Randomized Phase III Trial Results of Panitumumab, a Fully Human Anti–Epidermal Growth Factor Receptor Monoclonal Antibody, in Metastatic Colorectal Cancer

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Abstract

Monoclonal antibodies against the epidermal growth factor receptor have proven efficacy as monotherapy and in combination with chemotherapy in patients with metastatic colorectal cancer (CRC; mCRC). Initial clinical trials in CRC used the human-murine chimeric monoclonal antibody cetuximab. Ongoing studies are being conducted to evaluate the efficacy and safety of the fully human anti–epidermal growth factor receptor monoclonal antibody panitumumab. The results of a phase III trial, which compared panitumumab as a single agent to best supportive care in patients with previously treated metastatic CRC, have recently been reported. Panitumumab therapy resulted in a 46% reduction in the risk of tumor progression and a partial response rate of 8%. Rash was reported in 90% of patients, with increased severity significantly correlated with improved median overall survival (OS). Further clinical studies are ongoing and planned to test panitumumab in combination with chemotherapy in first-line therapy of advanced-stage CRC and adjuvant treatment of colon cancer.

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Introduction

Dysregulation of the epidermal growth factor (EGF) signaling pathway, caused by mutation or overexpression of the EGF receptor (EGFR), plays an important role in the growth and progression of tumor cells. The consequence of EGFR overexpression in neoplastic tissues is uncontrolled signal transduction through the receptor, which leads to increased proliferation, resistance to apoptosis, increased expression of angiogenic factors, and increased metastases. In patients with CRC, overexpression of EGFR has been reported in up to 85% of tumors and has been associated with poor prognosis and metastatic spread.[1]

The high prevalence of EGFR overexpression in neoplastic tissues has spawned the development of targeted therapies designed to inhibit this pathway. Monoclonal antibodies are 1 class of agents that block EGFR activation to prevent binding of the EGF ligand to its receptor. In the past several years, chimeric, humanized, and fully human anti-EGFR monoclonal antibodies have been developed and are currently in different stages of investigation in clinical trials for mCRC.

In the pivotal BOND1 randomized phase II trial, cetuximab, a human-murine chimeric immunoglobulin (Ig) G1 monoclonal antibody, demonstrated activity as a single agent (overall response rate of 11%) and in combination with irinotecan chemotherapy (overall response rate of 23%) in patients with irinotecan-refractory advanced-stage CRC.[2] These results led to the US Food and Drug Administration approval of cetuximab in this patient population.

In recent years, advances in hybridoma technology have stirred an evolution in antibody therapeutics from chimeric to humanized to fully human antibodies generated in transgenic mice. Panitumumab, a fully human anti-EGFR monoclonal antibody, was developed by replacing the murine Ig loci with human sequences via XenoMouse® technology.[3] Panitumumab has an IgG2 isotype, suggesting that its primary mechanism of action is EGFR blockade with no contribution by immunologic-mediated mechanisms. This is in contrast to antibodies of the IgG1 type, such as cetuximab, which can mediate antibody-dependent cell-mediated cytotoxicity. In preclinical studies, panitumumab has been observed to bind EGFR with pmol/L affinity ($K_D = 5 \times 10^{-11}$ mol/L) and inhibit tumor growth more potently than other EGFR-targeted antibodies. Several clinical trials have demonstrated tolerable safety profile and efficacy with panitumumab as a single agent and in combination with chemotherapy in a broad range of solid tumors.[4,5]

In 2005, results from a phase II trial investigating panitumumab as monotherapy in patients with heavily pretreated mCRC demonstrated promising activity.[4] In that study, 148 patients with a median age of 59 years and Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤ 1 received panitumumab 2.5 mg/kg intravenously once every week in 8-week cycles. A partial response (PR) lasting for a median of 4.2 months was seen in 9% of patients, and dis-

ease stabilization was noted in 29% of patients. At a median follow-up of 7 months, median OS was 8.7 months, and median progression-free survival (PFS) was 3.1 months. Panitumumab was well tolerated, with skin toxicity (grade 1/2, 87%; grade 3, 7%) being the most frequently reported adverse event. Three percent of patients in the study had to discontinue panitumumab because of skin-related toxicities. It is of note that, in this trial, only 1 patient experienced an infusion reaction, which resolved rapidly after antihistamine administration and allowed further continuation of panitumumab in subsequent cycles.

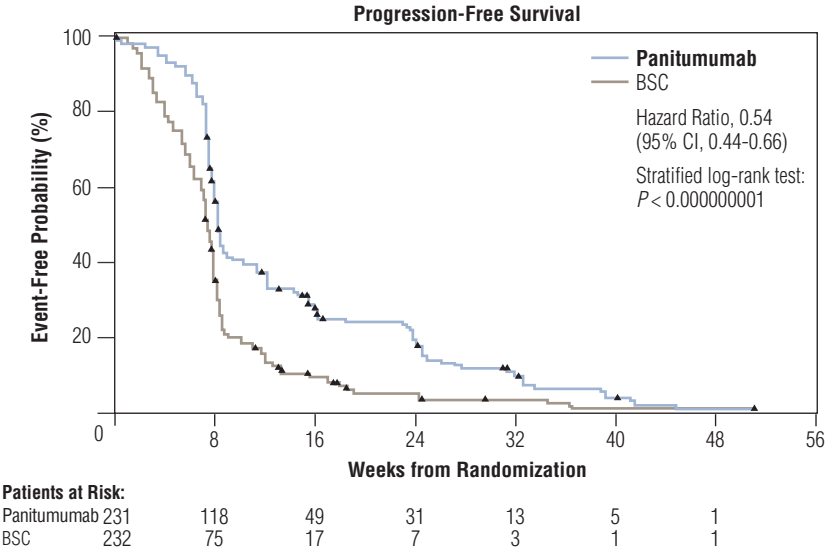
Phase III Trial of Single-Agent Panitumumab plus Best Supportive Care

Based on the encouraging results from the phase II study, a multicenter, randomized phase III trial was conducted to compare the efficacy and safety of panitumumab plus best supportive care (BSC) with BSC alone in patients with 5-fluorouracil–, oxaliplatin-, and irinotecan-refractory mCRC.[6] The results from this trial were presented by Peeters and colleagues at the 97th Annual Meeting of the American Association for Cancer Research held in Washington, DC, in April 2006.

In this study, patients with metastatic colorectal adenocarcinoma expressing EGFR in ≥ 1% of tumor cells were randomized to receive panitumumab 6 mg/kg every 2 weeks plus BSC or BSC alone until disease progression. Crossover to the panitumumab plus BSC arm was allowed for patients who progressed on BSC alone. The primary endpoint of the study was PFS, and secondary endpoints included OS, overall objective response, median duration of response, median time to response, and safety.

A total of 1040 patients were screened, and 463 patients (median age, 63 years) were randomized 1:1 to the 2 treatment arms. Of the 232 patients in the BSC arm, 174 patients (75%) crossed over to the panitumumab plus BSC arm. Of all patients, 63% were men, 67% had colon cancer, and 33% had rectal cancer. Approximately 85% of patients in both treatment arms had an ECOG PS ≤ 1, and 70% had 1-2 metastatic sites. All patients had received ≥ 2 lines of previous chemotherapy, and 35% had received previous adjuvant chemotherapy.

Figure 1: Phase III Trial of Panitumumab plus BSC in mCRC: Progression-Free Survival[6]



At a median follow-up of 19 weeks, treatment with panitumumab plus BSC yielded a 46% decrease in the tumor progression rate compared with BSC alone ($P < 0.000000001$; Figure 1).[6] The PFS rates were consistently higher for the panitumumab plus BSC arm from the first scheduled assessment at week 8 through week 40 (49% vs. 30% for BSC alone at week 8; 18% vs. 5%, respectively, at week 24; and 4% vs. 1%, respectively, at week 40). The favorable effect on PFS with panitumumab plus BSC was demonstrated among all patients, irrespective of age, PS, number of previous treatments, number of metastatic sites, or even EGFR expression levels. Patients treated with panitumumab plus BSC had a significantly higher PR rate of 8% versus 0 for those treated with BSC alone ($P < 0.0001$), with disease stabilization in 28% of patients versus 10%, respectively (Table 1), according to central review.[6] The median time to response with panitumumab plus BSC was 8 weeks, and the median response duration was 17 weeks. Among the patients who crossed over to the panitumumab plus BSC arm, 1% exhibited a complete response, 9% exhibited PRs, and 32% exhibited stable disease; responses in the crossover arm were assessed by the investigators. There was no significant difference in the survival between the 2 arms when all patients were included in the interim analysis, perhaps because of the high number of patients on the BSC arm who crossed over to panitumumab plus BSC treatment. In support of this possibility, a 22% reduction in the risk of death with panitumumab plus BSC was

Table 1: Phase III Trial of Panitumumab plus BSC in mCRC: Efficacy[6]

Efficacy	Panitumumab 6 mg/kg plus Best Supportive Care (n = 231)	Best Supportive Care (n = 232)
Partial Response	19 (8%)	0
Stable Disease	64 (28%)	24 (10%)
Median Time to Response	8 Weeks (2 months)	–
Median Duration of Response	17 Weeks (4 months)	–
Progression-Free Survival	Hazard ratio, 0.54; $P < 0.000000001$	
Overall Survival	Hazard ratio, 0.93; $P = 6065$	

Table 2: Phase III Trial of Panitumumab plus BSC in mCRC: Adverse Events[6]

Adverse Event	Panitumumab 6 mg/kg plus Best Supportive Care (n = 229)	Best Supportive Care (n = 234)
Grade 3/4 Skin Toxicity		
Overall	14	0
Dermatitis acneiform	7	0
Erythema	5	0
Pruritis	2	0
Rash	1	0
Grade 3/4 Hypomagnesemia	3	0

Values are percentages.

observed when patients who crossed over were excluded.

Skin-related toxicities (any grade) were reported in 90% of patients with panitumumab plus BSC compared with 9% with BSC alone. Grade 3/4 skin toxicities were seen in 14% of patients with panitumumab plus BSC (dermatitis acneiform 7%, erythema 5%, pruritis 2%, and rash 1%) versus none with BSC alone (Table 2).[6] Interestingly, patients who had a higher grade of skin toxicity (grades 2-4) had a statistically significant improvement in median OS compared with those with grade 1 toxicity (hazard ratio, 0.61; $P = 0.0278$), which mirrors experience with cetuximab. Other drug-related adverse events included hypomagnesemia (38% vs. 0, respectively); only 3% of these events were considered serious (grade 3/4). One patient had to discontinue treatment because of a grade 2 hypersensitivity reaction. Potential infusion reactions as defined by the National Cancer Institute Common Toxicity Criteria for Adverse Events 3.0 guidelines were low (all grades, 5%), with no grade 3/4 reactions. No patients had detectable levels of anti-panitumumab antibodies after treatment.

Discussion

This recent phase III trial data demonstrate that single-agent panitumumab provides a novel option for the treatment of mCRC. It is of note that this trial provides the first results of a comparison of an EGFR antibody against BSC; in the pivotal randomized phase II trial (BOND1), both treatment arms contained cetuximab.[2] Panitumumab monotherapy significantly improved the PFS rate, particularly in the early phase of treatment before patients in the BSC arm crossed over to panitumumab. Overall, this therapy was well tolerated, and skin toxicity and hypomagnesemia were the primary adverse events associated with panitumumab.

Several observations from this study are noteworthy in evaluating the significance of these results. First of all, the patient population in this study was younger (median age, 63 years) than most patients with advanced CRC, and the majority of the study population had a good PS going into the trial (ECOG PS 0/1, 86%). Furthermore, although there was a 46% decrease in the tumor progression rate with panitumumab therapy compared with BSC, median PFS duration appeared to be comparable with cetuximab monotherapy (approximately 8 weeks vs. 6 weeks).[2,6] Similarly, the overall response rates for panitumumab and cetuximab as single agents are comparable in previously treated patient populations (8% and 11%, respectively). There was no OS advantage conferred by panitumumab treatment in this phase III study; however, this was not a primary endpoint of the study, and differences in survival might have been blurred by the fact that the majority of patients (75%) crossed over to the panitumumab treatment arm upon progression. Lastly, panitumumab did not elicit severe infusion reactions, whereas cetuximab therapy is more likely to cause hypersensitivity reactions because of the formation of human antimouse antibodies. Therefore, panitumumab could be administered without hypersensitivity premedication. In addition, the phase III trial used panitumumab in an every-2-week schedule, which bodes well for combination with modern 2-weekly chemotherapy regimens such as FOLFOX (5-fluorouracil/oxaliplatin/leucovorin) and FOLFIRI (5-fluorouracil/irinotecan/leucovorin). It should be emphasized, though, that data on panitumumab in combination with conventional chemotherapy are quite limited thus far. It has yet to be demonstrated whether panitumumab shows the same synergistic effect in combination with irinotecan as cetuximab does.

Several ongoing trials are evaluating the efficacy of panitumumab in combination with chemotherapy and other biologic agents as first-line and adjuvant therapy for CRC. A phase III trial (PACCE [Panitumumab Advanced Colorectal Cancer Evaluation]) has been initiated to evaluate the FOLFOX or FOLFIRI regimen (physician's choice) plus bevacizumab with or without panitumumab in patients with previously untreated mCRC.[7] The use of panitumumab in a future generation of adjuvant trials in stage II/III colon cancer is in discussion. Continued clinical studies of the optimal sequencing with chemotherapy and direct comparison of these EGFR-targeted agents in patients with mCRC are warranted.

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