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Original Research

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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Abstract ***Objective:*** To investigate the cost-effectiveness of panitumumab plus mFOLFOX6 (oxaliplatin, 5-fluorouracil and leucovorin) compared with bevacizumab plus mFOLFOX6 in first-line treatment of patients with wild-type *RAS* metastatic colorectal cancer (mCRC).
Design: A semi-Markov model was constructed from a French health collective perspective, with health states related to first-line treatment (progression-free), disease progression with and without subsequent active treatment, resection of metastases, disease-free after successful resection and death.
Methods: Parametric survival analyses of patient-level progression-free and overall survival data from the only head-to-head clinical trial of panitumumab and bevacizumab (PEAK) were performed to estimate transitions to disease progression and death. Additional data from PEAK informed the amount of each drug consumed, duration of therapy, subsequent therapy use, and toxicities related to mCRC treatment. Literature and French public data sources were used to estimate unit costs associated with treatment and duration of subsequent active therapies. Utility weights were calculated from patient-level data from panitumumab trials in the first-, second- and third-line settings. A life-time perspective was applied. Scenario, one-way, and probabilistic sensitivity analyses were performed.

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Results: Based on a head-to-head clinical trial that demonstrates better efficacy outcomes for patients with wild-type *RAS* mCRC who receive panitumumab plus mFOLFOX6 versus bevacizumab plus mFOLFOX6, the incremental cost per life-year gained was estimated to be €26,918, and the incremental cost per quality-adjusted life year (QALY) gained was estimated to be €36,577. Sensitivity analyses indicate the model is robust to alternative parameters and assumptions.

Conclusions: The incremental cost per QALY gained indicates that panitumumab plus mFOLFOX6 represents good value for money in comparison to bevacizumab plus mFOLFOX6 and, with a willingness-to-pay ranging from €40,000 to €60,000, can be considered cost-effective in first-line treatment of patients with wild-type *RAS* mCRC.

1. Introduction

Colorectal cancer (CRC) represents a significant social and healthcare burden. It is the second most common cancer in Europe, with an estimated 447,000 new cases occurring in 2012, and is also the second most common cause of cancer death in Europe, accounting for an estimated 215,000 deaths in 2012 [1]. In France, CRC is the third most common cancer in men and the second in women with incidence rates comparable to those found in other high-risk areas of Western Europe, North America, Australia/New Zealand and Japan [2].

Of patients with CRC, 20–25% have metastatic disease (mCRC) at diagnosis, and metastases eventually develop in up to 50% of all patients [3]. Patients with mCRC experience significant morbidity and diminished quality of life. The 5-year relative survival rate is only 5–15% in patients with widespread metastatic disease, indicating that there is a need to improve treatment outcomes [4]. Although the goal of treatment for most patients with mCRC is to prolong survival for as long as possible while maintaining quality of life, surgical resection of metastases can achieve cure for a small proportion of patients [5].

According to the European Society for Medical Oncology (ESMO) clinical practice guidelines for advanced CRC, panitumumab and cetuximab, monoclonal antibodies against the epidermal growth factor receptor (EGFR), and bevacizumab, which binds the vascular endothelial growth factor (VEGF), can be considered in combination with chemotherapy as first-line options for selected patients with mCRC [6]. The ESMO recommendations are based on the improved outcomes reported for these biologics versus chemotherapy alone in clinical trials.

While panitumumab and bevacizumab are recommended options in first-line treatment of patients with mCRC, additional evidence (e.g. a head-to-head clinical trial) and updated labels for the EGFR inhibitors should be considered when deciding between EGFR- and VEGF-targeted treatments. Since the initial European Medicines Agency (EMA) approval of panitumumab in 2007, 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) predicts lack of response to panitumumab in combination with oxaliplatin-based chemotherapy, and has driven new labels for the EGFR inhibitors. Use of the extended *RAS* biomarker selection reduces the patient population eligible to receive panitumumab by approximately 17% compared with the wild-type *KRAS* exon 2 mCRC population, and improves the efficacy of panitumumab without altering its safety profile [7]. 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.

Moreover, data from a prospective-retrospective analysis of the phase II PEAK trial (NCT00819780) of panitumumab versus bevacizumab in first-line mCRC have recently been reported [8,9]. The PEAK trial is an open-label, randomised, multicenter clinical study designed to compare head-to-head panitumumab plus oxaliplatin, 5-fluorouracil and leucovorin (mFOLFOX6) ($n = 142$) versus bevacizumab plus mFOLFOX6 ($n = 143$). Results from patients with wild-type *RAS* mCRC, as defined by the extended *RAS* analysis ($n = 88$ for panitumumab plus mFOLFOX6; $n = 82$ for bevacizumab plus mFOLFOX6), showed a statistically significant incremental progression-free survival (PFS) benefit of 2.9 months ($p = 0.03$) and a strong trend in terms of overall survival (OS) incremental benefit (12.4 months) favouring the panitumumab arm [8,9].

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 healthcare costs challenges faced in France and in Europe generally. To our knowledge only one cost-effectiveness manuscript has been published comparing panitumumab versus bevacizumab in first-line mCRC, but it is of limited relevance because it is constrained to an outdated label population (wild-type *KRAS*) and it does not make use of the informative data from the PEAK trial [10].

Therefore, to evaluate the cost-effectiveness of panitumumab versus bevacizumab in the wild-type *RAS* setting, which is consistent with current labels for EGFR inhibitors in mCRC, we developed a semi-Markov model based on the PEAK clinical trial conducted in patients with wild-type *RAS* mCRC in the first-line setting, and applied a French health collective perspective.

2. Methods

2.1. Population

The model population was based on a subset of the patient population from PEAK, the only first-line clinical trial of panitumumab plus mFOLFOX6 versus bevacizumab plus mFOLFOX6 conducted in patients with mCRC. This subset population was defined as adults (age $\geqslant$ 18 years) who have been diagnosed with wild-type *RAS* (i.e. no mutation in exons 2, 3, or 4 of *KRAS* and *NRAS*) mCRC and who have not previously been treated with chemotherapy or investigational agents for mCRC.

2.2. Model structure

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. This approach was similar to cost-effectiveness models of mCRC and other metastatic and/or advanced cancers found in the literature [11–14]. The model uses a 2-week cycle length; the time horizon is that of the lifetime of a patient with mCRC (which is assumed to be no more than 20 years post treatment initiation). The model begins with a cohort of patients initiating first-line mCRC treatment and concludes when the entire patient cohort has died. The semi-Markov model structure and allowed transitions between health states are presented in Fig. 1.

2.3. Transition probabilities

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. The parametric survival modelling was coded in SAS (version 9.3; Cary, NC) using the LIFEREG procedure. Parametric survival curves were estimated using exponential, Weibull and log-logistic statistical distributions for each treatment. The PFS Kaplan–Meier plot and the fitted PFS curves for panitumumab plus mFOLFOX6 and bevacizumab plus mFOLFOX6 are displayed in Fig. 2. The OS Kaplan–Meier plot and the fitted OS curves for panitumumab plus mFOLFOX6 and bevacizumab plus mFOLFOX6 are displayed in Fig. 3. The Weibull distribution was selected as the best-fitted curve for both PFS and OS based on graphical overlay of the curves and the Kaplan–Meier plot, goodness-of-fit statistics (Akaike information criterion) and face validity of long-term survival projections.

Resection-related transition probabilities were based on data from the PEAK clinical trial and used to model the number of resection attempts, the probability that an attempt results in complete removal or reduction of the tumour, and the mean time to resection for patients with wild-type *RAS* mCRC. 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 patients with mCRC that was initially unresectable, but became resectable after chemotherapy [15].

Following disease progression, patients could be treated with an active subsequent treatment (modelled treatments were anti-EGFR treatment plus FOLFIRI, bevacizumab plus FOLFIRI) or best supportive care (BSC), with distribution of active treatment or BSC taken from data from the PEAK clinical trial. Based on clinical guidelines from the National Comprehensive Cancer Network, patients switched to second-line therapy of a different class (e.g. anti-EGFR to anti-VEGF and vice versa) [16,17]. The length of therapy for active second-line treatment was defined by the treatment's PFS in second-line treatment, as reported in the published literature, as this information was not collected in the PEAK trial. The median active second-line treatment PFS was converted to an estimated mean PFS by assuming an exponential distribution. Following disease progression on any subsequent active treatment, patients were treated with BSC until death. Second-line therapies did not directly affect OS, as it was referenced to the OS as observed in the PEAK trial, but they influenced costs and quality of life.

Transition probabilities from subsequent active therapy to BSC were calculated from the weighted average PFS of each subsequent therapy modelled; transition probabilities to death were calculated from the selected best-fitting OS curve; and the transition probability from the progression-free health state to the health state Progressive Disease: Treat With Subsequent Active Therapy was calculated by multiplying the transition probability to disease progression in each cycle by the percentage of patients receiving active second-line treatment. Similarly, the transition probability to the health state Progressive Disease: Treat With BSC was calculated by multiplying the transition probability to disease progression in each cycle by the percentage of patients receiving BSC (1 minus the percentage of patients receiving active second-line treatment).

2.4. Costs

Drug-acquisition costs were calculated from costs using French Health National Insurance [18,19], using 2013 costs. Consumption of drugs, defined as the

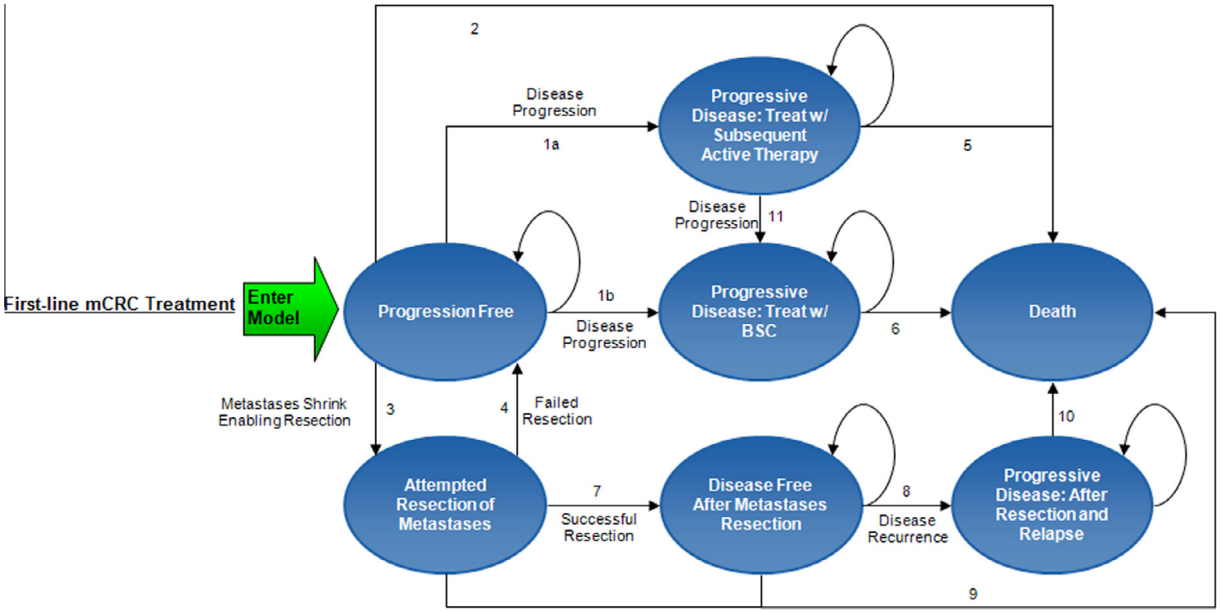

Fig. 1. Model structure. BSC, best supportive care; mCRC, metastatic colorectal cancer. *Health-states transition probability sources:* [1a]Progression Free to Progressive Disease: Treat With Subsequent Active Therapy (*source:* parametric survival modelling of patient-level data [i.e. progression-free survival]; percentage of patients utilising active treatment postprogression from PEAK trial). [1b]Progression Free to Progressive Disease: Treat With BSC (*source:* parametric survival modelling of patient-level data [i.e. progression-free survival]; percentage of patients utilising BSC postprogression from PEAK trial). [2]Progression Free to Death (*source:* parametric survival modelling of patient-level data from PEAK trial [i.e. overall survival]). [3]Progression Free to Attempted Resection of Metastases (*source:* percentage of patients undergoing resection attempt from PEAK trial). [4]Attempted Resection of Metastases to Progression Free (*source:* percentage of patients with failed resection attempt from PEAK trial). [5]Progressive Disease: Treat With Subsequent Active Therapy to Death (*source:* parametric survival modelling of patient-level data from PEAK trial [i.e. overall survival]). [6]Progressive Disease: Treat With BSC to Death (*source:* parametric survival modelling of patient-level data from PEAK trial [i.e. overall survival]). [7]Attempted Resection of Metastases to Disease Free After Metastases Resection (*source:* percentage of patients with successful resection attempt from PEAK trial). [8]Disease Free After Metastases Resection to Progressive Disease: After Resection and Relapse (*source:* parametric survival modelling of progression-free survival data from Adam et al. [15]). [9]Disease Free After Metastases Resection to Death (*source:* parametric survival modelling of overall survival data from Adam et al. [15]). [10]Progressive Disease: After Resection and Relapse to Death (*source:* parametric survival modelling of overall survival data from Adam et al. [15]). [11]Progressive Disease: Treat With Subsequent Active Therapy to Progressive Disease: Treat With BSC (*source:* weighted average of published progression-free survival values for second-line treatment options).

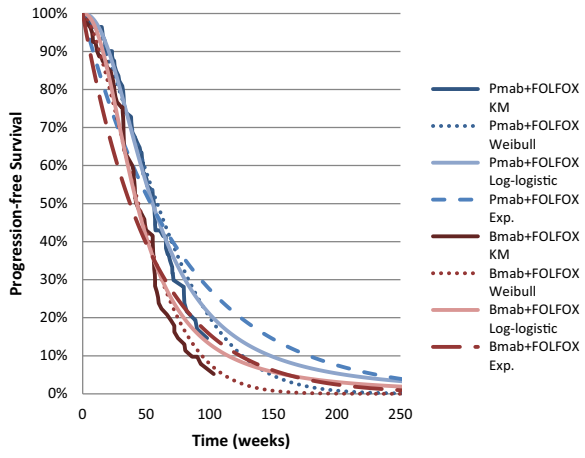

Fig. 2. Progression-free survival Kaplan–Meier plot and fitted curves. Bmab, bevacizumab; Exp, exponential; FOLFOX, leucovorin, 5-fluorouracil, and oxaliplatin; KM, Kaplan–Meier; Pmab, panitumumab. Akaike information criterion for goodness-of-fit: Weibull = 359.46, exponential = 390.42; log–logistic = 360.44.

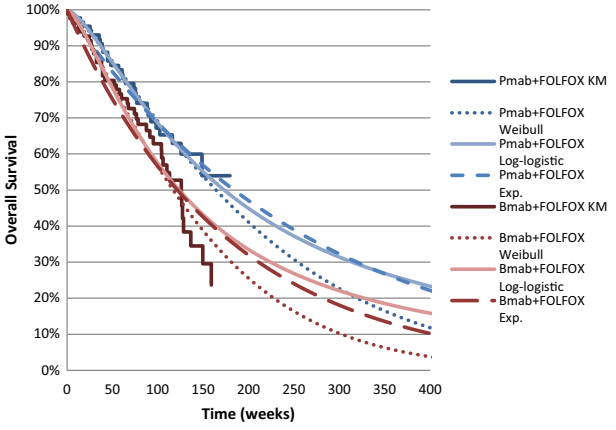

Fig. 3. Overall survival Kaplan–Meier plot and fitted curves. Bmab, bevacizumab; Exp, exponential; FOLFOX, leucovorin, 5-fluorouracil, and oxaliplatin; KM, Kaplan–Meier; Pmab, panitumumab. Akaike information criterion for goodness-of-fit: Weibull = 348.29, exponential = 350.65; log–logistic = 352.60.

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. Drug-acquisition costs and drug-consumption inputs are presented in Table 1, along with sources and assumptions. Non-drug medical costs considered by the model include *RAS*

Table 1
Regimen-specific input parameters.

Input parameter	Panitumumab + mFOLFOX6	Bevacizumab + mFOLFOX6	Source
Biologic drug-acquisition cost	€387	€278	French Health Ministry [18,19]
Chemotherapy drug-acquisition and chemotherapy/ biologic drug-administration cost (note: biologic drug-acquisition costs are separate)	€440	€473	Weighted average DRG costs for the health collective perspective (70% inpatient; 30% day case) from HEVA [20]
Number of treatment cycles			Estimated from the average number of observed panitumumab, bevacizumab, and mFOLFOX6 infusions for patients with wild-type *RAS* mCRC from the PEAK trial, the projected PFS beyond the data collection period, and the ratio of actual to observed treatments in the data collection period
Panitumumab	19.82	–	
Bevacizumab	–	14.10	
mFOLFOX6	12.23	10.50	
Serious adverse events (incidence)			Incidence of serious adverse events occurring in >2% of patients with wild-type *RAS* mCRC in either treatment arm (May 30, 2012, data cutoff) from PEAK trial [9]
Pulmonary embolism	4.7%	2.5%	
Diarrhoea	3.5%	1.3%	
Sepsis	3.5%	1.3%	
Dehydration	2.3%	0.0%	
Febrile neutropenia	2.3%	2.5%	
Gastroesophageal reflux disease	2.3%	0.0%	
Pneumonia	2.3%	3.8%	
Deep vein thrombosis	1.2%	3.8%	
Pyrexia	1.2%	3.8%	
Urinary tract infection	1.2%	2.5%	
Vomiting	1.2%	2.5%	
Infection	0.0%	2.5%	
Intestinal perforation	0.0%	2.5%	
Syncope	0.0%	2.5%	
Subsequent therapy use			Subsequent antitumour therapies from PEAK trial [9] and other assumptions
Anti-EGFR + FOLFIRI	–	69.3%	
Bevacizumab + FOLFIRI	65.5%	–	
Best supportive care	34.5	30.7%	
Subsequent therapy duration			
Anti-EGFR + FOLFIRI			Peeters et al. [21]; Giantonio et al. [22]. Reported medians converted to means for use in the model by assuming an exponential distribution
PFS (median)	25.65 weeks		
Treatment cycles (median)	11.8		
Bevacizumab + FOLFIRI			
PFS (median)	31.74 weeks		
Treatment cycles (median)	10.0		
Resection attempts	13.6%	11.0%	Resection attempts for liver metastases for patients with wild-type *RAS* mCRC from the PEAK trial
Successful resection	66.7%	77.8%	Successful resection (complete removal) of liver metastases for patients with wild-type *RAS* mCRC from the PEAK trial

DRG, diagnosis-related group; EGFR, epidermal growth factor receptor; FOLFIRI, leucovorin, 5-fluorouracil and irinotecan; FOLFOX, leucovorin, 5-fluorouracil, and oxaliplatin; mFOLFOX6, oxaliplatin + 5-fluorouracil + leucovorin; PFS, progression-free survival.

mutation testing, drug administration, chemotherapy, physician visits, diagnostic tests, serious adverse events treatment, resection, subsequent treatment and BSC (Table 2).

2.5. Utility weights

Utility weights used in the model were based on EuroQol-5 Dimension (EQ-5D) questionnaire responses from patients with wild-type *RAS* mCRC in the first-line PRIME (NCT00364013) clinical trial [7,32], patients with wild-type *KRAS* mCRC in the second-line panitumumab clinical trial [21] and BSC patients with wild-type *KRAS* mCRC in the third-line panitumumab clinical trial [6] (Table 2). For second-line and beyond, we assumed that utility weights for patients with wild-type *RAS* mCRC were similar to utility weights for those with wild-type *KRAS* mCRC due to lack of biomarker analysis for wild-type *RAS* utilities in these trials at the time of the present analysis. Utility weights were calculated by averaging all EQ-5D responses before disease progression in each of the respective trials and treatment lines, using the Dolan algorithm [33]. Utility weights for patients living disease-free after a successful resection were assumed to be equivalent to the progression-free utility weight for all patients with wild-type *RAS* mCRC. Disease-recurrence utility weights were assumed to be the average of subsequent active treatment and BSC in the disease progression health state.

2.6. Analyses

The model outcomes calculated for each first-line treatment regimen included patient survival (life-years), quality-adjusted life-years (QALYs) and costs for healthcare resources. Briefly, QALYs are calculated as the time (i.e. years) spent in a health state multiplied by utility weights corresponding to patient health at that time. Utility weights generally range from zero, representing death, to one, representing perfect health. By adjusting survival (time) by quality of life (utility weights), the cost-effectiveness of treatments across a range of conditions is standardised so that decision makers can allocate resources using comparable statistics, i.e. incremental cost-effectiveness ratios (ICERs). ICERs are calculated as the difference in total costs divided by difference in total life years. In the case of this analysis, the incremental costs per life-year and per QALY gained were calculated. 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 [34].

To test the robustness of the model methods, assumptions, and specific parameters, we examined the effect of using alternative methods and data sources for the model inputs in a series of focused scenario analyses conducted around the assumptions and methods used to calculate drug-acquisition costs, subsequent treatment and utility weights. We also examined the effect of changing parameters individually as part of one-way sensitivity analyses.

In addition to one-way sensitivity analyses, a probabilistic sensitivity analysis was performed to examine the effects of joint uncertainty across all the parameters of the model. The results of the probabilistic sensitivity analysis were summarised using cost-effectiveness scatter plots (not shown) and cost-effectiveness acceptability curves.

3. Results

The cost-effectiveness model is based on a head-to-head clinical trial that demonstrates better efficacy outcomes for patients with wild-type *RAS* mCRC who receive panitumumab plus mFOLFOX6 versus bevacizumab plus mFOLFOX6. Table 3 summarises the cost-effectiveness results of the deterministic (base-case) analysis. The model projected 3.58 life-years for panitumumab plus mFOLFOX6 and 2.73 life-years for bevacizumab plus mFOLFOX6 (both arms discounted 4% per annum). Adjusting for quality of life, panitumumab plus mFOLFOX6 was estimated to produce 2.68 QALYs, while bevacizumab plus mFOLFOX6 was estimated to produce 2.05 QALYs (both arms discounted 4% per annum). Monoclonal antibody drug-acquisition costs made up 40–44% of total costs modelled, with BSC costs contributing the second greatest proportion of costs (23–25% of total). Due to greater PFS (longer duration of therapy) and higher drug-acquisition costs, total drug costs were higher for panitumumab plus mFOLFOX6 than for bevacizumab plus mFOLFOX6 (€42,843 versus €29,871). Similarly, costs for administration, chemotherapy drugs and BSC were higher for panitumumab plus mFOLFOX6 than for bevacizumab plus mFOLFOX6 due to longer survival.

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. The one-way sensitivity analysis indicated that drug-acquisition costs, costs of BSC and costs of subsequent treatments were the most sensitive parameters.

Scenario analysis conducted around major model assumptions indicated that the model was robust to alternative assumptions of PFS and OS distributions, resection modelling and subsequent treatment following disease progression (Table 4).

Mean net monetary benefits from 10,000 simulations of the probabilistic sensitivity analysis ranged from €10,211 to €64,176 for panitumumab plus mFOLFOX6 and from €9106 to €50,489 for bevacizumab plus mFOLFOX6 for willingness-to-pay thresholds ranging from €40,000 to €60,000, respectively. The cost-effectiveness acceptability curve displayed in Fig. 4 indicates that 54.0% of simulations were below a willingness-to-pay threshold of €40,000 and 82.5% of simulations were

Table 2
Other input parameters.

Input parameter	Value	Source
KRAS and *RAS* test	€123	One *KRAS* (exon 2) and one *KRAS* (exons 3–4)/*NRAS* (exons 2–4) test performed. Costs from Qjagen [23]
RAS frequency	46.2%	In the NCT00364013 study, 506 out of 1096 patients randomised who had a tumour sample available for *RAS* testing had wild-type *RAS* mCRC
FOLFOX alone drug-acquisition and administration cost	€437	Mean costs per case for collective perspective from HEVA [20]
General practitioner office visit cost	€23	General practitioner visits were assumed to occur every 4 weeks. Costs were from French Health Insurance [24][a]
Oncology specialist office visit cost	€28	Visits to an oncology specialist are assumed to occur every treatment cycle (2 weeks). Costs were from French Health Insurance [24]
Computed tomography scan cost	€50	It was assumed that disease progression would be monitored every 8 weeks, similar to the protocol from the panitumumab clinical trial Costs were for a computed tomography scan of the abdomen and pelvis from the Classification Commune des Actes Médicaux [25]
Serious adverse events cost (hospital costs)		
Pulmonary embolism	€3984	Assumed similar to costs for an arterial thrombolic event from Mickisch et al. [26]
Diarrhoea	€1991	Average of mean hospitalisation costs from Mickisch et al. [26] and Douillard et al. [27]
Sepsis	€3954	Assumed similar to febrile neutropenia
Dehydration	€3563	Hospitalisation costs from Vergnenegre et al. [28]
Febrile neutropenia	€3954	Mean hospitalisation costs from Durand-Zaleski et al. [29]
Gastroesophageal reflux disease	€3563	Assumed similar to dehydration
Pneumonia	€3954	Mean hospitalisation costs from Durand-Zaleski et al. [29]
Deep vein thrombosis	€1447	Mean hospitalisation costs for a venous thromboembolic event from Mickisch et al. [26]
Pyrexia	€3954	Assumed similar to febrile neutropenia
Urinary tract infection	€3954	Assumed similar to febrile neutropenia
Vomiting	€1991	Assumed similar to diarrhoea
Infection	€3954	Assumed similar to febrile neutropenia
Intestinal perforation	€3984	Assumed similar to costs for an arterial thrombolic event from Mickisch et al. [26]
Syncope	€3563	Assumed similar to costs of dehydration
Resection surgery and hospitalisation cost	€14,428	HEVA [20]
Disease relapse following resection cost per cycle	€1913	Average of subsequent therapies modelled postprogression
End-of-life cost	€7653	French Health Ministry [18–19]
Best supportive care costs per cycle	€564	Remak and Brazil [30] estimated the monthly costs for supportive care to be £675 per month. This value was divided by 2 to estimate a per-cycle cost, inflated to 2011–2012 lb [31] and converted to Euros (£1 = €1.15)
Utility weights		
Progression free	0.821	Wild-type *RAS* from first-line NCT00364013 trial
Progressive disease		
Subsequent active treatment	0.782	Wild-type *KRAS* from second-line 20050181 trial
Best supportive care	0.681	Patients with wild-type *KRAS* mCRC treated with best supportive care in the third-line 20020408 trial

FOLFOX, leucovorin, 5-fluorouracil and oxaliplatin.
[a] Scheduled physician visits did not include visits for serious adverse events treatment or management that occurred on days other than the day of treatment administration. Also, costs of scheduled physician visits during best supportive care after disease progression were captured as part of the best supportive care costs and were not included in these cost estimates, because the frequency of office visits was likely to be different.

below a willingness-to-pay threshold of €60,000. Additionally, 97% of simulations performed showed panitumumab plus mFOLFOX6 to be more effective and more costly or more effective and less costly than bevacizumab plus mFOLFOX6.

4. Discussion

We developed a semi-Markov model based on the first-line PEAK study to investigate the cost-effectiveness of panitumumab plus mFOLFOX6 compared with bevacizumab plus mFOLFOX6 in patients with wild-type *RAS* mCRC. Based on the model projections, treatment with panitumumab plus mFOLFOX6 resulted in longer survival and greater QALYs than bevacizumab plus mFOLFOX6. Accordingly with increased survival, total costs for panitumumab plus mFOLFOX6 were also greater.

To our knowledge, this is the first cost-effectiveness publication reporting analyses for the wild-type *RAS* mCRC population, and the first head-to-head study between panitumumab and bevacizumab using patient-level data. Lawrence et al. [10] recently published a first-line cost-effectiveness analysis comparing panitumumab,

Table 3
Deterministic results.

Outcome/cost category	Panitumumab + mFOLFOX6	Bevacizumab + mFOLFOX6	Difference Between Panitumumab + mFOLFOX6 and Bevacizumab + mFOLFOX6
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	€9507	€1829
Toxicity treatment and management	€873	€1058	€−185
Physician visits	€1581	€1247	€334
Monitoring for disease progression	€506	€99	€407
Best supportive care	€24,418	€17,140	€7278
Resection related	€8823	€8006	€817
End-of-life costs	€6554	€6811	€−257
Total costs	€97,203	€74,440	€22,763
Incremental cost-effectiveness ratios of panitumumab + mFOLFOX6 versus bevacizumab + mFOLFOX6			
Incremental cost per life-year gained	€26,918		
Incremental cost per QALY gained	€36,577		

mFOLFOX6, oxaliplatin + 5-fluorouracil + leucovorin; QALY, quality-adjusted life-year.

bevacizumab and cetuximab within the wild-type *KRAS* mCRC population. However, the analysis is outdated as it does not use the current labelled population of patients with wild-type *RAS* mCRC, nor does it make use of recent informative head-to-head clinical trial results.

The model described in this article, like all models, has its limitations, although we feel that adequate sensitivity and scenario analyses around modelling assumptions have shown those limitations to result in similar conclusions of value for money. The PEAK trial is a phase 2 trial with a lower number of enrolled patients ($N = 285$) than a phase 3 trial. In the wild-type *RAS* mCRC patient population of PEAK, the primary end-point (PFS) was significantly in favor of panitumumab and a secondary end-point (OS) showed a strong trend in terms of incremental benefit (12.4 months) favouring the panitumumab arm, despite low power to detect differences. Our probabilistic sensitivity analysis takes issues related to lower sample sizes into account with its uncertainty around the treatment variable included in the parametric survival modelling. Despite increased uncertainty due to a lower sample size, the cost-effectiveness acceptability curves show good value for money for panitumumab plus mFOLFOX6.

Models based on clinical trials can have inherent limitations due to the design of the trial and the inclusion criteria for patients, which may mean that the trial population is not completely representative of 'real world' clinical patients. Therefore, for our model, we compared the clinical characteristics of the wild-type *RAS* mCRC population in the bevacizumab arm of PEAK with a recently published real-life French mCRC patient cohort from the ETNA study.[35] ETNA only included mCRC patients treated with bevacizumab and did not select by *RAS* tumour status. The clinical characteristics of the PEAK bevacizumab cohort show some differences versus the ETNA population, but these differences likely balance each other out from a prognostic perspective: there were no ECOG 2 patients in PEAK versus 12% in ETNA and median age was 60 years in PEAK versus 65 years in ETNA; however, only 40% of patients in PEAK had a single metastatic site versus 57% in ETNA. Patient survival rates in PEAK versus ETNA were similar at 1 year (79% versus 80%), 2 years (59% versus 54%) and 3 years (30% versus 29%), which supports the proposal that the PEAK population can be considered representative of the French population.

Additionally, a limitation of the PEAK trial, and the majority of all other trials in oncology, is that most data collection stops at the point of disease progression. Our knowledge of subsequent treatments is limited to the types of drugs patients received post progression. Based on this information, we attempted to model the costs associated with those treatments to reflect a real-world treatment scenario. We did not model subsequent therapy costs of the newer agents to market (e.g. aflibercept, regorafenib), but we do not expect that the inclusion of these therapies would change the conclusions of the model given the first-line focus of the analysis and that cost differences would wash out between arms. Over a

Table 4
Scenario analysis results.

Alternative input parameter scenario	Incremental cost per QALY gained	Change from base case (%)
Base case analysis	€36,577	
Parametric survival analysis		
Log–logistic PFS	€40,973	12.02
Log–logistic OS	€36,041	−1.47
Log–logistic PFS and OS	€40,169	9.82
Drug consumption		
No vial wastage (vial sharing)	€35,834	−2.03
Wastage	€37,926	3.69
Number of treatment cycles		
Observed number of treatment cycles preprogression	€30,384	−16.93
Resection		
No resection modelled	€35,589	−2.70
Subsequent therapy postprogression		
All patients receive BSC postprogression	€50,390	37.76
No drug, BSC, or end-of-life costs postprogression	€38,310	4.74

BSC, best supportive care; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year.

range of alternative assumptions conducted in scenario analyses, conclusions of the model did not change.

While our analysis focused on a first-line treatment comparison between an anti-EGFR, panitumumab, and an anti-VEGF, bevacizumab, it would be of interest to decision makers to examine costs and outcomes within the anti-EGFR class. To date, no first-line trials have been conducted between panitumumab and cetuximab. However, the ASPECCT trial examined these treatments as monotherapies in the third-line setting [36]. In the *KRAS* population, PFS and OS hazard ratios were 1.00 (95% confidence interval (CI) 0.88, 1.14) and 0.97 (95% CI 0.84, 1.11), respectively. There are no *RAS* available data for this trial. If we were to assume equivalent efficacy in the first-line setting and modelled both treatments, we would expect, for cetuximab relative to panitumumab, higher administration costs (cetuximab must be administered weekly and panitumumab is administered every 2 weeks), higher costs due to infusion reactions (rates of any grade infusion reaction were 14% with cetuximab versus 3% with panitumumab in ASPECCT) and higher premedication costs (as premedication for cetuximab is required to reduce infusion reactions). Additional modelling taking into account the potential uncertainty of PFS and OS differences between the products would be needed to confirm this assumption.

Utility weights for our model were estimated from other panitumumab trials that included the EQ-5D as a part of data collection. In some of these trials, wild-type *RAS* data were not available at the time of the present analysis. In examining utility weights calculated from the PRIME trial with both wild-type *KRAS* and *RAS* biomarkers, we found little difference in progression-free utility weights between the groups. Additionally, our model assumes no difference in utility weights between treatments, so any change to the utility weights would have equal impact on both treatments compared.

Finally, the basis of this analysis assumes that treatment of mCRC with first-line agents is acceptable from the payer perspective. This is indeed the case in a majority of countries. However given the high total costs of treatment, an analysis that examines the cost-effectiveness of first-line mCRC treatment compared with no treatment (i.e. best supportive care) may be of interest to decision makers and patients in areas that have not approved first-line mCRC treatment for reimbursement.

Based on results of this model, panitumumab plus mFOLFOX6 represents good value for money compared with a current standard of care bevacizumab plus mFOLFOX6 and, with a willingness-to-pay ranging

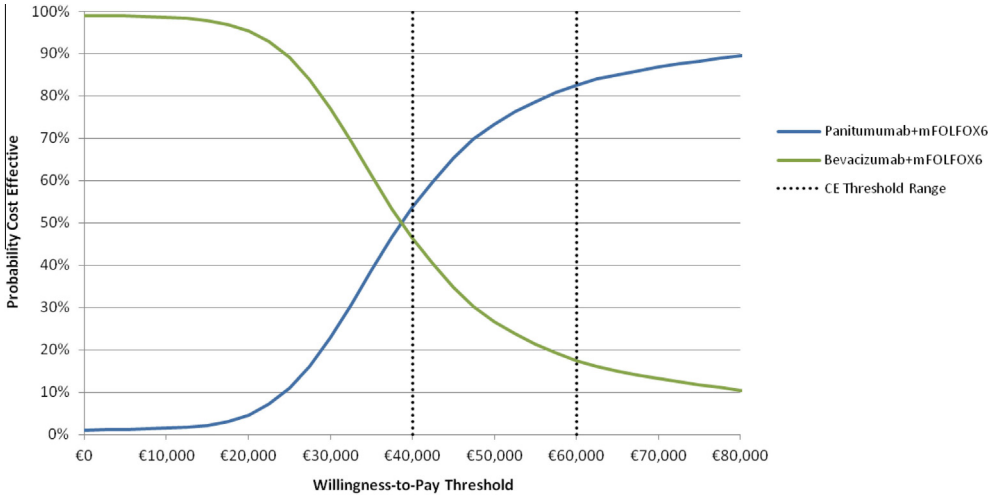

Fig. 4. Cost-effectiveness acceptability curve. CE, cost-effectiveness; mFOLFOX6, oxaliplatin + 5-fluorouracil + leucovorin.

from €40,000 to €60,000 can be considered cost-effective in first-line treatment of patients with wild-type *RAS* mCRC. Future research extending treatment comparisons to other active regimens will produce a clearer picture of the cost effectiveness of treatments for patients with wild-type *RAS* mCRC.

Conflict of interest statement

This study was conducted by RTI Health Solutions under the direction of Amgen and was funded by Amgen. Guy Hechmati, Jonas Hjelmgren, Frédérique de Liège, Julie Lanier and Beth Barber are employees of Amgen. Christopher Graham and Hediyyih Knox are employees of RTI Health Solutions.

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