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FDA Drug Approval Summary: Panitumumab (Vectibix[™])

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Key Words. Panitumumab • Colorectal cancer • Advanced resistant/refractory disease • Drug approval

LEARNING OBJECTIVES

After completing this course, the reader will be able to:

1. Add panitumumab (Vectibix[™]) to the armamentarium of drugs for colorectal cancer.
2. Identify the patient group that is eligible for panitumumab therapy.
3. Identify biologic agents that have activity in colorectal cancer.
4. List the FDA criteria for the analysis of progression-free survival and for accelerated approval.

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ABSTRACT

On September 27, 2006, the U.S. Food and Drug Administration granted approval to panitumumab (Vectibix[™], Amgen, Inc., Thousand Oaks, CA) for the treatment of patients with epidermal growth factor receptor (EGFR)-expressing, metastatic colorectal carcinoma with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. Panitumumab approval is based on the results of a single, open-label, randomized, multinational study that enrolled 463 patients with EGFR-expressing (at least 1+ membrane staining in $\geq 1\%$ of tumor cells) metastatic colorectal cancer. Patients were randomized to either best supportive care (BSC) alone or BSC plus panitumumab, 6 mg/kg i.v., every other week. The primary study endpoint was progression-free survival (PFS), determined by an independent review committee that was blinded as to treatment assignment. BSC patients who progressed were eligible to receive panitumumab.

The study patients' median age was 62 years, with 40%

aged ≥ 65 ; 63% were male, 99% were white, 86% had a baseline Eastern Cooperative Oncology Group performance status score of 0 or 1, and 67% had colon cancer. The median time from diagnosis of metastases was approximately 19 months and the median number of prior therapies was 2.4. The PFS duration was significantly longer among patients randomized to receive panitumumab in addition to BSC ($n = 231$) compared with BSC alone ($n = 232$). The median and mean PFS times were 56 and 96.4 days, respectively, for patients receiving panitumumab and 51 and 59.7 days, respectively, for patients receiving BSC alone. Nineteen partial responses (8%, 95% confidence interval [CI], 5.3%–12.5%) were observed in panitumumab treated patients. The median duration of response was 17 weeks (95% CI, 16–25 weeks). Approximately 75% of patients in the BSC alone arm crossed over to receive panitumumab after disease progression. There was no difference in overall survival between the two study arms. The most common adverse events were skin rash, hypomagnesemia, paronychia, fatigue, abdominal pain,

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nausea, and diarrhea. The most serious adverse events were pulmonary fibrosis, severe dermatologic toxicity complicated by infectious sequelae and septic death, infu-

sion reactions, abdominal pain, hypomagnesemia, nausea, vomiting, diarrhea, and constipation. *The Oncologist* 2007; 12:577–583

Disclosure of potential conflicts of interest is found at the end of this article.

INTRODUCTION

Panitumumab is a human IgG₂ monoclonal antibody that binds to the epidermal growth factor receptor (EGFR), a transmembrane receptor tyrosine kinase of the ErbB (HER) family [1]. Binding of panitumumab to the EGFR inhibits phosphorylation and activation of EGFR-associated kinases, including EGF and transforming growth factor- α , resulting in inhibition of cell growth and decreased production of growth factors such as vascular endothelial growth factor and interleukin-8. EGFR is constitutively expressed in many normal epithelial tissues, including the skin follicle, placenta, and mammary gland [2–4]. Overexpression of EGFR is also detected in many human cancers including those of the colon and rectum [5–7].

Panitumumab administered as a single agent exhibits nonlinear pharmacokinetics [8]. Following a single 1-hour infusion the area under the concentration–time curve (AUC) increased in a greater than dose-proportional manner, and clearance (CL) of panitumumab decreased from 30.6 ml/kg per day to 4.6 ml/kg per day as the dose increased from 0.75 mg/kg to 9 mg/kg. However, at doses above 2 mg/kg, the AUC of panitumumab increased in an approximately dose-proportional manner.

Following the recommended dose regimen (6 mg/kg given once every 2 weeks as a 1-hour infusion), panitumumab concentrations reached steady-state levels by the third infusion with mean ($\pm$ standard deviation [SD]) peak and trough concentrations of 213 ± 59 and 39 ± 14 $\mu\text{g/ml}$, respectively. The mean ($\pm$ SD) $\text{AUC}_{0-\tau}$ and CL were $1,306 \pm 374$ $\mu\text{g} \cdot \text{day/ml}$ and 4.9 ± 1.4 ml/kg per day, respectively. The elimination half-life was approximately 7.5 days (range, 3.6–10.9 days).

A population pharmacokinetic analysis was performed to explore the potential effects of selected covariates on panitumumab pharmacokinetics. Results suggest that age, gender, race, mild-to-moderate renal dysfunction, mild-to-moderate hepatic dysfunction, and EGFR membrane-staining intensity (1+, 2+, 3+) in tumor cells had no apparent impact on the pharmacokinetics of panitumumab [8].

PATIENTS AND METHODS

A phase III, randomized, controlled, open-label study evaluating the efficacy and safety of panitumumab plus best supportive care (BSC) versus BSC alone was submitted.

This trial enrolled 463 patients, at 81 non-U.S. sites, who had progressed on or following treatment with regimen(s) containing a fluoropyrimidine, oxaliplatin, and irinotecan. Patients had to have received at least two but no more than three prior chemotherapy regimens for metastatic colorectal cancer and they had to have measurable disease. All patients were required to have EGFR expression defined as at least 1+ membrane staining in $\geq 1\%$ of tumor cells by the Dako EGFR pharmDx™ (Dako North America, Inc., Carpinteria, California) test kit. The first patient was enrolled on January 16, 2004 and the last patient was enrolled on March 16, 2005. The date of data cutoff was June 20, 2005. Thirty-two subjects were still receiving treatment at the time of the data cutoff.

Patients were randomized 1:1 to receive panitumumab at a dose of 6 mg/kg given once every 2 weeks plus BSC ($n = 231$) or BSC alone ($n = 232$) until investigator-determined disease progression, intolerable side effects, or other reason for discontinuation. Randomization was stratified based on Eastern Cooperative Oncology Group (ECOG) performance status (PS) score (0–1 versus 2) and geographic region (western Europe, eastern/central Europe, or other). Patients randomized to the panitumumab arm were to receive panitumumab without routine premedication at a dose of 6 mg/kg (based on actual baseline body weight) in a minimum of 100 ml normal saline every other week, over 60–90 minutes (depending on volume). Patients in the panitumumab arm also received BSC, which included antibiotics, analgesics, radiation therapy for pain control limited to bone metastases only, corticosteroids, transfusions, psychotherapy, growth factors, palliative surgery, or any symptomatic therapy, as clinically indicated, at the discretion of the investigator according to institutional norms.

The primary endpoint for the study was progression-free survival (PFS). Secondary endpoints were survival time, objective response, and response duration. PFS and response were verified by an independent radiology review committee who were blinded to the assigned treatment arm and to the local assessment.

Upon investigator-determined disease progression, patients in the BSC alone arm were permitted to receive panitumumab (6 mg/kg every 2 weeks). All patients were followed for survival approximately every 3 months for up to 48 months from randomization.

Table 1. Patient demographics and disease characteristics

	P + BSC (n = 231), n (%)	BSC (n = 232), n (%)	Total (n = 463), n (%)
Gender			
Male	146 (63)	148 (64)	294 (63)
Age			
Median (range)	62.0 (27–83)	63.0 (27–82)	62.0 (27–83)
>65	94 (42)	91 (39)	187 (40)
Race			
White	229 (99)	228 (98)	457 (99)
Primary site			
Colon	153 (66)	157 (68)	310 (67)
Rectum	78 (34)	75 (32)	153 (33)
ECOG PS score			
0	107 (46)	80 (34)	187 (40)
1	94 (41)	115 (50)	209 (45)
2	29 (13)	35 (15)	64 (14)
3	1 (0)	2 (1)	3 (1)
n of disease sites			
1	64 (28)	53 (23)	117 (25)
2	97 (42)	108 (47)	205 (44)
3	45 (19)	51 (22)	96 (21)
4	23 (10)	13 (6)	36 (8)
5	2 (1)	5 (2)	7 (2)
Metastatic site			
Liver	178 (77)	194 (84)	372 (80)
Lung	147 (64)	139 (60)	286 (62)
Lymph nodes	52 (23)	66 (28)	118 (25)
Abdomen	37 (16)	29 (17)	76 (16)
Months since metastatic diagnosis			
Median	18.9	19.3	19.1
Range	5.2–129.2	4.6–68.6	4.6–129.2
Prior metastatic regimens			
1–2	147 (64)	144 (62)	290 (63)
3–4	81 (35)	87 (38)	169 (37)
>5	3 (1)	1 (0)	4 (0)

Abbreviations: BSC, best supportive care; ECOG PS, Eastern Cooperative Oncology Group performance status; P, panitumumab.

RESULTS

Demographics and disease characteristics of study patients are summarized in Table 1. While the two groups were generally similar, patients randomized to the panitumumab plus BSC arm tended to have a lower ECOG PS score, fewer disease sites, and less frequent liver involvement. The median number of prior metastatic regimens in both arms was 2.4.

EGFR expression levels are shown in Table 2. Most pa-

tients had a high level of EGFR expression, with 74% having $\geq 10\%$ positive staining, 77% having $\geq 10\%$ of cells with membrane staining, and 70% having a maximum staining intensity of 2+ or 3+. The two arms were similar in the distribution of percent staining, percent cells with membrane staining, and maximum staining intensity.

PFS results are summarized in Table 3 and in Figure 1. There was a statistically significant difference in PFS favoring the panitumumab plus BSC arm ($p < .0001$). The dif-

Table 2. Epidermal growth factor receptor expression level

	P + BSC (n = 231)	BSC (n = 232)	Total (n = 463)
Percentage of cells with positive staining			
<1%	2 (<1)	1 (<1)	3 (<1)
1%–9%	57 (25)	57 (25)	114 (25)
10%–20%	65 (28)	75 (32)	140 (30)
>20%–35%	14 (6)	28 (12)	42 (9)
>35%	93 (40)	71 (30)	164 (35)
Percentage of cells with membrane staining			
<1%	1 (<1)	0 (0)	1 (<1)
1%–9%	54 (23)	50 (22)	104 (22)
10%–20%	64 (28)	80 (34)	144 (31)
>20%–35%	12 (5)	24 (10)	36 (8)
>35%	100 (43)	78 (34)	178 (38)
Maximum staining intensity			
0	2 (<1)	0 (0)	2 (<1)
1+	60 (26)	78 (34)	138 (30)
2+	122 (53)	113 (49)	235 (51)
3+	47 (20)	41 (18)	88 (19)

Abbreviations: BSC, best supportive care; P, panitumumab.

Table 3. Progression-free survival (PFS) in the intent-to-treat (all randomized patients) population

	P + BSC (n = 231)	BSC (n = 232)
Progressed, n (%)	193 (84%)	208 (90%)
Censored, n (%)	38 (16%)	24 (10%)
PFS (days)		
Median	56	51
95% CI	(55–59)	(50–54)
Mean (SD)	96.4 (5.3)	59.7 (3.75)
Min, max	0, 357	0, 337

Abbreviations: BSC, best supportive care; CI, confidence interval; P, panitumumab; SD, standard deviation.

ference in the median PFS time between arms was 5 days and the difference in mean PFS time was 37 days. As noted in Figure 1, however, there was considerable divergence of the curves after the median was reached. Exploratory univariate analyses assessing the relationship between EGFR expression and PFS did not suggest that the PFS benefit differed as a function of EGFR staining intensity or percentage of EGFR-expressing tumor cells. PFS improvement in response to panitumumab was consistent across the following

subgroups: age, sex, disease site, and number of prior lines of chemotherapy.

Nineteen panitumumab-treated patients (8%) achieved a partial response (95% confidence interval [CI], 5.0%–12.6%). No patient in the control arm had an objective response. The median duration of response was 17 weeks (95% CI, 16–25 weeks). The median time to response was 7.9 weeks. Of the 232 patients randomized to BSC alone, 75% crossed over to receive panitumumab following disease progression. The median time to cross-over was 8.4 weeks (0.3–26.4 weeks). There was no difference in overall survival observed between the study arms.

Safety

Safety data are derived from 1,467 panitumumab-treated patients, 1,293 who received panitumumab alone and 174 who received panitumumab plus chemotherapy. The most common adverse events observed in these studies were skin rash, hypomagnesemia, paronychia, fatigue, abdominal pain, nausea, and diarrhea. The most serious adverse events observed were pulmonary fibrosis, severe dermatologic toxicity complicated by infectious sequelae and septic death, infusion reactions, abdominal pain, hypomagnesemia, nausea, vomiting, and constipation. Table 4 summarizes adverse events occurring in $\geq 5\%$ of patients in the

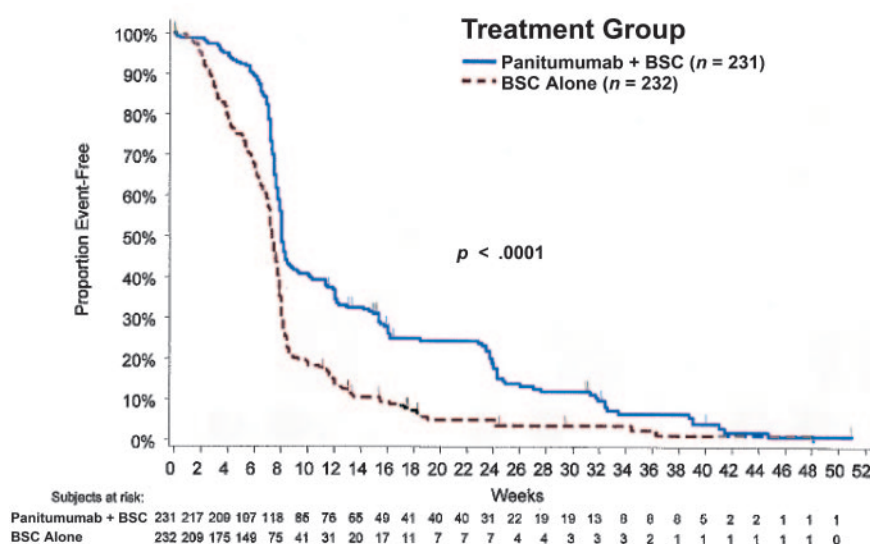


Figure 1. Kaplan-Meier plot of progression-free survival time. Abbreviation: BSC, best supportive care.

submitted clinical trial. The median number of panitumumab doses was five (range, 1–26 doses), and 71% of patients received eight or fewer doses.

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

Pulmonary fibrosis was reported in <1% (2/1,467) of patients enrolled in panitumumab clinical studies. One patient, with underlying idiopathic pulmonary fibrosis, received four doses of panitumumab in combination with chemotherapy. Pulmonary fibrosis worsened and the patient died. The second case was characterized by cough and wheezing 8 days following the initial dose, exertional dyspnea on day 192 of treatment, with the 7th dose, and persistent symptoms and computed tomography evidence of pulmonary fibrosis following the 11th dose of panitumumab as monotherapy. An additional patient died with bilateral pulmonary infiltrates of uncertain etiology with hypoxia, after 23 doses of panitumumab in combination with chemotherapy. Following the initial fatality, patients with a history of interstitial pneumonitis or pulmonary fibrosis, or evidence of interstitial pneumonitis or pulmonary fibrosis, were excluded from clinical studies.

In the submitted clinical trial, NCI-CTC grade 3 or 4 hypomagnesemia requiring oral or i.v. electrolyte repletion occurred in 4% of panitumumab-treated patients. In

some patients, hypomagnesemia was associated with hypocalcemia. Hypomagnesemia was generally observed 6 weeks or longer after the initiation of panitumumab.

In the randomized, controlled clinical trial, integument toxicities were reported in 90% of patients receiving panitumumab. Toxicity was severe (NCI-CTC grade 3 and higher) in 16% of patients. In addition to the skin-related toxicities listed in Table 4, cheilitis was identified in 6% of subjects. Ocular toxicities occurred in 34 (15%) patients in the panitumumab arm and five patients (2%) in the BSC arm. The most commonly occurring events were (in the panitumumab and BSC arms, respectively) conjunctivitis (4% and 1%), ocular hyperemia (3% and 0%), and increased lacrimation (2% and 1%). Nail toxicities were identified in 78 (34%) patients in the panitumumab arm. No nail toxicities were identified in the BSC arm. Nail adverse events included paronychia (24%), nail disorder (9%), onychorrhexis, nail bed infection, nail bed inflammation, nail discoloration, nail discomfort, and onycholysis (all 1%).

DISCUSSION

Two classes of biologics have recently been approved that expand the options for the treatment of metastatic colorectal cancer: angiogenesis inhibitors and EGFR inhibitors. Bevacizumab, a recombinant, humanized, monoclonal IgG₁ antibody directed against the vascular endothelial growth factor (VEGF), received full approval in the U.S. in February 2004 when used in combination with irinotecan-based chemotherapy for the first-line treatment of metastatic colorectal cancer. Approval was based on demonstration of su-

Table 4. Adverse events, irrespective of attribution, in $\geq 5\%$ of the study population

Body system	P + BSC (n = 229)		BSC alone (n = 234)	
	All grades (%)	Grade 3–4 (%)	All grades (%)	Grade 3–4 (%)
Body as a whole				
Fatigue	26	4	15	3
General deterioration	11	8	4	3
Digestive				
Abdominal pain	25	7	17	5
Nausea	23	1	16	<1
Diarrhea	21	2	11	0
Constipation	21	3	9	1
Vomiting	19	2	12	1
Stomatitis	7	0	1	0
Mucosal inflammation	6	<1	1	0
Metabolic/nutritional				
Peripheral edema	12	1	6	<1
Hypomagnesemia (lab)	39	4	2	0
Respiratory				
Cough	14	<1	7	0
Skin/integument toxicity (all)	90	16	9	0
Erythema	65	5	1	0
Acneiform dermatitis	57	7	1	0
Pruritus	57	2	2	0
Skin exfoliation	25	2	0	0
Rash	22	1	1	0
Skin fissures	20	1	<1	0
Dry skin	10	0	0	0
Acne	13	1	0	0
Nail	29	2	0	0
Paronychia	25	2	0	0
Other nail disorder	9	0	0	0
Hair	9	0	1	0
Growth of eyelashes	6	0	0	0
Eye	15	<1	2	0

Version 2.0 of the National Cancer Institute Common Toxicity Criteria was used for grading toxicities. Skin toxicity coded based on a modification of the National Cancer Institute Common Toxicity Criteria for Adverse Events, version 3.0. Abbreviations: BSC, best supportive care; P, panitumumab.

terior overall survival, PFS, and objective response rate [9–11].

Cetuximab, a chimeric monoclonal antibody directed against the extracellular binding domain of EGFR, received accelerated approval in the U.S. in February 2004 for use in combination with irinotecan for the treatment of a subgroup of patients with EGFR-expressing metastatic colorectal cancer who were refractory to irinotecan-based chemotherapy and as a single agent in patients who are intolerant of

irinotecan-based chemotherapy [12]. The accelerated approval was based on the surrogate endpoint of tumor response.

Panitumumab is the first fully human monoclonal antibody approved for the treatment of colorectal cancer. As a fully human agent, severe infusion reactions, including anaphylactic reaction, bronchospasm, fever, chills, and hypotension, are uncommon ($\sim 1\%$) [13]. Cetuximab is a recombinant human/mouse chimeric monoclonal antibody.

Severe infusion reactions occur in approximately 3% of treated patients [8]. Both drugs produce dermatologic toxicity. For neither drug did efficacy correlate with either the percentage of EGFR-positive cells or the intensity of EGFR expression.

Both panitumumab and cetuximab are indicated for the treatment of EGFR-expressing, metastatic colorectal carcinoma. Panitumumab approval is for patients with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. Cetuximab approval is for use in combination with irinotecan in patients who are refractory to irinotecan-based chemotherapy and as a single agent in patients who are intolerant to irinotecan-based chemotherapy. Panitumumab approval was based on PFS while cetuximab approval was based on objective response rate. Currently no data are available that demonstrate an improvement in disease-related symptoms or longer survival with either drug.

Drug approval in the U.S. requires adequate and well-controlled studies demonstrating that a drug is both safe and effective for the indication for which approval is sought. Approval requires the demonstration of either clinical benefit (e.g., prolongation of survival, relief of symptoms) or an effect on an established surrogate for clinical benefit.

The recommendation for accelerated approval for pani-

tumumab as a single agent for patients with metastatic colorectal cancer who have progressed following fluoropyrimidine-, irinotecan-, and oxaliplatin-containing chemotherapy regimens is based on PFS. From a regulatory perspective, PFS is not an established surrogate but is considered a surrogate endpoint that is likely to predict effects on overall survival. As such, PFS can be used to support the accelerated approval of panitumumab compared with BSC in this disease setting [14]. Progression-free survival is best determined in a blinded randomized trial with progression determined by independent reviewers who are blinded as to treatment assignment.

Accelerated approval requires that the sponsor conduct adequate and well-controlled studies to verify and describe clinical benefit (increased survival or improvement in disease related symptoms). Such studies must be conducted with due diligence.

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The views expressed are the result of independent work and do not necessarily represent the views and findings of the U.S. Food and Drug Administration.

DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST

The authors indicate no potential conflicts of interest.

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