The cost of survival gain in metastatic colorectal cancer (mCRC) in Spain

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BACKGROUND

- Chemotherapies are commonly used for the treatment of mCRC. Over the past 10 years, a number of targeted therapies (bevacizumab, cetuximab, panitumumab, aflibercept, and regorafenib) have been approved for the treatment of mCRC[1–5]
- Targeted therapies are more expensive than chemotherapies; therefore, their clinical benefit is associated with economic implications
  - Traditionally, the added value of a new therapy has been estimated through the use of cost–utility analyses
  - However, clinical trial data are often incomplete and incremental cost-effectiveness ratios (ICERs) are highly dependent on the assumptions used to extrapolate or adjust trial results. In the UK, ICERs for second-line cetuximab plus irinotecan versus irinotecan alone range from £45,237 to £370,044 depending on the assumptions used[6]
- Outside of cost-effectiveness analyses, the relative cost of overall survival (OS) gain has not been examined extensively in published literature. Thus, a basic cost-effectiveness analysis of targeted therapies in mCRC was conducted from the perspective of a Spanish national payer, using only observed data

OBJECTIVE

- To estimate the incremental cost per month of median OS gained with the use of approved targeted therapies, in addition to chemotherapy or best supportive care (BSC) alone, for first-, second-, and third-line treatment of mCRC

METHODS

- A review was conducted of product labels of bevacizumab, cetuximab, panitumumab, aflibercept, and regorafenib to identify pivotal phase 3 clinical trials. Studies were included if they demonstrated statistically significant improvement in median OS (Table 1)

***Table 1:** Summary of clinical trials assessing targeted therapies*

Regimen/source	Targeted therapies	Median treatment duration, months	Median PFS, months	Median OS, months
First-line				
IFL Hurwitz 2004[i,9]	Bevacizumab	9.3	10.6	20.3
	--	6.4	6.2	15.6
FOLFIRI Van Cutsem 2011[10]	Cetuximab	NR	9.9	23.5
	--	NR	8.4	20.0
FOLFOX4 Douillard 2014[ii,11]	Panitumumab	NR	10.0	23.9
	--	NR	8.6	19.7
Second-line				
FOLFOX4 Giantonio 2007[12]	Bevacizumab	4.6	7.3	12.9
	--	3.2	4.7	10.8
Oxaliplatin- or irinotecan-based chemotherapy Bennouna 2013[7]*	Bevacizumab	4.2	5.7	11.2
	--	3.2	4.1	9.8
FOLFIRI Van Cutsem 2012[13]	Aflibercept	4.9	6.9	13.5
	--	4.2	4.7	12.1
Third-line				
BSC Karapetis 2008[iii,14]	Cetuximab	NR	3.7	9.5
	--	NR	1.9	4.8
BSC Grothey 2013[15]	Regorafenib	1.7	1.9	6.4
	--	1.6	1.7	5.0

i. IFL is no longer standard of care.
ii. An updated exploratory analysis.
iii. A retrospective analysis; tumor samples were not available for all patients.
BSC, best supportive care; NR, not reported
*Bennouna *et al*[7] presented the average results for bevacizumab added to a variety of oxaliplatin- or irinotecan-based chemotherapies. The dosing regimens for the most common three regimens were used; these dosing regimens were taken from an ASCO presentation of the study.[8]

- Treatment duration was not consistently reported across all trials. For this analysis, median PFS was used as a proxy for treatment duration, which should be reasonable because most patients discontinue therapy due to progression or death.[15] The model considers the drug and administration cost over the treatment duration
  - Adverse event management and disease management costs are not included in the analysis

Drug costs estimation

- The acquisition costs for targeted therapies and chemotherapies were based on the 2015 public price including VAT from the Consejo General de Colegios Oficiales de Farmacéuticos (Portalfarma) with a 7.5% discount (Table 2)[16]
- The recommended dosing regimens were based on clinical trials identified in Table 1, and were used to estimate the costs in Table 3. Body surface area (men: 1.93 ± 0.19 m^2, women: 1.68 ± 1.8 m^2) and weight (men: 79.8 ± 15 kg, women: 65.3 ± 14 kg) are based on a study of cancer patients in the UK[17]
  - The analysis assumed that the population is 58% male, based on a study that estimated the percent of incident CRC cases in men and women in 2012[18]
- The drug cost per month of a treatment regimen was based on the recommended dose of each drug, the number of vials/capsules required to achieve dose, the cycle length, and the number of doses per cycle
  - The analysis assumed that vial sharing was not allowed (i.e., after administration, the remaining drug in a vial would be discarded)
- The number of vials/tablets required to achieve the specified dose were based on methods described by Sacco *et al*, 2010.[17] A sample calculation for cetuximab is presented in Table 4; similar calculations were performed for other drugs

***Table 2:** Drug acquisition cost*

Drug	Formulation	Cost per vial/tablet, €
5-FU	500 mg vial	3.12
	1000 mg vial	3.12
	5000 mg vial	12.61
Aflibercept	100 mg vial	433.78
	200 mg vial	823.39
Bevacizumab	100 mg vial	377.70
	400 mg vial	1278.30
Capecitabine	150 mg tablet	0.40
	500 mg tablet	1.25
Cetuximab	100 mg vial	229.16
Irinotecan	40 mg vial	13.46
	100 mg vial	33.64
	300 mg vial	100.92
	500 mg vial	107.75
Leucovorin	50 mg vial	4.23
	100 mg vial	8.46
	200 mg vial	16.91
Oxaliplatin	50 mg vial	99.25
	100 mg vial	180.00
	200 mg vial	317.46
Panitumumab	100 mg vial	414.65
	200 mg vial	784.91
	400 mg vial	1516.03
Regorafenib	40 mg tablets, 84 tablets per package	35.24

***Table 3:** Drug costs estimation*

Regimen/ source	Drug	Dose	Drug cost per dose, €	Doses per cycle	Cycle length, weeks	Drug cost per month, €
IFL + bevacizumab Hurwitz 2004[9]	Irinotecan	125 mg/m^2	83.68	4	6	223.15
	Fluorouracil	500 mg/m^2	3.81	4	6	10.17
	Leucovorin	20 mg/m^2	4.23	4	6	11.29
	Bevacizumab	5 mg/kg	1395.38	1	2	3031.63
FOLFIRI + cetuximab Van Cutsem 2011[10]	Irinotecan	180 mg/m^2	108.96	1	2	236.72
	Leucovorin	200 mg/m^2	32.99	1	2	71.68
	Fluorouracil*	400 mg/m^2	3.12	1	2	6.78
	Fluorouracil**	2400 mg/m^2	13.98	1	2	60.75
	Cetuximab	400 mg/m^2	1787.27	Initial loading dose	NA	NA
		250 mg/m^2	1160.22	1	1	5041.43
FOLFOX4 + panitumumab Douillard 2014[11]	Oxaliplatin	85 mg/m^2	328.55	1	2	713.81
	Leucovorin	200 mg/m^2	32.99	2	2	143.37
	Fluorouracil*	400 mg/m^2	3.12	2	2	13.57
	Fluorouracil**	600 mg/m^2	5.47	2	2	23.78
	Panitumumab	6 mg/kg	1892.87	1	2	4112.47
FOLFOX4 + bevacizumab Giantonio 2007[12]	Oxaliplatin	85 mg/m^2	328.55	1	2	713.81
	Leucovorin	200 mg/m^2	32.99	2	2	143.37
	Fluorouracil*	400 mg/m^2	3.12	2	2	13.57
	Fluorouracil**	600 mg/m^2	5.47	2	2	23.78
	Bevacizumab	10 mg/kg	2600.84	1	2	5650.64
FOLFOX6 + bevacizumab Arnold 2012[8]	Oxaliplatin	85 mg/m^2	328.55	2	4	713.81
	Leucovorin	400 mg/m^2	63.87	2	4	138.77
	Fluorouracil*	400 mg/m^2	3.12	2	4	6.78
	Fluorouracil**	2400 mg/m^2	13.98	2	4	60.75
	Bevacizumab	5 mg/kg	1395.38	2	4	3031.63
XELOX + bevacizumab Arnold 2012[8]	Capecitabine	1000 mg/m^2	4.83	28	3	195.97
	Oxaliplatin	130 mg/m^2	435.01	1	3	630.07
	Bevacizumab	7.5 mg/kg	2020.56	1	3	2926.60
FOLFIRI + bevacizumab Arnold 2012[8]	Irinotecan	180 mg/m^2	108.96	1	2	236.72
	Leucovorin	400 mg/m^2	63.87	1	2	138.77
	Fluorouracil*	400 mg/m^2	3.12	1	2	6.78
	Fluorouracil**	2400 mg/m^2	13.98	1	2	60.75
	Bevacizumab	5 mg/kg	1395.38	1	2	3031.63
FOLFIRI + aflibercept Van Cutsem 2012[13]	Irinotecan	180 mg/m^2	108.96	1	2	236.72
	Leucovorin	400 mg/m^2	63.87	1	2	138.77
	Fluorouracil*	400 mg/m^2	3.12	1	2	6.78
	Fluorouracil**	2400 mg/m^2	13.98	1	2	60.75
	Aflibercept	4 mg/kg	1475.30	1	2	3205.26
Cetuximab + BSC Karapetis 2008[14]	Cetuximab	400 mg/m^2	1787.27	Initial loading dose	NA	NA
		250 mg/m^2	1160.22	1	1	5041.43
Regorafenib + BSC Grothey 2013[15]	Regorafenib	160 mg	140.95	21	4	3215.48

*Bolus.
**Continuous infusion.

***Table 4:** Estimation of number of units: sample calculation for cetuximab*

Number of 100 mg vials	Body surface area, m^2	Males			Females		
		Proportion of patients, %		Number of 100 mg vials per dose	Proportion of patients, %		Number of 100 mg vials per dose
		Cumulative	Per dose		Cumulative	Per dose	
1	0.3	0	0	1	0	0	1
2	0.5	0	0	2	0	0	2
3	0.8	0	0	3	0	0	3
4	1.0	0	0	4	0	0	4
5	1.3	0	0	5	1	1	5
6	1.5	1	1	6	16	15	6
7	1.8	17	16	7	65	49	7
8	2.0	64	47	8	96	31	8
9	2.3	95	31	9	100	4	9
10	2.5	100	5	10	100	0	10
		Mean vials per dose		8.22	Mean vials per dose		7.22
		Cost per vial, €		229.16	Cost per vial, €		229.16
		Mean cost per dose €		1883.38	Mean cost per dose, €		1654.53

Administration costs estimation

- The unit cost of chemotherapy administration is €250.12, which is the average cost of chemotherapy administration across 9 regions reporting administration costs in price bulletins (Asturias, Baleares, Canary Islands, Castilla-León, Galicia, La Rioja, Murcia, Navarra, and País Vasco)
- For each regimen, the administration cost per month was based on the unit cost of administration per visit, the cycle length, and the number of doses per cycle

RESULTS

- Table 5 reported the results incremental median OS (mOS) gain and incremental cost associated with introducing targeted therapies over chemotherapies
  - In first-line, targeted agents were associated with 3.5–4.7 months of mOS gain with an additional cost of €8044 to €16,370/month
  - In second-line, the 1.4–2.1 months of mOS gain had an additional cost of €13,274 to €22,096/month
  - In third-line, the cost per month of mOS gain was the lowest, ranging from €4364 to €4958, with mOS gains of 1.4–4.7 months

***Table 5:** Analysis results*

Trial/source	Intervention	Median PFS, months	Median OS, months	Incremental mOS, months	Drug cost, €	Administration cost, €	Incremental cost, €	Incremental cost, €/ incremental month mOS
First-line								
Hurwitz 2004[9]	IFL + bevacizumab	10.6	20.3	4.7	34,632	9600	37,808	8044
	IFL	6.2	15.6		809	5615		
Van Cutsem 2011[10]	FOLFIRI + cetuximab	9.9	23.5	3.5	54,259	10,760	57,296	16,370
	FOLFIRI	8.4	20.0		3158	4565		
Douillard 2014[11]	FOLFOX4 + panitumumab	10.0	23.9	4.2	50,070	10,868	43,899	10,452
	FOLFOX4	8.6	19.7		7693	9347		
Second-line								
Giantonio 2007[12]	FOLFOX4 + bevacizumab	7.3	12.9	2.1	47,780	7934	46,401	22,096
	FOLFOX4	4.7	10.8		4204	5108		
Arnold 2012[8]	FOLFOX6 + bevacizumab (5 mg/kg)	5.7	11.2	1.4	22,525	3097	19,622	14,016
	FOLFOX6	4.1	9.8		3772	2228		
Arnold 2012[8]	XELOX + bevacizumab	5.7	11.2	1.4	21,390	2065	18,583	13,274
	XELOX	4.1	9.8		3387	1485		
Arnold 2012[8]	sFOLFIRI + bevacizumab	5.7	11.2	1.4	19,806	3097	18,859	13,470
	sFOLFIRI	4.1	9.8		1816	2228		
Bennouna 2013[7]	Fluoropyrimidine + oxaliplatin or irinotecan + bevacizumab	5.7	11.2	1.4	21,240*	2753*	19,021	13,587
	Fluoropyrimidine + oxaliplatin or irinotecan	4.1	9.8		2992*	1980*		
Van Cutsem 2012[13]	FOLFIRI + aflibercept	6.9	13.5	1.4	25,173	3750	24,316	16,886
	FOLFIRI	4.7	12.1		2069	2538		
Third-line								
Karapetis 2008[14]	Cetuximab (wild-type *KRAS*)	3.7	9.5	4.7	19,280	4021	23,302	4958
	BSC (wild-type *KRAS*)	1.9	4.8		0	0		
Grothey 2013[15]	Regorafenib	1.9	6.4	1.4	6109	0	6109	4364
	Placebo	1.7	5.0		0	0		

*Weighted average of costs for FOLFOX6 + bevacizumab, XELOX + bevacizumab, and FOLFIRI + bevacizumab from Arnold 2012.

CONCLUSIONS

- Based on this analysis, which considered only observed data without extrapolation, the incremental cost per month of mOS gain varies greatly in Spain, both by treatment and by line
- The survival gain on targeted therapies is the highest in first-line treatment compared with second- or third-line treatment. The addition of a targeted agent gives the highest additional cost per month of OS gain in second-line treatment, followed by first-line treatment, with the lowest cost per month of mOS gain provided by third-line treatment. Regorafenib was the most cost-effective treatment in this analysis
- The impact of this analysis on the management of targeted agents in Spain should be explored further, and future analyses should consider other treatment-related costs, such as adverse event management and disease management costs, as well as dose adjustments to manage toxicities

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