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Clinical Trial Results

Phase II Study of Panitumumab in RAS Wild-Type Metastatic Adenocarcinoma of Small Bowel or Ampulla of Vater

Pat Gulhati,[a] Kanwal Raghav,[b] Rachna Shroff,[b] Gauri Varadhachary,[b] Milind Javle,[b] Wei Qiao,[c] Huamin Wang,[d] Jeffrey Morris,[c] Robert Wolff,[b] Michael J. Overman[b]

[a]Hematology/Oncology Fellowship Program, Division of Cancer Medicine, Departments of [b]Gastrointestinal Medical Oncology, Division of Cancer Medicine, [c]Biostatistics and Applied Mathematics, and [d]Pathology, The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Trial Information

- **ClinicalTrials.gov Identifier**: NCT01202409
- **Sponsor(s)**: Amgen
- **Principal Investigator**: Michael J. Overman
- **IRB Approved**: Yes

Lessons Learned

- Panitumumab has no clinical activity in metastatic RAS wild-type small bowel adenocarcinoma (SBA) and ampullary adenocarcinoma (AAC), possibly due to the foregut and midgut derivation of small bowel and ampulla.
- These results, along with findings from genomic characterization of SBA, suggest that SBA represents a unique intestinal malignancy and treatments should not be habitually extrapolated from colorectal cancer.
- Further studies evaluating the benefit of targeted therapies exclusively in SBA and AAC are warranted.

Abstract

Background. Given the benefit of epidermal growth factor receptor (EGFR) monoclonal antibodies in colorectal cancer (CRC), we sought to evaluate the efficacy of panitumumab in metastatic RAS wild-type small bowel adenocarcinoma (SBA) and ampullary adenocarcinoma (AAC).

Methods. We conducted a single-center, open-label, single-arm, Bayesian phase II trial. The primary objective was response rate (RR). Panitumumab was administered at a dose of 6 mg/kg intravenously (IV) every 14 days.

Results. Nine patients (male/female 7:2, median age: 61 years [range: 40–74], Eastern Cooperative Oncology Group [ECOG] performance status 0/1: 2/7) were enrolled from September 2013 to October 2015. One patient had AAC (pancreaticobiliary subtype) and eight patients had SBA (three duodenal, five jejunal/ileal). Acneiform rash was the most common toxicity. The study was stopped early due to futility with no responses, stable disease (SD) in two patients, and progression of disease (PD) in seven patients. Median progression-free survival (PFS) and overall survival (OS) were 2.4 and 5.7 months, respectively. No patients had extended RAS mutations (exons 2/3/4), but two patients had BRAF G469A and one patient had PIK3CA H1074R mutations.

Conclusion. Panitumumab had no clinically meaningful activity in patients with metastatic RAS wild-type SBA and AAC. Our findings may relate to the primarily midgut and foregut derivation of the small bowel and ampulla. ***The Oncologist*** 2018;23:277–e26

Discussion

Panitumumab is a U.S. Food and Drug Administration-approved anti-EGFR monoclonal antibody with a demonstrated RR of 31% and improvement in mean PFS from 1.7 to 5.2 months when compared with best supportive care in RAS wild-type refractory metastatic CRC. Given their rarity and proximity to the large bowel, SBA and AAC are often treated in a similar manner to CRC with treatment data extrapolated from studies in CRC.

We performed a single-arm trial evaluating efficacy of panitumumab monotherapy in refractory metastatic RAS wild-type SBA and AAC. The primary endpoint of this study was RR. A sample size of 17 was required to demonstrate an RR of 17% using a binomial one-sample test with two-sided alpha of 0.05 and power of 90%. Between September 2013 and October 2015, nine patients were enrolled. Per continuous Bayesian monitoring criteria, the study was stopped early when the probability of determining a 17% RR was $<5\%$.

Median age of the study population was 61 (range 40–74) years. One patient had AAC (pancreaticobiliary subtype) and

Correspondence: Michael J. Overman, M.D., Department of Gastrointestinal Medical Oncology, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Boulevard, Unit 426, Houston, Texas 77030, USA. Telephone: 713-792-2828; e-mail: moverman@mdanderson.org Received September 18, 2017; accepted for publication October 13, 2017; published Online First on December 19, 2017. http://dx.doi.org/10.1634/theoncologist.2017-0568

eight patients had SBA (duodenal in three, jejunal/ileal in five). Of nine patients, poorly differentiated histology was present in five (55.6%) and mucinous histology was present in three (33.3%). Inflammatory bowel disease was present in one (11.1%) patient, and two (22.2%) patients had a known history of Lynch syndrome.

In nine patients, panitumumab demonstrated no responses, two SD, and seven PD (Fig. 1). Median PFS was 2.4 months and median OS was 5.7 months at median follow-up time of 16.6 months. Treatment was otherwise well tolerated, with expected common toxicities of acneiform rash (100%), anemia (33%), fatigue (22%), hypomagnesemia (22%), and skin infection (22%).

We evaluated several key mutational hotspots (*BRAF*, *PIK3CA* and *ERBB2* genes) associated with resistance to EGFR blockade in RAS wild-type metastatic CRC and identified two patients with *BRAF G469A* mutation, and one patient with *PIK3CA H1047R* mutation. Given recent findings suggesting that right-sided colon cancers (midgut derivation) benefit less from anti-EGFR therapy compared with left-sided colon cancers (hindgut derivation), we propose that our findings may relate to the primarily midgut (distal duodenum to ileum) and foregut (proximal duodenum) derivation of the small bowel and ampulla.

To our knowledge, this is the first prospective clinical trial evaluating anti-EGFR therapy in SBA and AAC. Taken together with recent findings from the first large-scale genomic comparison of SBA with colorectal and gastric cancers, we propose that SBA is a molecularly unique intestinal malignancy and treatment paradigms should not be extrapolated from CRC to SBA and AAC without dedicated investigations. Further studies evaluating the benefit of targeted therapies in SBA and AAC are warranted.

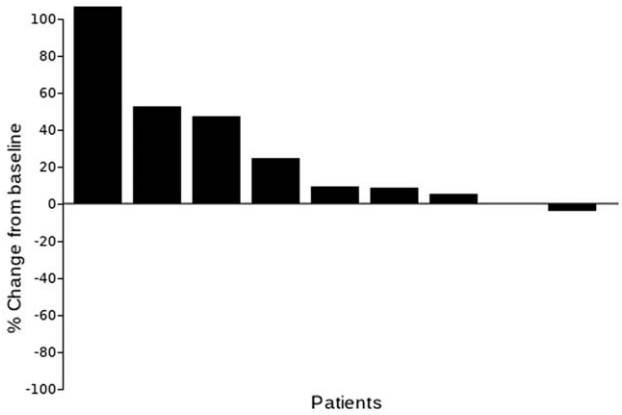

Figure 1. Waterfall plot with best tumor response as per Response Evaluation Criteria in Solid Tumors v1.1.

Trial Information	
Disease	Small bowel and ampullary cancer
Stage of Disease/Treatment	Metastatic/advanced
Prior Therapy	1 prior regimen
Type of Study - 1	Phase II
Type of Study - 2	Single arm
Primary Endpoint	Overall response rate
Secondary Endpoint	Progression-free survival
Secondary Endpoint	Overall survival
Secondary Endpoint	Toxicity

Additional Details of Endpoints or Study Design

Study Design The study was an open-label, single-arm, single-institution, Bayesian phase II study conducted at University of Texas MD Anderson Cancer Center. This clinical trial was originally designed to evaluate the addition of panitumumab to capecitabine and oxaliplatin in patients with SBA and AAC. Oxaliplatin was dosed at 110 mg/m^2 on day 1, panitumumab was dosed at 9 mg/kg on day 1, and capecitabine 750 mg/m^2 p.o. b.i.d. on days 1–14 every 21 days (1 cycle). However, due to toxicity, the trial was modified to investigate single-agent panitumumab administered at a dose of 6 mg/kg intravenously every 14 days (1 cycle). Imaging studies were conducted every 4 cycles. Treatment was continued until progression of disease, intercurrent illness preventing further administration of treatments, severe predefined treatment-related toxicities, or treatment delay of more than 4 weeks due to toxicity.

Statistical Analysis The primary endpoint of this study was RR to single-agent panitumumab per Response Evaluation Criteria In Solid Tumors (RECIST) v1.1 criteria [1] in the evaluable population. Data from a previous study of single-agent panitumumab in KRAS wild-type CRC demonstrated a 17% response rate [2, 3]. Assuming a null hypothesis of $\leq$1% RR, a sample size of 17 patients would be able to demonstrate a RR of 17% using a binomial one-sample test with two-sided alpha of 0.05 and power of 90%. Continuous Bayesian monitoring for efficacy was conducted, requiring study termination if the probability of RR of 17% was $<$5% [4, 5]. Monitoring for response allowed up to 8 cycles from their first dose prior to nonresponder determination and study enrollment was continuous. Evaluable patients were defined as patients who had restaging imaging to enable response determination.

Secondary endpoints included toxicity rate, PFS, and OS. Toxicities to be included in toxicity monitoring included definite or probably treatment-related grade 3 or 4 nonhematological toxicities, excluding grade 3 rash and grade 3 hypomagnesemia, which are both expected and manageable toxicities. PFS was defined as the interval between start of treatment to the date of first documentation of progression or symptomatic deterioration or death due to any cause. OS was defined as the time from first study treatment to date of death or last follow-up. Comparisons were conducted using Wilcoxon rank sum test, Fisher's exact test, or log-rank test. Kaplan-Meier curves were used to estimate unadjusted OS and PFS time distributions. All computations were carried out in SAS version 9.4 (SAS Institute Inc., Cary, NC) and TIBCO Spotfire S+ version 8.2 (TIBCO Software Inc., Palo Alto, CA).

Investigator's Analysis	Inactive because results did not meet primary endpoint

Drug Information for Phase II Treatment	
Drug 1	
Generic/Working Name	Panitumumab
Trade Name	Vectibix
Company Name	Amgen
Drug Type	Antibody
Drug Class	EGFR
Dose	6 milligrams (mg) per kilogram (kg)
Route	IV
Schedule of Administration	6 mg/kg intravenously every 14 days

Patient Characteristics for Phase II Treatment	
Number of Patients, Male	7
Number of Patients, Female	2
Stage	IV
Age	Median (range): 61 (40–74)
Number of Prior Systemic Therapies	Median (range): 1
Performance Status: ECOG	0 — 2
	1 — 7
	2 — 0
	3 — 0
	Unknown — 0

Primary Assessment Method for Phase II Treatment	
Title	Total patient population
Number of Patients Screened	9
Number of Patients Enrolled	9
Number of Patients Evaluable for Toxicity	9
Number of Patients Evaluated for Efficacy	9
Evaluation Method	RECIST 1.1
Response Assessment CR	$n = 0$ (0%)
Response Assessment PR	$n = 0$ (0%)
Response Assessment SD	$n = 2$ (22.2%)
Response Assessment PD	$n = 7$ (77.8%)
Response Assessment OTHER	$n = 0$ (0%)
(Median) Duration Assessments PFS	16.6 months
(Median) Duration Assessments OS	16.6 months

Phase II Treatment Adverse Events

	All Dose Levels, Cycle 1						
Name	**NC/NA**	**1**	**2**	**3**	**4**	**5**	**All grades**
Pruritus	33%	56%	11%	0%	0%	0%	67%
Nausea	78%	22%	0%	0%	0%	0%	22%
Skin infection	78%	0%	22%	0%	0%	0%	22%
Hypomagnesemia	34%	44%	22%	0%	0%	0%	66%
Fatigue	78%	0%	22%	0%	0%	0%	22%
Anemia	56%	11%	22%	11%	0%	0%	44%
Rash acneiform	0%	100%	0%	0%	0%	0%	100%

Number of patients who experienced toxicities ($n = 9$).
Abbreviation: NC/NA, no change from baseline/no adverse event.

Assessment, Analysis, and Discussion

Completion	Study completed
Investigator's Assessment	Inactive because results did not meet primary endpoint

Small bowel adenocarcinoma (SBA) and ampullary adenocarcinoma (AAC) are rare tumors with an estimated incidence of 10,190 in the U.S. in 2017, of which approximately 40% will be adenocarcinomas [6]. The vast majority of patients present with metastatic disease secondary to frequent delays in diagnosis [6]. Although there are no randomized clinical trials comparing the efficacy of various chemotherapy regimens in patients with advanced SBA, there have been five prospective studies, four of which used fluoropyrimidine and oxaliplatin as the backbone chemotherapy [7–11]. We recently published the first prospective clinical trial evaluating the use of targeted therapies in SBA and AAC, in which we found that capecitabine and oxaliplatin (CAPOX) with bevacizumab is a safe and effective regimen [11].

Epidermal growth factor receptor (EGFR) plays a key role in tumor-associated proliferation, angiogenesis, invasion/metastasis, antiapoptosis, and chemotherapy resistance [12]. EGFR is expressed in approximately 67% cases of AAC [13] and 72% cases of SBA [14]. Panitumumab is a U.S. Food and Drug Administration-approved anti-EGFR monoclonal antibody that demonstrated response rate (RR) of 31% and improvement in mean progression-free survival (PFS) from 1.7 to 5.2 months when compared with best supportive care in RAS wild-type refractory metastatic colorectal cancer (CRC) patients [2, 3]. Given their rarity and proximity to the large bowel, SBA and AAC are treated in a similar manner to CRC [15]. Although several case reports have suggested benefit from anti-EGFR therapies in SBA [16–18], the role of anti-EGFR targeted agents has never been prospectively studied in the treatment of SBA and AAC.

This clinical trial was originally designed to evaluate the addition of panitumumab to CAPOX in patients with SBA and AAC. We initially enrolled three patients (two with SBA, one with AAC [pancreaticobiliary subtype]) to receive CAPOX (dosing as described previously [7]) along with panitumumab (9 mg/kg intravenously [IV] on day 1 of each 21-day cycle). Two of three patients had partial response at the time of the first restaging scan, whereas one of three patients had progression of disease. However, all three patients developed grade 3 toxicities, which led to dose reduction and/or discontinuation of treatment on protocol. More specifically, the first patient had grade 3 nausea and grade 3 vomiting requiring dose reduction of oxaliplatin, the second patient had grade 2 nausea and grade 3 diarrhea requiring dose reduction of both oxaliplatin and capecitabine, and the third patient had grade 3 mucositis, grade 2 hand-foot syndrome, and grade 3 paronychia requiring dose reduction of capecitabine and discontinuation of panitumumab. Based on the aforementioned toxicities and the subsequent publications of the COIN and REAL3 trials, which suggested an antagonistic interaction between oxaliplatin, capecitabine, and anti-EGFR antibodies [19, 20], we modified the protocol to maximize patient safety and instead performed a single-arm trial evaluating efficacy of panitumumab monotherapy dosed at 6 mg/kg IV on day 1 of each 14-day cycle in refractory metastatic RAS wild-type SBA and AAC.

Between September 2013 and October 2015, nine patients with advanced SBA or AAC were enrolled. The baseline characteristics of the study population are listed in Table 1. The median age of the study population was 61 (range 40–74) years. Of nine patients, one (11.1%) had AAC (pancreaticobiliary subtype) and eight (88.9%) had SBA (duodenal in three, jejunal/ileal in five). Poorly differentiated histology was present in five (55.6%) patients and mucinous histology was present in three (33.3%) patients. Inflammatory bowel disease was present in one (11.1%) patient, and two (22.2%) patients had a known history of Lynch syndrome.

Outcomes related to the efficacy of this regimen are listed in Table 2. The primary endpoint for this study was RR. We found that panitumumab has limited clinical activity in this population with no responses noted; two patients had stable disease, whereas the remaining seven patients had progression of disease. Figure 1 depicts a waterfall plot of best tumor response per Response Evaluation Criteria In Solid Tumors criteria. Secondary endpoints included PFS, overall survival (OS), and toxicity. At a median follow-up time of 16.6 months, median PFS was 2.4 months (95% confidence interval [CI]: 1.5 months – not applicable [N/A]) and median OS was 5.7 months (95% CI: 2.7 months – N/A; Fig. 2; Table 2). The most common treatment-related grade 1–4 adverse events are listed in Table 3. Treatment was well tolerated, with the most common toxicity being grade 1 acneiform rash (100% of patients). The most common grade 2/3 toxicities were anemia (33%), fatigue (22%), hypomagnesemia (22%), and skin infection (22%). There were no treatment-related deaths.

We evaluated several key mutational hotspots associated with resistance to EGFR blockade in metastatic CRC [21]. Extended RAS mutational testing identified no patients with mutations in KRAS or NRAS. Further genomic analysis of genes relevant to anti-EGFR activity (BRAF, PIK3CA and ERBB2) identified two of nine patients with BRAF G469A mutation, one of nine patients with PIK3CA H1047R mutation, and no patients with ERRB2 mutations. We recently reported the largest genomic profiling of SBA along with comparison to neighboring intestinal tumors, which demonstrated that SBA represents a unique genomic entity with distinct alterations compared with CRC [22]. In that study, we reported mutation rates of 9.1% (29/317), 16.1% (51/317), and 9.5% (30/317) for BRAF, PIK3CA and ERRB2 in SBA, respectively [22]. Given the large number of targetable genomic alterations (91% of patients) noted in SBA, further studies evaluating the benefit of targeted therapies in SBA and AAC are warranted [22].

In conclusion, panitumumab is a well-tolerated treatment with limited clinical activity in SBA and AAC. Toxicities were limited and there were no treatment-related deaths. To our knowledge, this is the first prospective clinical trial evaluating the use of EGFR-targeted antibodies in SBA and AAC. Given recent findings suggesting that right-sided colon cancers (midgut

derivation) benefit less from anti-EGFR therapy compared with left-sided colon cancers (hindgut derivation) [23], we propose that our findings may relate to the primarily midgut (distal duodenum to ileum) and foregut (proximal duodenum) derivation of the small bowel and ampulla.

Disclosures

Michael J. Overman: Amgen (RF). The other authors indicated no financial relationships.

(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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Figures and Tables

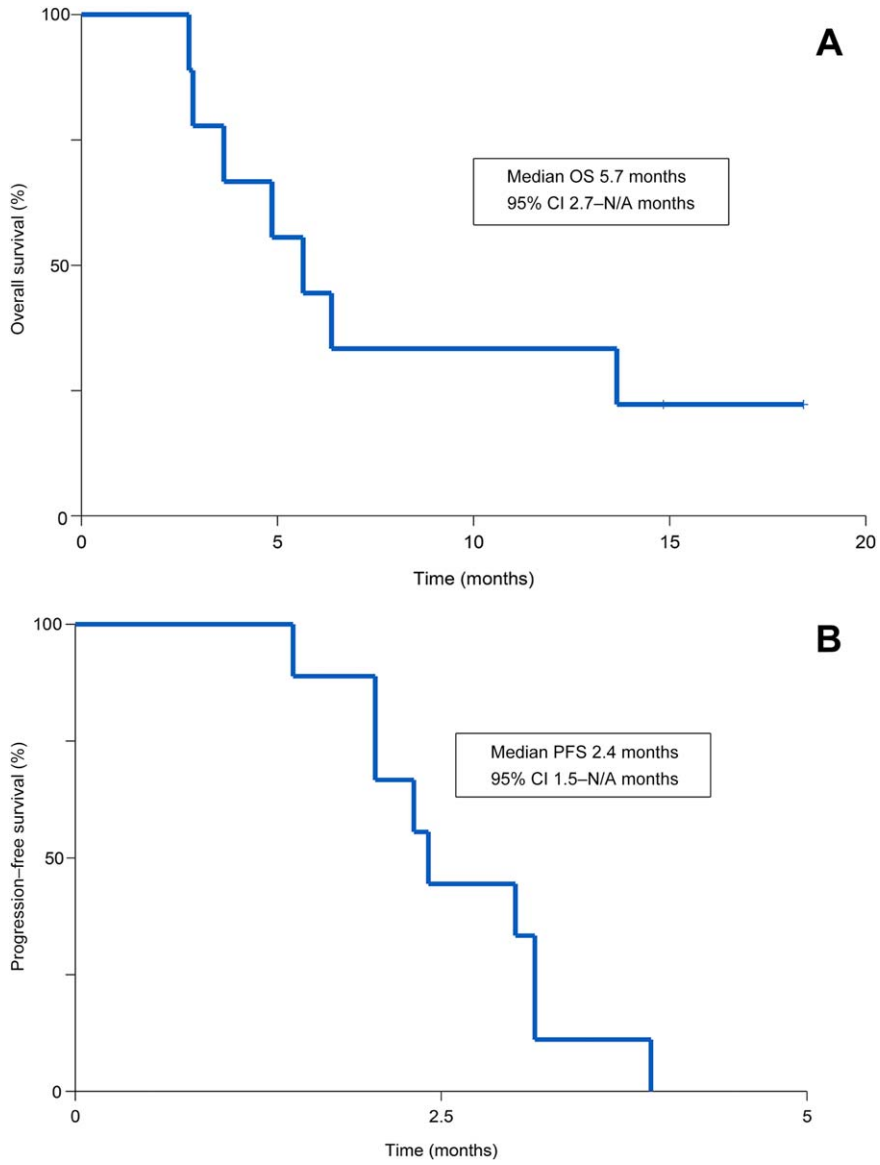

Figure 2. Kaplan-Meier estimates of overall survival **(A)** and progression-free survival **(B)** for panitumumab in metastatic RAS wild-type small bowel adenocarcinoma and ampullary adenocarcinoma.

Abbreviations: CI, confidence interval; N/A, not applicable; OS, overall survival; PFS, progression-free survival.

Table 1. Baseline patient characteristics ($n = 9$)

Variable	Patients, *n* (%)
Median age, years (range)	61 (40–74)
ECOG performance status	
0	2 (22.2)
1	7 (77.8)
Grade	
Moderate	4 (44.4)
Poor	5 (55.6)
Mucinous features	
None	6 (66.7)
Present	3 (33.3)
History of inflammatory bowel disease	
No	8 (88.9)
Yes	1 (11.1)
History of Lynch Syndrome	
No	7 (77.8)
Yes	2 (22.2)
Race	
Black	0 (0)
Hispanic	1 (11.1)
White	8 (88.9)
Gender	
Female	2 (22.2)
Male	7 (77.8)
Location	
Ampulla	1 (11.1)
Small bowel	8 (88.9)
Liver metastases	
No	7 (77.8)
Yes	2 (22.2)
Peritoneal metastases	
No	8 (88.9)
Yes	1 (11.1)

Table 2. Efficacy analysis ($n = 9$)

Outcome measure	Patients, *n* (%)
Response	
Yes	0 (0)
No	9 (100)
Median progression-free survival, months (95% CI)	2.4 (1.5–N/A)
Median overall survival, months (95% CI)	5.7 (2.7–N/A)

Abbreviations: CI, confidence interval; N/A, not applicable.

Table 3. Number of patients who experienced toxicities ($n = 9$)

	Toxicity grade			
Toxicity type	**1**	**2**	**3**	**4**
Hematologic				
Anemia	1	2	1	0
Thrombocytopenia	0	0	0	0
Neutropenia	0	0	0	0
Nonhematologic				
Abdominal pain	0	0	0	0
ALT elevation	0	0	0	0
Alkaline phosphatase elevation	0	0	0	0
Anorexia	0	0	0	0
AST elevation	0	0	0	0
Total bilirubin elevation	0	0	0	0
Cough	0	0	0	0
Diarrhea	0	0	0	0
Fatigue	0	2	0	0
Headache	0	0	0	0
Hypertension	0	0	0	0
Hypomagnesemia	4	2	0	0
Nausea	2	0	0	0
Paronychia	0	1	0	0
Pruritus	5	1	0	0
Acneiform rash	9	0	0	0
Skin fissures	0	0	0	0
Skin infection	0	2	0	0

Abbreviations: ALT, alanine transaminase; AST, aspartate transaminase.

