Epidermal Growth Factor Receptor-Targeted Therapy of Colorectal Cancer with Panitumumab

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Abstract: Panitumumab is a fully human monoclonal antibody directed against the epidermal growth factor receptor (EGFR), which when overexpressed may contribute to the development and progression of cancer and is present in several solid tumors, including colorectal cancer (CRC). Panitumumab is registered in USA for the treatment of patients with EGFR expressing CRC after disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. The present evidence of effectiveness of Panitumumab for the treatment of metastatic CRC is based on objective tumor respose as well as on progression-free survival. This review article summarizes the development of Panitumumab in preclinical and early phase trials in CRC and focuses on the most recent results available from advanced phase clinical trials, with an update on presentations at the 2007 annual meeting of the American Society of Clinical Oncology (ASCO).

Key Words: Panitumumab, colorectal cancer, monoclonal antibodies, EGFR, FISH, KRAS, BRAF.

INTRODUCTION

Colorectal carcinoma (CRC) is the second cause of cancer-related death in developed countries. [1]. Despite the prevalence of CRC, the overall incidence and death rates have declined over the past decades, possibly reflecting the increased utilization of screening procedures, earlier diagnosis, and better surgical and medical treatment modalities. Approximately 20% of patients with CRC present with metastatic disease. Treatment options in this stage include different chemotherapeutic and targeted agents, either in combination or as single agents: fluorouracil plus leucovorin, irinotecan, oxaliplatin, capecitabine, bevacizumab, and cetuximab [2]. Traditionally, the most active regimen utilized fluorouracil (either by bolus or continuous infusion) plus leucovorin, yielding an objective response rate of 20–25% and median overall survival (OS) of approximately 11 months. The further addition of irinotecan and oxaliplatin to fluorouracil/leucovorin-containing regimens has generated improved overall response rates and survival. Objective response rates between 31% and 55% for irinotecan-containing regimens (irinotecan plus bolus fluorouracil/leucovorin [IFL] or infusional fluorouracil/leucovorin plus irinotecan [FOLFIRI]) and up to 50% for oxaliplatin-containing regimens (fluorouracil/leucovorin plus oxaliplatin [FOLFOX]) have been reported. OS for irinotecan- and oxaliplatin-containing regimens approaches 20 months, approximately double that of traditional fluorouracil/leucovorin regimens [2,3].

The most recent advancements in the treatment of metastatic CRC are derived from the development of targeted therapy toward tumor growth factors, cell surface receptors and their associated intracellular effector molecules. In particular, therapeutic options have been expanded with the introduction of monoclonal antibodies (moAbs) against the vascular endothelial growth factor (VEGF) and the extracellular domain of epidermal growth factor receptor (EGFR). Bevacizumab is a chimeric humanized moAb that targets VEGF and is used for treatment of metastatic CRC in combination with fluorouracil/leucovorin-based chemotherapy. The addition of bevacizumab to IFL increased the median duration of survival from 15.6 months (IFL) to 20.3 months (bevacizumab plus IFL; $p < 0.001$) [4]. Cetuximab is a human–mouse chimeric moAb that binds specifically to the extracellular domain of the EGFR, inhibiting cellular growth and differentiation, promoting apoptosis, and inhibiting angiogenesis. Statistically significant improvement was demonstrated when cetuximab was given in combination with irinotecan (overall response rate 22.9%) versus cetuximab alone (10.8%) in patients with irinotecan-refractory colorectal cancer; OS for cetuximab alone versus cetuximab plus irinotecan was 6.9 months versus 8.6 months, respectively ($p = 0.48$) [5].

Panitumumab (Vectibix, ABX-EGF; Amgen Inc., Thousand Oaks, CA) is the first human monoclonal antibody that selectively targets the extracellular domain of the EGFR. It was approved by the Food and Drug Administration in September 2006 and is indicated for the treatment of EGFR-expressing, metastatic CRC with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens [6]. Panitumumab was developed using XenoMouse™ technology by which human immunoglobulin genes were introduced into mice lacking functional mouse immunoglobulin genes. The monoclonal antibody is produced by immunizing a XenoMouse strain of mice with human cervical epidermal carcinoma cell line

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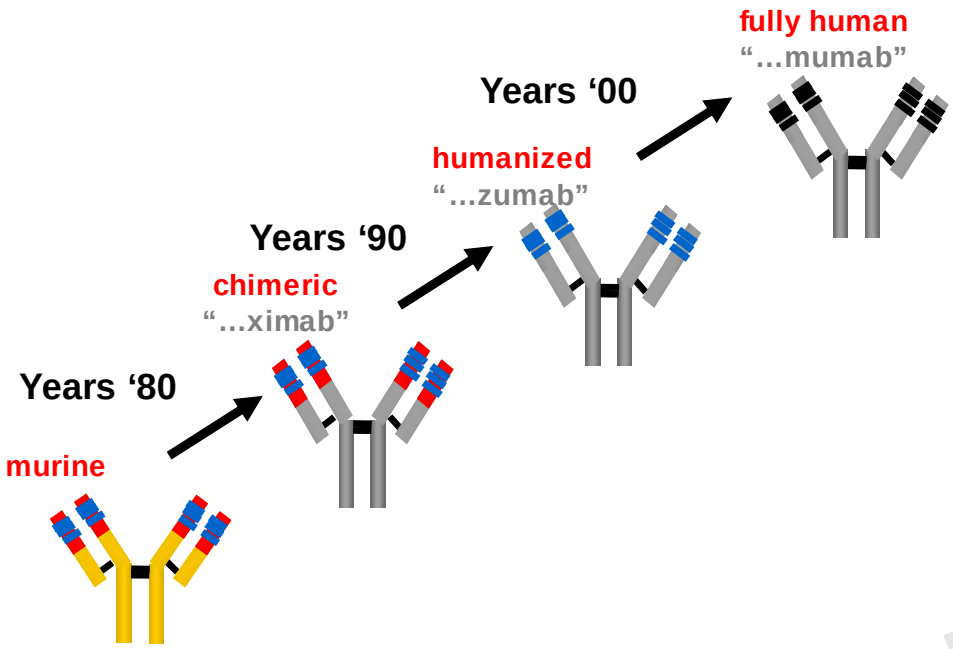

Fig. (1). Pharmaceutical evolution of therapeutic monoclonal antibodies for the treatment of solid tumors.

A431, a cell line known for overexpression of the EGFR [7]. Differently from chimeric antibodies such as cetuximab, which have about 34% mouse protein, and humanized antibodies such as bevacizumab, which comprise 5–10% mouse protein, fully humanized antibodies do not contain any mouse proteins (Fig. **1**), possibly overcoming the problems of immunogenicity, which can lead to allergic reactions during treatment administration, and induction of human anti-mouse antibodies, which can reduce the efficacy of the agent and lead to a need for repeated administration [8]. Panitumumab is a moAb of the IgG_2 isotype, which lacks effector functions, so that unlike in mechanism of action of cetuximab, antibody-dependent cell-mediated cytotoxicity does not play a role in its therapeutic efficacy. It binds with high affinity to EGFR (KD=5 x 10–11 mol/l in preclinical studies), effectively preventing the binding of TGF-α and EGF to the receptor, and receptor activation [9]. This article summarizes the development of panitumumab in CRC, from early phase trials to the most recent results available from ASCO 2007.

EFFICACY OF PANITUMUMAB IN CLINICAL TRIALS OF COLORECTAL CANCER THERAPY

Phase I Trials

The weekly dose of panitumumab was determined in a phase I trial by Figlin *et al*. [10] that included patients with colorectal, gastroesophageal, pancreatic, non–small-cell lung, renal and prostate cancer. Forty-three patients were enrolled in this trial, which did not observe dose-limiting toxicity in the first four weeks of treatment up to the 2.5 mg/kg/week dose level with no loading dose. No infusion reactions or human antihuman antibodies were detected in this cohort. The rash characteristic of EGFR blocking antibodies was observed in 100% of patients who were treated with 2.0 mg/kg/week or more of panitumumab. Serum concentrations of panitumumab achieved at the dose of 2.5 mg/kg/week were similar to the serum concentrations in xenograft mice, which resulted in inhibition of A431 tumor growth [11]. A partial response (PR) of 10 months was seen in one patients with CRC treated with 2.5 mg/kg and a stable disease (SD) was reported for 7 months in one patient with esophageal cancer (0.1 mg/kg). One patient with prostate cancer experienced a minor response for 6 months (0.75 mg/kg). An update on this study by Weiner *et al*. on 96 patients, including 39 CRC, showed that the maximum tolerated dose was not reached, and pharmacokinetics were noted to be stable over the range of dosing schedules [12]. Of particular note, all of the 5 responders were CRC, and in this histology response rate was 12.8%. Subsequent reports have also shown that administration of panitumumab is feasible at 6.0 mg/kg every two weeks and 9.0 mg/kg every three weeks, with similar drug exposure and toxicity profiles to the 2.5 mg/kg/week dose [13,14].

Phase II Monotherapy Trials

In metastatic CRC, data on the efficacy of panitumumab monotherapy are available from a phase II trial that enrolled 148 patients who had failed treatment with a fluoropyrimidine and either irinotecan or oxaliplatin [15]. Patients enrolled in this trial had to have EGFR staining by immunohistochemistry (IHC) in at least 10% or more of tumor cells. They were also prospectively divided into two cohorts according to whether they had 2+ and 3+ staining in 10% or more of cells, or 2+ and 3+ staining in less than 10% of cells. Treatment was with panitumumab at a dose of 2.5 mg/kg/week. Updated results of this trial reported an overall response rate (by central review) of 9% (all PR) with a further 29% having SD as their best response. The median progression-free survival (PFS) and OS for the group were 13.6 weeks and 37.6 weeks, respectively. There was no significant difference in the efficacy outcomes between the two EGFR staining cohorts. Rash was the major toxicity, followed by fatigue. The incidence of skin rash of any grade was 95%, although only 7% had grade 3 toxicity and none had grade 4 toxicity; it was the cause for treatment discontinuation in only four patients. Grade 3 fatigue was reported

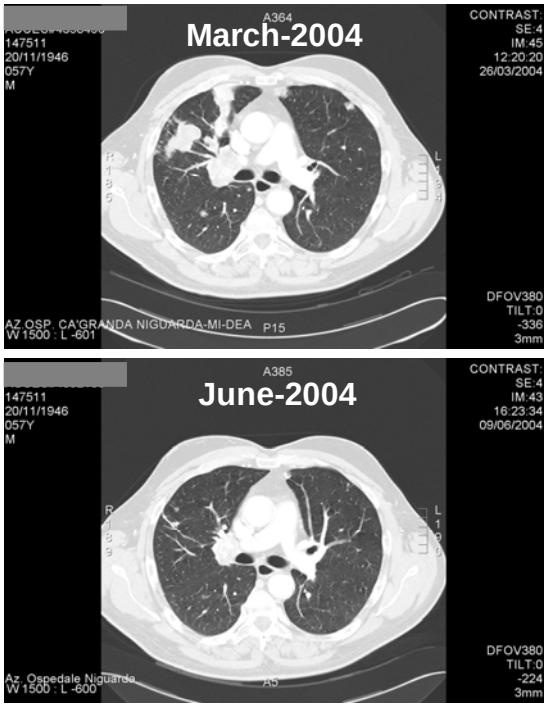

Fig. (2). Representative objective response of lung metastases of a patient with metastatic colorectal cancer in progression after fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens before (upper panel) and after (lower panel) treatment with panitumumab monotherapy at Ospedale Niguarda Ca' Granda.

in 9% of patients, with only 3% of cases considered to be treatment related. Another phase II monotherapy trial evaluated panitumumab activity in metastatic CRC patients with low (1%-9%) or negative (<1%) tumor EGFR levels by IHC. Results confirmed earlier findings that panitumumab has anti-tumor activity in patients with low (PR=8%, median PFS=8 weeks) or undetectable (PR=5%, median PFS=8 weeks) EGFR tumor membrane levels as measured by IHC [16].

Phase II Combination with Chemotherapy Trials

A phase II trial evaluated panitumumab in combination with irinotecan- and 5-fluorouracil–based treatment in previously untreated patients [17]. EGFR staining in 10% or more of tumor cells was required for study entry. Patients were treated with panitumumab 2.5 mg/kg/week. Initially, patients were treated with the bolus 5-fluorouracil–based IFL regimen (n=19), but the protocol was later amended so that patients received the infused 5-fluorouracil–based FOLFIRI regimen instead (n=24), due to the high incidence of severe diarrhea with IFL. The overall response rates observed in this trial were 46% with IFL and 42% with FOLFIRI, with a further 28% and 37% in each cohort, respectively, having SD as their best response. The median PFS at the time of reporting were 5.6 months for IFL and 10.9 months for FOLFIRI, with an OS of 17 months recorded for the IFL and 22.5 for the FOLFIRI cohort. Grade 3/4 diarrhea occurred in 11 patients (58%) for the IFL and 6 patients (25%) for FOLFIRI. Skin toxicity was the predominant toxicity observed, occurring at any grade in 84% and 75% of patients treated in the IFL and FOLFIRI cohorts, respectively. Other commonly occurring toxicities included fatigue, nausea, abdominal pain, anorexia, dehydration, dizziness, hypokalemia, hiccups and peripheral edema. In general, the incidence of these toxicities was much less in the FOLFIRI treated cohort.

Phase III Monotherapy Trials

A recently published randomized Phase III study showed that panitumumab improved PFS in patients with metastatic CRC who developed disease progression after standard chemotherapy, being the first to demonstrate in a randomized controlled trial the superiority of a targeted agent used as monotherapy in metastatic CRC compared to best-supportive care (BSC) alone [18]. The BOND trial indeed, which previously led to the licensing of cetuximab and the establishment of the cetuximab–irinotecan combination as a standard treatment for patients in this setting who have failed previous irinotecan treatment, did not include a BSC control arm [5]. In this phase III trial of panitumumab, a total of 463 patients with documented progression of disease during or following treatment with a fluoropyrimidine, irinotecan, and oxaliplatin were randomly assigned to receive panitumumab 6 mg/kg every 2 weeks plus BSC (n = 231) or BSC alone (control arm; n = 232). Tumor cell positivity for EGFR expression was 1% or more by IHC. Patients who received panitumumab plus BSC showed a 46% decrease in the rate of tumor progression compared with those who received BSC alone (hazard ratio = 0.54; $CI_{95\%}$= 0.44 to 0.66). Median PFS time was 8 weeks ($CI_{95\%}$= 7.9 to 8.4) for panitumumab and 7.3 weeks ($CI_{95\%}$= 7.1 to 7.7) for BSC. Mean PFS time was 13.8 ± 0.8 weeks for panitumumab and 8.5 ± 0.5 weeks for BSC. Objective response rates also favored panitumumab over BSC; after a 12-month minimum follow-up, response rates were 10% for panitumumab and 0% for BSC ($p<0.0001$). No difference was observed in OS (HR, 1.00; $CI_{95\%}$= 0.82 to 1.22), which was confounded by similar activity of panitumumab after 76% of BSC patients entered the cross-over study. In general, panitumumab was well tolerated; skin-related toxicities occurred in 90% of patients in the panitumumab group and in 9% of patients in the BSC group. One patient in the panitumumab group discontinued treatment because of grade 2 dermatitis acneiform. Deaths on study (including the long-term follow-up period) occurred in 186 (81%) patients in the panitumumab group and 194 (84%) patients in the BSC group. Nearly all deaths were related to disease progression. There were no treatment-related deaths. In the panitumumab group, 36% of patients had declines in blood magnesium levels versus 1% in the BSC group. Grade 3 or 4 hypomagnesemia occurred in 3% of patients and required magnesium supplementation. One patient discontinued treatment because of a grade 2 hypersensitivity reaction. Of 185 (83%) of 224 patients with both a baseline and post baseline sample available for testing, no patients tested positive for human antihuman antibodies. Subset analyses of this study, concerning elderly patients (<65 vs >65 years) and patients with poor performance status (ECOG score 0-1 vs 2-3) was presented at the 2007 ASCO Gastrointestinal Cancers Symposium [19]. The treatment effect on PFS favored panitumumab vs BSC regardless of age or ECOG status. Among the panitumumab patients, similar PFS and OS times and ORR were seen between elderly and younger patients and

within both ECOG status groups, showing that the efficacy and tolerability of panitumumab in metastatic CRC patients was similar regardless of age and ECOG status. Moreover, also patient-reported outcome (PRO)-assessed clinical benefit was evaluated in this trial, showing that among panitumumab patients with PFS > 56 days, those who had a best response of PR or SD experience significantly higher health-related quality of life and less CRC symptomatology than panitumumab patients without a response [20]. Results regarding patients randomized to the BSC arm who received panitumumab in a separate crossover study were presented at the 31st ESMO Congress in October 2006 [21]. Of 232 pts randomized to the BSC arm in the parental study, 194 had progressive disease and discontinued the phase III study. 175 of these had then enrolled in the crossover study. The objective response rate was 10% with 1% complete response, 9% PR and 32% SD; median PFS was 8.1 ($CI_{95\%}$= 8.0 to 12.4) weeks. These response and PFS rates were consistent with that seen in patients receiving panitumumab plus BSC in the phase III study as well as in previous panitumumab monotherapy studies.

Ongoing Studies of Panitumumab in Combination with Other Agents

Panitumumab is currently being evaluated in a number of trials in CRC. Registrational phase III studies evaluating the combination with chemotherapy in first- (FOLFOX + panitumumab vs FOLFOX alone) and second-line (FOLFIRI + panitumumab vs FOLFIRI alone) were initiated in 2006 and are still ongoing. Other Phase II studies in first- and second-line metastatic CRC were also initiated in 2006, to be conducted in the US, and include: the STEPP trial, evaluating the prophylactic treatment of skin toxicity for patients receiving second-line irinotecan-based chemotherapy concomitantly with panitumumab; the SPIRTT trial, comparing FOLFIRI regimen plus panitumumab vs FOLFIRI regimen plus bevacizumab as second-line treatment after first-line fluoropyrimidine and oxaliplatin-based chemotherapy with at least 4 doses of bevacizumab; and the PRECEPT trial, evaluating panitumumab in combination with FOLFIRI following first-line FOLFOX and bevacizumab [http:// clinicaltrials.gov/ct/search?term=panitumumab. Accessed June 10th, 2007]. Panitumumab is also being studied in combination with chemotherapy (FOLFIRI or FOLFOX) and motesanib diphosphate (AMG 706), an oral drug with activity against multiple tyrosine kinases including VEGFR, PDGFR and Kit. Preliminary data of this combination were presented at the 2007 ASCO Annual Meeting [22]. Forty-five patients were enrolled in a phase Ib study and received at least 1 dose of AMG 706 (FOLFIRI/FOLFOX n=33/12); 64% had prior chemotherapy. There were 6 dose-limiting toxicities: FOLFIRI n=4, all grade 3 (diarrhea n=2: 50 mg qd, 75 mg bid; deep vein thrombosis n=1: 75 mg qd; high GI output n=1: 75 mg bid); FOLFOX n=2 (all fatigue, grade 3: 50 mg qd). Treatment-related adverse events (AE) included: any AE, FOLFIRI/FOLFOX 88/92% of patients (grade 3, 21/58%); fatigue 55/58% (12/33%), anorexia 24/50% (0/0%), diarrhea 24/33% (0/8%), epistaxis 27/0% (0/0%) and hypertension 15/8% (0/0%). There were no grade 4/5 AEs. Two cases of cholecystitis (grade 3, n=1) occurred. This preliminary data showed that AMG 706 was tolerable when combined with panitumumab and FOLFIRI or FOLFOX, with little effect on AMG 706 pharmacokinetic. Objective overall tumor response (CR+PR) per RECIST was 11/22 (50%) for the biologics + FOLFIRI and 5/10 (50%) for biologics + FOLFOX [22].

Complex-Design Studies: the PACCE Trial and its Discontinuation

A non-registrational Phase IIIb study was also initiated in 2005 to assess whether the addition of panitumumab to first-line chemotherapy (either oxaliplatin-or irinotecan-based) plus bevacizumab would have improved PFS compared with treatment with chemotherapy plus bevacizumab alone (PACCE trial). Between 2005 and 2006, the PACCE trial enrolled 1,054 patients (824 patients were randomized to receive oxaliplatin-based chemotherapy, and 230 patients were randomized to receive irinotecan-based chemotherapy) at 240 trial sites in the United States. The PACCE trial design is so intricate (in terms of chemotherapy regimens, associations with either one or two monoclonal antibodies directed against VEGF or EGFR, number of participating institutions, and variety of safety as well as efficacy issues addressed at the same time in the absence of phase II data), that in our opinion this trial should not be taken as an example for future clinical studies, especially without the guide of biomarker(s) of tumor sensitivity or resistance to targeted therapy. In March 2007 Amgen discontinued panitumumab treatment in the trial, basing on a preliminary review of data from a pre-planned interim efficacy analysis scheduled after the first 231 events (death or disease progression). This analysis revealed a statistically significant difference in PFS in favor of the control arm. An unplanned analysis of OS also demonstrated a statistically significant difference favoring the control arm. A review of the interim analysis showed an increased incidence of grade 3 severe events of diarrhea, dehydration and infections in the panitumumab-treated patients. In addition, an increased incidence of pulmonary embolism was observed in patients who received Vectibix compared with those who did not (4 percent and 2 percent, respectively). One (<1%) fatal event of pulmonary embolism occurred in a patient receiving pantumumab [23]. Overall it is our opinion that, because of its methodological pitfalls, the failure of PACCE trial should not jeopardize the accurate ongoing development of panitumumab.

CLINICAL AND DIAGNOSTIC PARAMETERS ASSOCIATED WITH LIKELIHOOD OF RESPONSIVENESS OR RESISTANCE TO PANITUMUMAB THERAPY IN METASTATIC CRC

Cutaneous Toxicity as a Surrogate Marker of Efficacy

The identification of patients who are likely to benefit from EGFR targeted moAbs remains a considerable challenge, particularly because these treatments are expensive and benefit only a fraction of the target population [24]. Cutaneous toxicity (skin rash) is an on-target side effect that occurs with significant frequency with both cetuximab and panitumumab. Data from several clinical trials with cetuximab show a positive correlation between rash and response and/or survival [25]. As for panitumumab, the association between severity of skin toxicity and efficacy has been stud-

ied in a pooled analysis of five clinical trials (4 phase II studies and the phase III study [18]) including a total of 612 patients [26]. The median (95% CI) duration of PFS was 8.4 weeks (8.0 to 11.3), the median (95% CI) survival was 6.9 months (6.2 to 7.9), and the ORR (95% CI) was 9.0% (6.8 to 11.5). The most common skin toxicities (any grade, grade 3/4) were erythema (54%, 4%) pruritus (53%, 2%), dermatitis acneiform (52%, 5%), and rash (39%, 2%). ORR, PFS, and OS appeared to favor patients with grade 2-4 skin toxicity vs patients with grade 0- 1 skin toxicity, demonstrating that the severity of skin rash was correlated with increased efficacy of panitumumab in terms of overall clinical outcome. The use of skin rash as a tool to optimize anti-EGFR therapy is being currently explored also in other studies, but this is not a true predictive marker because it is only assessable after the therapy has been initiated, and it would be more appropriately defined as a surrogate marker of efficacy.

Tumor EGFR Gene Copy Number as a Predictive Factor of Clinical Outcome

In the last few years, considerable efforts have been made in order to identify molecular predictive factors of response to anti-EGFR therapies, including moAbs. Soon after the first large clinical trials with cetuximab, it was clear that in metastatic CRC patients the degree of EGFR expression in tumor tissue (as evaluated by IHC) does not correlate with clinical response [5], raising in the minds of investigators important questions about the concept of targeted therapy itself. This finding was confirmed also with panitumumab, as demonstrated by phase II [16] and phase III studies [18]. In 2005, we reported that objective tumor response to cetuximab and panitumumab is associated with increased gene copy number (GCN) of the EGFR, as assessed by fluorescent in situ hybridization (FISH) in individual tumor specimens [27]. In a larger and more homogeneous patients series, we subsequently analyzed the association between EGFR GCN and clinical outcome in a subset of patients from those enrolled in the registratory phase III trial [18] of panitumumab and BSC vs BSC only. In this study [28], we show that in patients treated with panitumumab, a mean EGFR GCN <2.5/nucleus or <40% of tumor cells displaying chromosome 7 polysomy within the tumor predict for shorter progression-free survival (p=0.039 and p=0.029, respectively) and overall survival (p=0.015 and 0.014). None of the treated patients with mean EGFR GCN <2.47/nucleus or <43% of chromosome 7 polysomy obtained indeed objective response, as compared to 6/20 and 6/19 in patients with values above these cut-off limits (p=0.0009 and 0.0007, respectively). Evaluation of BSC-treated patients showed no correlation between EGFR GCN or chromosome 7 polysomy status and progression-free survival, suggesting a predictive, rather than prognostic value of this genetic feature. Taken together, these findings suggest that patients with tumors distinguishable by FISH analysis of EGFR as homogenously disomic or with low chromosome 7 polysomy have a reduced likelihood of response to panitumumab.

KRAS and BRAF Mutations and their Antagonism to Anti-EGFR Monoclonal Antibody Therapy

KRAS and *BRAF* are cellular effectors that act downstream of EGF signaling and their malignant activation caused by mutations can independently impair the inhibitory effect of anti-EGFR therapy, with both small molecules tyrosine kinase inhibitors and moAbs [29-31]. The only available data regarding panitumumab come from a study performed by our group on 48 metastatic CRC patients (12 treated with cetuximab monotherapy, 25 with panitumumab monotherapy and 11 with cetuximab plus irinotecan–based chemotherapy) [31]. In this series, the presence of *KRAS* and/or *BRAF* mutations was negatively associated with partial response (p = 0.005) and PFS (p = 0.0443 for *KRAS* alone and 0.0259 for *KRAS* and/or *BRAF*), confirming that most patients with CRC carrying mutated *KRAS* or *BRAF* are not likely to experience significant benefit on either cetuximab or panitumumab treatment. However, the same patients should not be excluded from anti-EGFR moAbs treatment, as we found that there are few patients in which the presence of *KRAS* mutations is compatible with a clinical response to this therapeutic regimen. The molecular determinants of response in this subset of patients are presently unknown, and this observation therefore warrants further investigations.

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