

# Aflibercept in combination with FOLFIRI in patients with metastatic colorectal cancer: cost-effectiveness based on VELOUR best efficacy subgroup post-hoc analysis

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## Introduction

- Colorectal cancer (CRC) is the third most frequent type of cancer diagnosed in the world, with an incidence that increases with age<sup>1</sup>. In 2008, 1.2 million new cases were diagnosed and almost 25% of patients present with metastatic CRC (mCRC) at diagnosis<sup>2</sup>.
- In Spain, the most commonly treatment administered on first line are oxaliplatin-based combinations<sup>3</sup>. On those patients who have progressed to this first line, FOLFIRI is the recommended second line<sup>3</sup>.
- Aflibercept is a new option in the second-line treatment of mCRC for patients who have progressed to a first line Oxaliplatin-based therapy.

## Objective

To estimate the incremental cost per life-year gained (LYG) of aflibercept in combination with FOLFIRI as second-line treatment in metastatic colorectal cancer (mCRC) in Best Efficacy Subgroup (BES) patients previously treated with Oxaliplatin compared to FOLFIRI.

## Methods

- A Markov model with 3 health states (stable disease, progression and death) was used to estimate lifetime costs and outcomes. "Stable disease" state allowed transition to a sub-state for those patients who stopped treatment but did not have progression disease.
- 2-weeks cycle duration was established to set the frequency of chemotherapy administration.
- A post-hoc analysis<sup>4</sup> of the VELOUR clinical trial revealed an improvement of aflibercept efficacy in a specific subgroup. BES was composed by patients with performance status (PS) 0 with any number of metastatic sites or PS 1 with <2 metastatic sites, exclusive of adjuvant fast relapsers.
- The model started with the administration of the 2<sup>nd</sup> line treatment to the entire cohort of patients, which continue while the patient was in a state of "stable disease".
- Lifetime horizon was considered, which approximately corresponds to 15 years of modelization. According to the National Health System (NHS) perspective only direct costs were considered. Costs and outcomes were 3% annually discounted<sup>5</sup>.

- Efficacy and adverse events (AE) were obtained from VELOUR clinical trial<sup>6</sup>. After analyzing different distributions to extrapolate overall survival beyond the time horizon, the best fit was obtained by using log-logistic distribution<sup>7</sup>.
- Cost estimation (€, 2013) included pharmaceutical and administration cost, adverse event management and hospital and medical visits consumption (table 1). Ex-factory price<sup>8</sup> with mandatory deduction<sup>9</sup> was applied for drug cost estimation. Aggregated

chemotherapy costs for both alternatives considered in the model, disease management and AE costs<sup>10</sup> are recorded on table 1.

- Transition from stable disease to progression implied the interruption of second-line treatment and administration of a third-line chemotherapy (72%) or best supportive care (28%).
- Univariate deterministic and probabilistic sensitivity analysis (SA) were performed to confirm model robustness.

Table 1. Unitary costs (€ 2013)

Chemotherapy cycle cost		Costs (€ 2013)	Adverse events (aggregated cost)		Costs (€ 2013)
Aflibercept + FOLFIRI		€1,048.25	Asthenia		€107.85
FOLFIRI		€146.86	Diarrhea		€247.65
Management disease (aggregated cost)		Costs (€ 2013)	Febrile neutropenia		€4,740.07
Stable disease – on 2 <sup>nd</sup> line treatment		€176.14	Hemorrhage		€4,187.59
Stable disease – without chemotherapy treatment		€69.21	Hypertension		€10.35
Progressive disease – on 3 <sup>rd</sup> line chemotherapy treatment		€681.99	Nauseas		€28.46
Progressive disease – BSC treatment		€606.96	Neutropenia		€99.87
			Stomatitis		€1,517.50

BSC: Best Supportive Care

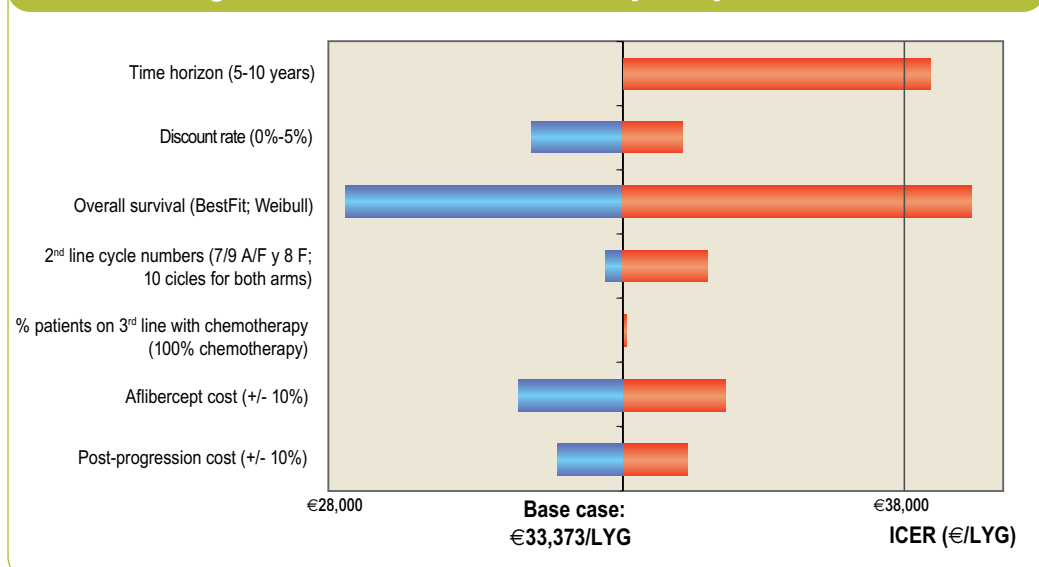
## Results

- Administration of aflibercept + FOLFIRI as second-line treatment on BES was more effective than FOLFIRI, yielding 1.92 LYG (23 life-months gained) compared to 1.55 LYG (18.6 months).
- Aflibercept + FOLFIRI accounted a total cost of €40,449, compared to €25,698 estimated for FOLFIRI.
- The incremental cost-effectiveness analysis provided a €33,373/LYG ratio for aflibercept in combination with FOLFIRI versus FOLFIRI for BES. (table 2).
- On deterministic SA, the most influencing parameters on results were time horizon and distribution that fits for overall survival data<sup>7</sup> (figure 1). The results of the remaining analysis varied were less than a variation of ±6% from base case result.
- On Figure 2 were represented probabilistic SA results. were 92.78% of simulations were equal or less than an acceptability threshold of €45,000/LYG<sup>11</sup>.

Table 2. Base case results of cost-effectiveness model

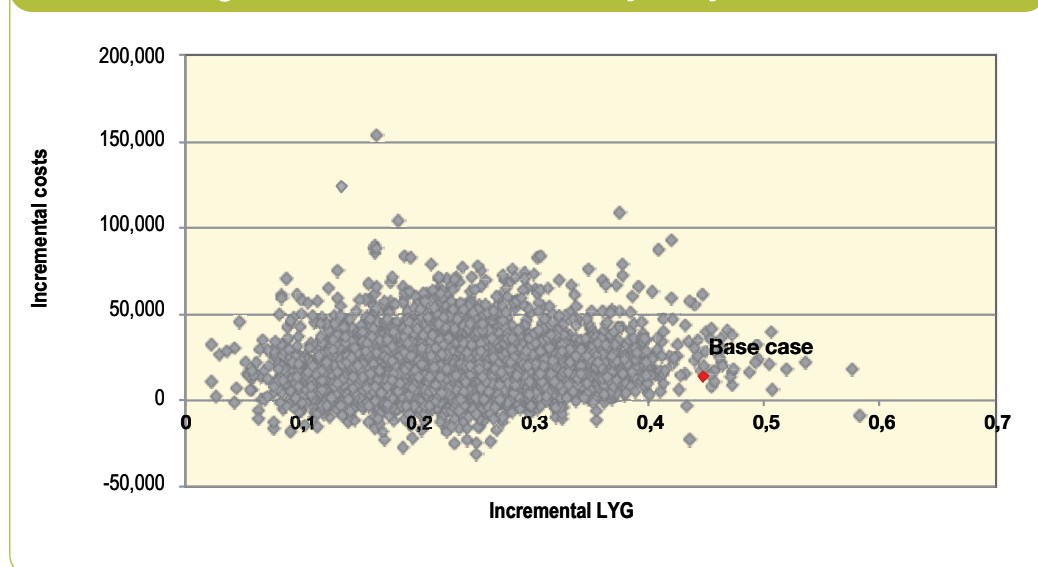
	Aflibercept + FOLFIRI	FOLFIRI	Incremental
Discounted Life-years (LYs) gained	1.92	1.48	0,44 (5.3 months)
Undiscounted Life-years (LYs) gained	2.05	1.55	0,50 (6 months)
Discounted total costs (€, 2015)	€40,449	€25,698	€14,751
Undiscounted total costs (€, 2015)	€42,723	€26,950	€15,773
Stable disease (undiscounted costs)	Drug costs	€9,776	€1,469
	Disease management	€5,149	€4,482
	AE costs	€658	€230
Progression (undiscounted costs)	Drug costs	€3,182	€2,892
	Disease management	€23,447	€17,375
ICER (€/LYG aflibercept + FOLFIRI vs. FOLFIRI)			€33,373/LYG

Figure 1. Deterministic sensitivity analysis results



A/F: aflibercept/FOLFIRI, LYG: life-year gained; ICER: incremental cost-effectiveness ratio

Figure 2. Probabilistic sensitivity analysis results



LYG: life-year gained

## Conclusions

- According to a post-hoc analysis, aflibercept in combination with FOLFIRI could increase overall survival versus FOLFIRI on BES.
- Aflibercept + FOLFIRI could be an efficient strategy for second-line treatment in specific mCRC patients for the Spanish NHS.
- Considering an acceptable threshold of willingness to pay for additional LYG is below €45,000 in Spain, aflibercept in combination with FOLFIRI can be considered a cost-effective strategy, since the ICER of aflibercept with FOLFIRI versus FOLFIRI is €33,373 per LYG.

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