COST-EFFECTIVENESS OF CETUXIMAB AS FIRST-LINE TREATMENT FOR METASTATIC COLORECTAL CANCER IN THE US

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Background

- Approximately 140,000 new colorectal cancer (CRC) cases are expected in the US in 2014.[1]
- 5-year survival for metastatic colorectal cancer (mCRC) is 13%, despite the approval of multiple new chemotherapeutics and targeted agents over the past decade.[1,2]
- Optimal use and sequencing of available systemic agents, as well as appropriate use of surgery and/or radiation, may have implications on survival, liver resectability, toxicity, and total cost of care for patients with mCRC.[3]
- Recent randomized clinical trials have demonstrated that cetuximab (Erbitux®), a recombinant anti-EGFR monoclonal antibody, may improve survival in *K-RAS* wild-type (WT) mCRC patients when given in combination with chemotherapy.[4-9]
- Clinical trials have also shown improved survival when bevacizumab (a monoclonal antibody against vascular endothelia growth factor) is combined with chemotherapy.[10-12]
- The multi-center Phase III study KRK-0306 (FIRE-3) is the first to directly compare biologics (bevacizumab vs. cetuximab) in combination with chemotherapy in first-line mCRC treatment.[4]

Objective

- This cost-effectiveness analysis uses FIRE-3 trial results to evaluate the clinical and economic tradeoffs associated with use of either FOLFIRI (irinotecan, 5FU, and LV) + cetuximab or FOLFIRI + bevacizumab in the first-line treatment of *K-RAS* WT mCRC patients in the United States.

Methods

Model Overview

Structure: Deterministic cost-effectiveness model
Population: Adult US mCRC patients with previously untreated (1st-line):
- Base case: *K-RAS* WT, EGFR-expressing tumors
- Alternate scenario analysis: *RAS* WT tumors[a]

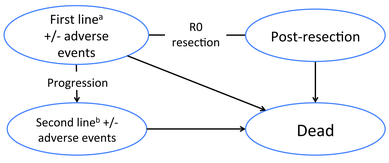
Perspective: Payer
Time horizon: Lifetime
Outcome measures:
- Survival (in life years, LYs; and quality adjusted life years, QALYs)
- Costs (in 2013 US$), including product, adverse event, and other direct medical costs
- Incremental cost-effectiveness ratios (ICERs, in $/LY and $/QALY)

[a] A preplanned sub-analysis was done to evaluate the effect of additional *K-RAS* mutations in exon 3 (codon 59/61), exon 4 (codon 117/146), NRAS exon 2 (codons 12/13), exon 3 (codons 59/61) and exon 4 (codons 117/146).

Model Structure

- Patients may progress from 1st line to 2nd line therapy, experience treatment-specific adverse events (in either line), or die at any point.
- Adverse events considered in the model include: acneiform rash, desquamation, diarrhea, infection, leukopenia, neutropenia, and thromboembolic events.
- Treatment cycles are assumed to be 2 weeks.
- Second-line treatment regimens varied by first-line treatment and are based on proportions reported in FIRE-3.
- Patients incurred costs associated with product acquisition and administration, adverse event treatment, and direct medical utilization.

Figure 1. Model Structure



[a] First-line treatments include cetuximab or bevacizumab, + FOLFIRI.
[b] Second-line treatments differ by initial treatment, and include regimens reported in FIRE-3 (See Table 4).

Analyses

- Base case: ICERs were calculated for cetuximab + FOLFIRI compared with bevacizumab + FOLFIRI.
- Alternate scenario analysis: Identical ICERs were calculated for the subset of patients with *RAS* WT tumors.
- One-way sensitivity analyses: All model parameters were independently varied by +/- 20%.

Table 1. Clinical Efficacy

Parameter	Value	Source
Median Overall Survival (months)		
Base Case[a]		
Bevacizumab + FOLFIRI	25.0	4
Cetuximab + FOLFIRI	28.7	
Alternate Scenario Analysis[a]		
Bevacizumab + FOLFIRI	25.6	4
Cetuximab + FOLFIRI	33.1	
R0 Resection	37.4	13
1st line Patients Receiving 2nd-Line		
Bevacizumab + FOLFIRI	76.4%	4
Cetuximab + FOLFIRI	78.5%	
Patients with R0 Resection		
Bevacizumab + FOLFIRI	6.5%	14
Cetuximab + FOLFIRI	12.2%	
Patients with Adverse Event(s) in 1st-line		
Bevacizumab + FOLFIRI	44.6%	4
Cetuximab + FOLFIRI	59.4%	

[a] For each initial treatment strategy.

Table 2. Health Utilities

		Source
mCRC:		
1st-line	0.77	15
2nd-line	0.75	15,16
Grade 3-4 adverse events[a]	-0.07	17
Liver resection surgery[b]	0.54	18
Survival after R0 resection	0.84	19

mCRC, metastatic colorectal cancer.
[a] Adverse event utilities expressed as a decrement.
[b] Utility applied for 1 month.

Table 3. 1st-line Regimens

Regimen	# Cycles per Regimen		Acquisition ($)		Administration ($)	
	Value	Source	Value	Source	Value	Source
1st-Line						
Bevacizumab + FOLFIRI	12	4	2,734	20,21	694	20,22
Cetuximab + FOLFIRI	10		5,289		837	
All 2nd-line therapies	7	12	See Table 4		See Table 4	

Table 4. 2nd-line Regimens Utilization and Costs

	Acquisition ($)		Administration ($)		2nd- Line Utilization, Among 1st-line:		
	Value	Source	Value	Source	Cetuximab Patients	Bevacizumab Patients	Source
Bevacizumab + 5-FU/ leucovorin	2,653		592		4.4%	4.7%	
Bevacizumab + FOLFIRI	2,734		694		12.4%	0.5%	
Bevacizumab + FOLFOX	3,053		694		29.4%	11.5%	
CapeOX	4,189		174		8.3%	7.9%	
Cetuximab	5,095		286		0.0%	5.5%	
Cetuximab + FOLFIRI	5,289	20,21	837	20,22	0.0%	14.4%	4
Cetuximab + FOLFOX	5,608		837		0.0%	17.4%	
FOLFOX	514		623		26.0%	30.4%	
Infusional 5-FU/leucovorin	114		521		6.4%	5.8%	
Panitumumab	4,454		143		4.9%	0.3%	
Panitumumab + FOLFIRI	4,649		694		2.0%	0.8%	
Panitumumab + FOLFOX	4,968		694		6.4%	0.9%	

Results

Base Case

- Compared with 1st line bevacizumab patients, those treated with cetuximab:
  - gained an additional 5.7 months of life (42.9 vs. 37.2 months).
  - incurred additional lifetime costs of $46,301.

Alternate Scenario Analysis

- Benefits of cetuximab were greater for the *RAS* WT subpopulation, with ICERs of $77,380 per LY and $99,636 per QALY.

Probabilistic Sensitivity Analyses

- Cetuximab would be considered cost effective 80% of the time at a societal willingness to pay of $150,000/LY.

Figure 2. Probabilistic Sensitivity Analyses

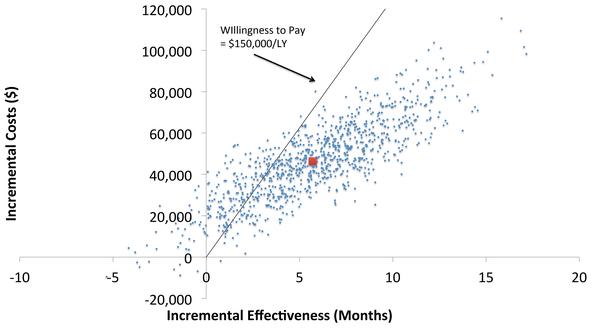


Table 5. Results[a]

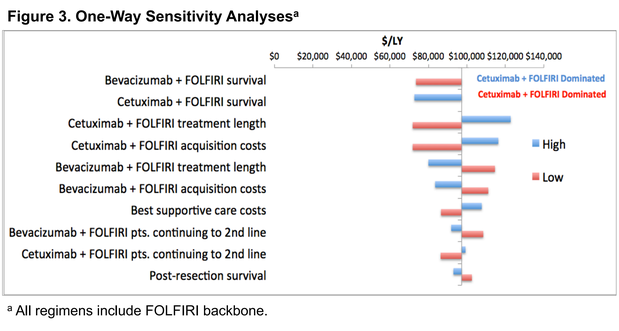
	Cost		LY		QALY		ICER	
Regimen	Total	Δ	Total	Δ	Total	Δ	$ per LY	$ per QALY
Base Case								
Bevacizumab	$234,632	-	3.10	-	2.38	-	-	-
Cetuximab	$280,933	$46,301	3.58	0.48	2.76	0.38	$97,297	$122,704
Alternate Scenario Analysis								
Bevacizumab	$238,255	-	3.17	-	2.43	-	-	-
Cetuximab	$305,727	$67,472	4.04	0.87	3.11	0.68	$77,380	$99,636

Δ, change in; ICER, incremental cost effectiveness ration; LY, life year; QALY, quality-adjusted life year.
[a] All regimens include FOLFIRI backbone.

One-way Sensitivity Analyses

- Results were most sensitive to first-line survival, treatment duration, and acquisition costs.

Figure 3. One-Way Sensitivity Analyses[a]



[a] All regimens include FOLFIRI backbone.

Conclusions

- Cetuximab + FOLFIRI resulted in an ICER of $97,297/LY compared with bevacizumab + FOLFIRI; this is below frequently cited societal willingness-to-pay thresholds.
- *RAS* WT subgroup analysis showed greater increase in survival for cetuximab patients.
- The analysis is the first of its kind to use pivotal clinical trial data to compare biologic agents and project economic outcomes in mCRC patients.
- Treatment with cetuximab + FOLFIRI in 1st-line mCRC patients may use financial resources more efficiently than would treatment with bevacizumab + FOLFIRI. This information can be useful to clinicians, payers, and policy makers in making treatment and resource allocation decisions for *K-RAS* WT and *RAS* WT mCRC patients.

References

1. American Cancer Society 2014; **2.** Cartwright *Clin Colorectal Cancer* 2012; **3.** Stein *World J Gastroenterol* 2014; **4.** Heinemann *J Clin Oncol* 2013; **5.** Erbitux Prescribing Information 2013; **6.** Bokemeyer *J Clin Oncol* 2009; **7.** Bokemeyer *Ann Oncol* 2011; **8.** Van Cutsem *N Engl J Med* 2009; **9.** Van Cutsem *J Clin Oncol* 2011; **10.** Avastin Prescribing Information 2013; **11.** Hurwitz *N Engl J Med* 2004; **12.** *Giantonio J Clin Oncol* 2007; **13.** Adam *J Clin Oncol* 2009; **14.** Stintzing *Ann Oncol* 2012; **15.** Meads *Health Technol Assess* 2010; **16.** Mittmann *J Natl Cancer Inst* 2009; **17.** Jonker *N Engl J Med* 2007; **18.** Gazelle *Radiology* 2004; **19.** Fryback *Med Decis Making* 1993; **20.** NCCN Clinical Practice Guidelines in Oncology, Colon Cancer (Version 3) 2012; **21.** PriceRx® Wolters Kluwer 2013; **22.** Physicians' Fee & Coding Guide 2013.

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