ELSEVIER

Critical Reviews in Oncology/Hematology 74 (2010) 193–202

CRITICAL REVIEWS IN
Oncology
Hematology
Incorporating Geriatric Oncology

www.elsevier.com/locate/critrevonc

Improving disease control in advanced colorectal cancer: Panitumumab and cetuximab

Javier Rodríguez [1], Antonio Viúdez [1], Mariano Ponz-Sarvisé, Isabel Gil-Aldea, Ana Chopitea, Jesús García-Foncillas, Ignacio Gil-Bazo *

Department of Oncology, Clínica Universidad de Navarra, Pamplona, Spain

Accepted 23 July 2009

Contents

Abstract

Colorectal cancer remains a major public health concern in Europe and North America. It is responsible for one million new cases and half a million deaths per year worldwide. During the past few years new effective treatments have evolved improving the outcome of patients with this disease. Several alternatives are currently available for advanced colorectal cancer patients including different chemotherapeutic regimens (fluoropyrimidines, irinotecan and oxaliplatin) and targeted therapies such as bevacizumab and cetuximab. Different combinations achieve a median survival of over 2 years. Intense efforts focus on identifying agents targeting growth factor receptors, signal transduction pathways or angiogenesis mediators. One of the last available drugs for the management of advanced colorectal cancer is panitumumab, a well-tolerated and effective anti-EGFR monoclonal antibody approved as a single agent in chemotherapy refractory patients. We discuss the

* Corresponding author at: Department of Oncology, Clínica Universidad de Navarra, Pío XII, 36, 31008 Pamplona, Spain. Tel.: +34 948 255400; fax: +34 948 255500.
E-mail address: igbazo@unav.es (I. Gil-Bazo).
[1] Both authors contributed equally.

doi:10.1016/j.critrevonc.2009.07.005

current evidence supporting panitumumab for metastatic colorectal cancer treatment, potential predictive biomarkers and ongoing clinical trials with different combinations including panitumumab.

Keywords: Advanced colorectal cancer; Panitumumab; EGFR; Targeted therapy; Biomarkers

1. Introduction to colorectal cancer

Advanced colorectal carcinoma (aCRC) remains a major public health concern in the current century worldwide. In fact, it represented the second most common cancer type among men and women in Europe in 2006 (412,900 new cases) [1]. Furthermore, aCRC constituted the second leading cause of death among cancer patients in that continent the same year (207,400 deaths) [1].

Surgical approaches provide low recurrence rates and high survival expectancy in localised-stage colorectal tumour patients [2]. In addition, adjuvant chemotherapy regimens have been shown to effectively improve outcomes in both stage III and high-risk stage II disease [3].

Unfortunately, metastatic colorectal cancer is still far away from being considered a curable disease. The ultimate aims in treating stage IV colorectal cancer are to decrease tumour-related symptoms and to prolong overall survival (OS) without affecting health-related quality of life parameters. In the frontline setting, the introduction of active new chemotherapeutic and biologically targeted agents (bevacizumab [4] or cetuximab [5]) has dramatically improved overall response rate (ORR), progression-free survival (PFS) and OS of subjects with this condition [6–8]. Despite these advances, response rate (RR) to standard second line therapy remain low, and median survival times are in the range of 6–12 months [9].

This fact has encouraged the active search for other targeted therapies directed to a variety of fundamental checkpoints in colorectal carcinogenesis. The epidermal growth factor receptor (EGFR) signalling pathway comprises a major target against which several new drugs are currently being developed. The last EGFR inhibitor to be approved by the U.S. FDA [10] for aCRC patients regardless *Kras* status and refractory to 5FU, irinotecan and oxaliplatin-containing chemotherapy regimens was panitumumab in 2006. In contrast, for EU and Canada, the European Committee for Medicinal Products for Human Use (CHMP), restricted its approval to *Kras* wild-type chemotherapy refractory patients.

This paper summarises and discusses the new pieces of evidence supporting the use of panitumumab in the systemic management of aCRC as well as the potential biomarkers for prediction of response and the currently ongoing clinical trials with this new drug.

2. The epidermal growth factor receptor family as a target for cancer therapy

The EGFR signalling pathway constitutes an attractive and effective target for developing cancer therapies since the molecular structure of the receptor and its tyrosine kinases are well determined [11]. The EGFR activation is the starting point for a variety of key processes involved in cancer cell growth and migration, including proliferation, angiogenesis and invasion. After the ligand has bound the receptor, EGFR suffers a conformational change leading to the receptor dimerisation and the subsequent autophosphorylation of several tyrosine residues. These tyrosine residues serve as binding sites for several signal transducers and adaptor molecules. This process fosters an intracellular mitogenic signalling cascade via multiple pathways, mainly RAS/RAF/MAPK, P3IK/AKT and phopholipase-C pathways [12,13] (Fig. 1).

In fact, one of the first targeted therapies shown to be effective against cancer was trastuzumab, a humanised anti-erbB2 monoclonal antibody [14] approved for its use in combination with chemotherapy against erbB2-expressing metastatic breast tumours. The addition of trastuzumab to first-line chemotherapy regimens was associated with improved patient's survival (a 20% reduction in the risk of death [15]) when compared to chemotherapy as a stand-alone therapy.

Other successfully developed EGFR signalling pathway inhibitors that have reached the clinic include cetuximab, commonly used in head and neck [16] and colorectal cancers [5,17–21], lapatinib [22], approved for metastatic breast cancer, gefitinib [23] and erlotinib, an active TKI in non-small cell lung cancer [24] and pancreatic cancer [25]. According to its biochemical structure, there are two basic types of EGFR inhibitors; monoclonal antibodies (Moabs) such as cetuximab or panitumumab binding to the extracellular domain of the receptor and small, orally available, molecules that inhibit the EGFR receptor tyrosine kinases (TKIs) such as erlotinib or gefitinib, as shown in Fig. 1.

3. Panitumumab in colorectal cancer treatment

Panitumumab is the first fully human IgG2 monoclonal antibody directed against the EGFR [26]. This agent binds to the extracellular domain of the EGFR (erbB1) and prevents receptor dimerisation. This union leads to the internalisation of the receptor–antibody complex and prevents ligand-induced EGFR-tyrosine autophosphorylation [27], and activation of downstream signalling proteins. The net effect is the inhibition of cellular proliferation and tumour growth and the induction of apoptosis (Fig. 1).

3.1. Preclinical development

Panitumumab was generated using XenoMouse strains, engineered to be deficient in mouse antibody production and

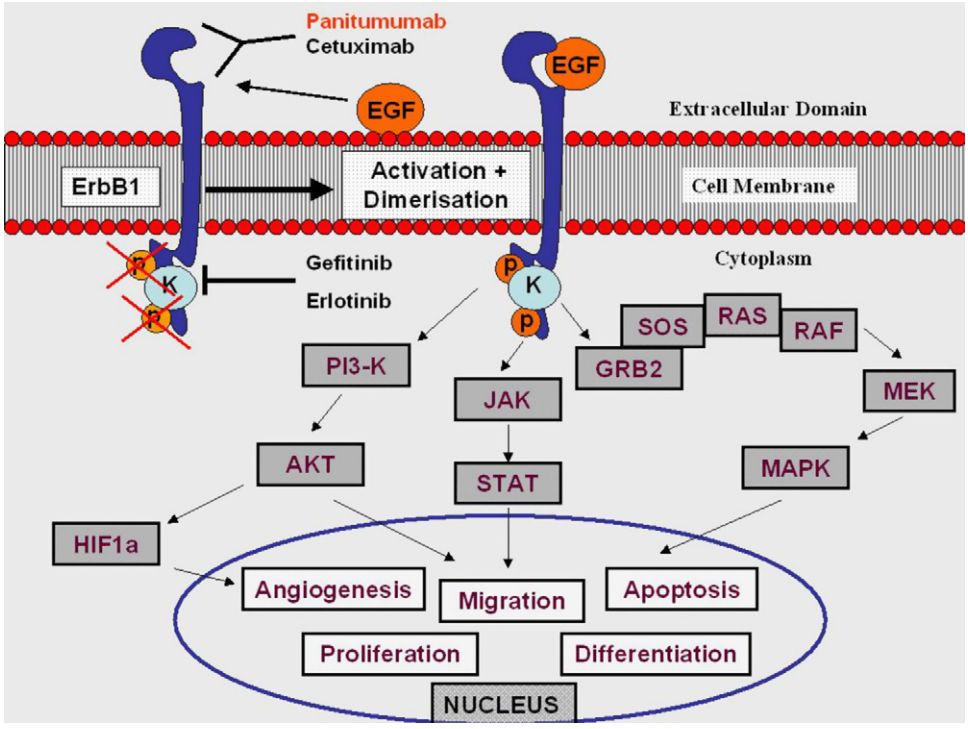

Fig. 1. EGFR (erbB1) and its signalling pathways. Monoclonal antibodies (Moabs); tyrosine kinase inhibitors (TKIs); epidermal growth factor (EGF).

to contain integrated fragments from the human heavy and Kappa light chain loci [28]. Panitumumab exhibited a high affinity to the EGFR, higher than that reported for other anti-EGFR Moabs [29], as well as the ability to neutralise both EGF and TGF-alfa binding to EGFR-expressing human carcinoma cell lines [30].

Besides EGFR signalling blockade, other mechanisms may account for panitumumab effect on different tumour cell lines, including antiangiogenic effects through inhibition of VEGF and IL-8 production and matrix metalloproteinases inhibition [31,32].

In vivo, panitumumab mediates therapeutic elimination of established tumours and shows synergies with chemotherapy in mediating tumour regression [33].

These observations provided the rationale for the design of a phase I multicentre, open-label, dose escalating clinical trial in 96 patients with a variety of EGFR-expressing human solid tumours. No infusion-related or serious adverse events were noted (a transient and dose dependent skin rash was the primary toxicity). No maximum tolerable dose (MTD) was reached. Pharmacokinetic (PK) exposure was similar between weekly 2.5 mg/Kg, 6 mg/Kg every 2 weeks and 9 mg/Kg on a 3-weekly basis, with low inter and intra-patient variability [34]. Since preliminary evidence of antitumoural activity was suggested in aCRC [35], specific phase II trials with this compound were initiated in this condition.

3.2. Clinical trials with single-agent panitumumab

The safety and efficacy of single-agent panitumumab has been recently summarised across five clinical studies involving 762 aCRC patients relapsed after oxaliplatin and/or irinotecan-based chemotherapy. This analysis that did not take into account patient's *Kras* status showed a disease control rate in the range of 29–44% and a median progression-free survival of 8–14 weeks [36]. In view of these consistent results, a single phase III, open-label, randomised, multinational study [37] was initiated (Table 1). 463 EGFR-

Table 1
Clinical trials with panitumumab in monotherapy or combination therapy. Number of patients (*n*); overall response rate (ORR); progression-free survival (PFS); overall survival (OS); best supportive care (BSC); weeks (w); months (m). Irinotecan, bolus 5-fluorouracil, and leucovorin (IFL). Irinotecan, infusional 5-fluorouracil and leucovorin (FOLFIRI).

Treatment	Patients (*n*)	ORR (%)	PFS	OS (m)	Pre-treated	Phase
Panitumumab vs. BSC [37]	231	10	8 w	–	Yes	III
	232	0	7 w	–		
Panitumumab after BSC [39]	176	11	9 w	6	Yes	III cross over
Panitumumab [52]	148	9	14 w	9	Yes	II
Panitumumab + IFL [41]	19	46	6 m	17	No	II
Panitumumab + FOLFIRI [41]	24	42	11 m	23	No	II
Panitumumab [53]	91	7	8 w	–	Yes	II

expressing (at least 1+ membrane staining in >1% of tumour cells) aCRC patients were randomly assigned to best supportive care (BSC) with or without panitumumab, 6 mg/kg i.v., every 2 weeks. The primary study endpoint was PFS. BSC patients who progressed were eligible to cross over to receive panitumumab on progression. All patients enrolled were refractory to standard chemotherapy regimens containing fluoropyrimidines and oxaliplatin or irinotecan. 100% and 37% of the patients had received 2 and 3 lines of previous treatment, respectively. The median PFS was 8 weeks in the panitumumab arm and 7.3 weeks in the BSC group, with 49% of the patients in the panitumumab group and 30% in the BSC group being alive and progression-free by week 8. Panitumumab reduced the risk of disease progression vs. BSC alone by almost half (hazard ratio = 0.54, 95%CI: 0.44–0.66, $p < 0.0001$). The mean PFS was longer in the panitumumab arm than in the BSC arm (13.8 vs. 8.5 weeks). In patients unselected for *Kras* status the ORR was 10% in the panitumumab group, with a median duration of response of 17.0 weeks, whereas no responses were observed in the BSC arm. Stable disease (SD) was observed in 27% and 10% in the panitumumab and BSC groups, respectively. No responders were identified in the panitumumab mutant *Kras* group, whereas wild-type *Kras* patients treated with panitumumab achieved a 17% ORR [38]. Among patients who crossed over to receive panitumumab after progression, ORR was 11% with an additional 33% of patients achieving SD [39]. All responders had wild-type *Kras*, for an overall response rate in this subgroup of patients of 22% [38]. Median progression-free survival was 9.4 weeks and median overall survival 6.3 months.

On this basis, the U.S. FDA approved panitumumab (Vectibix®), for the treatment of patients affected by EGFR-expressing metastatic colorectal cancer (with >1% EGFR tumour cell membrane staining) after disease progression on fluoropyrimidine, oxaliplatin and irinotecan containing chemotherapy regimens [10]. In addition, the European Committee for Medicinal Products for Human Use also issued a positive opinion, approving panitumumab for use in the European Union (EU) for patients with *Kras* wild-type, chemotherapy refractory aCRC [38].

3.3. Panitumumab-based combinations

The encouraging results seen with single-agent panitumumab in heavily pre-treated aCRC patients and the reported preclinical synergistic interactions [33] have prompted the design of several panitumumab-based combination trials.

Mature results of a two-part multicentre study with the combination of panitumumab and 5-fluorouracil (5-FU), leucovorin and irinotecan, either IFL or FOLFIRI [38], in aCRC patients are now available. For both chemotherapy regimens, ORR was more than 40% and disease control rate almost reached 80%. Despite previously reported lack of significant PK interactions between panitumumab, irinotecan and SN-38 when the combination of panitumumab and IFL was first analysed [40] these data suggest that panitumumab may have better tolerability when combined with FOLFIRI than with IFL. In fact, grades 3/4 diarrhoea occurred in 11 patients (58%) treated with IFL-panitumumab compared with only 6 patients (25%) in the FOLFIRI-panitumumab regimen [41].

Ongoing randomised phase III trials are evaluating the addition of panitumumab to either FOLFIRI [42] in pre-treated aCRC patients or to FOLFOX (PRIME study) [43] as frontline therapy. Preliminary data suggest no pharmacokinetic/pharmacodynamic interactions and an acceptable safety profile, as such both trials continue without modifications. Enrolment was anticipated to be completed by the end of 2008 and results are eagerly awaited. Other ongoing clinical trials with panitumumab are listed on-line at (http://clinicaltrials.gov/ct2/results?term=panitumumab+colorectal+cancer).

3.4. Safety profile

The most commonly reported adverse events in the available panitumumab studies are skin rash, hypomagnesemia, paronychia, fatigue, abdominal pain, nausea, and diarrhoea. The most serious adverse events, albeit rarely seen include pulmonary fibrosis, severe dermatological toxicity complicated by infectious sequelae and septic death, infusion reactions, abdominal pain, hypomagnesemia, nausea, vomiting, and constipation [44].

Skin related adverse events are seen in the vast majority of aCRC patients treated with EGFR inhibitors, although they result in discontinuation of therapy in only 2% of patients. The incidence of grade 3 skin toxicity is in the range of 15%. Most frequently reported dermatological manifestations include acneiform dermatitis, erythema, pruritus, rash, skin exfoliation, telangiectasia, trichomegaly and hirsuitism [45,46]. The most commonly occurring eye disorders are conjunctivitis (4%), ocular hyperemia (3%), and increased lacrimation (2%). Nail toxicities are identified in around 30% of the patients treated with panitumumab and include paronychia (24%), nail disorder (9%), onchorrhexis, nail bed infection, nail bed inflammation, nail discoloration, nail discomfort, and onycholysis (all 1%) [10,37].

Gastrointestinal toxicities are also commonly reported and include nausea, diarrhoea and anorexia. Most of them are mild, being grade 3 in only 2% of the treated patients [46].

Infusion reactions were noted in 4% of patients and in 1% reactions were graded as severe (National Cancer Institute Common toxicity Criteria [NCI-CTC] grades 3–4). Across all clinical studies, severe infusion reactions, including anaphylactic reaction, bronchospasm, fever, chills, and hypotension, occurred in less than 1% of patients. No infusion reaction was fatal [46].

Hypomagnesemia [47] appears in approximately 40% of patients treated with panitumumab. Hypomagnesemia often occurs after the 6–8 weeks and may be associated with hypocalcemia. NCI-CTC grade 3 or 4 hypomagnesemia requiring oral or i.v. electrolyte repletion occurred in 2% of panitumumab monotherapy-treated patients [48].

4. Predictive biomarkers of panitumumab's efficacy

4.1. Skin rash

A peculiar toxic effect of panitumumab, and other EGFR inhibitors, is a papulopustular skin rash, generally on face and upper torso, which is thought to be mechanism- and dose-related [49]. Several findings suggest that there is a correlation between intensity of skin rash and response and survival [5]. With respect to panitumumab, this correlation is particularly striking in a recently reported pooled analysis from 5 panitumumab clinical trials involving 612 aCRC patients. In this large combined analysis, severity of skin rash (grades 2–4 vs. grades 0–1) was significantly correlated with an increased RR (12.6% vs. 3.3%), longer median PFS (13.1 weeks vs. 8.0 weeks) and median OS (8.5 months vs. 4.5 months) [50].

The mechanism underlying the correlation between skin toxicity and tumour response is currently unclear, although some groups hypothesised that the rash is a surrogate indicator of an adequate degree of receptor saturation by anti-EGFR therapy. Pharmacokinetic data have shown that EGFR-mediated clearance of panitumumab was saturated at a dose of 2 mg/kg. A 100% skin rash incidence was achieved with increasing doses to 2.5 mg/kg, suggesting full receptor occupancy at this dose level [51].

Although skin rash may be a pharmacodynamic marker of drug action its predictive value and potential as a surrogate marker for response to EGFR-targeted agents depend on the correlation of HER-kinase signalling in paired skin and tumour tissue, an issue that requires further investigation.

4.2. HER family expression

To date, EGFR positivity by immunohistochemistry (IHC) analysis on tumour specimen has been mandatory for clinical use of panitumumab, as well as for eligibility in most clinical trials with this drug. In fact, a >1% EGFR tumour cell membrane staining was established as a necessary condition for panitumumab US FDA approval for this indication.

This biomarker however, has not demonstrated a clear role in predicting clinical response of aCRC to EGFR TKIs or Moabs [18,29]. All the reported trials with panitumumab have shown that tumour response does not correlate with the degree of EGFR expression. In fact, objective responses have been observed in patients with low or negative EGFR levels. Hetcht et al. reported a phase II open-label, multicentre study in 148 EGFR-positive aCRC patients who had progressed to fluoropyrimidine, irinotecan and/or oxaliplatin-based regimens (Table 1) [52]. All patients received weekly panitumumab 2.5 mg/kg, 8 of out of 9 weeks until disease progression. Interestingly, a 5% RR was seen in patients with low or non-EGFR staining. Mitchell et al. confirmed these results in a single-agent panitumumab trial in 91 pre-treated aCRC patients with negative or low EGFR expression by IHC. Disease control rate (DCR) was achieved in 36–42% of patients with a median duration of response of 20–22 weeks and a median PFS of 8 weeks, as shown in Table 1 [53]. Several factors might explain this apparent discrepancy, such as low sensitivity of IHC analysis, cytological heterogeneity of CRC and differential EGFR expression in primary and metastatic tumour tissue [54]. Finally, in some cancer cells, regardless the EGFR expression level, critical downstream signals may be activated via other receptors, or by other pathways [55]. Thus, a current important challenge in EGFR-targeted therapy is to better identify those tumours in which growth is most dependent on EGFR signalling.

In addition to EGFR, HER2 expression has been related to responsiveness to EGFR-targeted therapy. Her-2/neu is known to heterodimerise preferentially with EGFR [56], and to potentiate mitogenic signalling by increasing EGFR ligand affinities [57,58]. In human cancer cell lines, increased HER2 expression levels alone were associated with increased effectiveness of anti-EGFR therapy. Moreover, the presence of a combined EGFR and HER3 overexpression proved to be an even better predictor of response [59]. These findings have been confirmed in the clinical setting for lapatinib, a dual inhibitor of EGFR and HER2, since co-expression of pHER2 and pHER3, and not pEGFR, better correlated with clinical outcome [60]. Further research to confirm these data with other anti-EGFR therapies seems advisable.

4.3. Kras mutations

Alternative predictive biomarkers to EGFR IHQ expression are being actively pursued. Different studies suggest that *Kras* gene mutations are present in 30–50% of colorectal adenocarcinomas [61] and these mutations would be responsible for a constitutive activation of Kras protein downstream EGFR.

The status of *Kras* has been proven to be a major predictor of panitumumab efficacy. In a study by Amado et al. [38] *Kras* status was analysed in 427 of 463 aCRC patients treated with panitumumab. Median PFS was 12.3 weeks in the wild-type (WT) *Kras* group compared to 7.4 weeks in *Kras* mutant (MT) patients ($p < 0.0001$), and ORR was 17% and 0%, respectively. More recently, a pooled analysis from 4 clinical studies of panitumumab confirmed *Kras* as a valid predictive biomarker in selecting aCRC patients for panitumumab monotherapy. *Kras* genotype was identified using RT-PCR, from primary or metastatic tumour samples. ORR in patients with WT *Kras* samples was 13.7% whereas no responses were observed in patients with MT *Kras* samples. PFS and OS also favoured WT *Kras* group, with a HR of 0.42 (95%CI: 0.36–0.50) and 0.63 (95%CI: 0.53–0.74), respectively [62].

Although the presence of mutated *Kras* alleles is an independent predictive maker of anti-EGFR MoAb resistance it only accounts for 30–40% of non-responsive patients. Subsequently, efforts have focused on assessing whether the mutation status of the genes for other intracellular effectors (BRAF, PIK3CA) correlate with clinical response

to anti-EGFR MoAbs. In this sense, in a recent retrospective study of 113 aCRC patients who received cetuximab or panitumumab, *Kras* and *BRAF* point mutations in exons 2 and 15 were analysed, respectively [63]. The data confirmed that the presence of *Kras* mutations correlated with both, a lack of response to anti-EGFR MoAbs therapy and a shorter PFS. Since *Kras* and *BRAF* mutations are mutually exclusive, the authors analysed the *BRAF* mutational status on WT *Kras* tumours. Notably, the presence of *BRAF* mutations was inversely associated with response to therapy. None of the WT *Kras* patients who experienced response to therapy displayed *BRAF* mutations. In addition, in the subgroup of WT *Kras* patients, the presence of *BRAF* mutations correlated with shorter PFS and OS. The authors propose a combined analysis of both, *Kras* and *BRAF*, to prospectively select aCRC patients eligible for EGFR-targeted MoAbs therapy. Nevertheless, these findings need to be further evaluated in a large, prospective phase III trial, given that the number of patients in each subgroup was relatively small.

Besides *Kras* and *BRAF* mutations, key mechanisms involved in resistance to anti-EGFR therapy appear to emerge from the constitutive activation of other EGFR downstream signalling phosphoprotein expression. By using Bioplex phosphoprotein array in aCRC patients treated with cetuximab or panitumumab, Cox multivariate analysis adjusted for age and gender found Kras and pMEK to be two independent prognostic makers [64]. These data highlight the importance of EGFR downstream signalling phosphoprotein expression as predictive biomarkers in this setting.

4.4. EGFR gene amplification

It has been assumed that aCRC responsiveness to anti-EGFR MoAbs was linked to increased *EGFR* gene copy number (GCN) as measured by FISH. However, preliminary results have been inconclusive due to small sample size and treatment heterogeneity [65,66]. The predictive role of *EGFR* GCN has recently been suggested in 64 aCRC patients treated with panitumumab therapy [67]. A mean *EGFR* GCN of less than 2.5/nucleus or less than 40% of tumour cells displaying chromosome 7 polysomy within the tumour correlated with significantly shorter PFS and OS. The most appropriate cut-off values and the reproducibility of FISH results should be confirmed in larger trials. In addition, a prospective validation to find out whether detection of *EGFR* GCN together with downstream signalling phosphoprotein mutations (*Kras*, *BRAF*) can be clinically exploited for optimisation of anti-EGFR MoAb therapy warrants further research.

4.5. EGFR polymorphisms

EGFR polymorphisms have also been suggested as candidate predictors of clinical outcome in patients treated with anti-EGFR therapies. Carcereny et al. [68] analysed 84 aCRC patients who received cetuximab or panitumumab as second or third line therapy. They found single nucleotide polymorphisms (SNP) in codon 216 and 497 and a dinucleotide repeat polymorphism in intron 1. Interestingly enough, SNP 497 was significantly associated with a lower ORR and a shorter PFS and OS. Importantly, by multivariate analysis, pre-treatment CEA level, LDH and EGFR SNP 497 were identified as independent prognostic factors for PFS and OS. Prospective validation in a larger cohort of patients seems advisable.

5. Ongoing strategies in the development of panitumumab

5.1. Combination with other targeted therapies

Although activation of EGFR may be an important signal for tumour cell growth and survival, other growth factor receptors may be crucial for the proliferation and dissemination of neoplastic cells [69]. This assumption leads to the so-called "combined molecular targeting approach" in which more than one class of inhibitors is applied simultaneously. There are expanding series of such approach being currently tested in clinical trials. Among them, the combined blockade of angiogenic pathway and EGFR signalling pathway is being actively investigated.

The link between EGFR signalling and angiogenesis has been clearly identified in preclinical models [70,71]. Taking into account this rationale, as well as the promising results from the BOND-2 trial, a phase IIIB randomised, open-label clinical trial evaluating oxaliplatin- and irinotecan-based chemotherapy plus bevacizumab, with or without panitumumab, was initiated. Unexpectedly, preliminary data on this study showed an increased incidence of serious adverse events in the panitumumab arm as well as reduced median PFS and OS. Consequently, the Data Monitoring Committee recommended discontinuation of panitumumab [72]. The lack of benefit of adding panitumumab to standard chemotherapy plus bevacizumab reinforces the need for robust phase I/II-based clinical evidence before large phase III trials are conducted. In this sense, no data on the specific interaction between panitumumab and bevacizumab are currently available, nor on the possible PK/PD interactions with the use of two biological agents and full doses of chemotherapy. Another recently reported trial testing the combination of oxaliplatin, capecitabine and bevacizumab, with or without cetuximab also reported a detrimental effect on PFS with the double-antibody therapy, raising the possibility of a negative interaction between bevacizumab and anti-EGFR antibodies [73].

A more cautioned approach has been reported in a phase Ib, dose-finding study of panitumumab with FOLFIRI or FOLFOX plus AMG 706, an oral multikinase inhibitor with antiangiogenic activity that selectively targets VEGF, PDGF and Kit receptors. So far, described dose limiting toxicity (DLT) includes diarrhoea and fatigue. Preliminary data show that AMG 706 PK is comparable to data from monotherapy studies and no marked alterations have been observed in the

Table 2
Grade 3 or higher toxicities with an incidence of ≥5%. Nausea/vomiting (N/V); best supportive care (BSC).

	Cetuximab + BSC [21]	Panitumumab + BSC [37]
Fatigue	33%	4%
Anorexia	8%	3%
Constipation	4%	3%
N/V	6%	2%
Abdominal pain	13%	7%
Rash	12%	7%
Infusion reaction	4%	1%
Hypomagnesemia	6%	3%
Dyspnea	16%	5%
Fatigue	33%	4%

PK profiles of irinotecan or its metabolites. According to the preliminary data reported, radiological responses have been observed in 50% of the patients [74].

On the other hand, recent evidence has involved the insulin-like growth factor-1 receptor (IGF-1R) signalling through the type II receptor tyrosine kinase (RTK) family member and the acquisition of resistance to various anti-EGFR therapies [75]. In preclinical models, blockade of IGF-1R results in both, a potent inhibition of the PI3K/Akt signalling pathway and additive effects with panitumumab [76]. In the clinical scenario, a phase Ib of panitumumab plus AMG-479, a fully human anti-IGF-1R antibody, appeared tolerable and has shown preliminary evidence of activity in refractory aCRC [77].

5.2. Role of panitumumab in cetuximab-pre-treated patients

Panitumumab and cetuximab are the first anti-EGFR Moabs approved for the treatment of aCRC, showing both of them a similar safety and efficacy profile, when compared to BSC (Tables 2 and 3). By using flow cytometry and amino acid replacement scanning it was shown that both Moabs bind to comparable surface exposed amino acids (349, 355, 412 and 438) in domain III of EGFR [78]. Despite this structural homology some clinical differences have been observed. Given the fully human nature of panitumumab, a lack of cross reactivity with cetuximab regarding infusional reactions may be expected. However, this issue has not been prospectively explored. Retrospective data suggest however that panitumumab is not associated with hypersensitivity in patients who had prior grades 3–4 infusional reactions to cetuximab [79,80]. In addition, a differential response to these two anti-EGFR Moabs has also been suggested. Furthermore, single cases of CEA responses and minor responses to panitumumab have been suggested in patients who had evidence of progression to cetuximab [81]. Although theses data are so far inconclusive, due to the crucial therapeutic implications of this finding a thorough prospective validation in larger series of patients is warranted.

Table 3
Efficacy data comparing cetuximab and panitumumab. Overall survival (OS); progression-free survival (PFS); overall response rate (ORR); wild-type (WT); mutant-type (MT); weeks (w); months (m).

	Cetuximab [90]	Panitumumab [37]
Median OS		
WT	10 m	8 m
MT	5 m	5 m
Medias PFS		
WT	4 m	12 w
MT	2 m	7 w
ORR (%)		
WT	13	17
MT	1	0

6. Future directions

Since ErbB receptor downstream signalling can engage RAS/mitogen-activated protein kinase pathways, PI3K pathways, and STAT signalling molecules, a broad variety of molecular predictors are being tested from the available clinical material. In addition to total and phosphorylated EGFR, these include total and phosphorylated forms of AKT, mitogen-activated protein kinase (MAPK), mitogen-activated protein/ERK (MEK), ERK, signal transducers and activators of transcription (STAT), PTEN [82], NF-kB [83], mTOR, levels of the EGFR ligands epiregulin and amphiregulin [84] and others [12,85]. In addition, cDNA arrays have allowed the identification of series of genes that are differentially regulated by panitumumab in preclinical models [86], and clinical trials designed to validate these findings are currently in progress. Likewise, protein arrays may be used for quantitative analysis of signal pathway inhibition [87].

Given the links between angiogenesis, EGFR signalling pathway and the immunoresponse in human tumours, determination of circulating endothelial cells (CECs) has been proposed as a way to monitor antiangiogenic activity. In fact, preliminary data on panitumumab-based treated aCRC patients has recently suggested the use of a multiparameter flow cytometric determination of CECs, peripheral blood lymphocytes and dendritic cell immunophenotype as potential predictive biomakers of efficacy in the clinical setting [88]. Additionally, panitumumab-induced dynamic changes in EGFR expression on circulating tumour cells have been very preliminary shown to be of predictive value in aCRC under chemotherapy or panitumumab plus chemotherapy treatment [89]. Thus, further research in this field is necessary.

7. Conclusions

In recent years, three new biological drugs, cetuximab, bevacizumab and panitumumab have been approved for the treatment of aCRC patients. The addition of these new targeted therapies has clearly increased the therapeutic armamentarium for these patients and also offers prospects for

an increased chance of achieving longer survival expectancy. The major challenge now lies in how to customise cancer therapy for aCRC patients. The growing evidence summarised in this review points to the tumour molecular characteristics and/or pharmacogenomic profiles that may permit a rational selection of specific drug combinations for the treatment of each metastatic colorectal cancer patient.

Conflict of interest

The authors declare no conflict of interest.

Reviewer

Hans-Joachim Schmoll, Professor, Martin-Luther-Universitat Halle-Wittenberg, Klinik U Poliklinik fur Innere Medizin Hematologie/Onkologie Halle (Saale), Ernst-Gruber Strasse 40, Halle D-06120, Germany.

References

[1] Ferlay J, Autier P, Boniol M, et al. Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 2007;18:581–92.
[2] A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med 2004;350:2050–9.
[3] O'Connell MJ. Current status of adjuvant therapy for colorectal cancer. Oncology (Williston Park) 2004;18:751–5.
[4] Hurwitz H, Fehrenbacher L, Novotny W, et al. Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 2004;350:2335–42.
[5] Cunningham D, Humblet Y, Siena S, et al. Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. N Engl J Med 2004;351:337–45.
[6] Bengtsson G, Carlsson G, Hafström L, Jönsson PE. Natural history of patients with untreated liver metastases from colorectal cancer. Am J Surg 1981;141:586–9.
[7] de Brauw LM, van de Velde CJ, Bouwhuis-Hoogerwerf ML, Zwaveling A. Diagnostic evaluation and survival analysis of colorectal cancer patients with liver metastases. J Surg Oncol 1987;34:81–6.
[8] Gaffe BM, Donegan WL, Watson F, Sprat Jr JS. Factor influencing survival in patients with untreated hepatic metastases. Surg Gynecol Obstet 1969;127:1–11.
[9] Tournigand C, André T, Achille E, et al. FOLFIRI followed by FOLFOX6 or reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 2004;22:229–37.
[10] Giusti RM, Shastri KA, Cohen MH, Keegan P, Pazdur R. FDA drug approval summary: panitumumab (Vectibix). Oncologist 2007;12:577–83.
[11] Mendelsohn J, Baselga J. The EGF receptor family as targets for cancer therapy. Oncogene 2000;19:6550–65.
[12] Yarden Y, Sliwkowski MX. Untangling the ErbB signalling network. Nat Rev Mol Cell Biol 2001;2:127–37.
[13] Scaltriti M, Baselga J. The epidermal growth receptor pathway: a model for targeted therapy. Clin Cancer Res 2006;12:5268–72.
[14] Baselga J, Tripathy D, Mendelsohn J, et al. Phase II study of weekly intravenous recombinant humanized anti-p185HER2 monoclonal antibody in patients with HER2/neu-overexpressing metastatic breast cancer. J Clin Oncol 1996;14:737–44.
[15] Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. N Engl J Med 2001;344:783–92.
[16] Vermorken JB, Trigo J, Hitt R, et al. Open-label, uncontrolled, multicenter phase II study to evaluate the efficacy and toxicity of cetuximab as a single agent in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck who failed to respond to platinum-based therapy. J Clin Oncol 2007;25:2171–7.
[17] Saltz LB, Meropol NJ, Loehrer Sr PJ, et al. Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. J Clin Oncol 2004;22:1201–8.
[18] Sobrero AF, Maurel J, Fehrenbacher L, et al. EPIC: phase III trial of cetuximab plus irinotecan after fluoropyrimidine and oxaliplatin failure in patients with metastatic colorectal cancer. J Clin Oncol 2008;26:2311–9.
[19] Van Cutsem E, Nowacki M, Lang I, et al. Randomized phase III study of irinotecan and 5-FU/FA with or without cetuximab in the first-line treatment of patients with metatatic colorectal cancer: the Crystal trial. J Clin Oncol 2007;25 [abstract 4000].
[20] Bokemeyer C, Bondarenko I, Makhson A, et al. Cetuximab plus 5-FU/FA/oxaliplatin (FOLFOX-4) versus FOLFOX-4 in the first-line treatment of metastatic colorectal cancer: OPUS, a randomized phase II study. J Clin Oncol 2007;25 [abstract 4035].
[21] Jonker DJ, O'Callaghan CJ, Karapetis CS, et al. Cetuximab for the treatment of colorectal cancer. N Engl J Med 2007;357:2040–8.
[22] Ryan Q, Ibrahim A, Cohen MH, et al. FDA drug approval summary: lapatinib in combination with capecitabine for previously treated metastatic breast cancer that overexpresses HER-2. Oncologist 2008;13:1114–9.
[23] Kris MG, Natale RB, Herbst RS, et al. Efficacy of gefitinib, an inhibitor of the epidermal growth factor receptor tyrosine kinase, in symptomatic patients with non-small cell lung cancer: a randomized trial. JAMA 2003;290:2149–58.
[24] Gridelli C, Bareschino MA, Schettino C, et al. Erlotinib in non-small cell lung cancer treatment: current status and future development. Oncologist 2007;12:840–9.
[25] Moore MJ, Goldstein D, Hamm J, et al. Erlotinib plus gemcitabine compared with gemcitabine alone in patients with advanced pancreatic cancer: a phase III trial of the National Cancer Institute of Canada Clinical Trials Group. J Clin Oncol 2007;25:1960–6.
[26] Cohenuram M, Saif MW. Panitumumab the first fully human monoclonal antibody: from the bench to the clinic. Anticancer Drugs 2007;18:7–15.
[27] Freeman D, McDorman K, Bush T, et al. Mono and combination-therapeutic activity of panitumumab (ABX-EGF) on human A431 epidermoid and HT-29 colon carcinoma xenografts; correlation with pharmacodynamic parameters. Proc Amer Assoc Cancer Res 2004:27–31.
[28] Mendez MJ, Green LL, Corvalan JR, et al. Functional transplant of magabase human immunoglobulin loci recapitulates human antibody response in mice. Nat Genet 1997;15:146–56.
[29] Fan Z, Baselga J, Masui H, Maendelsohn J. Antitumor effect of anti-epidermal growth factor receptor monoclonal antibodies plus cis-diamminedichloroplatinum on well established A431 cell xenografts. Cancer Res 1993;53:4637–42.
[30] Yang XD, Jia XC, Corvalan JR, et al. Erradication of established tumors by a fully human monoclonal to the epidermal growth factor receptor without concomitant chemotherapy. Cancer Res 1999;59:1236–43.
[31] Jia XC, Corvalan JRF, Zhang L. Inhibition of vascular endothelial cell growth factor and interleukin-8 production in tumor and endothelial cell lines by a fully human monoclonal antibody to epidermal groth factor receptor. Proc Amer Assoc Cancer Res 2000:290.
[32] Yang XD, Corvalan JRF, Wang P. Inhibition of human cancer growth by ABX-EGF, a fully human anti-EGF receptor monoclonal antibody. Proc Am Assoc Cancer Res 2000:530.
[33] Lynch DH, Yang XD. Therapeutic potential of ABX-EGF: a fully antiepidermal growth factor reeptor monoclonal antibody for cancer treatment. Semin Oncol 2002;29:47–50.
[34] Arends R, Yang B, Schwab G, et al. Flexible dosing schedules of panitumumab in cancer patients. J Clin Oncol 2005;23 [abstract 3089].

[35] Weiner LM, Belldegrun A, Rowinsky E, et al. Updated results from a dose and schedule study of Panitumumab monotherapy in patients with advanced solid malignancies. J Clin Oncol 2005;23 [abstract 3059].
[36] Peeters M, Van Cutsem E, Hecht JR, et al. Efficacy and safety of panitumumab across five clinical studies in patients with metastatic colorectal cancer. J Clin Oncol 2007 [Gastrointestinal cancers symposium, abstract 336].
[37] Van Cutsem E, Peeters M, Siena S, et al. Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. J Clin Oncol 2007;25:1658–64.
[38] Amado RG, Wolf M, Peeters M, et al. Wild-type Kras is required for Panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol 2008;26:1626–34.
[39] Van Cutsem E, Siena S, Humblet YS, et al. An open-label, single-arm study assessing safety and efficacy of panitumumab in patients with metastatic colorectal cancer refractory to standard chemotherapy. Ann Oncol 2008;19:92–8.
[40] Hecht J, Berlin J, Malik I, et al. Panitumumab therapy with IFL in metastatic colorectal cancer patients: a pharmacokinetic analysis results. J Clin Oncol 2005 [Gastrointestinal cancers symposium, abstract 259].
[41] Berlin J, Posey J, Tchekmedyian S, et al. Panitumumab with irinotecan/leucovorin/5-fluorouracil for first-line treatment of metastatic colorectal cancer. Clin Colorectal Cancer 2007;6:427–32.
[42] Peeters M, Wilson G, Hotko Y, et al. Phase III study (20050181) of panitumumab with FOLFIRI compared to FOLFIRI alone as second-line treatment in patients with metastatic colorectal cancer (mCRC): preliminary safety results. J Clin Oncol 2008 [Gastrointestinal cancers symposium, abstract 335].
[43] Douillard J, Siena S, Cassidy J, et al. Phase III study (PRIME/20050203) of panitumumab with FOLFOX4 compared to FOLFOX4 alone in patients with previously untreated metastatic colorectal cancer (mCRC): preliminary safety data results. J Clin Oncol 2008 [Gastrointestinal cancers symposium, abstract 443].
[44] Drelich DA, Rose L, Ramirez M, Jacobs M, Mitchell E. Dermatological toxicities of panitumumab in the treatment of patients with metastatic colorectal cancer from three clinical studies. J Clin Oncol 2007;25 [abstract 14551].
[45] Segaert S, Van Cutsem E. Clinical signs, pathophysiology and management of skin toxicity during therapy with epidermal growth factor receptor inhibitors. Ann Oncol 2005;16:1425–33.
[46] Peeters M, Van Cutsem E, Berlin J, et al. Safety of panitumumab, a fully human monoclonal antibody against the epidermal growth factor receptor, in patients with metastatic colorectal cancer across clinical trials. J Clin Oncol 2007;25 [abstract 4138].
[47] Giusti RM, Shastri K, Pilaro AM, et al. U.S. Food and Drug Administration approval: panitumumab for epidermal growth factor receptor-expressing metastatic colorectal carcinoma with progression following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. Clin Cancer Res 2008;14(March (5)):1296–302.
[48] Anon. Vectibix (panitumumab) prescribing information. (v3, rev October 2007) Amgen Inc.: Thousand Oaks, CA. Available at: http://www.vectibix.com/pdfs/misc/vectibix_pi.pdf (accessed 10.03.2008).
[49] Perez-Soler R, Saltz L. Cutaneous adverse effects with HER1/EGFR-targeted agents: is there a silver lining? J Clin Oncol 2005;22:5235–41.
[50] Berlin J, Van Cutsem E, Peeters M, et al. Predictive value of skin toxicity severity for response to panitumumab in patients with metastatic colorectal cancer. A pooled analysis of five clinical trials. J Clin Oncol 2007;25 [abstract 4134].
[51] Figlin RA, Belldegrun AS, Crawford J, et al. ABX-EGF, a fully human anti-epidermal growth factor receptor monoclonal antibody in patients with advanced cancer. Phase I clinical results. J Clin Oncol 2002;21 [abstract 35].
[52] Hecht JR, Patnaik A, Berlin J, et al. Panitumumab monotherapy in patients with previously treated metastatic colorectal cancer. Cancer 2007;110:980–8.
[53] Mitchell EP, Hercht JR, Baranda J, et al. Panitumumab activity in metastatic colorectal cancer patients with low or negative tumor epidermal growth factor receptor levels: an updated analysis. J Clin Oncol 2007;25 [abstract 4082].
[54] Scartozzi M, Bearzi I, Berardi R, et al. Epidermal growth factor receptor (EGFR) status in primary colorectal tumors does not correlate with EGFR expression in related metastatic sites: implications for treatment with EGFR-targeted monoclonal antibodies. J Clin Oncol 2004;22:4772–8.
[55] Atkins D, Reiffen KA, Tegtmeier CL, et al. Immunohistochemical detection of EGFR in paraffin-embedded tumor tissues: variation in staining intensity due to choice of fixative and storage time of tissue sections. J Histochem Cytochem 2004;52:893–901.
[56] Graus-Porta D, Beerli R, Daly J, Hynes N. ErbB-2, the preferred heterodimerization partner of all ErbB receptors, is a mediator of lateral signalling. EMBO J 1997;16:1647–55.
[57] Tzahar E, Waterman H, Chen X, et al. A hierarchical network of interreceptor interactions determines signal transduction by Neu differentiation factor/neuregulin and epidermal growth factor. Mol Cell Biol 1996;16:5276–87.
[58] Lenferink A, Pinkas-Kramarski R, van de Poll M, et al. Differential endocytic of homo- and hetero-dimeric ErbB tyrosine kinases confers signalling superiority to receptor heterodimers. EMBO J 1998;17:3385–97.
[59] Emlet DR, Schwartz R, Brown KA, et al. HER-2 expression as a potential marker for response to therapy targeted to the EGFR. Br J Cancer 2006;94:1144–53.
[60] Johnston S, Trudeau M, Kaufman B, et al. Phase II study of predictive biomarker profiles for response targeting human epidermal growth factor receptor 2 in advanced inflammatory breast cancer with Lapatinib monotherapy. J Clin Oncol 2008;26:1066–72.
[61] Bos JL, Fearon ER, Hamilton SR, et al. Prevalence of ras gene mutations in human colorectal cancers. Nature 1987;327:293–7.
[62] Freeman D, Amado R, Wolf M, et al. Efficacy of Panitumumab monotherapy in relation to KRAS mutational status for treating metastatic colorectal cancer from four clinical studies. J Clin Oncol 2008 [abstract 47].
[63] Di Nicolantonio F, Martini M, Molinari F, et al. Wild-type BRAF is required fo response to panitumumab or cetuximab in metastatic colorectal cancer. J Clin Oncol 2008;26:5705–12.
[64] Merlin JL, Perkins G, Lievre A, et al. Additional value of EGFR downstream signaling phosphoprotein expression to KRAS mutation for response prediction to cetuximab in colorectal cancer. J Clin Oncol 2008;26 [abstract 4126].
[65] Moroni M, Veronese S, Benvenuti S, et al. Gene copy number of epidermal growth factor receptor and clinical response to anti-EGFR treatment in colorectal cancer: a cohort study. Lancet Oncol 2005;6:279–86.
[66] Lièvre A, Bachet JB, Le Corre D, et al. KRAS mutation status is predictive of response to cetuximab therapy in colorectal cancer. Cancer Res 2006;66:3992–5.
[67] Sartore-Bianchi A, Moroni M, Veronese S, et al. Epidermal growth factor receptor gene copy number and clinical outcome of metastatic colorectal cancer treated with Panitumumab. J Clin Oncol 2007;25:3238–45.
[68] Carcereny E, Castellvi-Bel S, Alonso V, et al. EGFR polymorphisms as predictors of clinical outcome in patients with advanced colorectal cancer treated with cetuximab and panitumumab. J Clin Oncol 2008;26 [abstract 4124].
[69] Gschwind A, Fischer OM, Ullrich A. The discovery of receptor tyrosine kinases: targets for cancer therapy. Nat Rev Cancer 2004;4:361–70.
[70] Petit AMV, Rak J, Hung MC, et al. Neutralizing antibodies against epidermal growth factor and ErbB-2/neu receptor tyrosine kinases down-regulate vascular endothelial growth factor production by tumor cells *in vitro* and *in vivo*: angiogenic implications for signal transduction therapy of solid tumors. Am J Pathol 1997;151:1523–30.

[71] Ciardiello F, Bianco R, Daminao V, et al. Antiangiogenic and antitumor activity of anti-epidermal growth factor receptor C225 monoclonal antibody in combination with vascular endothelial growth factor antisense oligonucleotide in human GEO colon cancer cells. Clin Cancer Res 2000;6:3739–47.
[72] Hecht JR, Mitchell E, Chidiac T, et al. A randomized phase IIIB trial of chemotherapy, bevacizumab and panitumumab compared with chemotherapy and bevacizumab alone for metastatic colorectal cancer. J Clin Oncol 2009;27:672–80.
[73] Punt CJ, Tol J, Rodenburg CJ, et al. Randomized phase III study of capecitabine, oxaliplatin and bevacizumab with or without cetuximab in advanced colorectal cancer, the CAIRO2 study of yhe Dutch Colorectal Cancer Group. J Clin Oncol 2008;26(Suppl.):180s [abstract LBA 4011].
[74] Schwartzberg LS, Hurwitz H, Stephenson J, et al. Safety and pharmacokinetics of AMG706 with Panitumumab plus FOLFIRI or FOLFOX for the treatment of patients with metastatic colorectal cancer. J Clin Oncol 2007;25 [abstract 4081].
[75] Jones HE, Goddard L, Gee JMW, et al. Insulin-like growth factor-1 receptor signalling and acquired resistance to gefitinib (ZD1839; Iressa) in human breast and prostate cancer cells. Endocrine-Related Cancer 2004;11:1–22.
[76] Beltran PJ, Mitchell P, Moody G, et al. AMG 479, a fully human anti IGF-1 receptor antibody, inhibits P3IK/Akt signalling and exerts potent antitumor effects in combination with EGFR inhibitors in pancreatic xenograft models. J Clin Oncol 2007 [Gastrointestinal cancers symposium, abstract 208].
[77] Sarantopoulos J, Mita AC, Mulay M, et al. A phase Ib of AMG479, a type 1 insulin-like growth factor receptor antibody in combination with Panitumumab or Gemcitabine. J Clin Oncol 2008;26 [abstract 3583].
[78] Freeman D, Sun J, Bass R, et al. Panitumumab and cetuximab epitope mapping and in vitro activity. J Clin Oncol 2008;26 [abstract 14536].
[79] Langerak AD, Mitchell E, Cheema G, River L, Shing M. Institutional experiences with panitumumab monotherapy in metastatic colorectal cancer patients intolerant to cetuximab. J Clin Oncol 2007;25 [abstract 14579].
[80] Helbling D, Borner M. Successful challenge with the fully human EGFR antibody panitumumab following an infusion reaction with the chimeric EGFR antibody cetuximab. Ann Oncol 2007;18: 963–4.
[81] Asmis TR, Shah MA, Haviland D, Kemeny N. Panitumumab with or without chemotherapy on metastatic colorectal cancer: safety and unusual activity, even following progression on Cetuximab. J Clin Oncol 2008 [Gastrointestinal cancers symposium, abstract 484].
[82] Frattini M, Saletti P, Romagnani E, et al. PTEN loss of expression predicts Cetuximab efficacy in metastatic colorectal cancer patients. Br J Cancer 2007;97:1139–45.
[83] Scartozzi M, Bearzi I, Pierantoni C, et al. Nuclear factor-kB tumor expression predicts response and survival in irinotecan-refractory metastatic colorectal cancer treated with cetuximab-irinotecan therapy. J Clin Oncol 2007;25:3930–5.
[84] Khambata-Ford S, Garrett CR, Meropol NJ, et al. Expression of epiregulin and amphiregulin and K-ras mutation status predict disease control in metastatic colorectal cancer patients treated with cetuximab. J Clin Oncol 2007;25:3230–7.
[85] Grunwald V, Hidalgo M. Developing inhibitors of the epidermal growth factor receptor for cancer treatment. J Natl Cancer Inst 2003;95:851–67.
[86] Boedigiemer M, Freeman D, Fitzpatrick D, et al. Gene expression profiles can predict panitumumab monotherapy responsiveness in xenograft models: a balanced approach. Proc Amer Assoc Cancer Res 2005;46 [abstract 1].
[87] Liotta LA, Espina V, Mehta AI, et al. Protein microarrays: meeting analytical challenges for clinical applications. Cancer Cell 2003;3:317–25.
[88] Bencardino K, Ronzoni M, Manzoni M, et al. In vivo biological effects of Panitumumab plus chemotherapy in advanced colorectal cancer patients. J Clin Oncol 2008;26 [abstract 14576].
[89] Hendlisz A, Marechal R, Durbecq V, et al. Modulation and prognostic value of epidermal growth factor receptor expression in circulating tumour cells during chemotherapy in patients with metastatic colorectal cancer. J Clin Oncol 2008;26 [abstract 15038].
[90] Karapetis CS, Khambata-Ford S, Jonker DJ, et al. *K-ras* mutations and benefit from cetuximab in advanced colorectal cancer. N Engl J Med 2008;359:1757–65.

Biography

Ignacio Gil-Bazo, MD, PhD, completed his medical oncology training at the Clínica Universidad de Navarra of the University of Navarra in Pamplona, Spain. He holds a PhD in medicine from the same university. After a fellowship at Memorial Sloan-Kettering Cancer Center in New York City, USA, he was appointed attending physician of the Department of Oncology as well as assistant professor of the University of Navarra.