Cost-effectiveness Analysis of Panitumumab Plus mFOLFOX6 Compared With Bevacizumab Plus mFOLFOX6 for First-Line Treatment of Patients With Wild-Type *RAS* Metastatic Colorectal Cancer

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BACKGROUND

- Colorectal cancer (CRC) is the second most commonly diagnosed cancer and cause of cancer death in Europe, with an estimated 447,000 new cases and 215,000 deaths occurring in 2012.[1]
- Approximately 20% to 25% of patients with CRC have metastatic disease (mCRC) at diagnosis, and up to 50% of all patients will develop metastases, which are associated with significant morbidity and diminished quality of life.[2]
- Panitumumab (a monoclonal antibody against epidermal growth factor receptor [EGFR]), as well as bevacizumab (a vascular endothelial growth factor [VEGF] inhibitor) in combination with chemotherapy are both options in the treatment of patients with wild-type *RAS* mCRC.[3,4]
- In 2007, panitumumab was initially approved by the European Medicines Agency (EMA) for patients with refractory mCRC with nonmutated (wild-type) *KRAS* genes.[3]
- Identification of additional *RAS* mutations beyond *KRAS* exon 2 (i.e., mutations in *KRAS* exons 3 and 4 and *NRAS* exons 2, 3, and 4) predict lack of response to panitumumab and have driven new labels for EGFR inhibitors.[5]
- The European Committee for Medicinal Products for Human Use (CHMP) stated recently that the benefit-risk balance of panitumumab has improved in its newly approved wild-type *RAS* indications, due to the exclusion of patients with additional *RAS* mutations outside those initially investigated in the *KRAS* exon 2 analyses.
- In such a context of improved benefit-risk balance of panitumumab, a legitimate question arises regarding the relative value for money of panitumumab versus bevacizumab given the health care costs challenges faced in France and in Europe generally.
- Head-to-head data are available from a prospective-retrospective analysis of the phase 2 PEAK (NCT00819780) trial, the only first-line clinical trial of panitumumab plus mFOLFOX6 (oxaliplatin, 5-fluorouracil, and leucovorin) versus bevacizumab plus mFOLFOX6 conducted in patients with mCRC (extended *RAS* analysis of panitumumab plus mFOLFOX6 [n = 88] and bevacizumab plus mFOLFOX6 [n = 82]; incremental benefit in favor of panitumumab: progression-free survival [PFS] = 2.9 months, $P = 0.03$; overall survival [OS] = 12.4 months, $P = 0.06$; event rate = 41.1%, hazard ratio = 0.63; 95% CI 0.39-1.02, $P = 0.06$).[6]

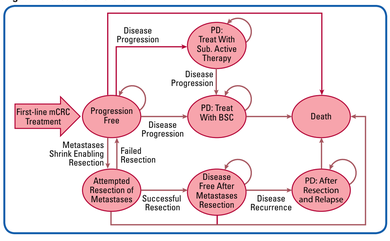
OBJECTIVE

- To evaluate the cost-effectiveness of first-line treatment with panitumumab plus mFOLFOX6 versus bevacizumab plus mFOLFOX6 in patients with mCRC in the wild-type *RAS* setting using data from the head-to-head PEAK trial.[6]

METHODS

- A semi-Markov model structure was selected to assess the cost-effectiveness of panitumumab plus mFOLFOX6 relative to bevacizumab plus mFOLFOX6 in the first-line treatment of patients with mCRC (Figure 1).[7]
- The model used a 2-week cycle length and lifetime time horizon of a patient with mCRC. The analysis began with a cohort of patients initiating first-line mCRC treatment and concluded when the entire patient cohort had died.[7]
- The analysis was performed from a French health collective perspective using data from a prospective-retrospective analysis of the phase 2 PEAK clinical trial of panitumumab versus bevacizumab in first-line mCRC treatment.[6,7]

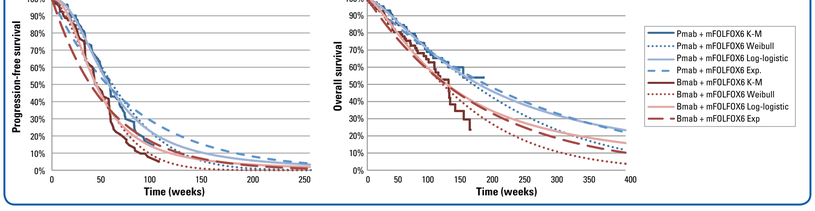
Figure 1. Model Structure



BSC = best supportive care; PD = progressive disease; Sub = subsequent.
Source: Graham et al. 2014.[7]

- The model population was based on a subset of the patient population from the PEAK trial and was defined as previously untreated adults (aged ≥18 years) who had been diagnosed with wild-type *RAS* (i.e., no mutation in exons 2, 3, or 4 of *KRAS* and *NRAS*) mCRC.[4,7]
- Transition probabilities to disease progression and death for panitumumab plus mFOLFOX6 and bevacizumab plus mFOLFOX6 were based on parametric survival curves estimated in a patient-level analysis of PFS and OS from the PEAK clinical trial (coded in SAS [version 9.3; Cary, North Carolina] using the LIFEREG procedure). The PFS and OS Kaplan-Meier (K-M) plots and the fitted PFS and OS curves for panitumumab plus mFOLFOX6 and bevacizumab plus mFOLFOX6 were estimated using exponential, Weibull, and log-logistic statistical distributions for each treatment (Figure 2).[4,7]
- The Weibull distribution was selected as the best-fitted curve for both PFS and OS based on graphical overlay of the curves and the K-M plot, goodness-of-fit statistics (Akaike information criterion), and face validity of long-term survival projections.[7]

Figure 2. PFS and OS K-M Plots and Fitted Curves



Bmab = bevacizumab; Exp = exponential; Pmab = panitumumab.
Source: Graham et al. 2014.[7]

- Resection-related transition probabilities based on PEAK clinical trial data were used to model the number of resection attempts, the probability that an attempt results in complete removal or reduction of the tumor, and the mean time to resection for patients with wild-type *RAS* mCRC.[6,7]
- Disease-free survival and OS for patients with a successful resection were modelled using parametric survival modelling and data from a study describing a population of unresectable patients that became resectable after chemotherapy.[8]
- Drug-acquisition costs were calculated from 2013 French Health National Insurance costs.[9,10] Consumption of drugs, defined as the average number of vials consumed per administration per patient, and the average number of cycles administered were calculated from data in the PEAK clinical trial for direct treatment comparators (Table 1).
- Nondrug medical costs considered by the model include *RAS* mutation testing, drug administration, chemotherapy, physician visits, diagnostic tests, resection, subsequent treatment, and BSC (Table 2).
- Costs of serious adverse events were modeled based on the incidence seen in the PEAK trial[6] and costs extracted from the literature.[11-14]
- Duration of subsequent therapy was modeled via median PFS for second-line treatments from the published literature by assuming an exponential distribution.[15,16]
- Utility weights used in the model were calculated from the EuroQol-5 Dimensions (EQ-5D) questionnaire responses[17] from patients with wild-type *RAS* mCRC in the first-line PRIME (NCT00364013) clinical trial (0.821),[5] patients with wild-type *KRAS* mCRC in the second-line panitumumab (NCT00339183) clinical trial (0.782),[15] and patients receiving BSC in the third-line panitumumab (NCT00113763) clinical trial (0.681).[18]
- The model outcomes calculated for each first-line treatment regimen included patient survival (life-years), quality-adjusted life-years (QALYs), costs for health care resources, and incremental cost-effectiveness ratios.
- To test the robustness of the model, one-way sensitivity analyses and a probabilistic sensitivity analysis were conducted.
- All costs were reported in 2013 Euros, and all costs and outcomes (benefits) in the model were discounted using the suggested discount rate in France of 4.0% per annum.[19]

Table 1. Regimen-Specific Base-Case Input Parameters

Input Parameter	Pmab + mFOLFOX6	Bmab + mFOLFOX6	Source
Biologic drug-acquisition cost	€387.00	€278.13	French Health Ministry[9,10]
Chemotherapy drug-acquisition and chemotherapy/biologic drug-administration cost	€440.03	€473.39	Weighted average DRG costs for the health collective perspective (70% inpatient, 30% day case) from HEVA[20]
Number of treatment cycles			Estimated from average number of observed Pmab, Bmab, and mFOLFOX6 infusions for patients with wild-type *RAS* mCRC from PEAK trial[6]; projected PFS beyond the data collection period
Pmab	19.82	—	
Bmab	—	14.10	
mFOLFOX6	12.23	10.50	
Subsequent therapy use, % (n/N)			Subsequent antitumor therapies from PEAK trial[6] and other assumptions
Anti-EGFR + FOLFIRI	—	69.3% (52/75)	
Bmab + FOLFIRI	65.5% (55/84)	—	
BSC	34.5% (29/84)	30.7% (23/75)	
Resection attempts, % (n/N)	13.6% (12/88)	11.0% (9/82)	Resection attempts for liver metastases for patients with wild-type *RAS* mCRC from the PEAK trial[6]
Successful resection, % (n/N)	66.7% (8/12)	77.8% (7/9)	Successful resection (complete removal) of liver metastases for patients with wild-type *RAS* mCRC from the PEAK trial[6]

DRG = diagnosis-related group; FOLFIRI = leucovorin, 5-fluorouracil, and irinotecan.

Table 2. Additional Base-Case Input Parameters

Input Parameter	Value	Source
KRAS and *RAS* test	€124	One *KRAS* (exon 2) and one *KRAS* (exons 3-4)/*NRAS* (exons 2–4) test performed; costs from Qiagen[21]
RAS frequency	46.2%	NCT00364013 study, Douillard[5]
mFOLFOX6 alone drug-acquisition and administration cost	€438	Mean costs per case for collective perspective from HEVA[20]
General practitioner office visit cost	€23	Assumed to occur every 4 weeks; costs from French Health Insurance[22]
Oncology specialist office visit cost	€28	Assumed to occur every treatment cycle (2 weeks); costs were French Health Insurance[22]
Computed tomography scan cost	€51	Assumed to occur every 8 weeks; costs from the Classification Commune des Actes Médicaux[23]
Resection surgery and hospitalization cost	€14,428	HEVA[20]
Disease relapse following resection cost per cycle	€1,913	Average of subsequent therapies modelled postprogression
End-of-life cost	€7,654	French Health Ministry[9,10]
BSC costs per cycle	€564	Estimated from monthly supportive care costs from Remak and Brazil[24]

RESULTS

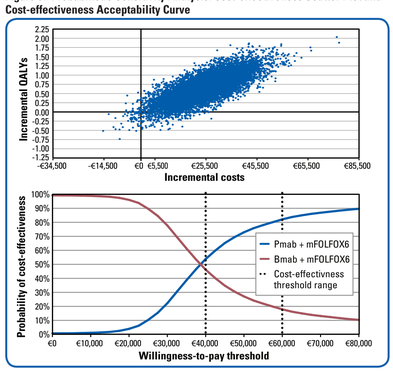
- In the base-case analysis of the cost-effectiveness model, head-to-head clinical trial data incorporated from the PEAK study led to greater projected life-years and QALYs for patients with wild-type *RAS* mCRC who received panitumumab plus mFOLFOX6 versus bevacizumab plus mFOLFOX6.
- Key cost drivers included monoclonal antibody drug-acquisition costs (40% to 44% of total costs) followed by BSC costs (23% to 25% of total costs); costs for serious adverse event treatment accounted for a minor percentage of the total cost in both treatments.
- Most costs were logically higher for panitumumab plus mFOLFOX6 due to greater PFS (longer duration of therapy) and greater OS (longer duration of BSC) (Table 3).
- The incremental cost per life-year gained was estimated to be €26,918, and the incremental cost per QALY gained was estimated to be €36,577.

Table 3. Base-Case Results: Patient Survival Outcomes and Costs

Outcome/Cost Category	Pmab + mFOLFOX6	Bmab + mFOLFOX6	Difference
Outcome			
Patient survival (undiscounted)	4.06	3.02	1.039
Life-years	3.58	2.73	0.846
QALYs	2.68	2.05	0.622
Cost category			
RAS test	€268	€0	€268
Biologic drug	€42,843	€29,871	€12,972
Administration and chemotherapy drug	€11,336	€9,507	€1,829
Adverse event treatment and management	€873	€1,058	€–185
Physician visits and monitoring for progression	€2,455	€2,305	€150
Resection related	€8,823	€8,006	€817
BSC and end-of-life costs	€30,972	€23,951	€7,021
Total costs	€97,203	€74,440	€22,763

- The one-way sensitivity analysis indicated that drug-acquisition costs, costs of BSC, and costs of subsequent treatments were the most sensitive model parameters.
- Results of the cost-effectiveness scatter plot showed panitumumab plus mFOLFOX6 generally to be more effective than bevacizumab plus mFOLFOX6 in a majority of the runs of the probabilistic sensitivity analysis, with more than 96% of simulations performed falling in the first/northeast (more effective, more costly) cost-effectiveness quadrant (Figure 3).
- Given no specified willingness-to-pay threshold in France, we examined cost-effectiveness across a range of possible thresholds. Mean net monetary benefits from 10,000 simulations of the probabilistic sensitivity analysis indicated that 54.0% of simulations were below a willingness-to-pay threshold of €40,000, and 82.5% of simulations were below a willingness-to-pay threshold of €60,000 (Figure 3).

Figure 3. Probabilistic Sensitivity Analysis: Cost-effectiveness Scatter Plot and Cost-effectiveness Acceptability Curve



- Table 4 lists the standard distribution for each set of model inputs varied in the probabilistic sensitivity analysis.

Table 4. Distributions Used in the Probabilistic Sensitivity Analysis

Input(s)	Distribution
PFS and OS survival curves	Multivariate normal
Number of vials consumed and mean number of treatments observed	Normal
Subsequent-treatment distribution	Dirichlet
Toxicity probabilities and utility weights	Beta
Costs	Gamma

CONCLUSION

- Model results indicated that panitumumab plus mFOLFOX6 represented good value for money compared with a current standard of care, bevacizumab plus mFOLFOX6 and, with a willingness-to-pay ranging from €40,000 to €60,000, can be considered cost-effective in the first-line treatment of patients with wild-type *RAS* mCRC.

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