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Original Research

Cost-effectiveness of capecitabine and bevacizumab maintenance treatment after first-line induction treatment in metastatic colorectal cancer

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Abstract ***Aim:*** Capecitabine and bevacizumab (CAP-B) maintenance therapy has shown to be more effective compared with observation in metastatic colorectal cancer patients achieving stable disease or better after six cycles of first-line capecitabine, oxaliplatin, bevacizumab treatment in terms of progression-free survival. We evaluated the cost-effectiveness of CAP-B maintenance treatment.

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Bevacizumab

Methods: Decision analysis with Markov modelling to evaluate the cost-effectiveness of CAP-B maintenance compared with observation was performed based on CAIRO3 study results (n = 558). An additional analysis was performed in patients with complete or partial response. The primary outcomes were the incremental cost-effectiveness ratio (ICER) defined as the additional cost per life year (LY) and quality-adjusted life years (QALY) gained, calculated from EQ-5D questionnaires and literature and LYs gained. Univariable sensitivity analysis was performed to assess the influence of input parameters on the ICER, and a probabilistic sensitivity analysis represents uncertainty in model parameters.

Results: CAP-B maintenance compared with observation resulted in 0.21 QALYs (0.18LYs) gained at a mean cost increase of €36,845, yielding an ICER of €175,452 per QALY (€204,694 per LY). Varying the difference in health-related quality of life between CAP-B maintenance and observation influenced the ICER most. For patients achieving complete or partial response on capecitabine, oxaliplatin, bevacizumab induction treatment, an ICER of €149,300 per QALY was calculated.

Conclusion: CAP-B maintenance results in improved health outcomes measured in QALYs and LYs compared with observation, but also in a relevant increase in costs. Despite the fact that there is no consensus on cost-effectiveness thresholds in cancer treatment, CAP-B maintenance may not be considered cost-effective.

1. Introduction

Recently, the results of the phase 3 CAIRO3 study showed that metastatic colorectal cancer (mCRC) patients with stable disease or better after 6 cycles of treatment with capecitabine, oxaliplatin and bevacizumab (CAPOX-B) had a significant benefit from capecitabine and bevacizumab (CAP-B) maintenance treatment compared with observation [1]. In this trial, reintroduction of CAPOX-B treatment was planned in all patients who had progressive disease following either CAP-B maintenance or observation. A statistically significant improvement in the primary endpoint of second progression-free survival (PFS-2), defined as the time from randomisation until progression of disease after CAPOX-B reintroduction, was shown for maintenance treatment versus observation, 11.7 months and 8.5 months, respectively (hazard ratio [HR] 0.67, 95% confidence interval [CI] 0.56–0.81). Although the study was not designed to detect a difference in overall survival (OS), an absolute median OS benefit of 3.5 months was observed, which was not statistically significant (HR 0.89, 95% CI 0.73–1.07). Median OS from the time of randomisation was 21.6 months for patients receiving maintenance treatment and 18.1 months for observation [1]. A statistically significant OS benefit in favour of CAP-B maintenance treatment was demonstrated in patients achieving complete response (CR) or partial response (PR) during induction treatment (24.1 months and 18.8 months, respectively [log-rank p = 0.0002]) [1]. However, results for this subgroup analysis require further validation. Maintenance treatment did not impair quality of life (mean change in global quality of life 0.03, 95% CI: 0.35–0.41) [1]. Our findings are supported by the results of the AIO 0207 study, which had a comparable study design [2].

Despite these results, economic concerns may hamper the implementation of CAP-B maintenance therapy in daily practice. Multiple cost-effectiveness analyses of bevacizumab-containing first-line regimens for mCRC treatment have been published with different results: some analyses did [3–6], but others did not show that the addition of bevacizumab to chemotherapy was cost-effective [7–12]. This diversity in results arises due to differences in methodology applied for these cost-effectiveness studies, such as therapy of comparison and country of origin [13]. In addition, as recently described, a cost-effectiveness study can be fully designed and calculated based on assumptions, such as duration of bevacizumab treatment continuation, which might importantly influence cost and effect outcomes [3,14].

Cost-effectiveness of CAP-B maintenance treatment has not been previously evaluated. Therefore, we evaluated the cost-effectiveness of CAP-B maintenance compared with the observational strategy following first-line CAPOX-B induction treatment for mCRC patients based on the CAIRO3 study.

2. Methods

2.1. Patient population

Results of the CAIRO3 study (NCT00442637) [1] were used for this post hoc cost-effectiveness model. The CAIRO3 study was a Dutch multicenter randomised clinical study in which mCRC patients (n = 558) with

stable disease or better after six cycles of CAPOX-B induction therapy were either assigned to observation or capecitabine (625 mg/m^2 orally twice daily continuously) and bevacizumab (7.5 mg/kg intravenously every 3 weeks) maintenance treatment. On progression, patients were scheduled to receive reintroduction of CAPOX-B therapy. Progression-free survival 1 (PFS1), time to second progression and OS were used for this cost-effectiveness model. PFS1 was defined as the interval between randomisation and the date of first progression while under maintenance or observation, or until death, or discontinuation, or end of trial for patients who did not progress. The time to second progression on any treatment including reintroduction of CAPOX-B (time to second progression) was defined as the interval between randomisation and the date of second progression (for those who had a first progression). In patients for whom no further treatment was registered beyond PFS1, time to second progression on any treatment was similar to OS (i.e. death as endpoint or censored if still alive). We defined OS as the interval between randomisation and the date of death (or censored if still alive). Mean values from the CAIRO3 data set were used for base case deterministic analysis.

2.2. Model structure

A Markov decision analytic model was designed (using TreeAge Pro Healthcare v.2014, TreeAge Software, Williamstown, MA, USA) incorporating both the observation and CAP-B maintenance treatment strategies and subsequent treatments for the management of mCRC. The Markov model (Fig. 1) consisted of four health states throughout the treatment of mCRC (post-induction, reintroduction or other treatment, salvage and death) and included probabilities of adverse events with related costs. Health-related quality of life (HRQoL) and costs were attributed to each health state. A lifetime horizon, based on a median duration of follow-up of 48 months in the CAIRO3 study, with

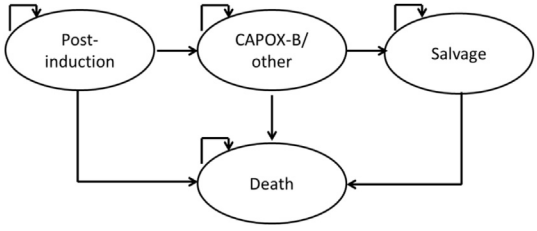

Fig. 1. Markov model with 3-week cycle length. All patients start in the post-induction phase. After 3 weeks, a patient can remain in this health state or transition to another health state: on progression CAPOX-B reintroduction/other treatment or death. Patients transitioned to CAPOX-B reintroduction/other treatment could remain in this health state or transition to salvage treatment on progression or death every Markov cycle. Patients in the salvage health state remained in this health state until death. CAPOX-B, capecitabine, oxaliplatin, bevacizumab.

Markov transition cycles of three weeks was chosen, to reflect the original treatment cycle length in the CAIRO3 study.

2.3. Health state transitions and clinical probability estimates

Time-dependent transition probabilities (time to first and second progression and survival) were derived directly from the CAIRO3 data set on a patient-level in 3-week intervals using Life Tables in IBM SPSS Statistics software, version 23 (Armonk, NY, IBM Corp.). Although, the CAIRO3 study was not designed to analyse specific subgroups, such as patients achieving CR or PR on CAPOX-B induction, we performed a separate analysis on this patient subgroup as CAP-B maintenance resulted in significantly improved PFS2 and OS. As a result, transition probabilities for this subgroup analysis were based on a smaller patient population (n = 366). In addition, time-dependent transition probability tables were also derived for the subgroup of patients with CR/PR after CAPOX-B induction treatment, since this subgroup appeared to benefit most from maintenance treatment. Clinical probabilities for grade 3 and 4 adverse events were derived from the CAIRO3 data set and a literature search in the PubMed database (Supplementary Table S1) [15–18]. Assumptions on incidence and treatment of grade 3 and 4 adverse events were validated following expert opinion within the study team.

2.4. Health-related quality of life scores and outcomes

HRQoL scores were calculated using the EQ-5D (3L) questionnaires for 492 patients (n = 250 and 242 for the observation and maintenance arm, respectively) for the post-induction health state. EQ-5D questionnaires were completed at baseline and every 9 weeks thereafter. For 96 patients, no EQ-5D questionnaires were available. HRQoL scores for the reintroduction or other treatment and salvage health states were derived from literature (Table 1) [4,5,7,9,19–26]. HRQoL scores reflect quality of life in a range between 0 (worst imaginable health/death) to 1 (optimal health) and were calculated with the Dutch EQ-5D tariff [27]. Quality-adjusted life years (QALYs) were subsequently calculated as the product of utility and time [28]. QALY is a measure reflecting years lived adjusted for quality of life and is widely used to compare health outcomes between treatment strategies [29].

2.5. Resource use and cost-estimates

Resource use was determined based on the CAIRO3 clinical data set and retrospective additional data collection for 146 patients (n = 75 in the observation arm and n = 71 in the maintenance arm) in six hospitals

Table 1
Model parameters—probabilities and HRQoL scores.

	Base case	Range tested in sensitivity analysis	Source
Probabilities of 1st progression and 2nd progression	Life-time tables	–	CAIRO3 data set [1]
Probabilities of death	Life-time tables	–	CAIRO3 data set [1]
HRQoL score maintenance health state	0·84	0·74–0·95	Base case: CAIRO3 data set and range: [4,5,7,9,19–22]
HRQoL score observation health state	0·83	0·74–0·95	Base case: CAIRO3 data set and range: [4,5,7,9,19–22]
HRQoL score for the reintroduction or 2nd line health state	0·73	0·58–0·78	Base case and range: [5,9,19,20,23–25]
HRQoL score for the salvage health state	0·69	0·64–0·73	Base case and range: [20,22,23,25,26]

participating in the CAIRO3 study (2 academic centers, 2 teaching hospitals and 2 general hospitals), listed in the Supplementary Table S1. Data collected in selected hospitals were regarded as a reflection of average daily practice. Only medical resource use data within the hospital participating to the CAIRO3 study were collected from the time of randomisation until death or last date alive. Medical resource utilisation of patients outside the participating center was outside the scope of the retrospective data collection.

A hospital payer's perspective was chosen in this study, which include drug costs for the treatment of mCRC and associated adverse events, hospital and physician fees, and all work-up performed within the hospital. Cost calculations for medication were based on an average patient of 79 kg with a body surface area of 1.92 m^2 (derived from the CAIRO3 data set). Medication costs included to this study are limited to inpatient medication for adverse events and medication prescribed by the medical oncologist. Treatment costs were derived from the Dutch Healthcare Institute, and medication costs were derived from the Healthcare Insurance Board [30–33]. The Dutch Healthcare institute provides standardised information on costs for i.e. physician fees, medical work-up and so forth, averaged for hospital types (academic, teaching and general hospitals). All costs are presented in Euros and indexed to 2014 using consumer price indices, if necessary, in the Supplementary Table S2. Costs and health outcome effects were discounted at an annual rate of 4% and 1.5%, respectively, as per Dutch guidelines (base case) [30]. In addition, both cost and health outcome effects were also discounted at an annual rate of 3% [34], and no discounting for costs and effects was also applied for comparison.

2.6. Outcomes and sensitivity analysis

Our primary outcomes were the incremental cost-effectiveness ratios (ICERs): the ratio of incremental costs per QALY and per life year (LY) gained. Univariable sensitivity analyses was used to demonstrate the influence of all model parameters, including a ratio reflecting the difference in the HRQoL scores between CAP-B maintenance and observation on the ICER (ranges tested as shown in Table 1). In addition, the mean cost-effectiveness and CIs were computed in a probabilistic sensitivity analysis using Monte Carlo simulation (n = 10,000) on the costs (gamma distributions), rates (normal distributions), probabilities (beta distributions) and utilities (beta distributions) with a 25% standard deviation used per parameter (Supplementary Table S2).

Cost-effectiveness outcomes were also calculated based on clinical outcomes of patients with PR or CR on induction treatment with CAPOX-B, as this subgroup appeared to derive the most benefit of maintenance treatment in CAIRO3 study [1].

3. Results

HRQoL scores from the CAIRO3 data set for the observation (mean 0.83) and CAP-B maintenance (mean 0.84) health states were not significantly different between treatment arms. HRQoL scores for reintroduction or other treatment, and salvage treatment were averaged from previously reported HRQoL scores and shown in Table 1. The mean systemic treatment costs (including mean costs for prophylaxis and handling of systemic agents by the hospital pharmacist) per 3-week cycle of CAP-B maintenance and salvage therapy were €2165 and €1,338, respectively (Table 2). In the CAIRO3 study, a median of 11 treatment cycles were administered to patients in the CAP-B maintenance treatment arm eventuating in a systemic therapy cost of €23,815.

Table 2
Average chemotherapy costs[a] in euro's for a patient with mean weight 79 kg, mean BSA 1,92 m^2 per Markov cycles of 3 weeks—base case.

Cost category	Cost (€)	Range tested in sensitivity analysis	Source
CAPOX-B induction treatment (for a total of 6 cycles)	16,473	–	[33]
CAP-B maintenance	2165	1624–2706	[33]
CAPOX-B reintroduction	2743	2057–3429	[33]
Other systemic treatment (defined as 1.5 cycles of FOLFIRI)	1470	1103–1838	[33]
Salvage treatment[b]	1338	1004–1673	[33]

[a] Includes costs for systemic treatment including prophylaxis and preparation of systemic agents by the (hospital) pharmacist.
[b] Based on additional data collected retrospectively for 146 patients.

In the deterministic analysis of this cost-effectiveness model, CAP-B maintenance treatment resulted in mean incremental cost of €36,845 with a mean incremental benefit of 0.21 QALYs and 0.18 LYs gained. This yields an ICER of €175,452 per QALY (quality-adjusted life year) gained and €204,694 per life year gained (Table 3). For patients achieving CR or PR following six cycles of CAPOX-B induction treatment, CAP-B maintenance treatment resulted in a mean incremental cost of €46,283 with a mean incremental benefit of 0.31 QALYs and 0.31 LYs, yielding an ICER of €149,300 per QALY and per LY gained. No important differences were observed between survival curves based on the cost-effectiveness model and the CAIRO3 study (Fig. 2).

3.1. Sensitivity analyses

Univariable sensitivity analyses for influence of model parameters showed that the model was most influenced by a larger difference in HRQoL between patients receiving CAP-B maintenance treatment and observation in the post-induction treatment phase. The ICER reduced to €94,454 per QALY if the HRQoL score of maintenance was 1 or equal to perfect health and the HRQoL score for observation remained 0.83. In contrast, observation dominated (i.e. higher HRQoL and lower costs) maintenance if the HRQoL for maintenance was 0.8 times the HRQoL score for observation. The second most influential parameter in the model was the HRQoL score during the post-induction phase (while the difference in HRQoL scores between CAP-B maintenance and observation remained constant) for both maintenance and observation (range: 0.74–0.95). This yielded an ICER range of €134,288 per QALY (for a utility of 0.95) to €231,172 per QALY (for a utility of 0.74). The third most influential parameter on the model was the cost of bevacizumab, yielding an ICER of €218,168 and €136,758 for a 25% bevacizumab cost increase or decrease, respectively. The ICER range (in € per QALY) of the ten most influential parameters are listed in Table 4.

Univariable sensitivity analyses were also performed on cost parameters only. The following three cost parameters were of most influence on the ICER, the cost of bevacizumab (see above for the ICER range), cost of salvage (ICER range €172,353–182,574 per QALY) and cost of hospitalisation (ICER range €174,207–180,720 per QALY). The ICER range (in € per QALY) of the ten most influential cost parameters are listed in Table 5.

With a probabilistic sensitivity analysis for 10,000 samples (plotted in Fig. 3) a mean incremental cost of €36,832 (95% CI €36,660–37,004) with a mean incremental benefit of 0.21 QALYs (95% CI 0.21–0.21), resulted in a mean ICER of €181,346 per QALY (95% CI €102,271–260,421).

4. Discussion

In our analysis, patients with mCRC receiving CAP-B maintenance treatment after CAPOX-B induction treatment generate more costs at an improved effectiveness in terms of gained QALYs or LYs gained compared with observation. The CAP-B maintenance treatment strategy results in an incremental cost per additional QALY ratio (ICER) of €175,452 compared to the treatment strategy with observation. Patients achieving CR or PR after CAPOX-B induction treatment appear to have a somewhat more beneficial ICER of €149,300 per QALY. However, the predictive value of CR/PR after induction treatment for the outcome of maintenance treatment should be further validated. Presently, subgroup analyses of the CAIRO3 study are being performed to identify patients that benefit most from CAP-B maintenance treatment strategy.

Previously, contradictory conclusions have been reported for cost-effectiveness studies regarding the addition of bevacizumab to first-line systemic treatment. However, none of these cost-effectiveness models evaluated bevacizumab-containing maintenance treatment. Koeberle *et al.* [35], who reported about costs—but not cost-effectiveness—found average costs of €4443/month for bevacizumab maintenance and €1558/month for the observation strategy (cost converted to Euros and corrected for inflation and power parity). Unfortunately, lack of a reported ICER hampers proper comparison with our results. The previously reported ICERs for the addition of bevacizumab to systemic treatment (converted in Euros and corrected for inflation and power parity) ranged from €42,272 to €438,444 per QALY and €10,567–336,776 per LY [13]. These different cost-effectiveness models all compared different first-line

Table 3
Incremental cost per effectiveness ratio (ICER in € per QALY or € per LY).

	Observation	CAP-B maintenance	Difference	ICER (€) discount: 4% for costs, 1.5% for effect	ICER (€) discount: 3% for costs and effects	ICER (€) without discounting
Cost (€)	94,111	130,956	36,845			
QALY	1.42	1.62	0.21	175,452	186,815	177,413
LY	2.25	2.43	0.18	204,694	207,572	205,426

Abbreviations: CAP-B, capecitabine and bevacizumab; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

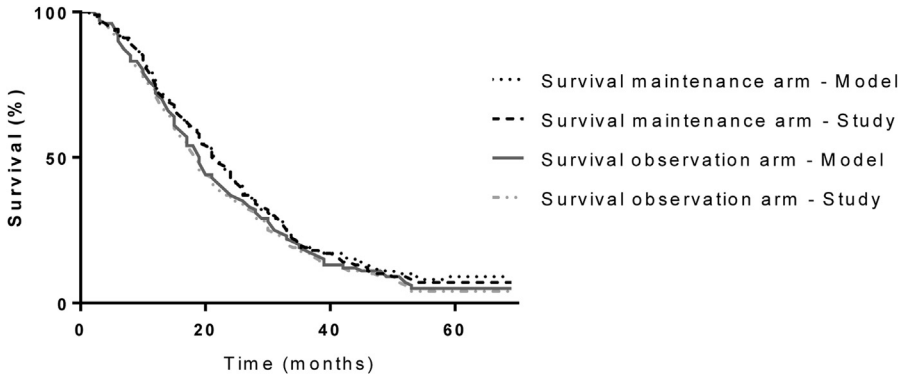

Fig. 2. Survival curves for patients for the maintenance and observation arm of the CAIRO3 study and survival curves for the maintenance and observation arm generated from the cost-effectiveness model.

Table 4
ICER ranges (in € per QALY) of the ten most influential model parameters.[a]

		Low value (€)	High value (€)
1	Post-induction HRQoL ratio maintenance:observation	Dominated[b]	491,270
2	HRQoL post-induction	134,288	231,172
3	Cost of bevacizumab	136,758	218,168
4	HRQoL re-induction	158,504	184,666
5	Cost salvage	172,353	182,574
6	Duration of hospitalisation	172,849	182,078
7	Cost of hospitalisation	174,207	180,720
8	Physician visit	174,513	180,414
9	Day-care hospital admission	174,632	180,294
10	Discount rate for costs	176,422	178,504

Abbreviations: HRQoL, health-related quality of life; ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

[a] A 25% percent range around the base case value was used for each model parameter.

[b] If the post-induction HRQoL of maintenance is 25% lower compared with the HRQoL of observation, then the observation treatment arm is regarded as superior in terms of both effectiveness and costs.

Table 5
ICER ranges (in € per QALY) of the ten most influential cost parameters.[a]

		Low value (€)	High value (€)
1	Bevacizumab	136,758	218,168
2	Salvage	172,353	182,574
3	Hospitalisation	174,207	180,720
4	Physician visit	174,513	180,414
5	Day-care hospital admission	174,632	180,294
6	Capecitabine	175,110	179,817
7	Oxaliplatin	175,653	179,273
8	Blood count & chemistry	176,022	179,008
9	Radiotherapy	176,088	178,841
10	CT-scan	176,422	178,505

Abbreviations: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.

[a] A 25% percent range around the base case value was used for each cost parameter.

treatment strategies, yielding important differences in incremental costs and effects. Differences in costs originate for instance from differences in cost-perspectives (e.g. hospital perspective or third-party payer perspectives), assumptions made (e.g. treatment duration), different health-care systems between countries and differences in medical practice [13,14].

Even though the CAIRO3 study did not include a cost-effectiveness evaluation in the study design, we are able to develop a robust model incorporating data from both the original data set of the CAIRO3 study as well as detailed retrospective data of a patient subset (n = 146) of the CAIRO3 patient population. The probabilistic sensitivity analysis confirms the outcomes of the deterministic analysis.

We have shown that our model outcome is most influenced by the difference in HRQoL score between patients in the maintenance and observation arm in the post-induction health state, i.e. when different HRQoL scores are assigned to patients in the maintenance and observation arm. The calculated post-induction HRQoL scores in our model were directly derived from the CAIRO3 study and are not significantly different between treatment arms. Furthermore, we have previously shown that the EORTC QLQ-C30 quality of life results of the CAIRO3 study were not clinically relevantly different between treatment arms in the post-induction

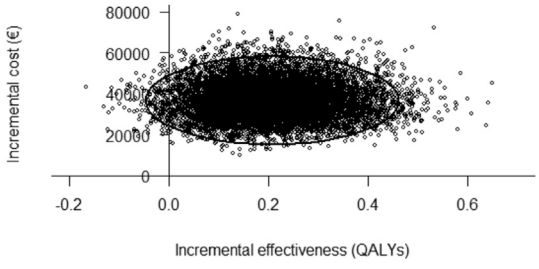

Fig. 3. Probabilistic Sensitivity Analysis (n = 10,000) for the incremental cost-effectiveness of CB maintenance versus observation. Each dot represents an ICER, ⬭ = 95% confidence incidence. ICER, incremental cost-effectiveness ratio.

health state [1]. As a result, we do not expect the post-induction HRQoL scores to have an important influence on the interpretation of our results towards daily practice even though these HRQoL scores demonstrated to be the most influential parameter on model outcomes by univariable sensitivity analysis.

In our decision-analytic model, the cost of bevacizumab is the most influential cost parameter in the model, with a range of €136,758–218,168 per QALY gained. A reduction in the cost of bevacizumab will therefore yield a more favourable cost-effectiveness outcome. The second most influential cost parameter in the model was the cost of salvage treatment (ICER range €172,353–182,574 per QALY). The influence of salvage treatment costs on model outcomes is limited as can be derived from the ICER range. A standard cost for all patients achieving the salvage treatment health state was used in our model. Detailed data, including information on systemic treatment dosage and duration of treatment, collected retrospectively on salvage treatment were only available for a subset of the patients included in the CAIRO3 study (n = 146). However, real life costs of subsequent treatment lines may differ between response subgroups and treatment arms.

There are some limitations to our study. First, our results may not reflect the cost-effectiveness in the general mCRC population due to inclusion and exclusion criteria of the study. For instance, one of the inclusion criteria was stable disease or better after six cycles of CAPOX-B induction treatment. Thus, costs and effects for patients achieving no more than progressive disease on CAPOX-B induction treatment were not included in the model. Although the general population is dissimilar to patients participating in clinical trials, we have previously demonstrated external validity of trial outcomes for patients not included in clinical trials, but fulfilling inclusion criteria [36]. Our outcomes may therefore, with caution, be externalised towards patients in general practice who meet the CAIRO3 study inclusion criteria. Second, the analysis was performed from a hospital perspective for which data on medical resource utilisation was collected retrospectively for a subset of 146 patients. A societal perspective may provide a more accurate estimate of costs, a better insight of the impact of treatment choices on society and is to be preferred. Unfortunately, it was not feasible to perform this analysis from a societal perspective due to the retrospective nature of this cost-effectiveness study. Finally, a survival benefit or clinically relevant improvement in quality of life for CAP-B maintenance treatment has not been demonstrated previously [1,2]. Therefore, the clinical relevance of the QALYs or LYs gained in this cost-effectiveness study should be interpreted with caution.

In conclusion, our data show that CAP-B maintenance treatment in mCRC incurs a relevant increase in costs. Given the increased burden of costs of systemic cancer treatment for healthcare budgets, cost-effectiveness analyses are increasingly being included in the decision-making on the implementation of treatments with clinically meaningful benefits in daily practice. Clearly, evaluation of costs versus clinical benefit should be included in the design of treatment guidelines [37]. Differences between cost-effectiveness models (e.g. costs included in the model) and the lack of a general consensus on defined financial thresholds complicate model comparisons, which hamper the adoptability of cost-effectiveness results towards treatment guidelines [13,38]. Even so, CAP-B maintenance treatment may not be considered as cost-effective.

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Role of funding source

Roche provided funding solely and did not participate in the design or analysis of this cost-effectiveness study, nor did Roche participate in manuscript writing.

Conflict of interest statement

E. van Rooijen is currently employed at Novartis. *A.J. ten Tije* has acted in advisory boards of Roche and Celgene. Research funding to the institution has been received from Roche, Celgene, Astra-Zeneca and Novartis. *C.J.A. Punt* is principal investigator of the CAIRO3 study, a randomised controlled-trial sponsored by the DCCG. He has acted in advisory boards for Amgen, Roche, Bayer and Merck-Serono. The DCCG received research grants for data management and statistical analysis from the Commissie Klinische Studies of the Dutch Cancer Foundation (KWF), Roche and Sanofi-Aventis. The DCCG additionally received a research grant for the cost-effectiveness evaluation of the CAIRO3 study from Roche. *M. Koopman* is principal investigator of the CAIRO3 study and has acted in advisory boards for Amgen, Roche, Servier, Merck and Bayer. *M. van Oijen* has received research funding from Bayer, Lilly, Roche, Merck and Roche. Research funding to the institution has been received from Amgen and Merck. The remaining authors declare no conflicts of interest.

Author contributions

M.F. has performed a retrospective data collection on medical resource utilisation of 146 CAIRO3 patients,

designed and performed the cost-effectiveness analysis and drafted this manuscript.

E.v.R. contributed in the design and analysis of the cost-effectiveness analysis.

H.v.T. performed the statistical analysis of the CAIRO3 study results.

L.M. performed data-management of the CAIRO3 study.

A.T., *G.C*, *A.V.*, *B.T.* collected data for the CAIRO3 study and facilitated the retrospective data collection on medical resource utilisation.

A.M. contributed in the analysis of quality of life outcomes.

H.K. contributed in the analysis and interpretation of the cost-effectiveness analysis outcomes.

C.U. provided intellectual support in the design and analysis of the cost-effectiveness analysis.

C.P. designed the CAIRO3 study, provided expert opinion and drafted the manuscript.

M.K. designed the CAIRO3 study, provided expert opinion and drafted the manuscript.

M.v.O. provided intellectual support in the design and analysis of the cost-effectiveness analysis and drafted the manuscript.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2017.01.019.

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