BEVACIZUMAB IN THE TREATMENT OF KRAS WILD TYPE METASTATIC COLORECTAL CANCER: AN ECONOMIC ANALYSIS BASED ON THE CALGB 80405 TRIAL

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1 – INTRODUCTION

- Bevacizumab (Avastin) is an anti-angiogenic humanized monoclonal antibody which binds to vascular endothelial growth factor (VEGF) to inhibit angiogenesis for continuous tumour control.
- Avastin is approved in combination with fluoropyrimidine-based chemotherapy for the treatment of adult patients with metastatic carcinoma of the colon or rectum [1].
- Cetuximab (Erbitux) is approved for the treatment of patients with epidermal growth factor receptor (EGFR) - expressing, RAS wild-type metastatic colorectal cancer (mCRC) in combination with irinotecan-based chemotherapy, in first-line in combination with FOLFOX, as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan [2].
- Both treatments have been shown to bring similar efficacy for the KRAS wild type population [3]. However, cetuximab is recognized to be more expensive than bevacizumab in Portugal.
- **The objective of this study was to perform a cost-effectiveness analysis comparing bevacizumab versus cetuximab in combination with FOLFOX or FOLFIRI in patients with KRAS wild type mCRC.**

2 – METHODS

Model	Partitioned survival model with three health states - progression free survival (PFS), progression, death- and weekly cycles
Population	Patients with KRAS wild type mCRC, 60 years, 69 kgs, 165 cm, 1,76 cm2, 57.6% KRAS not mutated
Treatment arms	• Bevacizumab (Avastin): 5 mg/kg every 2 weeks + FOLFOX or FOLFIRI • Cetuximab (Erbitux): 400 mg/m^2 initial dose, then 250 mg/m^2 weekly + FOLFOX or FOLFIRI • Patients in FOLFOX / FOLFIRI: 73.4% / 26.6%. FOLFOX every 2 weeks: Oxaliplatin: 85 mg/m^2 on day 1 of each cycle; Leucovirin: 200 mg/m^2 on day 1 and 2 of each cycle; Fluorouracil Bolus: 400 mg/m^2 on day 1 and 2 of each cycle; Florouracil IV: 600 mg/m^2 on day 1 and 2 of each cycle // FOLFIRI every 2 weeks: Irinotecan: 180 mg/m^2 on day 1 of each cycle; Leucovirin: 200 mg/m^2 on day 1 of each cycle; Fluorouracil Bolus: 400 mg/m^2 on day 1 each cycle; Florouracil IV: 3000 mg/m^2 on day 1 of each cycle (over 48h)
Treatment duration	• Treatment duration has been modelled using PFS estimates as a proxy and adjusting down the curve using a hazard ratio for bevacizumab and cetuximab of 1.5 • Median treatment durations: 9.0 months for bevacizumab and 8.3 months for cetuximab
Time horizon	12 years (after 12 years, less than 1% of patients are expected to be alive)
Efficacy, quality of life and safety data	• PFS and overall survival (OS) from CALGB 80405 trial • Gamma / Weibull distributions to extrapolate PFS / OS after trial period. • QALYs based on EQ-5D questionnaire • Incidence of grade 3/4 adverse events from CALGB 80405 trial
Costs	• Direct medical costs: drugs costs (including wastage), drug administration costs (infusion cost every two weeks for bevacizumab and every week for cetuximab), health state (PFS and progression) costs, adverse event (AE) treatment costs and KRAS testing cost only applicable in cetuximab arm • Health resource use was based on experts' opinion • Unitary costs were obtained using Portuguese official sources. • Costs were expressed in euros for the year of 2016.
Discount rate	5% per annum in costs and health consequences [4].
Perspective	Portuguese National Health Service (NHS).

Table 1 – Costs and sources

	Costs	Source
Drugs		
Bevacizumab	€ 2.057,00/month	[5]
Cetuximab	€ 3.592,00/month	[5]
Oxaliplatin 50 mg - 100 mg	€ 4,98 - € 7,27	[5]
Irinotecan 40 mg - 300 mg	€ 5,21 - € 18,59	[5]
Leucovorin 50 mg - 300 mg	€ 1,49 - € 5,57	[5]
Fluorouracil 500 mg - 1000 mg	€ 1,34 - € 2,16	[5]
Administration		
Drug infusion	€ 20,20	DRG 99350 [6]
Supportive care		
PFS/month	€ 292,28/month	Expert panel, [5], [6], [7]
Progression/month	€ 1.019,70/month	Expert panel, [5], [6], [7]
Diagnostic		
KRAS test	€ 110,70	DRG 36058 [6]
AE treatment		
Neuropathy (grade 3-4)	€ 108,85	Expert panel, [5], [6], [7]
Rash (grade 3-4)	€ 432,75	Expert panel, [5], [6], [7]
Diarrhea (grade 3-4)	€ 2.700,91	Expert panel, [5], [6], [7]
Hypertension (grade 3-4)	€ 520,63	Expert panel, [5], [6], [7]
Gastrointestinal events (grade 3-4)	€ 2.700,91	Assumption (=diarrhea)

3 – RESULTS

- Bevacizumab and cetuximab presented no statistically significant difference in terms of clinical benefit – PFS, OS and QALYs.
- The model predicted total cost of €84.268 or €103.305 for treating a mCRC patient with bevacizumab or cetuximab, respectively (Table 2).
- Acquisition cost of bevacizumab is lower than cetuximab (-€15.449 €/patient) as well as supportive care while on progressive disease (-€4.458/patient); supportive care while on PFS is slightly higher in bevacuzimab arm (+€953/patient) (Figure 1).
- One way sensitivity analysis tested major assumptions and showed the robustness of the results (Figure 2).

Table 2 – Incremental cost analysis (bevacizumab vs cetuximab)

Costs	Bevacizumab arm	Cetuximab arm	Incremental (bevacizumab vs cetuximab)
PFS*	€ 45.050	€ 59.629	-€14.580
Progression	€ 39.218	€ 43.676	-€4.458
Total	€ 84.268	€ 103.305	-€19.037

*Includes acquisition and administration of drugs, KRAS test, PFS supportive care and treatment of AEs costs.

Figure 1 – Cost components

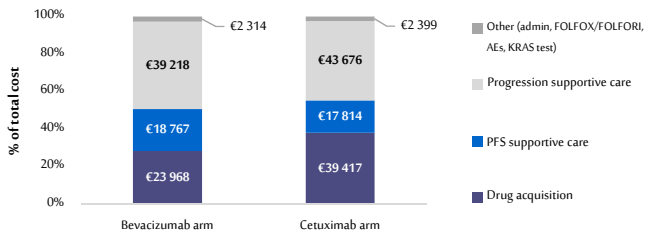
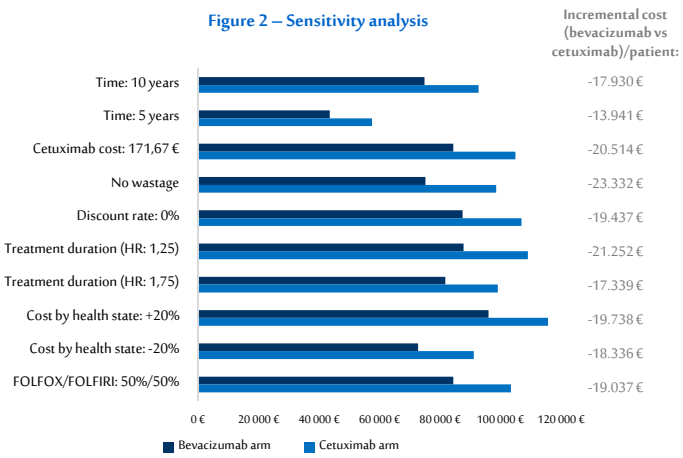


Figure 2 – Sensitivity analysis



4 – CONCLUSIONS

- The proposed model predicts similar health consequences - efficacy - for bevacizumab and cetuximab.
- Bevacizumab treatment results in a cost-saving of €19.000 per mCRC patient to the Portuguese NHS vs cetuximab treatment.
- Major cost drivers are acquisition drug costs and patients' management in the progression health state.
- The use of bevacizumab in KRAS wild type mCRC patients permit to achieve substantial cost-savings by the Portuguese NHS representing a cut of 39% on the biologic drug costs over a 12-year horizon.

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