, Atlan D, et al. 2005. Impact of EGFR expression on colorectal cancer patients prognosis and survival. *Ann Oncol*, 16:102–8.
- Tabernero J, Cervantes A, Martinelli E, et al. 2006. Optimal dose of cetuximab (C) given every 2 weeks (q2w): a phase I pharmacokinetic (PK) and pharmacodynamic (PD) study of weekly (q1w) and q2w schedules in patients (pts) with metastatic colorectal cancer (mCRC) [abstract]. *J Clin Oncol*, 24(18S):3085. Abstract 3085.
- Tournigand C, André T, Achille E, et al. 2004. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol*, 22:229–37.
- Vallböhmer D, Lenz H-J. 2005a. Epidermal growth factor receptor as a target for chemotherapy. *Clin Colorectal Cancer*, 5(Suppl 1):S19–27.
- Vallböhmer D, Zhang W, Gordon M, et al. 2005b. Molecular determinants of cetuximab efficacy. *J Clin Oncol*, 23:3536–44.
- Van Cutsem E, Nowacki M, Lang I, et al. 2007. Randomized phase III study of irinotecan and 5-FU/FA with or without cetuximab in the first-line treatment of patients with metastatic colorectal cancer (mCRC): the CRYSTAL trial [abstract]. *J Clin Oncol*, 25(18S):4000. Abstract 4000.
- Van Cutsem E, Humblet Y, Gelderblom J, et al. 2007. Cetuximab dose-escalation study in patients with metastatic colorectal cancer (mCRC) with no or slight skin reactions on cetuximab standard dose treatment (EVEREST): pharmacokinetic and efficacy data of a randomized study [abstract]. *Proc Am Soc Clin Oncol GI*, Abstract 237.
- van Sorge NM, van der Pol WL, van de Winkel JGJ. 2003. FcγR polymorphisms: implications for function, disease susceptibility and immunotherapy. *Tissue Antigens*, 61:189–202.
- Venook AP, Blanke CD, Goldberg RM, et al. 2006a. Assessing the combination of FOLFOX or FOLFIRI with bevacizumab, cetuximab, or both in metastatic colorectal cancer. *Commun Oncol*, 3:593–8.
- Venook A, Niedzwiecki D, Hollis D, et al. 2006b. Phase III study of irinotecan/5FU/LV (FOLFIRI) or oxaliplatin (FOLFOX) ± cetuximab for patients (pts) with untreated metastatic adenocarcinoma of the colon or rectum (mCRC): CALGB 80203 preliminary results [abstract]. *J Clin Oncol*, 2006:3509.

- Wainberg Z, Hecht JR. 2006. Panitumumab in colon cancer: a review and summary of ongoing trials. *Expert Opin Biol Ther*, 6:1229–35.
- Wells A. 1999. EGF receptor. *Int J Biochem Cell Biol*, 31:637–43.
- Weng W-K, Levy R. 2003. Two immunoglobulin G fragment C receptor polymorphisms independently predict response to rituximab in patients with follicular lymphoma. *J Clin Oncol*, 21:3940–7.
- Whang R, Hampton EM, Whang DD. 1994. Magnesium homeostasis and clinical disorders of magnesium deficiency. *Ann Pharmacother*, 28:220–6.
- Yarden Y, Sliwkowski MX. 2001. Untangling the ErbB signaling network. *Nature Rev Mol Cell Biol*, 2:127–137.
- Zhang W, Gordon M, Schultheis A, et al. 2007. FCGR2A and FCGR3A polymorphisms associated with clinical outcome of epidermal growth factor receptor expressing metastatic colorectal cancer patients treated with single-agent cetuximab. *J Clin Oncol*, 25:3712–18.

