

Economic Analysis of Panitumumab Compared With Cetuximab in Patients With Wild-Type *KRAS* Metastatic Colorectal Cancer That Progressed After Standard Chemotherapy

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ABSTRACT

Purpose: In this analysis, we compared costs and explored the cost-effectiveness of subsequent-line treatment with cetuximab or panitumumab in patients with wild-type *KRAS* (exon 2) metastatic colorectal cancer (mCRC) after previous chemotherapy treatment failure. Data were used from ASPECCT (A Study of Panitumumab Efficacy and Safety Compared to Cetuximab in Patients With *KRAS* Wild-Type Metastatic Colorectal Cancer), a Phase III, head-to-head randomized non-inferiority study comparing the efficacy and safety of panitumumab and cetuximab in this population.

Methods: A decision-analytic model was developed to perform a cost-minimization analysis and a semi-Markov model was created to evaluate the cost-effectiveness of panitumumab monotherapy versus cetuximab monotherapy in chemotherapy-resistant wild-type *KRAS* (exon 2) mCRC. The cost-minimization model assumed equivalent efficacy (progression-free survival) based on data from ASPECCT. The cost-effectiveness analysis was conducted with the full information (uncertainty) from ASPECCT. Both analyses were conducted from a US third-party payer perspective and calculated average anti-epidermal growth factor receptor doses from ASPECCT. Costs associated with drug acquisition, treatment administration (every 2 weeks for panitumumab, weekly for cetuximab), and incidence of infusion reactions were estimated in both models. The cost-effectiveness model also included physician visits, disease progression monitoring, best supportive

care, and end-of-life costs and utility weights estimated from EuroQol 5-Dimension questionnaire responses from ASPECCT.

Findings: The cost-minimization model results demonstrated lower projected costs for patients who received panitumumab versus cetuximab, with a projected cost savings of \$9468 (16.5%) per panitumumab-treated patient. In the cost-effectiveness model, the incremental cost per quality-adjusted life-year gained revealed panitumumab to be less costly, with marginally better outcomes than cetuximab.

Implications: These economic analyses comparing panitumumab and cetuximab in chemorefractory wild-type *KRAS* (exon 2) mCRC suggest benefits in favor of panitumumab. ClinicalTrials.gov identifier: NCT01001377. (*Clin Ther.* 2016;■:■■■-■■■) © 2016 The Authors. Published by Elsevier HS Journals, Inc.

Key words: cetuximab, colorectal cancer, cost-effectiveness, cost-minimization, panitumumab, subsequent-line.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer in both men and women in the United States

Accepted for publication March 14, 2016.

<http://dx.doi.org/10.1016/j.clinthera.2016.03.023>
0149-2918/\$ - see front matter

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and the second leading cause of cancer death.¹ In 2015, it was estimated that there would be 132,700 new cases of colon and rectum cancer and an estimated 49,700 people would die of this disease. Approximately 20% have metastatic CRC (mCRC) at diagnosis, and metastases eventually develop in 50% to 60% of all patients.¹⁻³ Patients with mCRC experience significant morbidity and diminished quality of life. The 5-year relative survival rate is <13% in patients with mCRC, indicating a continued need to improve treatment outcomes.¹ Surgical resection of metastases is curative in a very small proportion of patients; therefore, the goal of treatment for most patients with mCRC is to prolong survival while maintaining quality of life.

Chemotherapy is the first treatment option for metastatic disease when tumor lesions are not fully resectable. Regimens consisting of fluoropyrimidine and oxaliplatin (ie, FOLFOX) or irinotecan (ie, FOLFIRI) can be considered standard options for first-line treatment of mCRC. In randomized trials in which patients received either FOLFIRI followed by FOLFOX or FOLFOX followed by FOLFIRI, median progression-free survival (PFS) ranged from 7 months to 8.5 months.^{4,5} In addition to various chemotherapeutic regimens, current treatments for mCRC include targeted monoclonal antibodies directed against the epidermal growth factor receptor (EGFR), such as panitumumab and cetuximab, and bevacizumab, a humanized monoclonal antibody that binds the vascular endothelial growth factor. Trials comparing the use of these types of targeted therapies in patients with mCRC have demonstrated a significant increase in survival.⁶⁻¹²

Patients with *RAS* gene mutations should not be treated with an anti-EGFR agent because these mutations are predictive of a lack of response to panitumumab and cetuximab.^{2,3} Approximately 50% of patients with mCRC have tumors exhibiting *RAS* mutations,¹³ including 40% with *KRAS* (exon 2) mutations.¹⁴ Therefore, 50% to 60% of patients with mCRC would be eligible for treatment with panitumumab and cetuximab. Identifying *KRAS* status and ultimately *RAS* status through genotyping may reduce treatment costs by allowing physicians to target patients who are likely to benefit from treatment with EGFR inhibitors and to minimize the number of patients receiving anti-EGFR agents who are unlikely to respond favorably.

Several clinical trials have been conducted to study targeted therapies in the treatment of mCRC. The ASPECCT (A Study of Panitumumab Efficacy and Safety Compared to Cetuximab in Patients With *KRAS* Wild-Type Metastatic Colorectal Cancer) clinical trial was designed to evaluate the efficacy and safety of treatment with panitumumab ($n = 499$) versus cetuximab ($n = 500$) in patients with previously treated, chemotherapy-resistant, wild-type *KRAS* (exon 2) mCRC. This therapy resulted in an estimated median PFS of 4.1 months (95% CI, 3.2–4.8) in the panitumumab arm and 4.4 months (95% CI, 3.2–4.8) in the cetuximab arm. The estimated median overall survival (OS) was 10.4 months (95% CI, 9.4–11.6) in the panitumumab arm and 10.0 months (95% CI, 9.3–11.0) in the cetuximab arm.¹⁵ These results indicate noninferior OS in patients with wild-type *KRAS* (exon 2) mCRC (panitumumab vs cetuximab hazard ratio [HR], 0.97 [95% CI, 0.84–1.11]). Although the difference in OS between treatments is not statistically significant, it does highlight a trend in OS slightly favoring panitumumab.

Economic modeling can be used to help decision-makers determine the relative monetary value of 1 treatment versus another given the health care cost challenges and constraints that payers face. Cost-minimization analysis is a method that should be used only to measure and compare the costs of different medical interventions in economic evaluations of trials demonstrating no statistically significant difference in efficacy. However, Briggs and O'Brien¹⁶ suggest that even noninferior efficacy results, such as those reported in the ASPECCT study, can benefit from probabilistic cost-effectiveness modeling, as the uncertainty around the point estimates are considered in the Monte-Carlo sampling.

Recently, the American Society of Clinical Oncology announced an initiative focusing on value in cancer care.¹⁷ The value framework will consider a particular treatment regimen's effectiveness, the severity of the expected side effects, and the treatment's costs to evaluate the relative value of the treatments that are available and to determine the best treatment approach. To this point, economic modeling of noninferior trial results can assist with estimation of treatment costs (drug acquisition and administration) as well as the costs of side effects or toxicities between 2 treatments.

Published cost-effectiveness studies evaluating subsequent-line treatment with cetuximab or panitumumab in patients with wild-type *KRAS* (exon 2) mCRC have only examined the cost-effectiveness of these anti-EGFR therapies relative to best supportive care (BSC).^{18–20} To our knowledge, an economic model that directly compares panitumumab versus cetuximab in the treatment of patients with mCRC after prior chemotherapy treatment failure has not yet been published.

Given the noninferior efficacy results demonstrated in the ASPECCT study, we developed a decision-analytic model to perform a cost-minimization analysis, assuming equivalent efficacy (PFS), between panitumumab (intravenous infusion, 6 mg/kg every 2 weeks until disease progression) and cetuximab (intravenous infusion, loading dose of 400 mg/m² and weekly maintenance doses of 250 mg/m² until disease progression) monotherapy in chemorefractory patients with wild-type *KRAS* (exon 2) mCRC. Data from the head-to-head ASPECCT trial were used.

To examine the benefit suggested by Briggs and O'Brien¹⁶ of probabilistic cost-effectiveness modeling using noninferiority trial results, we also developed a semi-Markov model to evaluate the cost-effectiveness of panitumumab monotherapy versus cetuximab monotherapy in chemotherapy-resistant patients with wild-type *KRAS* (exon 2) mCRC using the full information (uncertainty) from the ASPECCT trial. Both analyses were conducted from a US third-party payer perspective.

MATERIALS AND METHODS

Population

The model population in both models was based on the patient population included in the head-to-head ASPECCT clinical trial comparing panitumumab and cetuximab in the treatment of mCRC. Briefly, this population was defined as adults (age ≥ 18 years) with wild-type *KRAS* (exon 2) with a diagnosis of mCRC for whom previous treatment with regimens containing irinotecan and oxaliplatin had failed and for whom at least 1 thymidylate synthase inhibitor had been received. In addition, enrolled patients had an Eastern Cooperative Oncology Group status of 0, 1, or 2 and adequate hematologic, renal, hepatic, and metabolic function.

Model Structure

The cost-minimization analysis assumed panitumumab and cetuximab had equivalent PFS and estimated the costs associated with drug acquisition, treatment administration frequency (biweekly for panitumumab, weekly for cetuximab), and incidence of infusion reactions. Costs were estimated over the time horizon of the model, which was determined according to the length of therapy as reflected by the average PFS. The cost-minimization model structure is illustrated in [Figure 1](#).

The cost-effectiveness analysis took the form of a probabilistic semi-Markov model, allowing patients to transition to various health states over time ([Figure 2](#)). In the cost-effectiveness analysis, the model begins with a cohort of patients initiating subsequent mCRC treatment after discontinuing failed chemotherapy after progression. Patients cycle through the model every 2 weeks. During each cycle, patients may transition to different mutually exclusive health states or stay in the same health state based on health state transition probabilities; each health state has a corresponding cost and outcome. For the base-case time horizon, Markov cycles are repeated for the lifetime of a patient. The semi-Markov model concludes when the entire patient cohort has died. Total costs and outcomes are calculated by summing across cycles.

Inputs

Transition Probabilities

In clinical trials of oncology products, Kaplan-Meier plots for PFS and OS are often right-censored because data collection ends before all patients experience disease progression and/or death. Because of the right censoring of the curves, parametric survival curves can be fit to patient-level survival data to extrapolate beyond the data collection period.

In the cost-minimization analysis, data from the ASPECCT clinical trial were used to conduct parametric survival analyses on the PFS of wild-type *KRAS* (exon 2) patients treated with panitumumab. The parametric survival modeling was coded in SAS version 9.3 (SAS Institute, Inc, Cary, North Carolina) by using the LIFEREG procedure. Three parametric models were tested, based on the intrinsic assumptions they make regarding changes to the hazard rate over time. The models were exponential, Weibull, and log-logistic. Based on graphical overlay of the curves and the Kaplan-Meier plot, goodness-of-fit statistics

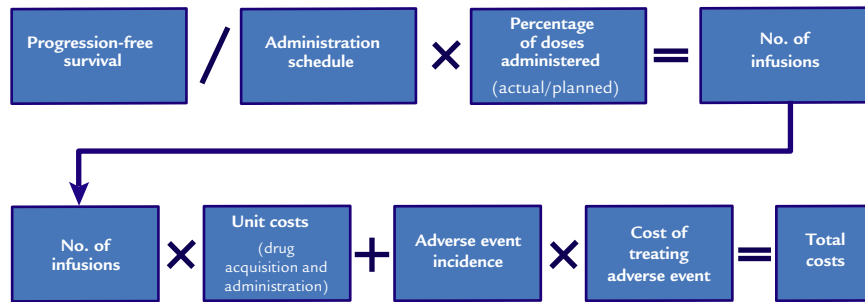


Figure 1. Cost-minimization model structure.

(Akaike information criterion), and face validity of long-term survival projections (as suggested by Latimer²¹), the best-fit survival curve for panitumumab was the Weibull, which was selected as the base-case estimate of mean PFS for panitumumab as well as cetuximab given that the model assumed both treatments had the same efficacy.

In the cost-effectiveness analysis, transition probabilities to disease progression and death for panitumumab and cetuximab were based on parametric

survival curves estimated in a patient-level analysis of PFS and OS from the ASPECCT clinical trial. In contrast to the cost-minimization analysis, separate parametric survival curves were estimated for panitumumab and cetuximab by including a covariate for panitumumab treatment in the regression equations; this approach accounted for noninferior ASPECCT trial results (OS HR, 0.97) and the difference in efficacy between panitumumab and cetuximab. Using the same criteria as the cost-minimization analysis, the

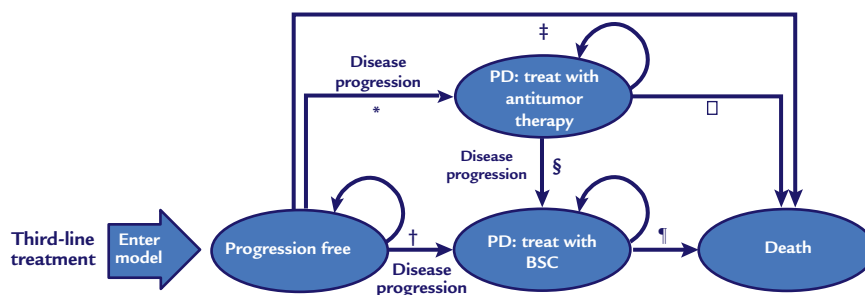


Figure 2. Cost-effectiveness model structure. After disease progression, patients discontinued their current treatment (panitumumab or cetuximab) and began treatment with another therapy. *Progression free to progressive disease (PD)—treat with antitumor therapy: parametric survival modeling of patient-level data; percentage of patients utilizing active treatment postprogression from ASPECCT (A Study of Panitumumab Efficacy and Safety Compared to Cetuximab in Patients With KRAS Wild-Type Metastatic Colorectal Cancer) trial (ie, progression-free survival [PFS]). †Progression free to PD—treat with best supportive care (BSC): parametric survival modeling of patient-level data; percentage of patients utilizing BSC postprogression from the ASPECCT trial (ie, PFS). ‡Progression free to death—parametric survival modeling of patient-level data from the ASPECCT trial (ie, overall survival [OS]). §PD—treat with antitumor therapy to PD: Treat with BSC; assumptions on length of fourth-line treatment. ¶PD—treat with antitumor therapy to death: parametric survival modeling of patient-level data from the ASPECCT trial (ie, OS). ¶PD—treat with BSC to death: parametric survival modeling of patient-level data from the ASPECCT trial (ie, OS).

Weibull was selected as the best-fit curve for panitumumab and cetuximab for both PFS and OS in the cost-effectiveness model (Figures 3 and 4).

Costs

Aside from the efficacy input parameters, sources were consistent for the input parameters used in both models. Drug acquisition costs in the base-case analysis were modeled by using Medicare average sales prices from the payment allowance limits for Medicare Part B drugs.²² Wholesale acquisition costs from Red Book²³ were examined in scenario analyses. Product exposure, defined as the average dose delivered, percentage of doses administered, and therapy duration (for subsequent therapy), were calculated from data in the ASPECCT clinical trial for direct treatment comparators. Premedication, drug acquisition and administration costs, dosing, duration, and other regimen-specific inputs are presented in Table I, along with sources and assumptions. Adverse event treatment incidence and cost inputs are presented in Table II, and non-regimen-specific

inputs and costs considered by the models (ie, *KRAS* mutation testing, physician visits, diagnostic tests, BSC, end-of-life care) are presented in Table III. All costs were inflated to 2014 US dollars by using the medical component of the Consumer Price Index.²⁴

Utility Weights

Utility weights, used only in the cost-effectiveness model, were based on EuroQol-5 Dimension questionnaire responses of patients with wild-type *KRAS* (exon 2) mCRC from the ASPECCT clinical trial during the progression-free period (average of screening and treatment visits during the progression-free period) and during the disease progression period (safety follow-up visit responses). Utility weights were estimated from the questionnaire responses by using the algorithm of Shaw et al²⁵ for US patients (Table III).

Outcomes Modeled

The model outcomes calculated for each treatment regimen in the cost-minimization analysis included the cost per treated patient, the cost per 100 treated

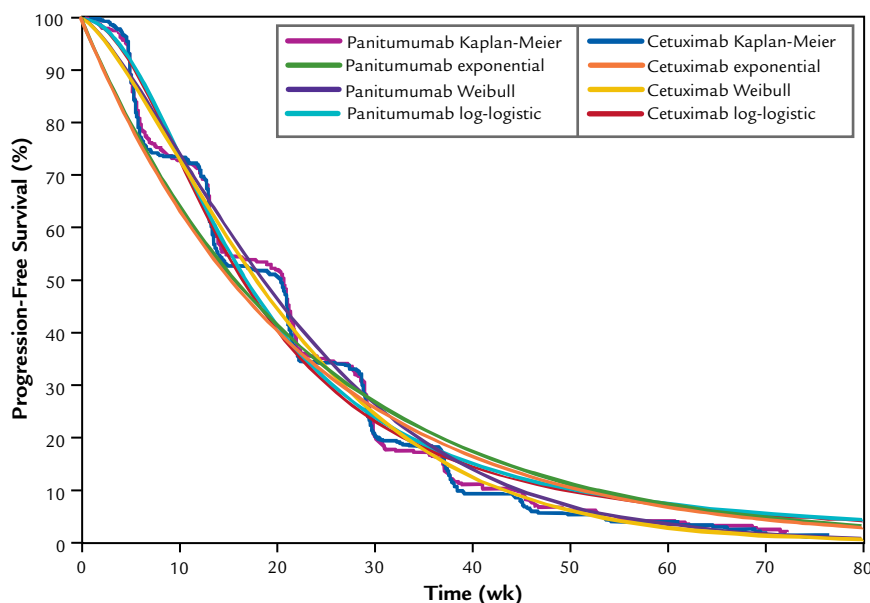


Figure 3. Progression-free survival Kaplan-Meier and fitted curves. Akaike information criterion for goodness-of-fit of progression-free survival curves: Weibull, 2384.95; exponential, 2261.54; log-logistic, 2272.89. Source: Parametric survival analyses were performed on the February 5, 2013, data cut from ASPECCT (A Study of Panitumumab Efficacy and Safety Compared to Cetuximab in Patients With *KRAS* Wild-Type Metastatic Colorectal Cancer).

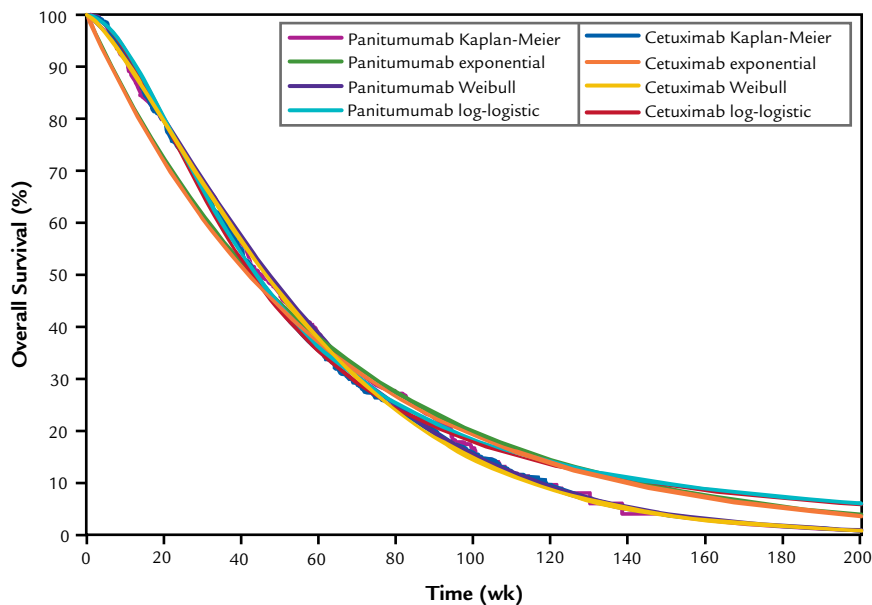


Figure 4. Overall survival Kaplan-Meier and fitted curves. Akaike information criterion for goodness-of-fit of overall survival curves: Weibull, 2585.46; exponential, 2506.62; log-logistic, 2515.79. Source: Parametric survival analyses were performed on the February 5, 2013, data cut from ASPECCT (A Study of Panitumumab Efficacy and Safety Compared to Cetuximab in Patients With *KRAS* Wild-Type Metastatic Colorectal Cancer).

patients, the cost savings per treated patient, and the cost savings per 100 treated patients receiving panitumumab monotherapy relative to cetuximab monotherapy.

The model outcomes calculated for each treatment regimen in the cost-effectiveness analysis included patient survival life-years, quality-adjusted life-years (QALYs), and costs for health care resources. The incremental costs and total life-years and QALYs were calculated to obtain an incremental cost per life-year gained and per QALY gained. All costs and outcomes (benefits) in the model were discounted by using the suggested discount rate in the United States of 3.0% per annum.²⁶

In the cost-effectiveness analysis, the robustness of the model methods, assumptions, and specific parameters were tested by examining the effect of using alternative methods and data sources for the model inputs in a series of focused scenario analyses conducted around the assumptions and methods used to calculate drug acquisition costs and subsequent treatment. We also examined the effect of changing parameters individually as part of 1-way sensitivity

analyses. In addition to 1-way sensitivity analyses, a probabilistic sensitivity analysis was performed to examine the effects of joint uncertainty across all the parameters of the model.

RESULTS

Deterministic Results

The results of the cost-minimization analysis (Table IV) revealed lower projected drug acquisition, administration, and adverse event costs for patients with wild-type *KRAS* (exon 2) mCRC who received panitumumab versus cetuximab. The projected total cost savings was \$9468 (16.5%) per patient treated with panitumumab.

Results from the cost-effectiveness model (Table V) demonstrated slightly better outcomes for patients with wild-type *KRAS* (exon 2) mCRC who received panitumumab versus cetuximab. The model projected 1.072 life-years for panitumumab and 1.051 life-years for cetuximab. Adjusting for quality of life, panitumumab was estimated to produce 0.736 QALY, whereas cetuximab was estimated to produce 0.726

Table I. Regimen-specific input parameters: cost-minimization and cost-effectiveness models.

Input Parameter	Panitumumab	Cetuximab	Source	
Biologic therapy				
Drug acquisition cost				
ASP	\$91.23	\$52.52	Payment allowance limits for Medicare Part B drugs ²² (per 10-mg dose)	
WAC	\$926.50	\$514.55	Red Book ²³ (per 100-mg vial)	
Chemotherapy IV infusion 2-week administration cost				
Average dose delivered	5.98 mg/kg	LD: \$294.46 MD: \$266.52	Panitumumab is administered over 60 minutes ^{27,28} Cetuximab loading dose is administered over 120 minutes and maintenance doses over 60 minutes ^{28,29}	
Percentage of doses administered	92.9	94.1	ASPECCT Clinical Study Report Table 14-05.002.001 for panitumumab and ASPECCT Ad Hoc Analysis Table us-2.5.800.001 for cetuximab Ratio of actual to planned doses from ASPECCT Clinical Study Report Table 14-05.002.002	
Premedication				
Drug acquisition cost				
ASP	\$0.68	\$0.68	HCPCS code J1200 for 50-mg dose of diphenhydramine ²²	
WAC	\$0.82	\$0.82	WAC per 50-mg dose of diphenhydramine, NDC 00641-0376-21 ²³	
Administration cost	\$30.09	\$30.09	Centers for Medicare & Medicaid Services ²⁸	
Percentage of doses requiring premedication			Minimum premedication for cetuximab is an H ₁ antagonist (eg, 50 mg of diphenhydramine) IV 30–60 minutes before the first dose (ASPECCT protocol and Eli Lilly ²⁹); premedication for panitumumab is not required (ASPECCT protocol)	
First dose	0	100.0	Assumed no panitumumab-treated patients and all cetuximab-treated patients were given premedication for first infusion	
Maintenance doses	2.8	12.5	Assumed percentage of patients observed to have an infusion reaction (any grade) in ASPECCT would require premedication maintenance doses	
Subsequent-line therapy use (CE model only)				
5-Fluorouracil	25.9%	28.2%	ASPECCT Clinical Study Report Table 14-04.001.008.001	
Irinotecan	12.6%	14.2%		
Oxaliplatin	11.4%	12.2%		
Cetuximab	7.8%	8.2%		
Panitumumab	1.0%	2.4%		
Bevacizumab	6.0%	6.4%		
Leucovorin	6.2%	5.0%		
Any antitumor therapy for mCRC*	41.1%	42.2%		
Percentage of doses administered		93.5		Assumed average ratio of actual to planned doses for third-line panitumumab and cetuximab (ASPECCT Clinical Study Report Table 14-05.002.002)
Treatment duration		10 wk		Assumed one half the duration of third-line treatment
Subsequent-line therapy drug acquisition cost				
5-Fluorouracil				
ASP		\$2.123	Payment allowance limits for Medicare Part B drugs ²² (per 500-mg dose)	
WAC		\$2.75	Red Book ²³ (per 500-mg vial)	
Irinotecan				
ASP		\$4.539	Payment allowance limits for Medicare Part B drugs ²² (per 20-mg dose)	
WAC		\$12.34	Red Book ²³ (per 40-mg vial)	
Oxaliplatin				
ASP		\$0.269	Payment allowance limits for Medicare Part B drugs ²² (per 0.5-mg dose)	
WAC		\$86.63	Red Book ²³ (per 50-mg vial)	
Cetuximab				
ASP		\$52.520	Payment allowance limits for Medicare Part B drugs ²² (per 10-mg dose)	
WAC		\$514.55	Red Book ²³ (per 100-mg vial)	
Panitumumab				
ASP		\$91.231	Payment allowance limits for Medicare Part B drugs ²² (per 10-mg dose)	
WAC		\$926.50	Red Book ²³ (per 100-mg vial)	
Bevacizumab				
ASP		\$65.664	Payment allowance limits for Medicare Part B drugs ²² (per 10-mg dose)	
WAC		\$649.14	Red Book ²³ (per 100-mg vial)	

(continued)

Clinical Therapeutics

Table I. (continued).

Input Parameter	Panitumumab	Cetuximab	Source
Leucovorin ASP	\$4.308		Payment allowance limits for Medicare Part B drugs ²² (per 50-mg dose)
WAC	\$4.40		Red Book ²³ (per 50-mg vial)

ASP = average sales price; ASPECCT = A Study of Panitumumab Efficacy and Safety Compared to Cetuximab in Patients With *KRAS* Wild-Type Metastatic Colorectal Cancer; CE = cost-effectiveness; HCPCS = Healthcare Common Procedure Coding System; IV = intravenous; LD = loading dose; mCRC = metastatic colorectal cancer; MD = maintenance dose; NDC = National Drug Code; WAC = wholesale acquisition cost.

*Any antitumor activity is less than the sum of the individual drugs because some patients received combination therapy.

Table II. Serious adverse event input parameters: cost-minimization and cost-effectiveness models.

Serious Adverse Event	Incidence, %		Hospital Cost, \$	Source
	Panitumumab	Cetuximab		
Hypomagnesemia (CE model only)	7.3	2.6	6939	Incidence: ASPECCT Clinical Study Report Table 12-8: Overall Subject Incidence of Adverse Events of Interest (Safety Analysis Set)
Infusion reactions, grades 1 and 2	2.6	10.7	3387	
Infusion reactions, grades 3 and 4	0.2	1.8	14,454	Cost: Costs extracted from Burudpakdee et al ³⁰ for all adverse events except cardiac arrhythmia and infusion reactions Cardiac arrhythmia costs estimated from ICD-9 427.31 (atrial fibrillation) from HCUPNet ³¹
Hypokalemia (CE model only)	3.2	1.8	6401	
Hypocalcemia (CE model only)	1.2	1.2	6401	Costs for infusion reaction extracted from Foley et al ³² and calculated as the incremental cost of having a reaction versus not having a reaction (ie, total costs for those with a reaction minus total costs for those without a reaction)
Acute renal failure (CE model only)	0.8	1.2	12,013	
Embolic and thrombotic events, unspecified (CE model only)	1.0	0.6	9832	Assumed outpatient setting for grades 1 and 2 infusion reactions and emergency department visit or inpatient hospitalization for grades 3 and 4 infusion reactions
Venous thromboembolism (CE model only)	1.2	0.8	9832	
Cardiac arrhythmia (CE model only)	0.2	0.2	9021	
Ischemic heart disease (CE model only)	0.2	0.2	22,867	
Arterial thromboembolic events (CE model only)	0.2	0.0	22,867	

ASPECCT = A Study of Panitumumab Efficacy and Safety Compared to Cetuximab in Patients With *KRAS* Wild-Type Metastatic Colorectal Cancer; CE = cost-effectiveness; HCUPNet = Healthcare Cost and Utilization Project's online query system; ICD-9 = *International Classification of Diseases, Ninth Revision*.

Table III. Other input parameters: cost-minimization and cost-effectiveness models.

Input Parameter	Value	Source
Other medical costs		
<i>KRAS</i> test	\$197.48	Final CMS 2014 <i>KRAS</i> genetic test national limit amount (CPT code 81275) ²⁸
General practitioner office visit cost* (CE model only)	\$107.83	Level 4 visit for an established patient (CPT code 99214) ²⁸ ; assumed to occur every 4 weeks
Oncology specialist office visit cost* (CE model only)	\$144.37	Level 5 visit for an established patient (CPT code 99215) ²⁸ ; assumed to occur every 2 weeks
Computed tomography scan cost (CE model only)	\$327.42	Computed tomography scan with contrast of the abdomen and pelvis (CPT code 74177) ²⁸ ; assumed disease progression was monitored every 8 weeks, similar to ASPECCT clinical trial protocol
BSC and end-of-life cost (CE model only)		
BSC costs per cycle	\$4493	End-of-life costs from Chastek et al ³³ for months 2–5 before death were used to estimate costs for BSC treatment
End-of-life cost	\$24,563	End-of-life costs from Chastek et al ³³ for the last month before death were used to estimate end-of-life/transition-to-death costs
Utility weights (CE model only)		
Progression free		Utility weights estimated from analysis of EQ-5D responses from ASPECCT during the progression-free period (average of screening and treatment visits during the progression-free period) by using the algorithm of Shaw et al ²⁵ for US patients
Pooled	0.803	
By treatment		
Panitumumab	0.7962	
Cetuximab	0.8096	
Progressive disease		Utility weights estimated from analysis of EQ-5D responses from ASPECCT during the disease progression period (safety follow-up visit responses) by using the algorithm of Shaw et al ²⁵ for US patients
Subsequent antitumor therapy	0.749	
BSC	0.602	

ASPECCT = A Study of Panitumumab Efficacy and Safety Compared to Cetuximab in Patients With *KRAS* Wild-Type Metastatic Colorectal Cancer; BSC = best supportive care; CE = cost-effectiveness; CMS = Centers for Medicare & Medicaid Services; CPT = Current Procedural Terminology; EQ-5D = EuroQol 5-Dimension questionnaire.

*Scheduled physician visits did not include visits for grade 3/4 toxicity treatment or management that occurred on days other than the day of treatment administration. Also, costs of scheduled physician visits during BSC after disease progression were captured as part of the BSC costs and were not included in these cost estimates because the frequency of office visits was likely to be different.

QALY. BSC costs contributed the greatest proportion of total costs modeled (46.0% for panitumumab; 43.5% for cetuximab), followed by monoclonal antibody drug acquisition costs (33.4% for panitumumab; 35.9% for cetuximab). Total drug costs for panitumumab were lower than total drug costs for cetuximab (\$50,360 vs \$56,377). Costs for administration, adverse events, and end-of-life care were also slightly

lower for panitumumab than for cetuximab. However, costs for physician visits, monitoring for disease progression, and BSC were slightly higher for panitumumab than for cetuximab due to longer projected survival. The incremental cost per life-year gained and the incremental cost per QALY gained indicate that with both end points, panitumumab dominated cetuximab (ie, panitumumab was less costly and had

Table IV. Deterministic results: cost-minimization analysis.

Cost	Per 1 Treated Patient, \$			Per 100 Treated Patients, \$		
	Panitumumab	Cetuximab	Savings per 1	Panitumumab	Cetuximab	Savings per 100
			Treated Patient			
<i>KRAS</i> test	197	197	—	19,748	19,748	—
Drug acquisition	46,179	53,609	−7430	4,617,853	5,360,863	−743,010
Anti-EGFR	46,178	53,606	−7428	4,617,836	5,360,625	−742,789
Premedication	0.18	2.38	−2.20	18	238.40	−220.45
Administration	1382	2916	−1534	138,209	291,599	−153,391
Outpatient	1382	2916	−1534	138,209	291,599	−153,391
Hospitalization	—	—	—	—	—	—
Adverse events	118	622	−504	11,790	62,220	−50,430
Infusion reactions						
Grades 1 and 2	89	364	−275	8876	36,358	−27,481
Grades 3 and 4	29	259	−229	2914	25,862	−22,948
Total	47,876	57,344	−9468	4,787,601	5,734,431	−946,830

EGFR = epidermal growth factor receptor.

slightly better outcomes than cetuximab). The results from the cost-effectiveness analysis are consistent with the ASPECCT primary analysis (HR, 0.97) showing noninferiority of panitumumab relative to cetuximab and slightly favoring panitumumab.

Sensitivity Analyses

The 1-way sensitivity analysis from the cost-effectiveness model indicated that model outcomes were most sensitive to changes to the Weibull OS treatment coefficient, panitumumab drug costs, BSC costs, and end-of-life costs. Scenario analyses conducted around major model assumptions indicated that the model was robust to alternative assumptions of PFS and OS distributions, wastage, drug acquisition costs, postprogression costs, and the progression-free utility weight method used (Table VI).

The probabilistic sensitivity analysis from the cost-effectiveness model was conducted by using the observed uncertainty measures of the PFS, OS, and other model inputs. Cost-effectiveness acceptability curves were calculated from 10,000 iterations by using the net monetary benefit statistic across a range of willingness-to-pay thresholds. The cost-effectiveness

scatter plot (Figure 5) and acceptability curves (Figure 6) indicate that 92.5% of simulations were below a willingness-to-pay threshold of \$50,000 and 98.5% of simulations were below a willingness-to-pay threshold of \$100,000. In addition, 45.8% of simulations revealed panitumumab to be less costly, with minimally better outcomes, than cetuximab.

DISCUSSION

Results Summary

Cetuximab or panitumumab monotherapy constitutes a standard-of-care treatment in the management of mCRC with wild-type *RAS* tumors.^{1–3} The ASPECCT clinical trial met its primary end point, reporting similar OS for both panitumumab and cetuximab (HR, 0.97 [95% CI, 0.84–1.11]) in the treatment of patients with chemorefractory wild-type *KRAS* (exon 2) mCRC. The cost-minimization model analysis conservatively used the panitumumab treatment effect (PFS HR) of 1.0 from ASPECCT. Deterministic results from the cost-minimization analysis projected panitumumab to be cost-saving relative to cetuximab (\$47,876 vs \$57,344) per patient. In a separate model, a cost-effectiveness analysis was

Table V. Deterministic results: cost-effectiveness analysis.

Outcome/Cost Category	Panitumumab	Cetuximab	Difference Between Panitumumab and Cetuximab
Outcome			
Patient survival (undiscounted)	1.100	1.078	0.022
Life-years	1.072	1.051	0.021
Before progression	0.421	0.406	0.016
After progression	0.651	0.645	0.006
QALYs	0.736	0.726	0.010
Before progression	0.336	0.328	0.007
After progression	0.401	0.398	0.003
Cost category			
<i>KRAS</i> test	\$197	\$197	\$0
Drug costs	\$50,360	\$56,377	−\$6016
Before progression			
Anti-EGFR	\$47,819	\$53,453	−\$5634
Premedication	\$0.19	\$1.45	−\$1.27
After progression	\$2541	\$2922	−\$381
Administration	\$2101	\$3635	−\$1535
Before progression	\$1431	\$2905	−\$1474
After progression	\$669	\$730	−\$61
Adverse events	\$1329	\$1334	−\$5
Physician visits	\$2591	\$2521	\$70
Monitoring for disease progression	\$1070	\$1041	\$29
BSC	\$69,238	\$68,321	\$917
End-of-life	\$23,771	\$23,786	−\$15
Total costs	\$150,657	\$157,213	−\$6556
Incremental cost-effectiveness ratios of panitumumab vs cetuximab			
Incremental cost per life-year gained			−\$307,432 (dominates [*])
Incremental cost per QALY gained			−\$648,345 (dominates [*])

BSC = best supportive care; EGFR = epidermal growth factor receptor; QALY = quality-adjusted life-year.

Note: Incremental cost-effectiveness ratios presented are calculated from model estimated cost, life-year, and QALY values before rounding.

*Panitumumab is more effective and less costly than cetuximab. The outcomes results are consistent with the ASPECCT (A Study of Panitumumab Efficacy and Safety Compared to Cetuximab in Patients With *KRAS* Wild-Type Metastatic Colorectal Cancer) primary analysis (hazard ratio, 0.97), showing noninferiority of panitumumab versus cetuximab and slightly favoring panitumumab (although this difference was not statistically significant).

conducted by using the actual treatment effect data from the ASPECCT trial (cetuximab vs panitumumab: PFS HR, 1.00 [95% CI, 0.88–1.14]; OS HR, 0.97 [95% CI, 0.84–1.11]) to compare the incremental cost per QALY gained for panitumumab and cetuximab. Results from the cost-effectiveness analysis projected

panitumumab to be dominant relative to cetuximab, with incrementally greater QALYs (0.736 vs 0.726) and lower costs (\$150,657 vs \$157,213) per patient. The outcomes estimated in this model were similar to those of the ASPECCT primary analysis (HR, 0.97) showing noninferiority of panitumumab versus

Table VI. Scenario analyses results: cost-effectiveness analysis.

Alternative Input Parameter Scenario	Base-case Parameter	Alternate Scenario Parameter	Incremental Cost per QALY Gained	ICER Change From Base-case, %	
Base-case analysis	—	—	−\$648,345	Dominates*	—
Wastage	Wastage	No wastage	−\$646,640	Dominates*	−0.3
Drug cost source	ASP	WAC	−\$468,555	Dominates*	−27.7
Cetuximab hospitalization for first administration	0%	100%	−\$648,345	Dominates*	0
Best-fit PFS curve	Weibull	Log-logistic	−\$909,743	Dominates*	40.3
	Weibull	Exponential	−\$715,855	Dominates*	10.4
Best-fit OS curve	Weibull	Log-logistic	−\$406,113	Dominates*	−37.4
	Weibull	Exponential	−\$379,303	Dominates*	−41.5
Cetuximab oncologist office visit	Every 2 weeks	Every week	−\$557,573	Dominates*	−14.0
Postprogression costs	ASPECCT %	All BSC	−\$609,028	Dominates*	−6.1
	ASPECCT %	All PD \$ equal	−\$670,409	Dominates*	3.4
Progression-free utility weight method	Pooled	By treatment	−\$418,472	Dominates*	−35.5

ASP = average sales price; ASPECCT = A Study of Panitumumab Efficacy and Safety Compared to Cetuximab in Patients With *KRAS* Wild-Type Metastatic Colorectal Cancer; BSC = best supportive care; ICER = incremental cost-effectiveness ratio; OS = overall survival; PD = progressive disease; PFS = progression-free survival; QALY = quality-adjusted life-year; WAC = wholesale acquisition costs.

Note: ICERs presented are calculated from model-estimated cost, life-year, and QALY values before rounding.

*Panitumumab is more effective and less costly than cetuximab. The outcomes results are consistent with the ASPECCT primary analysis (hazard ratio, 0.97), showing noninferiority of panitumumab versus cetuximab and slightly favoring panitumumab (although this difference was not statistically significant).

cetuximab, with a statistically nonsignificant OS trend favoring panitumumab. Scenario analyses indicated robust results, as modifications of key model assumptions consistently demonstrated panitumumab dominance. Furthermore, when accounting for uncertainty across all model parameters in the probabilistic sensitivity analysis, panitumumab was cost-effective at a willingness-to-pay threshold of \$50,000 or more in >92% of model simulations in the cost-effectiveness analysis.

Limitations

The strength of our models reside in the use of data from a well-conducted randomized Phase III head-to-head clinical trial in a homogeneous patient population. Considerable scrutiny was placed on toxicity collection in this study, allowing for a more accurate modeling of cost of toxicities amongst arms. However,

as with any model, there were several limitations to the analysis and modeling. Both models assumed dose modifications and dose interruptions in clinical practice that mimic the ASPECCT clinical trial recommendations. This scenario may not be necessarily true in actual clinical practice. For example, many physicians may carry through treatment with chronic aggressive intravenous magnesium supplementation in a setting in which no other treatment options may be available. In addition, the management of skin toxicity in clinical practice may vary from the ASPECCT clinical trial, with variations in the rate of dose interruptions or modifications and/or the implementation of dermatology or podiatry consults. Furthermore, the intensity of skin toxicity within a particular grade of toxicity can vary from 1 patient to another and may not be reflected adequately by the toxicity grading of the National Cancer Institute and Common Terminology

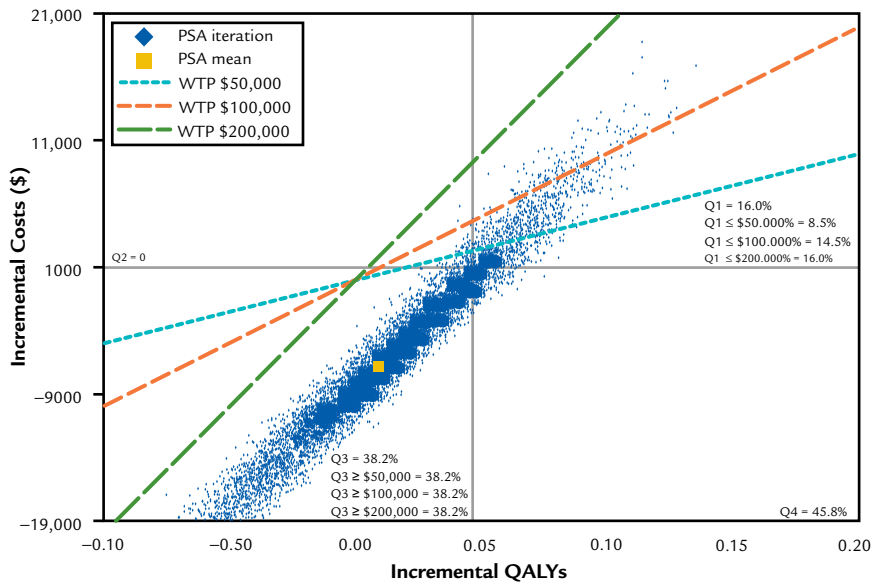


Figure 5. Probabilistic sensitivity analysis (PSA) cost-effectiveness scatter plot. *Quadrant 3 includes iterations in which cetuximab is more effective and more costly than panitumumab. Thus, the incremental cost-effectiveness ratio is switched and is interpreted as cetuximab compared with panitumumab. Iterations greater than the willingness-to-pay (WTP) threshold indicate situations in which panitumumab would be selected over cetuximab, given cetuximab is not cost-effective at the specified WTP threshold. Q1 = more costly, more effective; Q2 = more costly, less effective; Q3 = less costly, less effective; Q4 = less costly, more effective; QALY = quality-adjusted life-year.

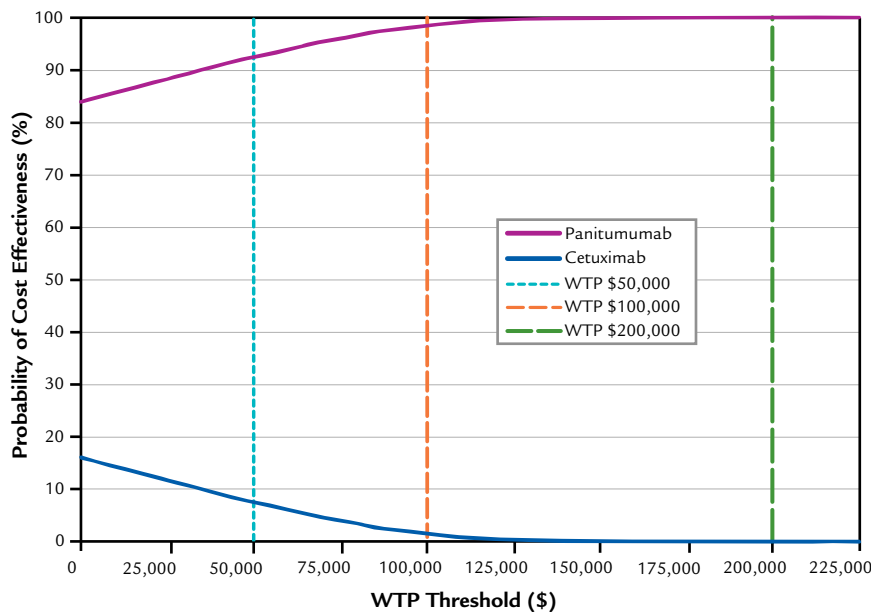


Figure 6. Probabilistic sensitivity analysis cost-effectiveness acceptability curve. WTP = willingness to pay.

Criteria for Adverse Events. Despite these limitations, the 1-way sensitivity analysis in the cost-effectiveness model indicated relatively minimal impact of panitumumab-related hypomagnesemia or grades 3 and 4 cetuximab infusion reactions on the cost-effectiveness results.

In addition, all models are abstractions from real clinical practice and do not take into account all costs and attributes of patient care. However, we have modeled costs that comprise the majority of total costs and those that are likely different between the 2 treatments (eg, drug, administration, adverse events).

Several assumptions were taken into account in the cost-modeling of an infusion reaction. Although most of the clinical sites in the ASPECCT trial were outside the United States, the rate of infusion reactions in the ASPECCT patient population was assumed to be similar for the US patient population. However, it is well known that geographic variations exist in terms of cetuximab infusion reactions.^{34–38} Therefore, the cost-savings and cost-effectiveness of panitumumab may vary across the United States, with likely higher cost savings and better cost-effectiveness outcomes with panitumumab than cetuximab in certain US regions.

CONCLUSIONS

These economic analyses comparing panitumumab and cetuximab in patients with wild-type *KRAS* (exon 2) mCRC suggest benefits in favor of panitumumab, with cost-savings of almost \$9500 per patient in the cost-minimization model, and an incremental cost per QALY gained demonstrating panitumumab to be less costly with marginally better outcomes than cetuximab in the cost-effectiveness model. Such cost-savings can add up, considering that >40,000 new patients are treated for mCRC every year, 40% to 50% of whom are eligible for anti-EGFR therapy. In addition to the potential economic advantage of panitumumab in this setting, panitumumab offers the convenience of biweekly administration over the weekly cetuximab administration, significantly reducing interruptions in patient and caretaker schedules. Furthermore, panitumumab has distinct advantages in terms of hypersensitivity reactions, which can be life-threatening in ~2% of patients receiving cetuximab but are rarely seen with panitumumab. The advantages of panitumumab in terms of hypersensitivity, scheduling, and

costs make it an attractive choice over cetuximab in patients with chemotherapy-refractory CRC.

Because the model was based on a monotherapy study in chemotherapy-resistant CRC, questions may remain regarding its applicability to irinotecan + anti-EGFR therapy in refractory CRC. The majority of patients in the United States receive cetuximab + irinotecan or panitumumab + irinotecan in late-treatment settings, rather than anti-EGFR monotherapy. Although a direct comparison of the costs of treatment with panitumumab and cetuximab has not been performed in such settings, there is little evidence to point to a discrepancy in interaction between these 2 monoclonal antibodies and variable chemotherapy backbones. Therefore, we believe that these results could be generalizable to anti-EGFR antibody + chemotherapy combinations; however, further analysis (particularly in first-line therapy) may be useful.

ACKNOWLEDGMENTS

This study was funded by Amgen Inc. Drs. Schwartzberg, Price, and Fakih received no compensation for their contributions to this manuscript. The sponsored research did not put limits on freedom to publish or the content of publication. Mr. Graham and Ms. Knox conducted the overall economic study design, analysis, and preparation of the manuscript. Dr. Maglinte, Dr. Hechmati, Mr. Hjelmgren, and Dr. Barber made clinical trial data available for analysis, offered analytical suggestions, and contributed to the economic study design, analysis, and manuscript preparation. Drs. Schwartzberg, Price, and Fakih contributed to the study design, data analysis, and preparation of the manuscript. All authors read and approved the final manuscript.

CONFLICTS OF INTERESTS

Mr. Graham and Ms. Knox are employees of RTI Health Solutions, a consultancy firm that has received compensation from Amgen Inc. Dr. Maglinte, Dr. Hechmati, Mr. Hjelmgren, and Dr. Barber are employees of Amgen and own Amgen stock. Drs. Schwartzberg and Fakih have previously served as consultants to Amgen and have also received honoraria from Amgen. Dr. Price has been a compensated member of an Amgen advisory board but has received no other honoraria from Amgen. The authors

have indicated that they have no other conflicts of interest regarding the content of this article.

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