

Cost-Effectiveness of Cetuximab as First-line Treatment for Metastatic Colorectal Cancer in the United States

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Purpose: We conducted a cost-effectiveness analysis incorporating recent phase III clinical trial (FIRE-3) data to evaluate clinical and economic tradeoffs associated with first-line treatments of *KRAS* wild-type (WT) metastatic colorectal cancer (mCRC).

Materials and Methods: A cost-effectiveness model was developed using FIRE-3 data to project survival and lifetime costs of FOLFIRI plus either cetuximab or bevacizumab. Hypothetical *KRAS*-WT mCRC patients initiated first-line treatment and could experience adverse events, disease progression warranting second-line treatment, or clinical response and hepatic metastasectomy. Model inputs were derived from FIRE-3 and published literature. Incremental cost-effectiveness ratios (ICERs) were reported as US\$ per life year (LY) and quality-adjusted life year (QALY). Scenario analyses considered patients with extended *RAS* mutations and CALGB/SWOG 80405 data; 1-way and probabilistic sensitivity analyses were conducted.

Results: Compared with bevacizumab, *KRAS*-WT patients receiving first-line cetuximab gained 5.7 months of life at a cost of \$46,266, for an ICER of \$97,223/LY (\$122,610/QALY). For extended *RAS*-WT patients, the ICER was \$77,339/LY (\$99,584/QALY). Cetuximab treatment was cost-effective 80.3% of the time, given a willingness-to-pay threshold of \$150,000/LY. Results were sensitive to changes in survival, treatment duration, and product costs.

Conclusions: Our analysis of FIRE-3 data suggests that first-line treatment with cetuximab and FOLFIRI in *KRAS* (and extended *RAS*) WT mCRC patients may improve health outcomes and use financial resources more efficiently than bevacizumab and FOLFIRI. This information, in combination with other studies investigating comparative effectiveness of first-line options, can be useful to clinicians, payers, and policymakers in making treatment and resource allocation decisions for mCRC patients.

Key Words: cost-effectiveness, colorectal cancer, *KRAS*, first-line therapy

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Over the last 15 years, median survival for patients with metastatic colorectal cancer (mCRC) has improved significantly, largely due to the introduction of chemotherapeutics (capecitabine, irinotecan, oxaliplatin) and targeted agents (bevacizumab, cetuximab, panitumumab, regorafenib). While studies have suggested that exposure to a greater number of chemotherapeutic agents over the course of disease is associated with improved survival,¹ no standard exists regarding the sequence of agents across lines of therapy. For the 40% of mCRC patients with the mutant form of *KRAS*,^{2–4} treatment sequencing is more straightforward as monoclonal antibodies against the epidermal growth factor receptor (EGFR) have been proven ineffective.^{4,5} For *KRAS* wild-type (WT) patients, the picture is more complex, as both cetuximab (anti-EGFR) and bevacizumab (monoclonal antibody against vascular endothelial growth factor) are approved in the first-line setting. Although bevacizumab has largely been the preferred first-line monoclonal antibody for mCRC, recent data have supported the role of EGFR inhibitors in this setting.

The CRYSTAL (Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer) randomized trial demonstrated a statistically significant improvement in median overall survival (OS) (hazard ratio [HR]=0.796, $P=0.0093$) in the subset of *KRAS*-WT patients receiving cetuximab and FOLFIRI compared with those receiving FOLFIRI alone.^{3,6} The OPUS (Oxaliplatin and Cetuximab in First-Line Treatment of Metastatic Colorectal Cancer) randomized trial demonstrated an improvement in overall response rate and progression-free survival (PFS) in *KRAS*-WT patients receiving cetuximab and FOLFOX4 compared with FOLFOX 4 alone, though OS was not significantly improved (HR=0.86, $P=0.39$).^{7,8} In both the CRYSTAL and OPUS studies, there was no benefit, and a trend toward poorer outcomes, in the *KRAS* mutant population.

Emerging data suggest that patients without evidence of mutations on extended *RAS* testing (*KRAS* (exon 3 [codon 59/61], exon 4 [codon 117/146]), *NRAS* (exon 2 [codon 12/13], exon 3 [codon 59/61], and exon 4 [codon 117/146])) may have further survival improvements when treated with cetuximab.^{9–14} With 15% to 25% of patients presenting with such mutations, broadening genetic screening to include additional exons with *KRAS* and *NRAS* mutations in multiple loci may be beneficial in refining the population of mCRC patients most likely to benefit from anti-EGFR therapy.^{15–18}

The recent German Phase III KRK-0306 (FIRE-3) study was designed to investigate whether bevacizumab or cetuximab is preferable in combination with irinotecan-containing chemotherapy in first-line treatment of patients with *KRAS*-WT mCRC.^{19,20} While overall response rate and PFS were similar between study arms, OS was greater in patients receiving cetuximab compared with bevacizumab, both with FOLFIRI

(28.7 vs. 25 mo; HR=0.77; 95% CI, 0.62-0.96). Among patients without mutations on extended *RAS* testing (85% of *KRAS*-WT population), the magnitude of OS benefit was even greater than observed in the *KRAS*-WT cohort (33.1 vs. 25.6 mo, HR=0.70, $P=0.011$).¹⁹

Recent findings from the CALGB/SWOG 80405 trial suggest that first-line bevacizumab and cetuximab in combination with chemotherapy are associated with similar survival.¹⁸ Unlike FIRE-3, however, the chemotherapy backbone in CALGB/SWOG 80405 was at the discretion of the treating physician, with the majority receiving FOLFOX. Further investigation into the impact of subsequent therapies on median survival with bevacizumab versus cetuximab is warranted to reconcile these discrepant findings. As such, the implications of first-line treatment choice on economic and clinical outcomes are still poorly understood.

Economic modeling is one method of estimating long-term costs and benefits of adding cetuximab to the therapeutic armamentarium in the United States. While several studies have investigated the cost-effectiveness of routine *KRAS* testing in mCRC patients²¹⁻²⁴ and first-line cetuximab relative to chemotherapy alone,²⁵⁻²⁷ few have compared cetuximab with other biologics in US mCRC patients. The present study determined the clinical and economic tradeoffs of cetuximab and bevacizumab in US mCRC patients, using FIRE-3 data and considering the impact of extended *RAS* testing and CALGB/SWOG 80405 results.

MATERIALS AND METHODS

Overview

A deterministic cohort model was developed to mimic the FIRE-3 protocol and evaluate results from that trial.^{19,20} The model projected, from the payer perspective, the lifetime cost-effectiveness of using cetuximab+FOLFIRI versus bevacizumab+FOLFIRI in first-line mCRC patients. For each treatment arm we estimated costs, life years (LYs), and quality-adjusted life years (QALYs), and calculated incremental cost-effectiveness ratios (ICERs). The model structure and data were based primarily on results of FIRE-3¹⁹ and supplemented with data from publicly available databases and published literature. Costs were reported in 2013 US\$, and discounting was not applied given the 2-year model duration reflecting mCRC survival. The model was developed using TreeAge Pro 2012 (TreeAge Software Inc., Williamstown, MA).

Model Structure

Figure 1 shows the patient flow through disease and therapies. The model evaluates a hypothetical cohort of treatment-naïve US *KRAS*-WT mCRC patients over a lifetime, comparing cetuximab+FOLFIRI with bevacizumab+FOLFIRI. Patients could experience either nonfatal or fatal grades 3 and 4 treatment-related adverse events, or progressive disease treated with second-line therapy or resulting in death. The proportion of patients on each second-line treatment was based on FIRE-3 and differed by first-line therapy (Tables 1 and 2). While receiving treatment, patients could experience treatment-specific adverse events that increased costs and decreased health-related quality of life (Table 1). Adverse events were included if they occurred in >5% of patients enrolled in FIRE-3 and incurred nontrivial treatment costs or health-related quality of life impact (based on clinical opinion). As in FIRE-3, a proportion of patients became eligible for liver resection after initiating first-line therapy. Those with R0

resection, that is, complete removal of entire tumor with microscopic examination of margins showing no tumor cells, were considered cured and not eligible for disease recurrence.

Clinical Inputs

Rates of progression were based on FIRE-3 data (Table 1). Median PFS and OS were converted to means and applied to all patients except those undergoing curative hepatic resection, for whom survival was based on CALGB/SWOG 80405.¹⁸ Liver resection was more likely for cetuximab-treated patients, based on FIRE-3 data.²⁸ First-line adverse event rates were also based on FIRE-3 (Table 1), and for second-line were estimated from published literature.²⁹⁻³¹ Mean estimates of clinical benefit were used in the calculation of ICERs in accordance with guidelines for performing cost-effectiveness analyses and commonly used methodology.³²⁻³⁴ The mean is preferred to the median when making projections for a population because it incorporates the impact of the small proportion of patients with extended survival on the desired model outcome of average life expectancy. In addition, the mean has certain properties that the median does not, including being able to be manipulated using standard mathematical operations.

Cost Inputs

The following model costs were included (Tables 2 and 3): product acquisition and administration, adverse event treatment, genetic testing, liver resection, postresection care, and supportive care. Costs were estimated from the payer perspective in 2013 US\$.

Product costs assumed recommended dosing schedules and Wholesale Acquisition Cost pricing (Table 2).⁴⁵⁻⁴⁷ Numbers of 2-week treatment cycles per patient were based on FIRE-3: 10 for cetuximab (400 mg/m² week 1, 250 mg/m² subsequent weeks); 12 for bevacizumab (5 mg/kg). Receipt of second-line therapy was based on FIRE-3 (Table 1) and second-line treatment duration of 7 cycles was based on published literature.³⁰

Adverse event costs other than diarrhea were estimated from a published economic analysis of mCRC patients, whereas diarrhea was from a study of all cancer patients (Table 3).^{39,40} Patients undergoing liver resection incurred surgery costs based on a 2011 study of patients with hepatic resection, and 5-year follow-up costs after R0 resection based on an economic analysis of colorectal cancer patients with liver metastases (Table 3).^{35,37} All patients received mCRC supportive care, with costs estimated from Medicare reimbursement (Table 3).³⁶ To reflect current standards of care, all patients were assumed to undergo *KRAS* and extended *RAS* testing, the costs for which were based on average mCRC tumor panel costs.³⁸

Utility Inputs

The impact of mCRC and treatment on health-related quality of life was incorporated using utility weights (Table 3), which range from 0 to 1, where 0 represents death and 1 represents perfect health. A literature search was conducted to identify the most appropriate sources of data, with emphasis on identifying estimates that were recent and from a mCRC patient population similar to that considered in the model. The utility estimates identified and used in the model were derived from published literature and varied by line of treatment, occurrences of grades 3+ adverse events, and liver resection.^{27,41-44}

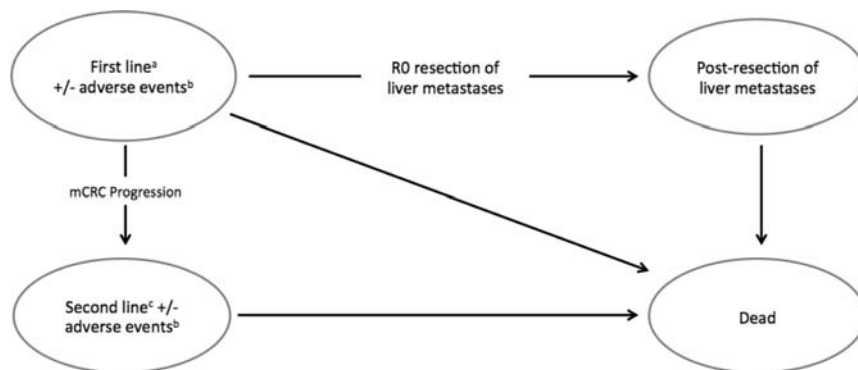


FIGURE 1. Model schematic. ^aFirst-line treatments include cetuximab+FOLFIRI or bevacizumab+FOLFIRI. ^bAdverse events include acneiform rash, desquamation, diarrhea, infection, leukopenia, neutropenia, and thromboembolic events. ^cSecond-line treatments differ by initial treatment, and include regimens reported in FIRE-3. mCRC indicates metastatic colorectal cancer.

Analyses

In the base case, the model calculated lifetime costs, absolute and quality-adjusted survival (as LYs, QALYs), and ICERs for cetuximab+FOLFIRI compared with bevacizumab+FOLFIRI. We compared ICERs to a willingness-to-pay (WTP) threshold to contextualize results and determine whether use of cetuximab+FOLFIRI would be considered an efficient use of resources. WTP represents the maximum additional spending a decision maker would be willing to undertake to gain 1 unit of benefit (eg, QALY). As this threshold value is currently the topic of much debate, we reviewed the body of literature describing currently used and recommended WTP thresholds, concluding that the \$150,000/QALY threshold was appropriate for this model.⁴⁸⁻⁵¹

As a primary scenario analysis, we evaluated the extended RAS-WT patient subgroup, using first-line survival data of 25.6 months for bevacizumab and 33.1 months for cetuximab.²⁸ Sensitivity analyses were conducted to determine the impact of parameter uncertainty on model outcomes. In 1-way sensitivity analyses, all model parameters were varied by

±20% of base case values. In probabilistic sensitivity analysis, 1000 model iterations were conducted with all parameters varying simultaneously; cost inputs followed γ -distributions, utility parameters were uniformly distributed with upper and lower bounds of ±20% of the base case, and clinical estimates followed normal distributions. To better relate our model assumptions to the CALGB/SWOG 80405 protocol and findings, we conducted 2 additional scenario analyses. First, we assumed that 26.6% of first-line patients received a FOLFIRI backbone and 73.4% received FOLFOX.¹⁸ Secondly, we used CALGB/SWOG 80405 OS estimates of 29.04 months for bevacizumab and 29.93 months for cetuximab.¹⁸ To further understand the impact of assuming the same utility weights for each first-line treatment, we also conducted scenario analyses in which the health utilities differed by ±10% for patients on each such treatment. To assess the impact of uncertainty in the rate of R0 resection, we conducted a final scenario analysis in which the resection rate of bevacizumab was set equal to that of cetuximab.

RESULTS

The model predicted that on average, first-line patients treated with cetuximab+FOLFIRI would live 7.6 months longer than those treated with bevacizumab+FOLFIRI (46.9 vs. 39.4 mo; Table 4). The mean quality-adjusted survival was also greater in the cetuximab arm (33.1 vs. 28.5 mo). With discounted mean lifetime costs of \$300,018 and \$245,485 per person, the ICER for first-line cetuximab relative to first-line bevacizumab was \$86,487/LY (\$107,630/QALY).

In the analysis of extended RAS-WT patients, total lifetime costs and benefits were higher in both arms. The cetuximab survival advantage increased to 12.3 months (52.5 vs. 40.2 mo) and 9.7 quality-adjusted months (40.6 vs. 30.9), and incremental costs increased to \$75,731 (\$324,809 vs. \$249,077). This led to ICERs of \$73,731/LY and \$93,785/QALY (Table 4).

The tornado diagram (Fig. 2A) shows the impact of uncertainty in model inputs on predicted outcomes. Results were most sensitive to first-line survival, treatment duration, and acquisition costs. A 20% increase in cetuximab survival caused the ICER to drop to \$70,297/LY, whereas a 20% decline increased the ICER to >\$800,000/LY. Corresponding changes in bevacizumab survival resulted in ICERs of \$286,860/LY and \$70,916/LY, respectively. Varying bevacizumab acquisition costs resulted in ICERs ranging from \$76,079 to \$96,899/LY, and varying those of cetuximab

TABLE 1. Clinical Parameters*

	Bevacizumab + FOLFIRI	Cetuximab + FOLFIRI
Median overall survival (mo)†		
KRAS-WT base case	25.0	28.7
RAS-WT alternate scenario	25.6	33.1
Mean overall survival (mo)†		
KRAS-WT base case	36.1	41.4
RAS-WT alternate scenario	36.9	47.8
Patients receiving second-line (%)	76.4	78.5
R0 resection (%)‡	6.5	12.2
Adverse events (%)		
Acneiform rash	0.0	16.8
Desquamation	0.7	6.7
Diarrhea	13.6	11.5
Infection	0.0	5.7
Leukopenia	11.2	12.8
Neutropenia	22.8	24.2
Thromboembolic events	5.8	5.1

*All data derived from FIRE-3 Phase III trial.

†Median survival estimates from the FIRE-3 trial were converted to mean survival estimates for use as model inputs, assuming that patient survival followed an exponential distribution.

‡Patients with R0 resection had 60 months' survival regardless of initial treatment.¹⁸

TABLE 2. Product Costs and Utilization per 2-Week Cycle and by Treatment Regimen

Regimen	Acquisition (\$)†#	Administration (\$)‡#	Second-line Utilization, by First-line Regimen*	
			Cetuximab (%)	Bevacizumab (%)
First-line				
Bevacizumab + FOLFIRI§	2734	694	—	—
Cetuximab + FOLFIRI§	5289	837	—	—
Second-line				
Bevacizumab + 5-FU/leucovorin§	2653	592	4.4	4.7
Bevacizumab + FOLFIRI§	2734	694	12.4	0.5
Bevacizumab + FOLFOX§	3053	694	29.4	11.5
CapeOX¶	4189	174	8.3	7.9
Cetuximab*§	5095	286	0	5.5
Cetuximab + FOLFIRI§	5289	837	0	14.4
Cetuximab + FOLFOX§	5608	837	0	17.4
FOLFOX	514	623	26.0	30.4
Infusional 5-FU/leucovorin	114	521	6.4	5.8
Panitumumab	4454	143	4.9	0.3
Panitumumab + FOLFIRI	4649	694	2.0	0.8
Panitumumab + FOLFOX	4968	694	6.4	0.9

*FIRE-3 Phase III trial.

†Source: NCCN Colon Cancer Guidelines 2013, PriceRx 2013.

‡Source: NCCN Colon Cancer Guidelines 2013, Physicians' Fee and Coding Guide 2013.

§Additional administration cost of \$31 applied for loading dose in first cycle.

||Additional acquisition cost of \$1528 applied for loading dose in first cycle.

¶Acquisition and administration cost per 3-week cycle, to reflect dosing schedule.

#In 2013 US\$; assumes 1.8 m² body surface area and 70 kg body weight.

NCCN indicates National Comprehensive Cancer Network.

resulted in ranges of \$67,278 to \$100,837/LY. Second-line treatments costs and adverse event costs and rates had the least impact on model results.

When all parameters were varied simultaneously in probabilistic sensitivity analysis over 1000 model iterations (Fig. 2B), cetuximab was cost-effective 92.3% of the time, considering a societal WTP \$150,000/LY.^{52,53} The average

increase in costs when using cetuximab was \$54,533, and the average increase in survival was 7.57 months.

When FOLFOX was included as backbone therapy for most patients, the costs of both model strategies increased. With the increase among bevacizumab patients greater than that in cetuximab patients, the ICER decreased to \$85,774/LY. When survival inputs reflected CALGB results, costs and life expectancy increased in both arms and cetuximab garnered a lower survival benefit than in the base case, with a resulting ICER of \$121,501/LY (Table 4).

In additional scenario analyses, we investigated the impact of differential utilities for patients on each first-line treatment. When the utility for patients receiving bevacizumab ranged from 0.69 to 0.85, the resulting ICER ranged from \$130,617/QALY to \$91,523/QALY. With a similar range of utilities for patients on cetuximab, the ICER ranged from \$92,690/QALY to \$128,061/QALY.

To assess the impact of liver resectability on model results, we conducted an analysis in which the R0 resection rate for bevacizumab was set equal to that for cetuximab. Relative to the base case, this analysis resulted in increased lifetime costs (\$260,380) and survival (42 mo) for bevacizumab patients, for a slightly lower ICER of \$101,451/LY.

DISCUSSION

Results from the FIRE-3 phase III trial and this economic analysis suggest that cetuximab added to FOLFIRI may be an attractive option as first-line therapy for treatment-naïve, RAS-WT mCRC patients. Use of this regimen compared with bevacizumab + FOLFIRI increased both LYs and QALYs. This clinical benefit can be explained, in part, by the greater proportion of cetuximab-treated patients becoming eligible for curative resection of liver metastases (12.2% vs. 6.5%). These findings differ from the results of the EPOC study, which suggest that chemotherapy with cetuximab resulted in poorer PFS than chemotherapy alone.⁵⁴ However, unlike in FIRE-3,

TABLE 3. Other Direct Medical Costs and Health Utilities

Parameters	Estimate	References
Direct medical costs*		
Care after resection (per year)	\$3797	Landman et al ³⁵
mCRC (per day)	\$146	Wong et al ³⁶
Resection (per event)	\$17,438	Abbott et al ³⁷
Genetic testing (per person)	\$1467	BMS Data on file ³⁸
Adverse events (per event)		
Acneiform rash	\$4737	Burudpakdee et al ³⁹
Desquamation	\$4737	Burudpakdee et al ³⁹
Diarrhea	\$8587	Elting and Shih ⁴⁰
Infection	\$6750	Burudpakdee et al ³⁹
Leukopenia	\$6750	Burudpakdee et al ³⁹
Neutropenia	\$6750	Burudpakdee et al ³⁹
Thromboembolic events	\$9368	Burudpakdee et al ³⁹
Health utilities		
mCRC		
First-line	0.77	Meads et al ⁴¹
Second-line	0.75	Meads et al ⁴¹ ; Mittmann et al ²⁷
Grade 3-4 adverse events‡	-0.07	Jonker et al ⁴²
Liver resection surgery†	0.54	Gazelle et al ⁴³
Survival after R0 resection	0.84	Fryback et al ⁴⁴

*In 2013 US\$.

†Utility applied for 1 month.

‡Utility for adverse events expressed as a decrement.

mCRC indicates metastatic colon cancer.

TABLE 4. Base Case and Select Scenario Analyses Results

Regimen	Total Cost	Δ Cost	LY		QALY		ICER	
			Total	Δ	Total	Δ	\$/LY	\$/QALY
Base case								
Bevacizumab + FOLFIRI	\$245,485	—	3.28	—	2.53	—	—	—
Cetuximab + FOLFIRI	\$300,018	\$54,533	3.91	0.63	3.03	0.51	\$86,487	\$107,630
<i>RAS</i> -WT scenario analysis*								
Bevacizumab + FOLFIRI	\$249,077	—	3.35	—	2.58	—	—	—
Cetuximab + FOLFIRI	\$324,809	\$75,731	4.37	1.03	3.39	0.81	\$73,731	\$93,785
FOLFOX scenario analysis†								
Bevacizumab + FOLFIRI	\$248,295	—	3.28	—	2.53	—	—	—
Cetuximab + FOLFIRI	\$302,360	\$54,064	3.91	0.63	3.03	0.51	\$85,744	\$106,706
CALGB 80405 scenario analysis‡								
Bevacizumab + FOLFIRI	\$269,748	—	3.73	—	2.87	—	—	—
Cetuximab + FOLFIRI	\$306,940	\$37,191	4.04	0.31	3.13	0.26	\$121,501	\$141,681

**RAS*-WT scenario analysis considered only those patients with *RAS*-WT. Median survival for cetuximab patients was 33.1 months, for bevacizumab patients was 25.6 months.

†FOLFOX scenario analysis assumes 73.4% of patients incur the costs of FOLFOX as the backbone regimen in combination with either cetuximab or bevacizumab, 26.6% incur the costs of FOLFIRI.

‡CALGB 80405 scenario analysis assumed survival consistent with results from that trial. Median survival for cetuximab patients was 29.9 months, for bevacizumab patients was 29.0 months.

ICER indicates incremental cost-effectiveness ratio; LY, life year; QALY, quality-adjusted life year.

the EPOC study did not include a bevacizumab arm and all patients received a fluoropyrimidine with oxaliplatin as the chemotherapy backbone. These discordant findings suggest that the choice of chemotherapy backbone (FOLFIRI vs. FOLFOX) to use in combination with a biologic may influence response rate and likelihood of curative hepatic resection.

In our model, differences in product costs resulted in higher lifetime costs for the cetuximab compared with bevacizumab arms. Despite this, cetuximab’s greater mean clinical benefit yielded an ICER of \$86,487/LY, well below frequently cited thresholds.⁴⁸ In a subgroup analysis of extended *RAS*-WT patients for whom cetuximab’s median survival advantage was greater (33.1 vs. 25.6 mo), the ICER was even more attractive at \$73,731/LY. Identifying patient subgroups, such as those without extended *RAS* mutations, for whom cetuximab treatment is more effective, could further optimize treatment outcomes and cost-effectiveness. Given the amount of variation in patient experiences and survival among the FIRE-3 population, including differences between those with and without extended *RAS* mutations and the large expected benefit of those patients eligible for hepatic resection, the choice of reporting results in terms of the mean OS as opposed to median is further supported to accurately reflect patient survival in estimation of population life expectancy. With model results most sensitive to survival and product costs, further research into the clinical benefit of each drug is warranted, and awareness of the impact of price negotiations may be beneficial.

Bevacizumab was approved for use in combination with first-line mCRC chemotherapy in 2004 and has largely been the preferred first-line monoclonal antibody since then. A recently published cohort study of 4877 US patients demonstrated that bevacizumab was used in 51% of patients as first-line therapy.⁵⁵ Cetuximab, in contrast, was used most frequently as second-line or third-line therapy in this cohort.⁵⁵ With emerging data supporting EGFR inhibitors in first-line, treatment decision making has become more complex. Often, first-line decisions are driven by factors including drug cost, anticipated toxicities, and practice patterns. Our study, which includes adverse events, costs, and survival, challenges the current preference for first-line bevacizumab. In particular, a trend toward better downstaging for hepatic metastasectomy

with first-line cetuximab may motivate patients and clinicians toward using EGFR inhibitors in the first-line setting.⁵⁶ Benefits of increased R0 resection among cetuximab-treated patients were demonstrated in a recent German economic analysis,⁵⁷ and a trend toward increased hepatic resection in cetuximab-treated patients was seen in CALGB/SWOG 80405. The randomized phase II PEAK trial results also suggest a benefit of EGFR inhibitor therapy as opposed to bevacizumab in first-line mCRC treatment.¹⁶

In FIRE-3, there were no differences in median PFS between treatment arms in both the *KRAS*-WT and extended *RAS*-WT populations, whereas median OS was higher in the cetuximab arm. These differences in OS but not PFS might suggest that observed differences in median OS were driven solely by subsequent-line therapy. However, a recent analysis of subsequent-line therapy in FIRE-3 patients demonstrated that decisions about second-line therapy were influenced to some extent by first-line efficacy.⁵⁸ Further, the proportion of complete responders in the intent-to-treat population was higher in the cetuximab arm, as were the number of partial responders in the response-assessable population. Greater partial and complete response to first-line therapy may not necessarily translate into improved PFS, but may have benefit in terms of hepatic resection feasibility, overall disease burden, and subsequent-line therapy tolerance. Next, recent data suggest that patients with left-sided compared with right-sided colon cancers are more likely to benefit from cetuximab therapy, which might also help explain the results observed in FIRE-3 patients, 80% of whom had left-sided tumors.⁵⁹ Further investigation into the impact of first-line therapy on subsequent-line treatment choice and benefit is warranted to further explain discrepancies between median PFS and median OS in this study.

The findings from FIRE-3 should also be considered in light of the somewhat divergent CALGB/SWOG 80405 results. With more patients in CALGB/SWOG 80405 receiving a FOLFOX backbone, use of a FOLFIRI backbone in FIRE-3 may have contributed to a greater proportion of cetuximab-treated patients undergoing hepatic metastasectomy; this, in turn, may have translated into clinical benefit and improved survival compared with that in CALGB/SWOG 80405.

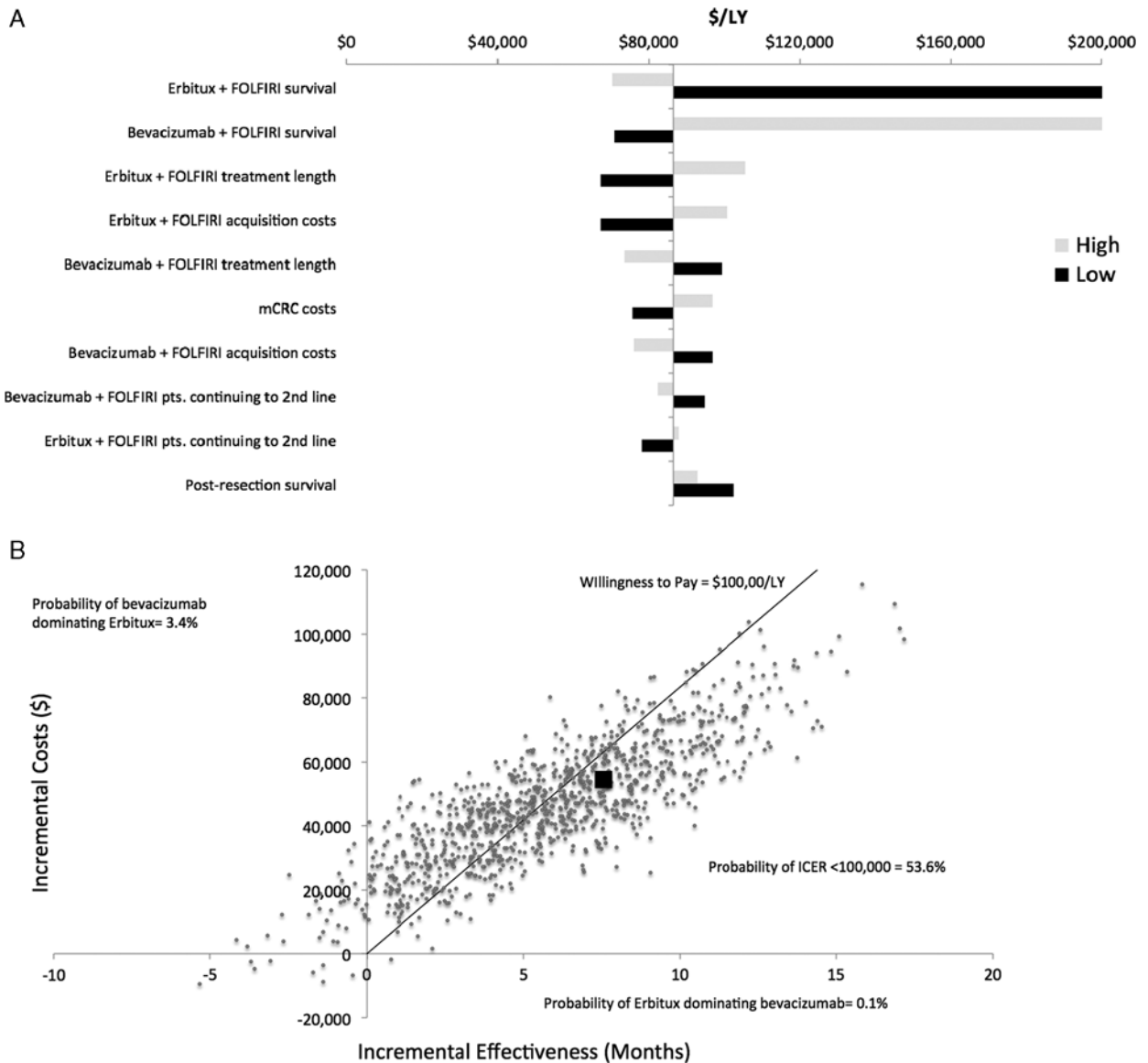


FIGURE 2. A, One-way sensitivity analysis results: tornado diagram. B, Probabilistic sensitivity analysis results: cost-effectiveness scatterplot. Dots represent ICERs when all parameters are varied simultaneously for 1000 model simulations; square represents base case ICER. ICER indicates incremental cost-effectiveness ratio; LY, life year; pts, patients.

Further, a larger number of patients in CALGB/SWOG 80405 than those in FIRE-3 received subsequent-line therapy (88% vs. 67%); this may also explain the divergent results of these 2 large trials. Higher subsequent-line biologics use among all CALGB/SWOG 80405 study patients may have contributed to improved and similar median survival in both arms relative to FIRE-3. Further investigation into the impact of extended *RAS* testing on treatment benefit may further corroborate the FIRE-3 results, as preliminary CALGB/SWOG 80405 findings suggest higher response rates with cetuximab in extended *RAS*-WT patients.⁶⁰ While it is important to acknowledge and reconcile the conflicting results of studies comparing biologics in first-line mCRC treatment, the FIRE-3 findings cannot be discounted based on those from CALGB/SWOG 80405. Nevertheless, future economic analyses that incorporate data

from CALGB/SWOG 80405 would be beneficial. Although not the primary focus of this manuscript, we did conduct 2 scenario analyses to assess the findings from CALGB. In the analyses using survival estimates and FOLFOX use reflecting CALGB/SWOG 80405, the general findings of cetuximab use resulting in greater survival at a reasonable cost were maintained.

Results of our analysis should be viewed taking into account its limitations. First, the model was primarily based on data from the FIRE-3 clinical trial. Generalizability of this model to real-world clinical settings is unclear, and additional observational cohort studies are needed to examine treatment patterns and associated costs with either treatment strategy. Of specific concern are differences between FIRE-3 and CALGB/SWOG 80405, as discussed above. It may also be that more US

patients than those in the German FIRE-3 setting would receive biologics in second-line, which could impact cost and clinical outcomes. However, model scenario and sensitivity analyses indicate that none of these factors would substantially impact model outcomes. In addition, the model considered two lines of therapy, even though third and subsequent lines were included in FIRE-3. As such, the model assumes that costs associated with treatment after second-line would not meaningfully differ between arms. While we do not have explicit data about third and subsequent-line biologics use in FIRE-3, it is possible that patients who received bevacizumab in first-line were less likely to receive cetuximab in later lines of treatment upon disease progression; such differences would have an impact on overall treatment costs and are not included in the model.

As in many cost-effectiveness analyses, the validity of utility weights is uncertain because of the need to combine data sources; however, the impact of varying these estimates in sensitivity analyses was small, indicating that increasing certainty in estimates would be of minimal value. Finally, we conducted the analysis from the payer perspective; therefore indirect costs (eg, productivity losses) were not included. While societal costs should be considered when making resource allocation decisions, the expected impact of such costs would be minimal compared with direct medical costs, for example, product costs and hospitalizations.

This analysis was the first of its kind to use data from a pivotal clinical trial to project economic outcomes comparing biologic agents for mCRC treatment. On the basis of FIRE-3 data, cetuximab has an ICER of \$86,487/LY compared with bevacizumab. Results were more favorable for cetuximab in *RAS*-WT patients, with an ICER of \$73,731/LY. While the economic efficiency of cetuximab treatment is uncertain as further clinical data emerges, these preliminary results based on FIRE-3 should be considered when making treatment decisions in first-line mCRC patients.

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