Panitumumab in Patients with KRAS Wild-Type Colorectal Cancer after Progression on Cetuximab

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ABSTRACT

Purpose Cetuximab and panitumumab are monoclonal antibodies that target the epidermal growth factor receptor (EGFR) and are approved for the treatment of patients with KRAS wild-type metastatic colorectal cancer. There are no data that describe the activity of panitumumab in patients with progressive disease on cetuximab. We performed a single-arm phase II trial of panitumumab in patients with KRAS wild-type metastatic colorectal cancer that had progressed on prior cetuximab.

Patients and Methods We used a two-stage study design to treat patients with panitumumab at 6 mg/kg every 14 days (cycle length = 28 days). Treatment was continued until disease progression, death, inability to tolerate panitumumab, or study withdrawal. The primary endpoint was response rate; secondary endpoints included progression-free survival and overall survival. Twenty patients were treated in the first stage, with plans to treat an additional twelve patients if there was at least one objective response. We collected blood samples at baseline and prior to cycles 2 and 3 to evaluate for the presence of anti-cetuximab and anti-panitumumab antibodies.

Results We treated twenty patients for a median of two cycles (range 1–4). No patients responded, and 45% had a best response of stable disease (no progression for at least two cycles). Median progression-free survival was 1.7 months and median overall survival was 5.2 months. Panitumumab was well tolerated. Thirteen patients (65%) had grade 1–2 dry skin or rash, and three patients had treatment-related grade 3 toxicities (one each with hyperglycemia, hyperbilirubinemia, and hypokalemia). No patients had detectable anti-cetuximab antibodies at any time point; one patient developed anti-panitumumab antibodies.

Conclusions Panitumumab has minimal benefit in patients with KRAS wild-type metastatic colorectal cancer that has progressed on prior cetuximab.

Discussion Both cetuximab and panitumumab competitively inhibit ligand binding to EGFR, thereby promoting receptor internalization and blocking receptor-mediated signaling. Although the two agents have never been compared directly in a randomized clinical trial, they produce similar response rates when used alone as well as in combination with cytotoxic agents. Cetuximab is a chimeric antibody with approximately 30% murine protein, while panitumumab is a fully human monoclonal antibody. Correspondingly, rates of severe hypersensitivity reactions are somewhat increased with cetuximab (3%) compared to panitumumab (1%). However, the potential efficacy of panitumumab in patients who have developed disease

progression on cetuximab has been an open question. Metges et al. (PANERB trial) prospectively treated 32 KRAS wild-type metastatic colorectal cancer patients with cetuximab and irinotecan followed by panitumumab monotherapy after progression. Remarkably, the authors reported an objective response rate of 22% to panitumumab, including a disease control rate (objective response plus stable disease) of 73% in 11 patients who had previously responded to cetuximab and irinotecan. In contrast, we found no responders and a stable disease rate of 45% with a median duration of only 1.7 months in our trial of 20 patients. Moreover, no patients had detectable anti-cetuximab antibodies at baseline. It is not clear to what extent the PANERB trial included patients without objective disease progression on cetuximab or for whom cetuximab-containing regimens may have been ceased due to toxicity in the absence of disease progression. In both circumstances, retreatment with panitumumab may be expected to demonstrate some degree of clinical activity. In our study, disease progression after at least 4 weeks of cetuximab documented radiographically or by increased carcinoembryonic antigen (CEA) levels was required for inclusion in order to ensure that the study population demonstrated unequivocal evidence of progression on cetuximab. While it remains possible that a small subset of patients may benefit from panitumumab after progression on cetuximab, our results suggest that this approach should not be adopted until predictive biomarkers for panitumumab response in this setting have been discovered and validated. Until then, patients who develop progression on cetuximab should be enrolled in trials of novel agents.

Waterfall plot showing best response assessment. RECIST data for 16 of the 20 patients enrolled. Four patients who had only a baseline scan are not included.

Full Clinical Trial Report, including disclosures, may be found online at: <http://clinicaltrialreports.theoncologist.com/reports/t11-452ctr-wadlow>

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