

Cost-effectiveness analysis based on response predictors for first-line therapies in metastatic colorectal cancer in Spain

Cristóbal Belda-Iniesta C,^{1,2} Victor Moreno,³ Brezo Martínez-Amores,⁴ Jorge Barriuso,³ Laura Mezquita,¹ Inmaculada Ibáñez de Cáceres,² Ángel Ayuso Sacido A,¹ José María Peña,⁵ Rosario Perona,² Enrique Grande,⁶ Zuleika Saz-Parkinson,⁷ José María Amate⁷

¹ Centro Integral Oncológico Clara Campal (CIOCC), GHM, Madrid, Spain; ² Unidad de Biomarcadores y Terapias Experimentales del Cáncer, IdiPAZ, Madrid, Spain; ³ Servicio de Oncología Médica, Hospital Universitario La Paz, Madrid, Spain; ⁴ Servicio de Oncología Médica, Hospital Rey Juan Carlos, Madrid, Spain; ⁵ Facultad de Informática, Universidad Politécnica de Madrid, Spain; ⁶ Hospital Universitario Ramón y Cajal, Madrid, Spain; ⁷ Agencia de Evaluación de Tecnologías Sanitarias, Instituto de Salud Carlos III, Spain

Objective

To assess the incremental cost-effectiveness ratio (ICER) per life-year gained (LYG) based on predictive markers for the available biological therapies in the treatment of metastatic colorectal cancer (mCRC) in Spain.

Methods

- Efficacy data were obtained from randomized clinical trials (RCT) on biological therapies for the first-line treatment of patients with mCRC.
- The RCT control arms were used as reference to calculate the ICERs.
- Moreover, the SmPCs of biological therapies, the clinical practice guidelines and the scientific evidence published were reviewed in search of clinical benefit markers (both biological and radiological) for their inclusion in the analysis.
- Toxicity was excluded as a predictor of efficacy of the therapies.
- Cost estimation was based on the mean duration of each treatment as reported in the RCT and therapy costs (ex-factory prices, € 2012), where an average patient of 70 Kg and 1.7 m² was assumed. [1]

Results

- In the review of the SmPCs of the biological therapies authorized as first-line treatment for patients with mCRC in Spain only one clinical benefit **biomarker** has been found:
 - The **mutational status of the K-RAS oncogene** constitutes a predictive biomarker for anti-EGFR therapies (cetuximab and panitumumab), that can only be administered in patients with wild-type K-RAS.
 - No predictive markers have been found for bevacizumab.
- After re-analysing the CRYSTAL and OPUS trials, it has been concluded that **early tumour shrinkage (≥20%) at week 8** of therapy with cetuximab constitutes a **radiological marker** of clinical benefit that translates into significant improvements of the overall survival (up to 28.3 and 26 months, respectively). [3, 4]
- This association between early tumour shrinkage and better health outcomes in the long term in patients with wild-type K-RAS tumours

- is independent of the chemotherapy regimens previously administered in said patients, while it is specific to cetuximab. [4]
- Joint consideration of both markers for cetuximab therapy yields not only the highest efficacy data as measured by overall survival but also significant cost savings when combined with standard chemotherapy (€ 4,875.95).
- Considering both markers together results in an ICER that is lower or in line with the threshold of 30,000 €/LYG (usual in literature about health technology assessment) when cetuximab, combined with FOLFIRI or FOLFOX is administered to patients with wild-type K-RAS who had presented with an early tumour shrinkage at week 8. (Table 1)
- The ICER estimated for the rest of the biological therapies in the first-line treatment of mCRC widely surpasses this threshold.

Table 1. ICER for each biological therapy according to the availability of biological and radiological markers and the chemotherapy regimen they are combined with.

THERAPEUTIC ALTERNATIVES	Biomarker of clinical benefit	Radiological marker of clinical benefit	SURVIVAL (MONTHS)	INCREMENTAL EFFICACY	INCREMENTAL COST	ICER (€/LYG)
FOLFIRI	No	No	18.6	-	-	-
Bevacizumab+IFL	No	No	20.3	1.7	24,980.92 €	176,335.91 €
Cetuximab+FOLFIRI	Wild-type K-RAS	Early tumour shrinkage at week 8	28.3	9.7	20,104.97 €	24,872.12 €
FOLFOX4	No	No	18	-	-	-
Bevacizumab+FOLFOX	No	No	21.3	3.3	19,466.64 €	70,787.78 €
Panitumumab+FOLFOX	Wild-type K-RAS	No	23.9	5.9	20,137.70 €	40,958.03 €
Cetuximab+FOLFOX	Wild-type K-RAS	Early tumour shrinkage at week 8	26	8	20,104.97 €	30,157.45 €

Conclusions

- The identification of patient groups that are most likely to obtain a clinical benefit allows for important improvements in the efficiency of resources allocated to the treatment of mCRC.
- Joint consideration of both markers for cetuximab therapy yields not only the highest efficacy data as measured by overall survival but also significant cost savings when combined with standard chemotherapy (€ 4,875.95).
- Thus, joint consideration of a biological marker (mutational state of K-RAS) and a radiological marker (early tumour shrinkage at week 8)

- for the treatment with cetuximab translates into ICERs that are lower or in line with the standard efficiency threshold (30,000 €/LYG).
- This scenario with two markers of clinical benefit for cetuximab is the only one that constitutes a cost-effective strategy for biological therapies in the first-line treatment of mCRC in Spain. It represents reductions of 26% compared to the ICER for panitumumab+FOLFOX, of 57% against bevacizumab+FOLFOX, and of 86% against combinations of irinotecan- and bevacizumab-based chemotherapies.

[1] Informe para la Comissió de Farmàcia i Terapèutica del Institut Català d'Oncologia (ICO): http://www.iconcologia.net/catala/professionals/comissio/informes/panitumumab_cetuximab_24_02_11.pdf
 [2] Cetuximab SmPC updated by the European Commission in November 2011: http://ec.europa.eu/health/documents/community-register/2011/20111024112249/anx_112249_es.pdf
 [3] Piessevaux, H., et al., Early tumor shrinkage for the prediction of efficacy of cetuximab in metastatic colorectal cancer (MCRC): analysis from the CRYSTAL study. *Annals of Oncology* 2010; 21 (Suppl 8):viii193, 2010.
 [4] Piessevaux, H., et al., Impact of early tumor shrinkage on long-term outcome in metastatic colorectal cancer (mCRC) treated with FOLFOX4 with or without cetuximab: Lessons from the OPUS trial. *J Clin Oncol* 29: 2011 (suppl 4; abstr 398), 2011.