Health Technology Appraisal

Bevacizumab (originator and biosimilars) with fluoropyrimidine-based chemotherapy for untreated metastatic colorectal cancer [ID6465]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

HEALTH TECHNOLOGY APPRAISAL

Bevacizumab (originator and biosimilars) with fluoropyrimidine-based chemotherapy for untreated metastatic colorectal cancer [ID6465]

Contents:

The following documents are made available to stakeholders:

1. Biosimilar pilot process
2. Evidence Assessment Report
3. Appendix to the EAG report

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

Appendix B – Biosimilar pilot process note

NICE is currently working on developing and piloting different approaches to our biosimilar appraisal processes against the process set out in the **health technology evaluation manual**. We have selected ID6465 bevacizumab (Avastin and biosimilars) with fluoropyrimidine-based chemotherapy for untreated metastatic colorectal cancer as a pilot for this "test and learn" approach to biosimilar appraisals.

We believe efficiencies can be made to the process which would result in a faster route to a recommendation, quicker access for patients and a less resource-intensive process for all involved.

We will use a blended approach that takes parts from the currently outlined biosimilars approach, the multiple technology appraisal (MTA) process and the single technology appraisal process (STA).

As outlined below, and as per the **health technology evaluation manual**, NICE can update guidance after loss of market exclusivity of a technology:

5.11.1 After the completion of surveillance in section 8.7, NICE will schedule a rapid update of the guidance to coincide with NHS Commercial Medicines Unit tenders for these technologies. The rapid update will focus on the active substance rather than the individual products. A rapid update cannot be used to update terminated guidance.

5.11.2 Companies that produce the biosimilar or generic technologies (including the originator company) will not need to provide an evidence submission to support a rapid update to guidance after loss of marketing exclusivity.

5.11.3 An EAG will develop a report that evaluates the economic model against a predetermined checklist. The report will include a targeted

literature review and clinical expert engagement. It will determine whether:

- there have been changes to the evidence base since the guidance was published
- there have been changes to the care pathway since the guidance was published
- cost was the key factor resulting in the technology not being recommended or recommended for optimised use.

5.11.4 NICE will not issue the report for technical engagement.

5.11.5 Participating companies will have 14 days to consider the report before it is considered by representatives of the committee who will act on behalf of the full committee. This will normally be the committee chair and a 3-member lead team.

5.11.6 The committee representatives will use the report to assess if there have been significant changes since the original guidance and whether the economic model can still be used for decision making. They will also decide on the threshold ICER for the technology to be considered cost effective, if this is not clearly identified in the original guidance.

5.11.7 If the committee concludes that the economic model can be used for decision making, final draft guidance will be developed using standard development timelines. New guidance will be published that will replace the original guidance.

5.11.8 If the committee concludes that the economic model cannot be used for decision making, no updated guidance will be produced. NICE will produce a statement indicating that the committee is unable to update the recommendations for the technology.

In the case of bevacizumab, NICE does not believe that the original economic model would be suitable for decision-making. As such, and as per the HTE manual (section 5.7.5), NICE proposes a proportionate approach to this decision problem. The EAG will create a streamlined economic model that considers bevacizumab in first line only and does not model downstream costs. This model can then be used for decision making. The manual makes allowances for proportionate decision making in the following sections:

5.7.5 When deciding on the suitability for streamlined decision making, NICE has taken into account the risks associated with the evaluation and the decision to streamline. This may include:

- the likelihood of decision error in the guidance, and its consequences
- the complexity of the technology, clinical pathway or evidence, and associated uncertainties
- the potential impact of the decision to streamline on:
    - resources for NICE, committees and stakeholders
    - service readiness
    - consistency and predictability of NICE decision making
    - openness and transparency in decision making.

NICE has worked with colleagues from NHS England to develop this approach. which falls within both the spirit and letter of the HTE manual.

As we are in the early stages of piloting the approach, further details will be developed as the pilot appraisal progresses. NICE welcomes feedback from stakeholders on new approaches.

Bevacizumab (originator and biosimilars) with fluoropyrimidine-based chemotherapy for metastatic colorectal cancer (including review of TA212) [ID6465]
A Pragmatic Multiple Technology Appraisal

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NIHR Evidence Synthesis Programme. Any errors are the responsibility of the authors.

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Contributions of authors

Mon Mon Yee built the cost-effectiveness model and ran and interpreted the results. Jessica E Forsyth undertook digitising of data and fitting distributions to time-to-event data. Amir Montazeri and Mark Saunders provided clinical advice. Matt Stevenson provided advice relating to health technology assessment throughout the project. All authors were involved in drafting and commenting on the final report.

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Abbreviations

5-FU	5 fluorouracil
AE	Adverse events
AIC	Akaike Information Criterion
BIC	Bayesian Information Criterion
BNF	British National Formulary
BSA	Body surface area
CAPOX	Capecitabine plus oxaliplatin
CEAC	Cost-effectiveness acceptability curve
CRC	Colorectal cancer
CVAD	Central venous access device
DSA	Deterministic sensitivity analyses
EAG	External Assessment Group
eMIT	electronic market information tool
EPP	Eligible patient population
ERG	Evidence Review Group
EQ-5D	EuroQol Five Dimension
FA	Folinic acid
FOLFIRI	Folinic acid plus fluorouracil plus irinotecan
FOLFOX	Folinic acid plus fluorouracil plus oxaliplatin
HR	Hazard ratio
HRQoL	Health-related quality of life
ICER	Incremental cost-effectiveness ratio
iNMB	Incremental net monetary benefit
IPD	Individual patient-level data
ITT	Intention-to-treat
IV	Intravenous
kg	kilogram
KM	Kaplan-Meier
mCRC	Metastatic colorectal cancer
mdG	Modified de Gramont
MTA	Multiple Technology Assessment
NG	NICE guidance
NHS	National Health Services
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OS	Overall survival
PFS	Progression-free survival
PSA	Probabilistic sensitivity analyses
PSS	Personal Social Services
PSSRU	Personal Social Services Research Unit
QALY	Quality-adjusted life year
RDI	Relative dose intensity
TA	Technology Appraisal
TTD	Time to treatment discontinuation
VEGF	Vascular endothelial growth factor

1. EXECUTIVE SUMMARY

1.1. Background

As part of piloting a new process developed by the National Institute for Health and Care Excellence (NICE) for evaluating the cost-effectiveness of biosimilars, bevacizumab (originator and biosimilars) with fluoropyrimidine-based chemotherapy for metastatic colorectal cancer (mCRC) was selected for assessment using a "*test and learn*" approach under an expedited multiple technology appraisal (MTA). Colorectal cancer (CRC), also known as bowel cancer, is a type of cancer that originates in the tissues of the colon or rectum. Between 2017 and 2019, it was the fourth most common cancer and the second leading cause of cancer-related death. mCRC refers to Stage IV disease, in which the cancer has spread beyond the colon or rectum to distant organs or tissues. Fluoropyrimidine-based chemotherapies (capecitabine monotherapy, Folinic acid plus fluorouracil plus oxaliplatin (FOLFOX), Folinic acid plus fluorouracil plus irinotecan (FOLFIRI) or Capecitabine plus oxaliplatin (CAPOX)) are currently recommended for treating patients with mCRC without known mutations in both first-and second-line settings. This report, written by the External Assessment Group (EAG) evaluates the clinical- and cost-effectiveness of bevacizumab (the originator and biosimilars) in combination with fluoropyrimidine-based chemotherapy for the treatment of adult patients with mCRC in first-and second-line settings.

1.2. Objectives

The main aim of the assessment is to appraise the clinical- and cost-effectiveness of bevacizumab (originator and biosimilars) with fluoropyrimidine-based chemotherapy within its marketing authorisation for treating adults with mCRC, excluding patients with known mutations. A secondary objective was to conduct the assessment as a pilot process to aid future biosimilar appraisals.

The objectives of the assessment are as follows:

- To conduct the assessment as a pilot process to biosimilar appraisals
- To review the clinical effectiveness evidence and develop a health economic model using a pragmatic approach to assess the cost-effectiveness of bevacizumab (originator and biosimilars) with fluoropyrimidine-based chemotherapy compared with fluoropyrimidine-based chemotherapy alone from the perspective of the NHS and Personal Social Services (PSS).

1.3. Methods

Clinical effectiveness methods

Given the pragmatic approach of this MTA, a systematic literature search was not conducted and instead the EAG reviewed previous NICE technology appraisals (TAs) and sought advice from clinical experts regarding newer data sources for the use of bevacizumab with fluoropyrimidine-based chemotherapy for treating mCRC.

Cost-effectiveness methods

Given the pragmatic approach of this MTA, the EAG reviewed the previous NICE TAs regarding the use of bevacizumab with fluoropyrimidine-based chemotherapy for the first- and second-line treatments of mCRC. The EAG developed a *de novo* economic model to assess the cost-effectiveness of bevacizumab plus fluoropyrimidine-based chemotherapy versus fluoropyrimidine-based chemotherapy alone in populations listed in the NICE final scope: (i) adults with untreated mCRC who would receive fluoropyrimidine-based chemotherapy, and (ii) adults with mCRC who have been previously received fluoropyrimidine-based chemotherapy and would be receiving second-line fluoropyrimidine-based chemotherapy. Capecitabine alone was not considered as a relevant comparator due to the lack of identified relevant studies evaluating bevacizumab in combination with capecitabine versus capecitabine alone.

Cost-effectiveness was evaluated through pair-wise comparisons over a 40-year (lifetime) time horizon from the perspective of NHS and PSS. The models used a partitioned survival model with three health states: (i) progression-free, (ii) post-progression and (iii) dead, deliberately assuming that no further active treatments were provided. This approach was deemed appropriate as long as it could be assumed that (i) treatments that would be provided subsequently were cost-effective, (ii) that the insertion of bevacizumab earlier in the treatment pathway would not affect the efficacy of subsequent treatments and (iii) that therefore a simple partition survival model evaluating one line of treatment was appropriate. As this approach resulted in an underestimation of life expectancy and quality-adjusted life years (QALYs) associated with the standard of care group, the EAG explored the impact by adding on the expected QALYs gained from later lines of treatments (based on values from the most recent NICE TAs) to the model base case estimates, to inform whether a disease severity modifier weighting should be used. However, this approach has also its own limitations: (i) allowing double counting of QALYs accrued during the period of time after progression to death, and (ii) assuming that all patients progress and receive the active subsequent treatment rather than the PFS event being death. The EAG has presented the results at the second-line setting with disease severity modifier weights of both 1.0 and 1.2.

Health outcomes and costs were discounted at a rate of 3.5% per annum. No subgroup analyses were conducted. Key model parameters were informed by the pivotal studies used in previous NICE TAs, routine costing sources, literature, and assumptions.

The incremental cost-effectiveness ratio (ICER), expressed in cost per quality-adjusted life years (QALYs) gained are provided for all comparisons. Sensitivity analyses were undertaken to explore the impact of alternative assumptions and data sources on model outcomes. The analyses were conducted using the mean price across 8 confidential tender prices, the median across these prices and each of the

8 individual prices as the EAG believes that assuming that the usage of drugs was independent of price (as the median and mean largely do) is not likely to be plausible when the range in prices is large.

1.4. Results

Clinical effectiveness

The EAG identified two relevant clinical studies related to the first-line treatment of mCRC with bevacizumab in combination with fluoropyrimidine-based chemotherapy: Study NO16966 for bevacizumab plus FOLFOX/CAPOX versus FOLFOX/CAPOX alone, and Study AVF2107g for bevacizumab plus FOLFIRI versus FOLFIRI alone. Within Study NO16966, the addition of bevacizumab 5 mg/kg or 7.5mg/kg to FOLFOX/CAPOX resulted in a statistically significant increase in median progression-free survival (PFS) of 1.4 months (HR = 0.83, $P = 0.0023$), and median overall survival (OS) of 1.4 months (HR = 0.89, $P = 0.0769$). Within Study AVF2107g, the addition of bevacizumab 5 mg/kg to FOLFIRI results in a statistically significant increase in median PFS of 4.4 months (HR = 0.54, $P < 0.001$) and median OS of 4.7 months (HR = 0.66, $P < 0.001$).

The EAG identified one relevant clinical study related to the second-line treatment of mCRC with bevacizumab in combination with FOLFOX compared with FOLFOX alone (Study E3200). Within the study, the addition of bevacizumab 10 mg/kg to FOLFOX resulted in a statistically significant increase in median PFS of 2.6 months (HR = 0.61, $P < 0.0001$) and median OS of 2.1 months (HR = 0.75, $P = 0.0011$).

Cost-effectiveness

In both first-and second-line settings, the EAG's models suggest that bevacizumab in combination with fluoropyrimidine-based chemotherapy is expected to generate more QALYs but incur higher costs than fluoropyrimidine-based chemotherapy alone. The main reasons underpinning these findings, within the bevacizumab plus fluoropyrimidine-based chemotherapy group, are: (i) extended PFS and OS when bevacizumab is provided, (ii) increased drug acquisition and administration costs associated with the addition of bevacizumab, (iii) higher overall disease management costs due to extended OS, and (iv) a slight increase in adverse event (AE) management costs.

The ICER for bevacizumab is strongly influenced by the assumed price of the intervention. Results when using the mean price are presented here, with the median-price ICERs being slightly lower; the appraisal committee has access to the confidential results using the 8 separate prices.

In the first-line setting, when the mean price is used the base case deterministic ICER for bevacizumab plus FOLFOX compared with FOLFOX is [redacted], the base case deterministic ICER for bevacizumab

plus FOLFIRI compared with FOLFIRI is [redacted], and the base case deterministic ICER for bevacizumab plus CAPOX compared with CAPOX is [redacted]. These ICERs were most sensitive to the assumed distributions for PFS and OS, however no ICER was greater than [redacted].

In the second-line setting, when the mean price is used, and the disease severity modifier is set to unity, the base case deterministic ICER for bevacizumab plus FOLFOX compared with FOLFOX is [redacted], and the base case deterministic ICER for bevacizumab plus CAPOX compared with CAPOX is [redacted]. These ICERs were most sensitive to the assumed distributions for PFS and OS. When the disease severity modifier was set to 1.2, the ICERs became [redacted] (FOLFOX comparison) and [redacted] (CAPOX comparison). The EAG believes that conditions are met to apply a disease severity modifier of 1.2 due to an estimated proportional shortfall of greater than 85%.

1.5. Conclusions

The results strongly suggest that the addition of bevacizumab to fluoropyrimidine-based chemotherapy results in an extension of life but at an increased cost. The ICER in each of the EAG's base cases are below [redacted]. The biggest uncertainty relates to the best distributions to model PFS and OS, although the EAG believes it unlikely that any further randomised comparative data will be generated to address this issue. Whilst it may not affect the conclusions for this appraisal, the EAG believes that further guidance should be provided on estimating the price of biosimilars where there are many tender prices that span a wide range of costs.

2. BACKGROUND

2.1. Background to the biosimilar pilot process

With this work, the NICE is piloting a new process for evaluating the cost-effectiveness of biosimilars. Bevacizumab (originator (Avastin) and biosimilars) with fluoropyrimidine-based chemotherapy for mCRC[1] has been chosen to be a pilot where a "*test and learn*" approach will be conducted. The pilot is intended be an expedited version of the MTA process with the EAG instructed to take a pragmatic approach throughout the evaluation process. This allows shorter timelines than a standard MTA, and also requires less resources, meaning that the costs of conducting the evaluation are cheaper. During the pilot, NICE increased the initial scope of the work to include treatment at second-line once clinical advice indicated that bevacizumab treatment in combination with fluoropyrimidine-based chemotherapies would not be either first-line or second-line but could be used at both lines. The final NICE scope[1] therefore included an evaluation of bevacizumab for both first- and second-line treatment. In both positions, patients with known mutations are excluded.

To fulfil its remit, the EAG has made some decisions that may not be optimal but are not resource-intensive, thus keeping in line with the pragmatic approach intended for this pilot. These decisions are believed to provide sufficient information to allow a decision to be made on the cost-effectiveness of bevacizumab for untreated mCRC and for second-line treatment. An example of this would be the lack of comprehensive systematic literature reviews where the key evidence is already known to the EAG and its clinical advisors. The appropriateness of the decisions made by the EAG can be assessed by external parties and this learning taken forward to future evaluations of biosimilar products.

2.2. Description of underlying health problem

CRC, also known as bowel cancer, is a type of cancer that originates in the tissues of the colon or rectum. Between 2017 and 2019, approximately 44,100 new cases of CRC were diagnosed annually in the UK, making it the fourth most common cancer and the second leading cause of cancer-related death.[2] CRC is staged from 0 to IV, with Stage 0 representing the earliest form of the disease and Stage IV indicating mCRC, in which the cancer has spread beyond the colon or rectum to distant organs or tissues, most commonly to the liver, lungs and peritoneum. In 2021, mCRC accounted for about 23% of new CRC cases in England, with one-year and five-year survival rates of approximately 44% and 11%, respectively.[3] The majority of patients with mCRC have unresectable disease, and treatment is therefore aimed at delaying disease progression, relieving tumour-related symptoms, prolonging survival, maintaining quality of life and minimising treatment-related side-effects.

2.3. Current service provision related to the decision problem.

For this decision problem, current standard of care in the first-and second-line treatments of mCRC includes four types of fluoropyrimidine-based chemotherapies: capecitabine monotherapy, FOLFOX, FOLFIRI and CAPOX, in accordance with NICE Guidance (NG) 151.[4] To align with the NICE final scope,[1] patients who are candidates for targeted treatments or immunotherapies are not mentioned here. Current recommendations on the use of specific technologies for treating mCRC from NICE are summarised in the Appendix (see Table 43).

3. DEFINITION OF THE DECISION PROBLEM

3.1. Decision problem

3.1.1. Population

Based on the final NICE scope,[1] this assessment focuses on the following two populations:

- Adults with untreated metastatic carcinoma of the colon or rectum who would receive fluoropyrimidine-based chemotherapy and
- Adults with metastatic carcinoma of the colon or rectum who have been previously received fluoropyrimidine-based chemotherapy and would be receiving second-line fluoropyrimidine-based chemotherapy.

Subgroup analyses are not considered. People who are candidates for targeted treatments or immunotherapies are excluded as the EAG has only assessed patients without known mutations.

Following conversations after the NICE final scope[1] was issued, the EAG has broadened the decision problem to include the use of bevacizumab at second-line, anticipating that there would be a subsequent scope published by NICE to cover second-line treatment. As many assumptions and parameters are shared between first- and second-line treatments combining both into one report was seen as more efficient than producing two separate reports.

3.1.2.Intervention

As listed in the final NICE scope,[1] the intervention under consideration is bevacizumab (the originator and biosimilars) given alongside fluoropyrimidine-based chemotherapy (described in Section 3.1.3). Bevacizumab is a recombinant humanised monoclonal antibody that targets vascular endothelial growth factor (VEGF). It inhibits angiogenesis (the formation of the new blood vessels) by binding to VEGF. It is thought to improve survival when used in combination with chemotherapy for the treatment of mCRC. Bevacizumab in combination with fluoropyrimidine-based chemotherapy is currently licensed for treatment of adult patients with metastatic carcinoma of the colon or rectum. The recommended dose of bevacizumab is either 5 mg/kg or 10 mg/kg of body weight given once every 2 weeks or 7.5 mg/kg or 15 mg/kg of body weight given once every 3 weeks. Bevacizumab is administered as an intravenous infusion, and it is recommended that treatment is continued until disease progression or until unacceptable toxicity. Dose reduction of bevacizumab for AEs is not recommended. Bevacizumab should not be administered as an intravenous push or bolus (rapid injection of medication directly into the vein).

Bevacizumab is subject to the following contraindications:

- Hypersensitivity to the active substance or to any of the excipients
- Hypersensitivity to Chinese Hamster Ovary cell products or other recombinant human or humanised antibodies
- Pregnancy

3.1.3.Comparators

The comparators are fluoropyrimidine-based chemotherapies used without bevacizumab. These are

- folinic acid plus fluorouracil plus oxaliplatin (FOLFOX)
- folinic acid plus fluorouracil plus irinotecan (FOLFIRI)
- capecitabine plus oxaliplatin (CAPOX)
- capecitabine monotherapy

Capecitabine monotherapy is not considered a relevant comparator in this assessment due to the lack of clinical evidence identified comparing the bevacizumab plus capecitabine versus capecitabine alone (see details in Section 4.24.3).

3.1.3.1. Fluorouracil plus folinic acid plus oxaliplatin (FOLFOX)

The FOLFOX regimen is a combination chemotherapy consisting of 5 fluorouracil (5-FU), folinic acid (FA) and oxaliplatin. The treatment is repeated every 2 weeks (14-day cycle). There are two variants of this regimen: FOLFOX-4 and FOLFOX-6, and details are summarised in Table 1.

Table 1: FOLFOX treatment regimen

Drug	Dosage	Route	Schedule
FOLFOX-4*			
Folinic acid	200 mg/m^2	IV infusion over 2 hours	Day 1 and 2
Fluorouracil	400 mg/m^2	IV bolus	Day 1 and 2
Fluorouracil	600 mg/m^2	IV infusion over 22 hours	Day 1 and 2
Oxaliplatin	85 mg/m^2	IV infusion over 2 hours	Day 1
FOLFOX-6†			
Folinic acid	400 mg/m^2	IV infusion over 2 hours	Day 1
Fluorouracil	400 mg/m^2	IV bolus	Day 1
Fluorouracil	2400-3000 mg/m^2	IV infusion over 46 hours	Day 1 and 2
Oxaliplatin	100 mg/m^2	IV infusion over 2 hours	Day 1

FOLFOX: folinic acid plus fluorouracil plus oxaliplatin, IV: intravenous
*per Study NO16966 protocol[5]
†based on the company's and Evidence Review Group (ERG)'s model in TA212,[6] using the modified de Gramont regimen and clinical experts' opinions

3.1.3.2. Fluorouracil plus folinic acid plus irinotecan (FOLFIRI)

The FOLFIRI regimen, using the modified de Gramont (mdG) regimen that the EAG's clinical advisors state is most widely used in England, is a combination chemotherapy consisting of 5-FU, FA, and irinotecan. The treatment is repeated every 2 weeks (14-day cycle) and the details are summarised in

Table 2. However, in Study AVF2107g,[7] the 5-FU was delivered as an IV bolus injection, and each component of the regimen was delivered weekly for 4 weeks, followed by 2 weeks of rest (6-week cycle).

Table 2: FOLFIRI treatment regimen

Drug	Dosage	Route	Schedule
FOLFIRI using the mdG regimen			
Folinic acid	400 mg/m^2	IV infusion over 2 hours	Day 1
Fluorouracil	400 mg/m^2	IV bolus	Day 1
Fluorouracil	2400-3000 mg/m^2	IV infusion over 46 hours	Day 1 and 2
Irinotecan	180 mg/m^2	IV infusion	Day 1
FOLFIRI based on Study AVF2107g protocol (Saltz regimen)			
Folinic acid	20 mg/m^2		Weekly for 4 weeks
Fluorouracil	500 mg/m^2	IV bolus	Weekly for 4 weeks
Irinotecan	125 mg/m^2	IV infusion	Weekly for 4 weeks

FOLFIRI: folinic acid plus fluorouracil plus irinotecan, IV: intravenous, mdG: modified de Gramont

3.1.3.3. Capecitabine plus oxaliplatin (CAPOX)

The CAPOX regimen is a combination chemotherapy consisting of oxaliplatin and capecitabine. The treatment is repeated every 3 weeks (21-day cycle). Oxaliplatin is delivered as a 130 mg/m^2 IV infusion on Day 1, while capecitabine is provided orally at 1000 mg/m^2 twice daily on Days 1-14.

3.1.3.4. Capecitabine monotherapy

Capecitabine is indicated as a first-line monotherapy of mCRC with a recommended dose of 1,250 mg/m^2 taken twice daily for 14 days, followed by a 7-day rest period before the next cycle.

3.1.4.Outcomes

The following outcomes are considered in this assessment, as described in the final NICE scope.[1]

- overall survival
- progression-free survival
- response rates
- adverse effects of treatment
- health-related quality of life

3.1.5.Economic analysis

Costs are considered from an NHS and PSS perspective. The cost-effectiveness of bevacizumab in combination with fluoropyrimidine-based chemotherapies versus fluoropyrimidine-based chemotherapies alone is expressed as an ICER in terms of the incremental costs per QALY gained.

Costs for consideration include:

- Costs of drug acquisition, administration, and monitoring
- Cost of follow-up
- Costs related to managing adverse events
- Costs of best supportive care
- Costs of terminal care

3.2. Aims and objectives of the review

The main aim of the assessment is to appraise the clinical and cost-effectiveness of bevacizumab (originator and biosimilars) with fluoropyrimidine-based chemotherapy within its marketing authorisation for treating adults with mCRC.

The objectives of the assessment are as follows:

- To conduct the assessment as a pilot process to biosimilar appraisals
- To review the clinical effectiveness evidence and develop a health economic model using a pragmatic approach to assess the cost-effectiveness of bevacizumab (originator and biosimilars) with fluoropyrimidine-based chemotherapy compared with fluoropyrimidine-based chemotherapy alone from the perspective of the NHS and PSS.

4. CLINICAL EFFECTIVENESS

4.1. Methods for reviewing effectiveness

Given the expedited approach of this MTA,[1] the EAG used a pragmatic approach for reviewing clinical effectiveness evidence. Therefore, a systematic literature search was not conducted and instead the EAG reviewed previous NICE technology appraisals (TAs) and sought advice from clinical experts regarding the use of bevacizumab with fluoropyrimidine-based chemotherapy for treating mCRC. The EAG identified two relevant NICE appraisals, TA118[8] (bevacizumab plus FOLFIRI) and TA212[6] (bevacizumab plus FOLFOX/CAPOX), for the first-line treatment, and one relevant appraisal, TA242[9] (bevacizumab plus FOLFOX), for the second-line treatment. The EAG did not identify any TAs for fluoropyrimidine-based chemotherapies alone as these have been standard of care for treating mCRC. Details of these TAs are summarised in Section 5.2. Additionally, two meta-analysis papers covering the use of bevacizumab with fluoropyrimidine-based chemotherapies as first- and second-line treatment were identified.[10, 11] This section is divided into clinical evidence related to the use of bevacizumab in the first-line setting (Section 4.2 and 4.3) and bevacizumab in the second-line setting (Section 4.4 and 4.5).

4.2. Results: first-line treatment of mCRC

The EAG identified two clinical studies related to the first-line treatment of mCRC with bevacizumab in combination with fluoropyrimidine-based chemotherapy. These were Study NO16966 reported by Cassidy *et al*.[5] (TA242) and Study AVF2107g reported by Hurwitz *et al.*[7](TA118). Additionally, a network meta-analysis report by Golfinopoulos *et al.*[10] was identified.

4.2.1. Study NO16966

4.2.1.1. Summary of the study

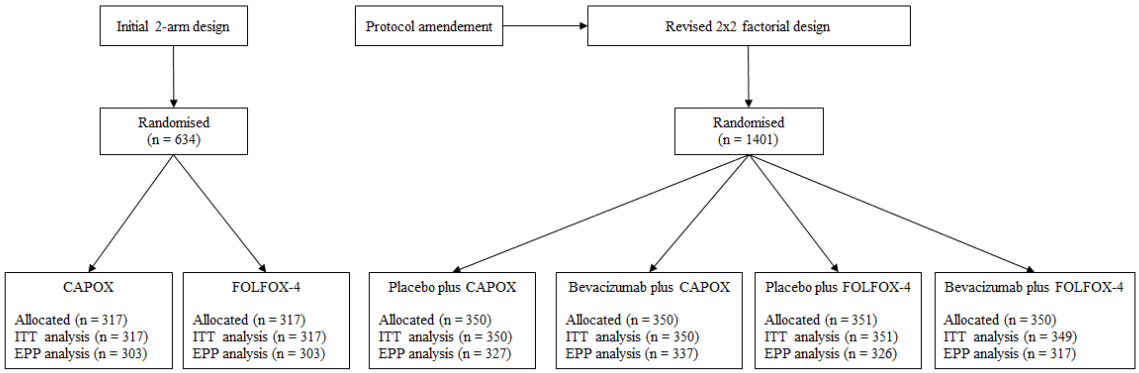
The Study NO16966 was a phase III, multicentre, multinational, two-arm, randomised, open label study with the primary objective of confirming the non-inferiority of CAPOX (termed XELOX in the paper) compared with FOLFOX-4 in adult patients with histologically-confirmed mCRC not previously treated (first-line therapy).[5]

Following randomisation of 634 patients, the open label study was amended to include a 2x2 factorial randomised (partially blinded for bevacizumab) phase III trial (n =1401) with the co-primary objective of demonstrating superiority of bevacizumab in combination with chemotherapy (either FOLFOX-4 or CAPOX) compared with placebo in combination with chemotherapy (FOLFOX-4 or CAPOX). Median follow-up was 28 months. The co-primary study endpoints after protocol modification were: (i) superiority of PFS in patients receiving bevacizumab plus chemotherapy (bevacizumab plus CAPOX/bevacizumab plus FOLFOX-4) over chemotherapy alone (placebo plus CAPOX/placebo plus FOLFOX-4) and (ii) non-inferiority of PFS in patients receiving CAPOX with or without bevacizumab

compared to FOLFOX-4 with or without bevacizumab. Secondary endpoints included PFS for superiority of CAPOX over FOLFOX, OS, overall rate of best response, time to response, duration of response, duration of complete response, time to treatment failure and safety.

The dose of bevacizumab was 5 mg/kg every two weeks (in combination with FOLFOX-4) or 7.5 mg/kg every three weeks (in combination with CAPOX) and administered as a 30-to-90-minute IV infusion before oxaliplatin. FOLFOX-4 consisted of FA given at a dose of 200 mg/m^2/day followed by bolus 5-FU 400 mg/m^2/day and a 22-hour infusion of 5-FU 600 mg/m^2/day for two consecutive days. Oxaliplatin was administered on day 1 at the dose of 85 mg/m^2 as a 2-hour infusion, concurrently with FA. The treatment was repeated every 2 weeks (14-day cycle). CAPOX consisted of a 2-hour IV infusion of oxaliplatin 130mg/m^2 on day 1 followed by oral capecitabine 1000mg/m^2 twice daily on days 1 through 14 (28 doses) of a 21-day cycle. The numbers of patients in each arm of the study are presented in Figure 1 and baseline characteristics of recruited patients are presented in the Appendix (see Table 44).

Figure 1: The numbers of patients in each arm of Study NO16966 (adapted from Cassidy *et al.*)



ITT: intention-to-treat; EPP: eligible patient population; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CAPOX: capecitabine plus oxaliplatin

4.2.1.2. Clinical outcomes of Study NO16966

Given the pragmatic nature of this pilot MTA, this section focuses only on the main drivers of the clinical effectiveness: OS and PFS. Time to treatment discontinuation (TTD) is discussed in the cost-effectiveness chapter (see details in Section 5.4.3.6.2.1).

4.2.1.2.1. Progression-free survival

The manufacturers' primary pooled analysis of superiority in the NO16966 trial (conducted by the manufacturer for TA212), which combined all patients in the trial (patients in the initial two-arm part plus patients in the 2x2 factorial part of the study) showed that the addition of bevacizumab to chemotherapy (CAPOX and FOLFOX-4 combined) significantly enhanced PFS compared with

chemotherapy alone (CAPOX and FOLFOX-4 combined with, or without, placebo). For the ITT population, the HR for remaining free of disease progression was 0.79 (97.5% CI: 0.72 to 0.87; *P* = 0.0001) at a median follow-up of 28 months with an increase in median PFS from 7.7 months in the chemotherapy group to 9.4 months in the bevacizumab plus chemotherapy group (a difference of 1.7 months).

A secondary pooled analysis of superiority, restricted to patients in the second 2x2 part of the NO16966 showed that the addition of bevacizumab to chemotherapy (bevacizumab plus CAPOX / bevacizumab plus FOLFOX-4 combined) significantly improved progression-free survival compared with chemotherapy alone (placebo plus CAPOX/ placebo plus FOLFOX-4 combined). For the intention to treat population in the 2x2 part of the trial, the HR for remaining free of disease progression was 0.83 (97.5% CI: 0.72 to 0.95; *P* = 0.0023) at a median follow-up of 28 months with an increase in median progression-free survival from 8.0 months in the chemotherapy group to 9.4 months in the bevacizumab plus chemotherapy group (a difference of 1.4 months). Figure 2 presents the Kaplan-Meier (KM) curves for PFS for bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX plus placebo. Further details for generating KM curves are discussed in Section 5.4.3.2.1.1.

The manufacturers' pooled analysis of non-inferiority (using the EPP and the ITT population) showed that the CAPOX (CAPOX/placebo plus CAPOX / bevacizumab plus CAPOX) and FOLFOX-4 (FOLFOX-4/ placebo plus FOLFOX-4/ bevacizumab plus FOLFOX-4) based regimens were equivalent for progression-free survival (see Table 3).

Figure 2: Kaplan-Meier curve for PFS in study NO16966 (generated by the EAG)

PFS: progression-free survival; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CAPOX: capecitabine plus oxaliplatin

Table 3: Summary of progression-free survival from the NO16966 trial (adapted from the EAG's report, TA212)

Interventions (Regimens)[a]	**Median follow up (months)**	**Numbers followed in each group (n)**	**Number of patients with event (n)**	**Median progression-free survival, (months)**	**Hazard Ratio (97.5% CI; p-value)**
Initial 2 arm design					
CAPOX	-	317	290 (91.5%)	7.1	Not applicable
FOLFOX-4 (control)	-	317	299 (94.3%)	7.7	Not applicable
2x2 factorial design					
B- CAPOX	-	350	295 (84.3%)	9.3	Not applicable
P- CAPOX	-	350	301 (86.0%)	7.4	Not applicable
B-FOLFOX-4	-	349	299 (85.7%)	9.4	Not applicable
P-FOLFOX-4 (control)	-	351	321 (91.5%)	8.6	Not applicable
Manufacturer's primary analysis (pooled results from both parts of study – all six groups)					
Superiority - Intention to treat analysis B- CAPOX / B-FOLFOX-4 combined vs. P- CAPOX / P-FOLFOX-4/ CAPOX / FOLFOX-4 combined	28	699 vs. 1335	594 (85.0%) vs. 1211 (90.7%)	9.4 vs. 7.7	0.79 (0.72, 0.87; *P* =0.0001)
Non inferiority[b] - Eligible patient population analysis CAPOX /P- CAPOX /B- CAPOX combined vs. FOLFOX-4/ P-FOLFOX-4/B-FOLFOX-4 combined	-	NR	NR	8.0 vs. 8.5	1.02 (0.92, 1.14; *P* = NR)[d]
Non inferiority[b] - Intention to treat analysis CAPOX /P- CAPOX /B- CAPOX combined vs. FOLFOX-4/ P-FOLFOX-4/B-FOLFOX-4 combined	-	NR	NR	8.0 vs. 8.5	1.01 (0.91,1.12; *P* =NR)[e]
Manufacturer's secondary analysis (analysis restricted to the 2 by 2 factorial design) [c]					
Superiority - Intention to treat analysis B- CAPOX / B-FOLFOX-4 combined vs. P- CAPOX / P-FOLFOX combined	-	699 vs. 701	513 vs. 547	9.4 vs. 8.0	0.83 (0.72, 0.95; *P* =0.0023)

NR: not reported; CI: confidence intervals

[a] CAPOX, oxaliplatin plus capecitabine; FOLFOX-4, oxaliplatin plus 5-fluorouracil and folinic acid; P-CAPOX, placebo plus CAPOX; B-CAPOX, bevacizumab plus CAPOX; P-FOLFOX-4; placebo plus FOLFOX-4; B-FOLFOX-4, bevacizumab plus FOLFOX-4, B- alone, Bevacizumab only

[b] Non-inferiority was concluded if the upper limit of the 97.5% confidence interval of the hazard ratio was ≤1.23

[c] Test of the hypotheses of no interaction for progression-free survival was 0.7025, which did not meet the conventional level of significance of less than 0.05

[d] Values are different to that report in the original published paper – hazard ratio, 1.05 (0.94,1.18)

[e] Values are different to that report in the original published paper – hazard ratio, 1.04 (0.93,1.16)

4.2.1.2.2. Overall survival

The primary pooled analysis of superiority in the NO16966 trial[5] (conducted by the manufacturer for TA212), which combined all patients in the trial (patients in the initial two-arm part plus patients in the 2x2 factorial part of the study) showed that the addition of bevacizumab to chemotherapy (CAPOX and FOLFOX-4 combined) significantly improved OS compared with chemotherapy alone (CAPOX and FOLFOX-4 combined with, or without, placebo) in patients not previously treated for metastatic disease. For the intention-to-treat (ITT) population, the hazard ratio (HR) for death was 0.83 (97.5% CI: 0.74 to 0.93; p = 0.0019) at a median follow-up of 28 months, with an increase in median OS from 18.9 months in the chemotherapy group to 21.2 months in the bevacizumab plus chemotherapy group (a difference of 2.3 months).

A secondary pooled analysis of superiority, restricted to patients in the second 2x2 part of the NO16966 trial (as per the original statistical trial plan), showed that the addition of bevacizumab to chemotherapy (CAPOX and FOLFOX-4 combined) improved OS compared with chemotherapy alone (CAPOX plus placebo and FOLFOX-4 plus placebo combined), although this was not statistically significant. For the ITT population of the 2x2 part of the NO16966 trial, the HR for death was 0.89 (97.5% CI: 0.76 to 1.03; *P* = 0.0769) at a median follow-up of 28 months, with an increase in median OS from 19.9 months in the chemotherapy group to 21.3 months in the bevacizumab plus chemotherapy group (a difference of 1.4 months). Figure 3 presents the KM curve for OS for bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX plus placebo. Further details for generating KM curves are discussed in Section 5.4.3.2.2.1.

The manufacturer performed two pooled analyses of non-inferiority, the first using the eligible patient population (EPP) defined as the ITT population who received at least one dose of a study drug, and who did not have a major protocol violation, and the second using the ITT population. Both analyses showed non-inferiority in OS between the CAPOX and FOLFOX-4 regimens. (see Table 4).

Figure 3: Kaplan-Meier curve for OS in study NO16966 (generated by the EAG)

OS: overall survival; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CAPOX: capecitabine plus oxaliplatin

Table 4: Summary of overall survival from the NO16966 trial (adapted from the EAG's report, TA212)

Interventions (regimens)	Median follow up (months)	Numbers followed in each group (n)	Number of patients with event (n)	Median overall survival, (months)	Hazard Ratio (97.5% CI; p-value)
Initial 2 arm design					
CAPOX	-	317	250 (78.9%)	18.8	NA
FOLFOX-4 (control)	-	317	262 (82.6%)	17.7	NA
2x2 factorial design					
Bevacizumab plus CAPOX	-	350	211 (60.3%)	21.4	NA
Placebo plus CAPOX	-	350	231 (66.0%)	19.2	NA
Bevacizumab plus FOLFOX-4	-	349	209 (59.9%)	21.2	NA
Placebo plus FOLFOX-4 (control)	-	351	224 (63.8%)	20.4	NA
Manufacturer's primary analysis (pooled results from both parts of study- all six groups)					
Superiority - Intention to treat analysis Bevacizumab plus CAPOX / Bevacizumab plus FOLFOX-4 combined vs. Placebo plus CAPOX/ Placebo plus FOLFOX-4/ CAPOX/ FOLFOX-4 combined	28	699 vs. 1335	420 (60.1%) vs. 967 (72.4%)	21.2 vs. 18.9	0.83 (0.74, 0.93; *P* =0.0019)
Non inferiority[b] - Eligible patient population analysis CAPOX/Placebo plus CAPOX/Bevacizumab plus CAPOX combined vs. FOLFOX-4/ Placebo plus FOLFOX-4/Bevacizumab plus FOLFOX-4 combined	-	NR	NR	19.7 vs. 19.5	1.00 (0.88, 1.13; *P* = NR)
Non inferiority[b] - Intention to treat analysis CAPOX/Placebo plus CAPOX/Bevacizumab plus CAPOX combined vs. FOLFOX-4/ Placebo plus FOLFOX-4/Bevacizumab plus FOLFOX-4 combined	-	NR	NR	19.8 vs. 19.6	0.99 (0.88, 1.12; *P* = NR)
Manufacturer's secondary analysis (analysis restricted to the 2 by 2 factorial design) *					
Superiority - Intention to treat analysis Bevacizumab plus CAPOX / Bevacizumab plus FOLFOX-4 combined vs. Placebo plus CAPOX/ Placebo plus FOLFOX combined	28	699 vs. 701	420 (60.1%) vs. 455 (64.9%)	21.3 vs. 19.9	0.89 (0.76, 1.03; *P* = 0.0769)

NR: not reported; NA: not applicable; CI: confidence intervals; CAPOX: oxaliplatin plus capecitabine; FOLFOX: oxaliplatin plus 5-fluorouracil and folinic acid

*Test of the hypotheses of no interaction for overall survival between the different treatment components (FOLFOX-4, CAPOX, bevacizumab, non-bevacizumab) was 0.94, which did not meet the conventional level of significance of less than 0.05.

4.2.2.Study AVF2107g

4.2.2.1. Summary of the Study

Study AVF2107g was a multicentre, international (United States, Australia and New Zealand) Phase III RCT comparing first-line bevacizumab plus FOLFIRI compared with FOLFIRI and placebo (FOLFIRI alone).[7] Within this study, patients could also be allocated to a third treatment arm of bevacizumab plus 5-FU/FA; however, after the safety of bevacizumab plus FOLFIRI had been determined, assignment to the bevacizumab plus 5-FU/FA arm was halted. Enrolment into the remaining arms was continued until 400 patients per arm had been included. Chemotherapies were delivered by bolus injection. The primary endpoint was OS and secondary endpoints included PFS, response rate and health-related quality of life (HRQoL).

The dose of bevacizumab was 5 mg/kg and administered every two weeks as a 30-to-90 minutes IV infusion. FOLFIRI consisted of irinotecan at a dose of 125 mg/m^2 as an IV infusion, bolus 5-FU at 500 mg/m^2 and bolus FA at 20 mg/m^2. The regimen was repeated weekly for 4 weeks, followed by 2 weeks of rest (6-week cycle). The baseline characteristics of recruited patients are presented in Appendix (see Table 45).

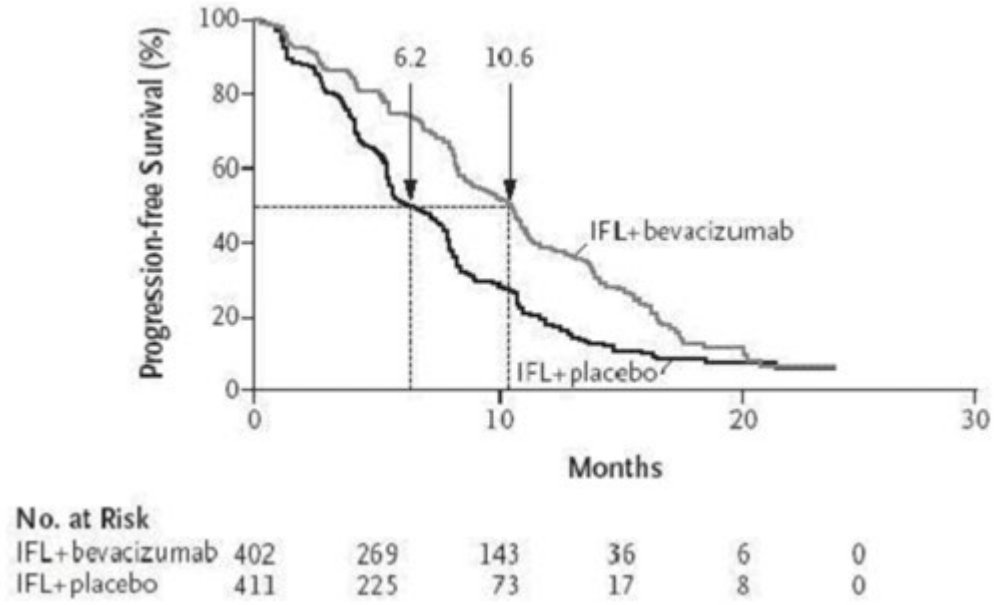
4.2.2.2. Clinical outcomes of Study AVF2107g

4.2.2.2.1. Progression-free survival

The PFS duration was estimated to be a median of 10.6 months for bevacizumab plus FOLFIRI and 6.2 months for FOLFIRI plus placebo, thereby improving the median PFS by 4.4 months (HR = 0.54, p<0.001) compared with FOLFIRI plus placebo.

Figure 4 presents the KM curves for PFS for bevacizumab plus FOLFIRI and FOLFIRI plus placebo.

Figure 4: Kaplan-Meier curves for PFS in study AVF2107g (reproduced from Hurwitz *et al*.)

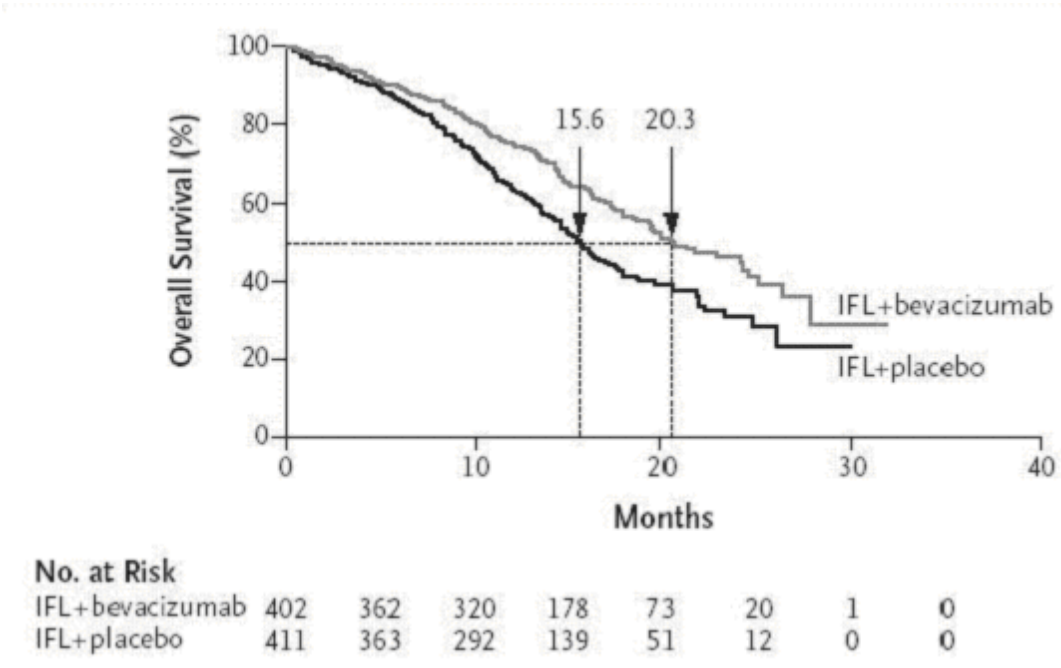


PFS: progression-free survival; IFL: folinic acid plus fluorouracil plus irinotecan (FOLFIRI)

4.2.2.2.2. Overall survival

The OS duration was estimated to be a median of 20.3 months for FOLFIRI plus bevacizumab and 15.6 months for FOLFIRI plus placebo, thereby improving median OS by 4.7 months (HR = 0.66, p<0.001). Figure 5 presents the KM curve for OS for bevacizumab plus FOLFIRI and FOLFIRI plus placebo.,

Figure 5: Kaplan-Meier curve for OS in study AVF2107g (reproduced from Hurwitz *et al*.)



OS: overall survival; IFL: folinic acid plus fluorouracil plus irinotecan (FOLFIRI)

4.2.3.Network meta-analysis of first-line treatments for metastatic colorectal cancer

Golfinopoulos *et al.*[10] conducted a random effects network meta-analysis (NMA) for treatments of mCRC, which was published in 2007. The outcomes considered within the NMA were HRs for OS and PFS, and the analyses were conducted considering: all lines of treatment, first-line only, non-first-line and non-bolus treatments.

The NMA included 40 studies (reporting results for first-, second- or third-line therapies) and included the data from the two studies discussed in Sections 4.2.1 and 4.2.2. HRs for bevacizumab in combination with FOLFIRI or FOLFOX compared with 5-FU plus FA (without irinotecan, oxaliplatin, bevacizumab, or cetuximab) as a first-line treatment are presented in Table 5, along with the corresponding HRs for FOLFIRI and FOLFOX alone.

Table 5: HRs for PFS and OS compared with 5-FU/FA, first-line comparison

Treatment	**HRs [95% CI] derived from the NMA relative to 5-FU plus FA (without irinotecan, oxaliplatin, bevacizumab, or cetuximab)**	
	PFS	**OS**
Bevacizumab plus FOLFIRI	0.41 [0.29, 0.59]	0.60 [0.44, 0.81]
Bevacizumab plus FOLFOX	0.56 [0.39, 0.80]	0.74 [0.57, 0.97]
FOLFIRI alone	0.74 [0.66, 0.83]	0.91 [0.83, 1.00]
FOLFOX alone	0.68 [0.59, 0.77]	0.84 [0.74, 0.94]

HR: hazard ratio; NMA: network meta-analysis; 5-FU: 5 fluorouracil; FA: folinic acid; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; PFS: progression-free survival; OS: overall survival

Within the NMA for first-line therapies, the direct comparison of bevacizumab plus FOLFIRI with FOLFIRI alone was informed by only one study (AVF2107g[7]). Due to this the EAG did not use the results from the NMA for bevacizumab plus FOLFIRI compared to FOLFIRI alone but opted to use the direct evidence from Study AVF2107g which meant that the analyses for PFS and OS were not forced to assume proportional hazards.

4.3. Discussion: first-line treatment of mCRC

(i) Bevacizumab plus FOLFOX/CAPOX versus FOLFOX/CAPOX alone

Study NO16966 was the primary source informing the clinical effectiveness of bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone in TA212. Although the Evidence Review Group (ERG) and the Appraisal Committee in TA212 preferred not to pool the FOLFOX-4 and CAPOX arms from the 2x2 factorial design of the study, separate analyses were not provided by the manufacturer. In the absence of additional studies evaluating the addition of bevacizumab to CAPOX, the EAG selected Study NO16966 to inform the clinical effectiveness of bevacizumab plus FOLFOX or CAPOX and

FOLFOX or CAPOX alone in the economic analysis by assuming comparable efficacy between FOLFOX-and CAPOX-containing regimens. This assumption was supported by the ERG's clinical advisors.

(ii) Bevacizumab plus FOLFIRI versus FOLFIRI alone

Study AVF2107g was the primary source informing the clinical effectiveness of bevacizumab plus FOLFIRI and FOLFIRI alone in TA118.[8] However, this study used the bolus (Saltz) regimen for the fluoropyrimidine-based therapy, which is not standard practice in the NHS in England. Furthermore, the Appraisal Committee in TA118 commented that there was potential confounding of OS outcomes in the study as patients continued to receive bevacizumab after disease progression, and the true impact of bevacizumab as a first-line therapy for mCRC was uncertain.

(iii) Bevacizumab plus capecitabine versus capecitabine alone

The EAG did not identify any previous NICE TAs or clinical studies evaluating bevacizumab in combination with capecitabine versus capecitabine alone for the first-line treatment of mCRC.

4.4. Results: second-line treatment of mCRC

The EAG identified two clinical studies related to the second-line treatment of mCRC with bevacizumab. These were Study E3200 reported by Giantonio *et al*.[12] and Study GERCOR reported by Tournigand *et al*.[13] Additionally, a meta-analysis report by Mocellin *et al*.[11] was identified.

4.4.1. Study E3200

4.4.1.1. Summary of the study

Study E3200[12] was a multicentre, open-label, randomised Phase III clinical trial evaluating treatment outcomes in patients diagnosed with advanced or mCRC who had received prior treatment with irinotecan and fluoropyrimidine-based chemotherapy for advanced disease. Patients with a history of oxaliplatin or bevacizumab use were excluded from participation. Eligible patients were randomly assigned to one of three treatment arms: arm A (n = 286), in which patients received bevacizumab plus FOLFOX-4, arm B (n = 291), in which patients received FOLFOX-4 alone, and arm C (n = 243), in which patients receive bevacizumab alone. Bevacizumab was delivered as a 10 mg/kg IV infusion over 30-90 minutes, oxaliplatin as an 85 mg/m^2 IV infusion over 120 minutes, leucovorin as a 200 mg/m^2 IV infusion over 120 minutes, fluorouracil as a 400 mg/m^2 IV bolus followed by a 600 mg/m^2 continuous IV infusion over 22 hours. The treatments were administered every 14 days. Baseline patient characteristics are presented in Appendix (see Table 46).

4.4.1.2. Clinical outcomes of the study

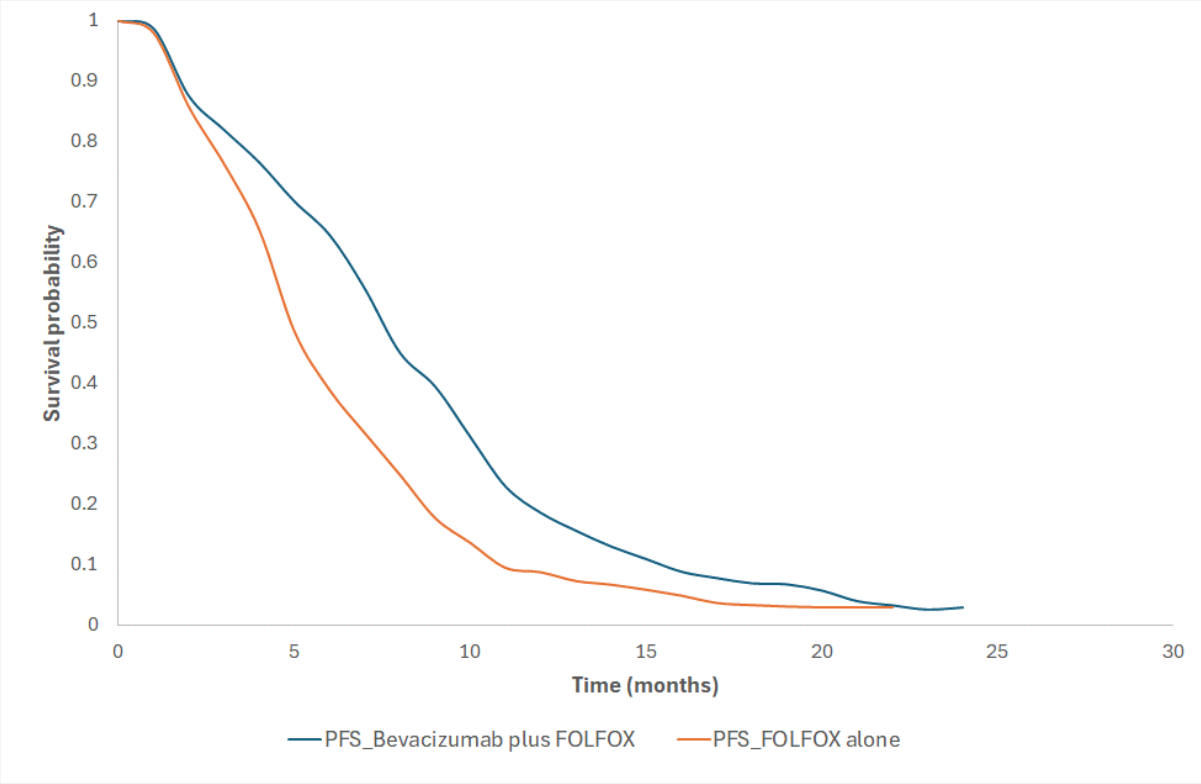
4.4.1.2.1. Progression-free survival

Bevacizumab plus FOLFOX, compared with FOLFOX alone, significantly improved median PFS by 2.6 months (P <0.0001). The median OS duration was 7.3 months of bevacizumab plus FOLFOX and 4.7 months for FOLFOX alone, with the HR for PFS equal to 0.61 (P <0.0001). Figure 6 presents the KM curve for PFS for bevacizumab plus FOLFOX-4 and FOLFOX-4 plus placebo.

4.4.1.2.2. Overall survival

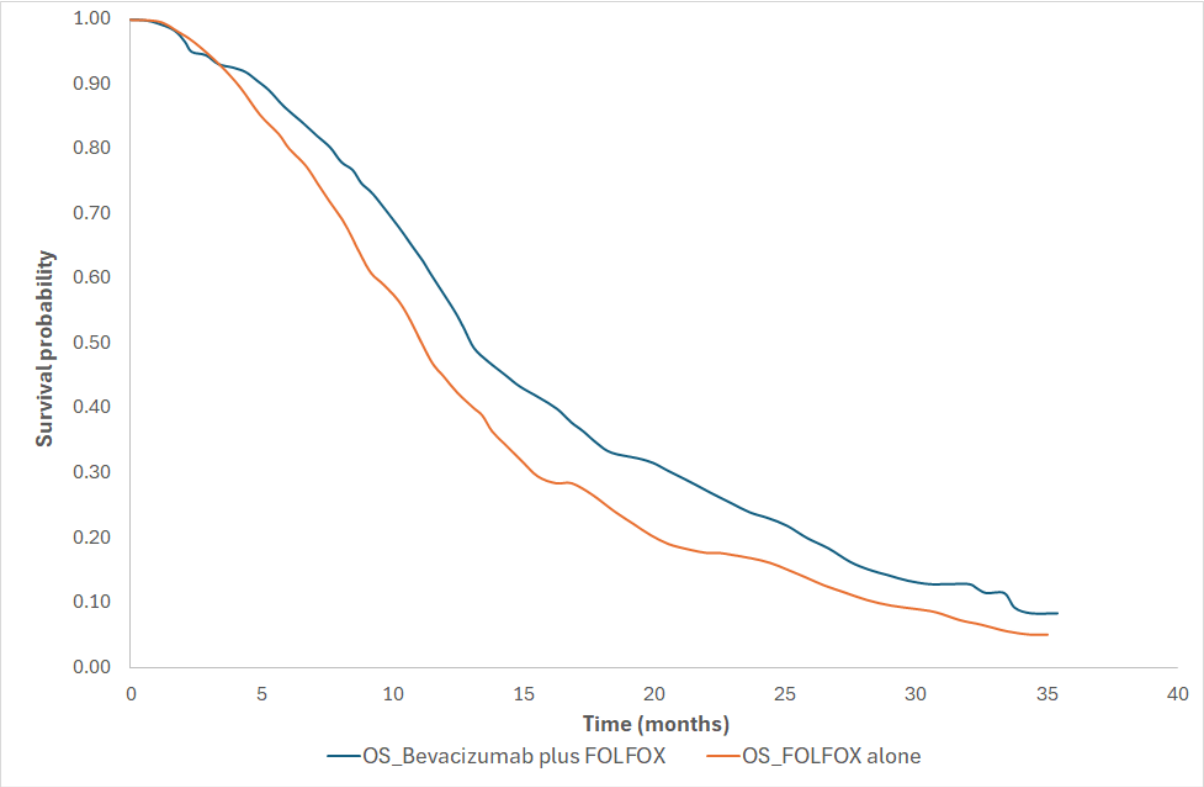
Bevacizumab plus FOLFOX, compared with FOLFOX alone, significantly improved median OS by 2.1 months (P = 0.0011). The median OS duration was 12.9 months of bevacizumab plus FOLFOX and 10.8 months for FOLFOX alone, with the HR for OS equal to 0.75 (P = 0.0011). Figure 7 presents the KM curve for OS for bevacizumab plus FOLFOX-4 and FOLFOX-4 plus placebo.

Figure 6: Kaplan-Meier curves for PFS in Study E3200



PFS: progression-free survival; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin

Figure 7: Kaplan-Meier curves for OS in Study E3200



OS: overall survival: FOLFOX: folinic acid plus fluorouracil plus oxaliplatin

4.4.2.Study GERCOR

4.4.2.1. Summary of the study

The Study GERCOR was a randomised open-label study evaluating FOLFIRI and FOLFOX-6 and determining the best sequence for treating patients with mCRC.[13]

The eligibility criteria for inclusion onto the study were: adenocarcinoma of the colon or rectum; unresectable metastases; at least one bidimensionally measurable lesion of ≥ 2 cm or a residual non-measurable lesion; adequate bone marrow, liver (alkaline phosphatases < 3 upper limits of normal [UNL], total bilirubin < 1.5 UNL, AST and ALT ≤ 3 UNL) and renal function (creatinine ≤ 135 µmol/L); WHO performance status (PS) of 0 to 2; age 18 to 75 years. Previous adjuvant chemotherapy, if given, must have been completed at least 6 months before inclusion. Patients with central nervous system metastases, second malignancies, bowel obstruction, current diarrhoea ≥ grade 2, symptomatic angina pectoris, or disease confined to previous radiation fields were excluded. FOLFIRI consisted of FA 200 mg/m^2 (levogyre leucovorin) or 400 mg/m^2 (dextro levogyre leucovorin) as a 2-hour IV infusion, and irinotecan 180 mg/m^2 given as a 90-minute IV infusion, followed by bolus 5-FU 400 mg/m^2 and a 46-hour IV infusion 5-FU 2,400 mg/m^2 for two cycles, increased to 3,000 mg/m^2 from cycle 3 where there were no AEs rated above grade 1 during the two first cycles, repeated every 2 weeks. FOLFOX-6 consisted of the same 5-FU/FA regimen, with the addition of oxaliplatin 100 mg/m^2

on day 1, given as a 2-hour IV infusion. Eligible patients randomly assigned to arm A (n =109) received FOLFIRI until progression or unacceptable toxicity followed by FOLFOX-6 if the patient was still alive. The opposite sequence (FOLFOX-6 followed by FOLFIRI) was administered in eligible patients randomly assigned to arm B (n =111). Patient characteristics are shown in Appendix (see Table 47).

4.4.2.2. Clinical outcomes of the study

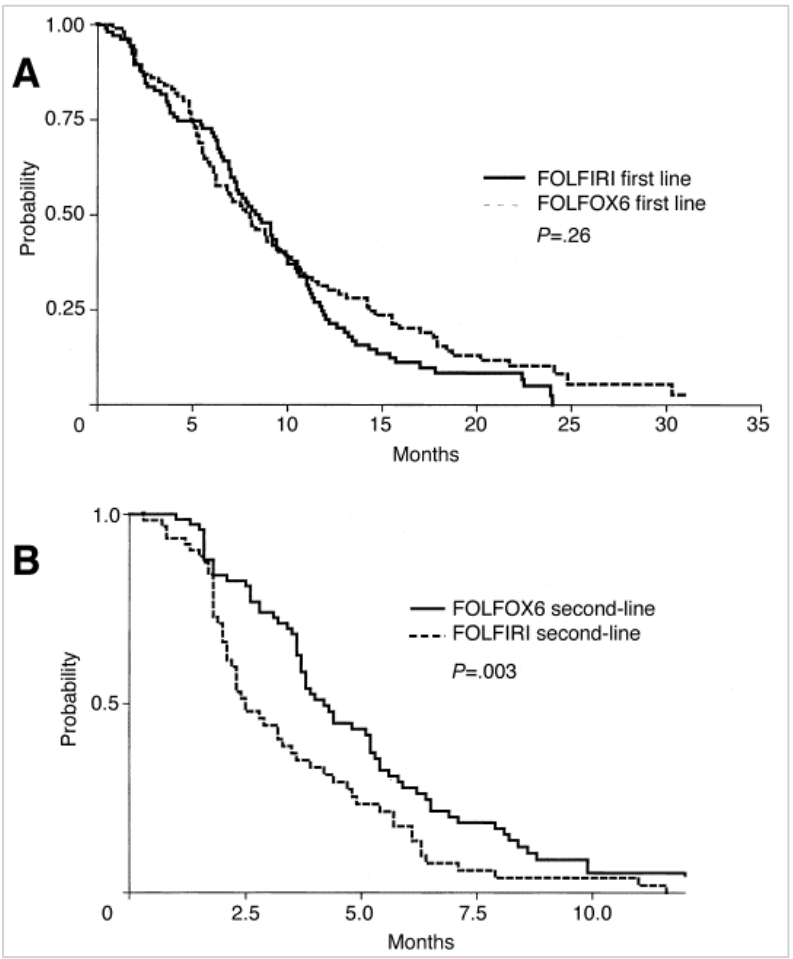
4.4.2.2.1. Progression-free survival

The median second PFS was 14.2 months for the FOLFIRI then FOLFOX-6 (arm A) group and 10.9 months for the FOLFOX-6 then FOLFIRI group (arm B) (P = 0.64). Figure 8 presents the KM curves for the PFS for the first-line and second-line treatments.

4.4.2.2.2. Overall survival

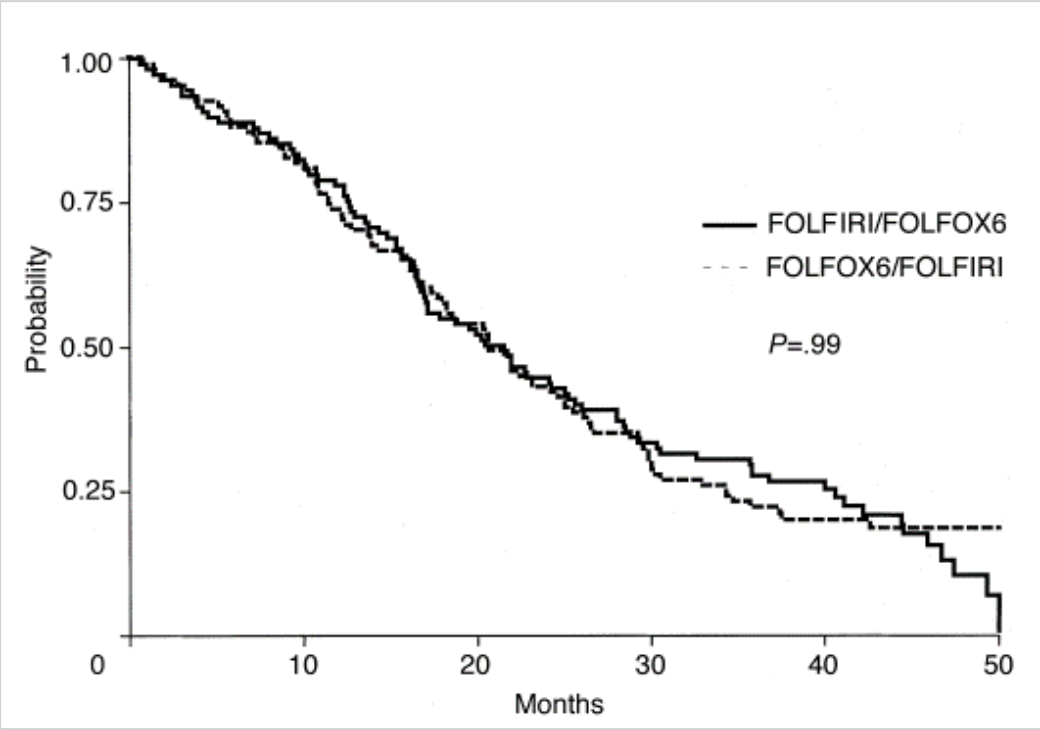
The median OS was 21.5 months for FOLFIRI then FOLFOX-6 group (arm A) and 20.6 months for FOLFOX-6 then FOLFIRI group (arm B) (P = 0.99). Figure 9 presents the KM curves for the OS.

Figure 8: Kaplan-Meier curves for PFS in Study GERCOR in (A) first-line therapy and (B) second-line therapy



PFS: progression-free survival; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan

Figure 9: Kaplan-Meier curves for OS in Study GERCOR



OS: overall survival; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan

4.4.3. Meta-analysis of second-line treatments for metastatic colorectal cancer

Mocellin *et al.*[11] conducted a meta-analysis of second-line systemic therapies in people with mCRC that progressed, recurred or did not respond to first-line therapy. The second-line therapies could be single therapies or combined treatments with any anticancer drug, at any dose or number of cycles. Primary outcomes assessed within the meta-analysis were OS and PFS. Thirty-one trials (both international and national trials) were deemed suitable for synthesis for OS and PFS outcomes. Multiple meta-analyses were conducted for different treatment comparisons, but for conciseness only the meta-analyses of OS and PFS outcomes for bevacizumab plus chemotherapy versus chemotherapy alone are summarised here. Four RCTs (1723 participants) compared bevacizumab plus chemotherapy and chemotherapy alone.[12, 14-16]

The studies by Bennouna *et al.*[14] and Masi *et al.*[16] included pooled chemotherapy regimens where participants could either receive irinotecan-based or oxaliplatin-based therapies. In the Bennouna *et al.* study, 59% and 58% of participants received irinotecan-based treatment in the bevacizumab plus chemotherapy arm and chemotherapy alone arm, respectively. In the Masi *et al.* study, 66% and 34% of patients in both arms received FOLFOX and FOLFIRI, respectively. In the study by Cao *et al.*[15] patients received either bevacizumab plus FOLFIRI or FOLFIRI alone, and in the Giantonio *et al.*[12] study patients received bevacizumab plus FOLFOX or FOLFOX alone.

HRs for OS and PFS were synthesised using a random effects meta-analysis with the results shown in Table 6. Both analyses demonstrated significant improvement in OS and PFS when chemotherapy was combined with bevacizumab compared with chemotherapy alone.

Table 6: Meta-analysis of PFS and OS for bevacizumab plus chemotherapy versus chemotherapy alone

Study	**PFS, HR (95% CI)**	**OS, HR (95% CI)**
Bennouna 2013 *(n = 820)*	0.68 (0.58, 0.80)	0.81 (0.69,0.95)
Cao 2015 *(n =142)*	0.71 (0.52, 0.97)	0.78 (0.55, 1.11)
Giantonio 2007 *(n = 577)*	0.61 (0.48, 0.78)	0.75 (0.60, 0.94)
Masi 2015 *(n = 184)*	0.70 (0.52, 0.94)	0.77 (0.56, 1.06)
Total *(n = 1723)*	**0.67 (0.60, 0.75)**	**0.79 (0.70, 0.88)**

HR: hazard ratio; CI: confidence interval, PFS: progression-free survival, OS: overall survival, n: number of study participants

4.4.3.1. Critique of the meta-analysis by Mocellin *et al*.

There are several differences between the populations in the studies included in the meta-analysis from Mocellin *et al.*.[11] As described earlier, the chemotherapy used varies between the four trials, with two of the studies pooling results from oxaliplatin-based therapies and irinotecan-based therapies. Additionally, in the study by Bennouna *et al.*,[14] bevacizumab is administered as 5 mg/kg every two weeks, whereas in the three other studies bevacizumab is administered as 10 mg/kg every two weeks. Furthermore, the study by Cao *et al.*[15] was conducted in China only, and the study by Masi *et al.*[16] was conducted in Italy only, the two remaining studies were international studies. An additional difference in the populations was that the participants of the study by Masi *et al.*, had received bevacizumab plus fluoropyrimidine, FOLFIRI or FOLFOX in the first-line setting, whereas the populations in the three other studies had not received bevacizumab until the second-line setting. Despite these differences in populations, the between study variability appears to be low in the meta-analysis (though this may be due to low study participant numbers), and individual study results similar, and therefore these differences are of low concern. The HRs from Masi *et al.* are fairly similar to those from the other studies which suggests that the use of bevacizumab in first-line may not affect the efficacy of bevacizumab in second-line which is a key assumption in the modelling undertaken.

Methodologically, the meta-analyses presented in Mocellin *et al.*,[11] are underpinned by the proportional hazards assumption. For these four studies, evidence of the applicability of the proportional hazards assumption has not been demonstrated for either OS or PFS. As the assessment of this assumption was not formally presented by Mocellin *et al.*,[11] there could be some uncertainty regarding the validity of the synthesised results.

4.5. Discussion: second-line treatment of mCRC

(i) Bevacizumab plus FOLFOX/CAPOX versus FOLFOX/CAPOX alone

Study E3200 was the only clinical evidence informing the effectiveness of bevacizumab plus FOLFOX and FOLFOX alone for the second-line treatment of mCRC in TA212 (included as part of the manufacturer's exploratory analysis although the manufacturer was seeking recommendation only in the first-line setting). Additionally, in TA242, both the ERG and company did not identify any further clinical studies comparing bevacizumab plus FOLFOX/CAPOX versus FOLFOX/CAPOX alone for the second-line use. Clinical advisors to the EAG were not aware of any other studies to inform this comparison.

Study GERCOR was used to extrapolate the PFS function of progressed patients who were treated with the second-line therapies in TA118. However, the EAG did not consider the study relevant for the decision problem because it evaluated only FOLFOX/FOLFIRI groups and the overall survival data for the second-line population could not be extracted from the published results.

Therefore, the EAG selected Study E3200 to inform the clinical effectiveness of bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone in the economic analysis. In line with the approach taken in the first-line setting, it was assumed that FOLFOX-and CAPOX-containing regimens have comparable efficacy. Study E3200 had not had prior bevacizumab use, which is a limitation as the model for second-line treatment does not consider previous treatments, data reported by Masi *et al.*[16] indicates that prior bevacizumab use may not influence the efficacy of bevacizumab.

The impact of applying HRs reported by Mocellin *et al*. to the modelled OS and PFS functions for FOLFOX alone group to generate OS and PFS curves for bevacizumab plus FOLFOX in the second-line setting was explored in a scenario analysis (see details in Section 5.4.4.2).

(ii) Bevacizumab plus FOLFIRI versus FOLFIRI alone

The EAG did not identify any previous NICE TAs or relevant clinical studies for the UK population evaluating bevacizumab in combination with FOLFIRI versus FOLFIRI alone for the second-line treatment of mCRC.

(iii) Bevacizumab plus capecitabine versus capecitabine alone

The EAG did not identify any previous NICE TAs or clinical studies evaluating bevacizumab in combination with capecitabine versus capecitabine alone for the second-line treatment of mCRC.

5. COST-EFFECTIVENESS

5.1. Overarching principles associated with the pilot MTA for bevacizumab biosimilars in treating metastatic colorectal cancer

Given the expedited approach of this MTA,[1] the EAG did not consider running full sequential treatment models including interventions used later in the mCRC treatment pathway. Instead, the following simplifying principles were used to allow a pragmatic approach which would provide indicative estimates of the ICER, which throughout this document have been presented in terms of cost per QALY gained.

The key principles used in the conceptualisation of the model are:

1) That subsequent NICE-recommended treatments after the relevant treatment line are cost-effective. Thus, extending the life of a person with first-line bevacizumab treatment would not result in patients receiving treatments that were not cost-effective and produce perverse results from a cost-effectiveness perspective.
2) That there is no interaction between the efficacy of duration of subsequent treatments and the use of bevacizumab treatment at an earlier line. Thus, the possibility that the early use of bevacizumab would dilute the effectiveness of a subsequent treatment has not been explicitly considered. Whilst this may be a limitation, this would not be a problem if interventions at later lines remain cost-effective, even if there is some dilution of effectiveness. This potential limitation is of particular importance when the decision problem was extended to explore the use of bevacizumab at both first- and second-line as often the same intervention is not used sequentially. The HRs reported by Masi *et al.,*[16] where bevacizumab was used in second-line treatment after treatment with bevacizumab in the first-line setting, are fairly similar to those from the other studies where bevacizumab was not used in the first-line (see Table 6) suggesting that the use of bevacizumab in first-line may not affect the efficacy of bevacizumab in second-line.
3) Based on the previous two points, a model that considers only one line of treatment represented by a simple partition survival model is deemed to be appropriate, with extrapolations of OS and PFS used to estimate the costs and QALYs associated with each treatment option. All costs that would be incurred and QALYs gained due to subsequent treatments are therefore intentionally excluded from the model on the premise that subsequent treatments would only increase the incremental net monetary benefit (iNMB) as these treatments are cost-effective (point 1) and there is no interaction between their relative effectiveness and the early use of bevacizumab (point 2).
4) The approach in 3), however, results in an underestimation of the life expectancy (and QALYs) associated with standard of care, which is an important component in determining whether a

disease severity modifier weighting should be used. The EAG has attempted to address this by adding on the expected QALYs gained through later lines of treatment to the QALYs estimated in the relevant line of treatment. However, this approach has limitations. Firstly, it allows for doubling counting of QALYs accrued during the period of time after a patient progresses to time of death, as there will be QALYs associated with both the initial treatment line (where the patient is in the progressed disease state) and the subsequent treatment where the patient would be in the progression-free state. A second limitation is that all patients progress and receive subsequent-line treatment rather than the PFS event being death. Both limitations are likely to overestimate the QALYs gained under current care and could be unfavourable to bevacizumab if the proportional or absolute QALY shortfall were marginally below the threshold required for an increased QALY weight. In this report, the EAG has run the results at second-line with disease severity modifier weights of both 1.0 and 1.2.

5) As instructed by NICE, the mean cost of the current tenders for biosimilar bevacizumab were used in the EAG's base case and median price in the sensitivity analysis. Additionally, the EAG has undertaken sensitivity analyses generating ICERs using all of the tender prices of bevacizumab. This was done as the EAG believes the median and means prices are likely to be overestimates of the real average price as these assume near independence between drug usage and tender price.

5.2. Review of existing cost-effectiveness evidence

Given the expedited approach of this MTA, the EAG used a pragmatic approach for reviewing the cost-effectiveness evidence. Therefore, a systematic literature search was not conducted and instead the EAG reviewed the previous NICE TAs regarding the use of bevacizumab with fluoropyrimidine-based chemotherapy for the first- and second-line treatments of mCRC. The EAG identified two NICE TAs for the first-line treatment, (TA118[8] and TA212[6]) and one NICE TA for the second-line treatment (TA242[9]).

Summary of key assumptions in previous appraisals for untreated metastatic colorectal cancer

The key parameter assumptions used in the company's models and ERG's models within TA118,[8] TA212[6] and TA242,[9] along with the Appraisal Committee's conclusions are summarised in Table 7.

Table 7: Summary of key issues and Appraisal Committee's preferred assumptions regarding the first-line treatment in TA118 and TA212

	First-line treatment		**Second-line treatment**
	TA118 (2007)	**TA212 (2010)**	**TA242 (2012)**
Scope			
Population	Adults with untreated mCRC	Adults with mCRC for whom oxaliplatin-based chemotherapy regimens are suitable	Adults with mCRC that has progressed after first-line chemotherapy
Intervention(s)	Bevacizumab in combination with FOLFIRI Bevacizumab in combination with 5-FU/FA without irinotecan	Bevacizumab in combination with FOLFOX Bevacizumab in combination with CAPOX (CAPOX)	Bevacizumab in combination with non-oxaliplatin chemotherapy
Comparators	Fluorouracil-containing or releasing regimens: FOLFIRI or 5-FU/FA alone	(i) Oxaliplatin-based chemotherapy: FOLFOX and CAPOX (main comparators) (ii) Irinotecan-based chemotherapy: FOLFIRI	Chemotherapy with oxaliplatin or irinotecan
Marketing authorisation	The licensed indication permits the use of bevacizumab in combination with fluoropyrimidine-based chemotherapy for metastatic carcinoma of the colon or rectum but does not specify a line of treatment.		
Outcomes	PFS, OS, Response rates, AEs, HRQoL		
Economic analysis			
Type of model	Partitioned survival model	Partitioned survival model	No economic model. Costing analysis for bevacizumab plus FOLFIRI versus cetuximab plus FOLFIRI was reported.
Time horizon	Lifetime horizon*	Lifetime horizon (8 years)	NA
Cycle length	Monthly cycle	Monthly cycle	NA
Discount rate	No discounting due to shorter lifetime horizon	3.5% per annum	NA
Perspective	NHS and PSS perspective		NR
Heath states in the model	Progression-free, post-progression and dead	Pre-progression on treatment, pre-progression off treatment, post-progression, dead	NA

Primary source of clinical effectiveness evidence for bevacizumab plus fluoropyrimidine-based chemotherapy versus fluoropyrimidine-based chemotherapy alone	Company's models OS, PFS: Hurwitz *et al.*[7] (AVF2107g) *ERG's models* OS, PFS: Hurwitz *et al.*[7] (AVF2107g) PFS for the 2nd line treatment Tournigand *et al.*[13] (FOLFIRI-FOLFOX treated group in the GERCOR trial) *Appraisal Committee's comments* - There is potential confounding of OS outcomes in the study as patients continued to get bevacizumab after disease progression. The true impact of bevacizumab as a first-line therapy for CRC is uncertain. - 5-FU was given by bolus, in real practice, it is administered by infusion. As bevacizumab effects are independent on the 5-FU, the Committee concluded that the trial results are generalisable to NHS practice England and Wales.	Company's model PFS, OS: Study NO16966[5] *ERG's and Appraisal Committee's preferences* - using 2x2 factorial design data of Study NO16966 - not pooling bevacizumab plus FOLFOX and bevacizumab plus CAPOX arms - not pooling FOLFOX and CAPOX arms - excluding patients who had received prior adjuvant therapy. This analysis was not provided by the company. *EAG's and Appraisal Committee's the next best alternative analysis†* - using 2x2 factorial design data of Study NO16966 - pooling bevacizumab plus FOLFOX and bevacizumab plus CAPOX arms - pooling FOLFOX and CAPOX arms ("*The Committee considered that CAPOX and FOLFOX could be equivalent, and FOLFOX-6 has similar efficacy as FOLFOX-4*") - excluding patients who had received prior adjuvant therapy	Both the company and the ERG did not identify any trials that compared bevacizumab in combination with non-oxaliplatin-based chemotherapy for patients with mCRC who have progressed after first-line chemotherapy. *"if bevacizumab plus a non-oxaliplatin-containing regimen is effective in the first-line setting, the combination would also be likely to be effective in second- and third-line setting."* The committee concluded that people receiving bevacizumab as second-line therapy would likely have smaller survival gains than people who have not previously received chemotherapy.
Parametric survival models used in the economic analysis	*Company's model* PFS, OS: Weibull model *EAG's model and Appraisal Committee's preferences* PFS, OS: Weibull model	*Company's model* PFS: KM for the first 28 months followed by fitted exponential model OS: KM for the first 28 months followed by fitted Weibull model *EAG's model and Appraisal Committee's preferences*	NA

		PFS: KM for the first 6 months followed by fitted Weibull model OS: KM for the first 28 months followed by fitted Weibull model	
HRQoL	<u>*Company's model*</u> Progression-free: 0.80 (Smith *et al*.[17]) Post-progression: 0.50 (Brown *et al*.[18]) <u>*ERG's models*</u> Progression-free: 0.80 Post-progression: 0.60 (assumption of a multiplier of 0.75 between progressed and stable states) <u>*Appraisal Committee's comments*</u> - The utility estimates remain uncertain. - The value is likely to reflect the lower end of the range (0.95- 0.71) based on the MABEL study.[19] - Disutilities due to AEs are not included in the model.	<u>*Company's model*</u> Pre-progression on treatment: 0.77 Pre-progression off treatment: 0.79 (subsequently changed to 0.77 by the company.) Post-progression: 0.68 <u>*ERG's comments*</u> - CAPOX group might have a higher utility value than FOLFOX. - Disutilities due to AEs are not included in the model. - ERG reduced all utility values by 20% within sensitivity analyses. <u>*Appraisal Committee's comments*</u> The utility estimates remain uncertain.	NA
Costs and resource use	<u>*Company's and ERG's models*</u> *Types of costs* Drug acquisition, infusional pumps, pharmacy costs, Hickman/PICC line insertion, hospital resources for chemo administration, management of AEs (both drug acquisition and hospital admissions), diagnostic tests, clinician consultations, primary care costs, terminal care/BSC costs *Dosing schedule*	<u>*Company's models*</u> *Types of costs* Drug acquisition, pharmacy, drug administration, monitoring *Dosing schedule* Mean treatment duration and dose intensity are from the Study NO16966. - No costs for second and third-line treatments are included in the model based	By taking into account of non-positive recommendations in TA118 and TA212, bevacizumab is likely to be less effective as a second-line therapy than as first-line therapy. Therefore, the Committee concluded that it was unlikely that bevacizumab plus non-oxaliplatin chemotherapy would be a cost-effective treatment for people with mCRC who had received first-line therapy.

	Used Hurwitz *et al.*[7] (AVF2107g) for dosing schedules of 1st line treatments and Tournigand *et al.* for 2nd line treatments. The Roswell Park treatment regimen was used for 5-FU/FA in the base case. BSC costs for mCRC is assumed to be the same as that for stage 4 breast cancer in the UK. <u>*Appraisal Committee's preferences*</u> - The true costs of treatment following disease progression are uncertain; these data were not collected within the included RCTs of bevacizumab.	on the assumption that costs are the same between treatment groups. - Supportive care cost is applied for the duration of post-progression survival. <u>*ERG and Appraisal Committee's preferences*</u> - Treatments other than oxaliplatin might continue until disease progression or unacceptable AEs. - Instead of FOLFOX-4 costs, FOLFOX-6 which is more common in UK practice is used for costing.	

TA: technology appraisal; mCRC: metastatic colorectal cancer; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; CAPOX: capecitabine plus oxaliplatin; 5-FU/FA: 5 fluorouracil and folinic acid; KM: Kaplan-Meier, RCT: randomised controlled trial; AEs: adverse events; BSC: best supportive care; NHS: National Health Services; PSS: Personal Social Services

* from randomisation until death, approximately 2.5 years

†as the EAG and Appraisal Committee's preferred analysis was not provided by the company

5.3. Review of manufacturers' submitted models

There were no economic models submitted by manufacturers for the current appraisal.

5.4. Independent economic assessments

5.4.1.Scope of the EAG's economic analysis

The EAG developed a *de novo* health economic model to assess the cost-effectiveness of bevacizumab in combination with fluoropyrimidine-based chemotherapy versus fluoropyrimidine-based chemotherapy alone, for patients with mCRC in both the first-line and the second-line treatment settings. The scope of the EAG's model is summarised in Table 8. The health outcomes and costs were assessed from the perspective of NHS and PSS over a lifetime horizon (up to 100 years of age) and were discounted at a rate of 3.5% per annum.[20] The economic analysis adopts the price year of 2023/24 including uplifted costs of older estimates using inflation indices, where necessary.

Table 8: Scope of the EAG's economic analysis

Population	People with mCRC who would normally receive chemotherapy • Adults with previously untreated mCRC (first-line treatment) • Adults with mCRC receiving second-line treatment
Intervention	Bevacizumab (originator and biosimilars) in combination with fluoropyrimidine-based chemotherapy
Comparators	Fluoropyrimidine-based chemotherapy alone • Folinic acid plus fluorouracil plus oxaliplatin (FOLFOX) • Folinic acid plus fluorouracil plus irinotecan (FOLFIRI) • Capecitabine plus oxaliplatin (CAPOX) • Capecitabine
Main economic outcome	Incremental cost per QALY gained
Additional model outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life
Perspective	NHS and PSS
Time horizon	Lifetime
Discount rate	3.5% per annum
Price year	2023/24

mCRC, metastatic colorectal cancer; NHS, National Health Services; PSS, Personal Social Services; QALY, quality-adjusted life-years; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan: CAPOX: oxaliplatin plus capecitabine

Population

The population included in the economic analysis relates to two main populations: (i) adult patients with previously untreated mCRC who would normally receive chemotherapy (first-line treatment),

and (ii) adult patients with mCRC who would normally receive chemotherapy as a second-line treatment. These populations are in line with the marketing authorisation for bevacizumab in mCRC. Patients who are candidates for targeted treatments or immunotherapies were excluded. At model entry, patients were assumed to have a mean age of 60 years with 40% female in the first-line population, and to have a mean age of 61 years with 39.5% female in the second-line population in line with the pivotal studies. Details are discussed in Section 5.4.3.1.

Intervention

Details on bevacizumab are provided in Section 3.1.2. The economic analysis considered bevacizumab in addition to three different combinations with fluoropyrimidine-based chemotherapy regimens: (i) bevacizumab with FOLFOX, (ii) bevacizumab with FOLFIRI, and (iii) bevacizumab with CAPOX. Given the lack of identified evidence regarding the clinical efficacy of bevacizumab plus capecitabine, this combination was excluded from the analysis.

Comparators

Details on the comparators are provided in Section 3.1.3. The economic analysis used FOLFOX, FOLFIRI and CAPOX as comparators. Capecitabine was not considered as a relevant comparator here as there was a lack of evidence for the effectiveness of bevacizumab plus capecitabine.

The interventions and comparators included in each pair-wise comparison, for both first- and second-line treatment, are shown in Table 9.

Table 9: Summary of the EAG's economic comparisons by each health economic model

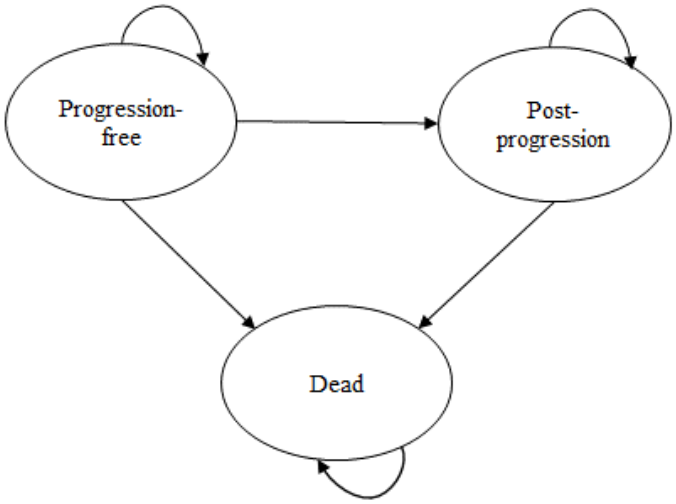
Model	**Treatment**
Model 1	
Intervention	Bevacizumab plus FOLFOX
Comparator	FOLFOX
Model 2	
Intervention	Bevacizumab plus FOLFIRI
Comparator	FOLFIRI
Model 3	
Intervention	Bevacizumab plus CAPOX
Comparator	CAPOX

FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; CAPOX: capecitabine plus oxaliplatin

5.4.2.Model structure and assumptions

The economic model adopts a partitioned survival approach, including three mutually exclusive and exhaustive health states: (i) progression-free, (ii) post-progression and (iii) dead (Figure 10).

Figure 10: Model structure



The partitioned survival model operates as follows. Patients enter the model in the progression-free state and receive treatment with either bevacizumab in combination with fluoropyrimidine-based chemotherapy, or fluoropyrimidine-based chemotherapy alone. For simplicity, the model assumes that patients only receive the best supportive care following progression. At any time *t*, health state occupancy is determined by the cumulative probabilities of PFS and OS, whereby: the probability of being alive and progression-free is determined by the cumulative probability of PFS; the probability of being alive following progression is given by the cumulative probability of OS minus the cumulative probability of PFS; and the probability of being dead is estimated as 1 minus the cumulative probability of OS. Patients are redistributed across three health states at the end of each monthly cycle. A half-cycle correction is applied in the model where appropriate. The model included two structural constraints: (i) the cumulative probability of PFS cannot be higher than the cumulative probability of OS at any timepoint, and (ii) the per-cycle risk of death in the target population cannot be lower than that of age-and sex-matched general population.

The cost-effectiveness of bevacizumab in combination with fluoropyrimidine-based chemotherapy versus fluoropyrimidine-based chemotherapy alone was evaluated using pair-wise comparisons over a 40-year (lifetime) time horizon.

Key assumptions employed in the economic model (both first-and second-line settings)

This section provides a list of key assumptions used in the base case model, and each assumption is elaborated on in more details in Section 5.4.3. Based on the Committee's preferred assumptions in TA118 and TA212, the economic model employs the following key assumptions in the base case:

- An agreed tender price of [redacted] for 100 mg/4 ml vial and [redacted] for 400 mg/16 ml vial (mean cost of current tenders for biosimilar bevacizumab) was used instead of the list price.

- The modelled population is 60 years of age at model entry, and 40% of patients are females in the first-line population. In the second-line population, the mean age is 61 years and 39.5% of patients are females.
- Using the precedent set in TA212 and clinical advice provided to the EAG, the efficacy of FOLFOX and CAPOX (with or without bevacizumab) was assumed to be identical.
- For the first-line treatment, the PFS and OS for bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone were modelled using gamma parametric survival models fitted to the pooled data from Study NO16966[5] (2x2 factorial design data).
- For the first-line treatment, the PFS and OS for bevacizumab plus FOLFIRI and FOLFIRI alone were modelled using Weibull parametric survival models which were fitted to the data from Study AVF2107g.[7]
- For the second-line treatment, the PFS and OS for bevacizumab plus FOLFOX and FOLFOX alone were modelled using gamma parametric survival models which were fitted to the data from Study E3200.[12] In line with assumptions for the first-line population, CAPOX (with and without bevacizumab) was considered clinically equivalent to FOLFOX (with and without bevacizumab).
- No studies were identified comparing bevacizumab plus FOLFIRI versus FOLFIRI alone in the second-line setting. An indication of the cost-effectiveness of bevacizumab plus FOLFIRI and FOLFIRI alone was estimated assuming that the relative difference in ICERs observed between bevacizumab plus FOLFOX/CAPOX versus FOLFOX/CAPOX alone and bevacizumab plus FOLFIRI versus FOLFIRI alone in the first-line setting was generalisable to the second-line setting.
- Following disease progression, patients were provided with best supportive care only.
- Drug wastage was included for both bevacizumab and comparators.
- Relative dose intensity (RDI), TTD, AEs and resource use for drug administration and monitoring were based on the data from Study NO16966 and Study AVF2107g for the first-line setting and Study E3200 for the second-line setting.
- The costs of central venous access devices (CVADs) were incurred by all patients and were applied as one-off costs in the first model cycle. Replacement costs were excluded.
- Health state resource use was independent of the type of treatment received but dependent on whether the patient was in pre-progression or had progressed disease.
- Utilities are independent of treatment received but were dependent on the health status (pre-progression or post-progression). Utilities were age-adjusted.
- Disutilities and additional costs associated with Grade ≥3 AEs were included as one-off values in the first model cycle. Caregiver disutilities were not considered.

- The disease severity modifier was assumed to be unity in the first-line setting and results are presented with values of unity and 1.2 in the second-line setting.

5.4.3. Evidence used to inform the model parameters

The majority of the parameters used in the base case model for the first-line setting were sourced from two clinical trials, Study AVF2107g[7] and Study NO16966[5], which were pivotal in informing the model parameters in TA118[8] and TA212,[6] respectively. Parameter values for the second-line setting were taken from the Study E3200.[12]

Table 10 summarises the evidence sources used to inform the model parameter values in the base case. The evidence sources and derivation of those values are described in detail in the subsequent sections.

Table 10: Summary of evidence used to inform the base case analysis

Parameter group	Source
Patient characteristics (age, proportion of female, body surface area [BSA], body weight)	Age and proportion of female based on average values from studies NO16966[5] and AVF2107g[7] (first-line setting), and from Study E3200[12] (second-line setting). BSA and body weight from Study NO16966 (both first-and second-line settings).
Time-to-event data (PFS and OS)	See details in Section 5.4.3.2 (first-line setting) and in Section 5.4.3.3 (second-line setting).
General population mortality risk	General population life tables for England, 2017-2019.[21] This year was taken to avoid the impacts of COVID-19.
AE frequency	Grade ≥3 AEs from Studies NO16966 and AVF2107g (first-line setting), and Study E3200 (second-line setting)
Health state utility values	Utilities for the progression-free and post-progression states were based on the values from TA212[6] (first-line setting) and TA1008[22] (second-line setting)
AE disutility values	Literature,[23-26] previous NICE TAs[27-29] and assumptions.
General population utility	Hernández Alava *et al*.[30]
Drug acquisition costs	Dosing schedules, RDI and TTD were based on Studies NO16966 and AVF2107g (first-line setting) and Study E3200 (second-line setting). Drug prices taken from eMIT 2024[31] and BNF 2025[32] apart from bevacizumab where the midpoint tender price of was applied.
Drug administration and monitoring costs	Resource use data from Studies NO16966 (both first-and second-line settings) and AVF2107g (first-line setting) with unit costs taken from NHS Reference Costs 2023/24.[33]
AE management costs	NHS Reference Costs 2023/24[33]
Best supportive care costs	Resource use data from previous NICE TAs[34-36] with unit costs taken from NHS Reference Costs 2023/24[33]
Terminal care costs	Round *et al*.,[37] uplifted from 2013/14 to 2023/24 prices.

PFS: progression-free survival; OS: overall survival; AE: adverse event; NICE: National Institute of Clinical Excellence; TA: technology appraisal; RDI: relative dose intensity; TTD: time to treatment discontinuation, eMIT: electronic market information tool; BNF: British National Formulary

5.4.3.1. Patient characteristics

On model entry, it was assumed that patients have a mean age of 60 years, a mean body weight of 70 kg, a mean body surface area (BSA) of 1.75 m^2, and that 40% are female in the first-line setting. The mean age and proportion of females were based on average values of Studies NO16966[5] and AVF2107g[7], while mean body weight and BSA were derived from Study NO16966 as the Study AVF2107g did not report them. Patients age in the model in synchronisation with the time cycles.

In the second-line population, patients were assumed to have a mean age of 61 years and proportion of females of 39.5% to reflect the patient characteristics from the Study E3200.[12] As the data for body weight and BSA were not reported in the study, these values were assumed to be the same as those used in the first-line setting.

5.4.3.2. Time-to-event data for the first-line treatment: progression-free survival and overall survival

Studies NO16966[5] and AVF2107g[7] were the primary sources of first-line clinical effectiveness evidence, comparing bevacizumab plus FOLFOX/CAPOX versus FOLFOX/CAPOX alone (TA212)[6] and bevacizumab plus FOLFIRI versus FOLFIRI alone (TA118),[8] respectively. The EAG did not have access to individual patient-level data (IPD) from these two studies. Therefore, the EAG either digitised KM curves from study publications or used provided KM estimates and generated pseudo-IPD for PFS and OS using the algorithm reported by Guyot *et al*.[38] The PFS and OS KM estimates for Study NO16966 were provided by NICE as commercial-in-confidence, and the data for Study AVF2107g were taken from Hurwitz *et al*.[7] The EAG independently fitted standard parametric survival models to the pseudo-IPD from Study NO16966 for bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone, and from Study AVF2107g for bevacizumab plus FOLFIRI and FOLFIRI alone. Seven parametric survival models were fitted, which were the exponential, Weibull, Gompertz, log-normal, log-logistic, gamma and generalised gamma distributions. The survival model selection process included: (i) examination of Akaike Information Criterion (AIC) and Bayesian Information Criterion (BIC), (ii) visual inspection of the fitted survival models against the KM survival functions and (iii) consideration of the clinical plausibility of the survival model predictions (based on hazard plots and input from clinical experts). Empirical hazard plots of the trial data were visualised using piecewise exponentials (via the *pehaz* function in R) and hazard functions smoothed using b-splines (via the *bshazard* function in R).

5.4.3.2.1. Progression-free survival

5.4.3.2.1.1. Progression-free survival for bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone

PFS was modelled independently for the bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone groups using pseudo-IPD from Study NO16966.[5] In the absence of

additional analyses for Study NO16966, the EAG's base case model followed the assumptions accepted by the Appraisal Committee in TA212, which include: (i) using the 2x2 factorial design data of the study, (ii) pooling the bevacizumab plus FOLFOX and bevacizumab plus CAPOX arms, (iii) pooling the FOLFOX and CAPOX arms, and (iv) excluding patients who had prior adjuvant chemotherapy. This data was provided by NICE as commercial-in-confidence.

Table 11 summarises AIC and BIC values for the fitted models, and Figure 11 and Figure 12 present the comparison of model-predicted versus observed PFS for bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone, respectively. Empirical and smoothed hazard plots are shown in Figure 13 and Figure 14, respectively. Parametric model-based hazard plots for each group are presented separately in Figure 15 (bevacizumab plus FOLFOX/CAPOX) and Figure 16 (FOLFOX/CAPOX alone).

Table 11: AIC and BIC statistics, PFS, bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone, first-line setting

Distribution	Bevacizumab plus FOLFOX/CAPOX		FOLFOX/CAPOX alone	
	AIC	BIC	AIC	BIC
Exponential	2969.02	2973.30	2699.32	2703.58
Weibull	2831.65	2840.21	2576.94	2585.46
Gamma	2819.39	2827.96	2549.03	2557.56
Gompertz	2896.54	2905.10	2654.62	2663.15
Log-logistic	**2810.39**	**2818.96**	**2524.45**	**2532.98**
Lognormal	2847.53	2856.09	2537.94	2546.46
Generalised gamma	2821.11	2833.96	2537.21	2550.00

AIC - Akaike Information Criterion; BIC - Bayesian Information Criterion; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CAPOX: capecitabine plus oxaliplatin
The best-fitting model is indicated by the lowest AIC or BIC value. Models that are the best fitting or within 5 points of the best-fitting are highlighted in bold.

Figure 11: Observed and model-predicted PFS, bevacizumab plus FOLFOX/CAPOX, first-line setting

PFS: progression-free survival; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CAPOX: capecitabine plus oxaliplatin; BevaFOLFOX: bevacizumab plus FOLFOX; BevaCAPOX: bevacizumab plus CAPOX; KM: Kaplan-Meier

Figure 12: Observed and model-predicted PFS, FOLFOX/CAPOX alone, first-line setting

OS: overall survival; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CAPOX: capecitabine plus oxaliplatin; KM: Kaplan-Meier

Figure 13: Empirical hazard plot for PFS (generated by the EAG), first-line setting

FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CAPOX: capecitabine plus oxaliplatin

Figure 14: Smoothed hazard plot for PFS (generated by the EAG), first-line setting

FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CAPOX: capecitabine plus oxaliplatin

Figure 15: Modelled hazard plots from standard parametric survival models for PFS, bevacizumab plus FOLFOX/CAPOX (generated by the EAG), first-line setting

Exp: exponential; gengamma: generalised gamma; llogis: log-logistic; lnorm: log-normal

Figure 16: Modelled hazard plots from standard parametric survival models for PFS, FOLFOX/CAPOX alone (generated by the EAG), first-line setting

Exp: exponential; gengamma: generalised gamma; llogis: log-logistic; lnorm: log-normal

5.4.3.2.1.2. Progression-free survival for bevacizumab plus FOLFIRI and FOLFIRI alone

PFS was modelled independently for the bevacizumab plus FOLFIRI and FOLFIRI alone groups using the pseudo-IPD generated from the PFS KM curves from Hurwitz *et al.*[7].

Table 12 summarises the AIC and BIC values for the fitted models, and Figure 17 and Figure 18 present the comparison of model-predicted versus observed PFS for bevacizumab plus FOLFIRI and FOLFIRI alone, respectively. Empirical and smoothed hazard plots are shown in Figure 19 and Figure 20, respectively. Parametric model-based hazard plots for each group are presented separately in Figure 21 (bevacizumab plus FOLFIRI) and Figure 22 (FOLFIRI alone).

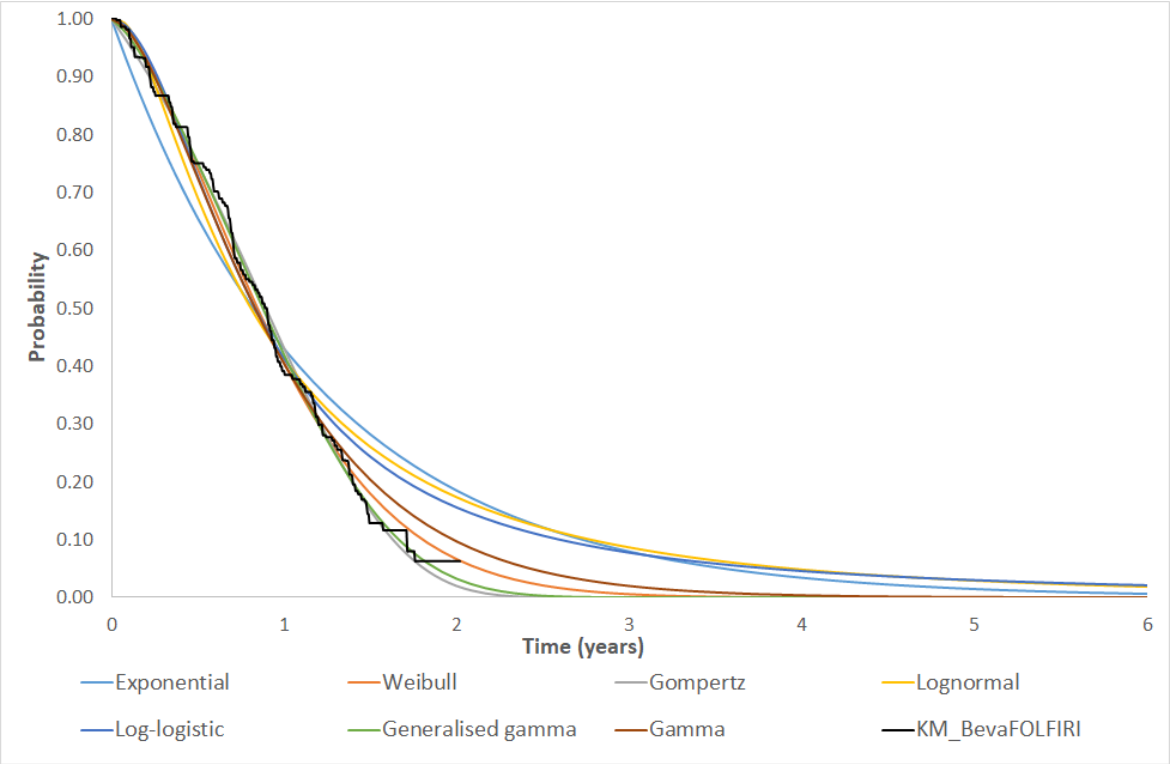
Table 12: AIC and BIC statistics, PFS, bevacizumab plus FOLFIRI and FOLFIRI alone, first-line setting

Distribution	Bevacizumab plus FOLFIRI		FOLFIRI alone	
	AIC	BIC	AIC	BIC
Exponential	1653.928	1657.924	1825.283	1829.301
Weibull	**1596.568**	**1604.561**	1773.169	1781.206
Gamma	1602.902	1610.895	**1766.725**	**1774.762**
Gompertz	**1596.739**	**1604.731**	1803.393	1811.431
Log-logistic	1618.649	1626.641	**1768.835**	**1776.872**
Lognormal	1633.937	1641.930	1774.200	1782.237
Generalised gamma	**1594.590**	**1606.580**	**1766.989**	**1779.045**

AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion, FOLFIRI: folinic acid plus fluorouracil plus irinotecan

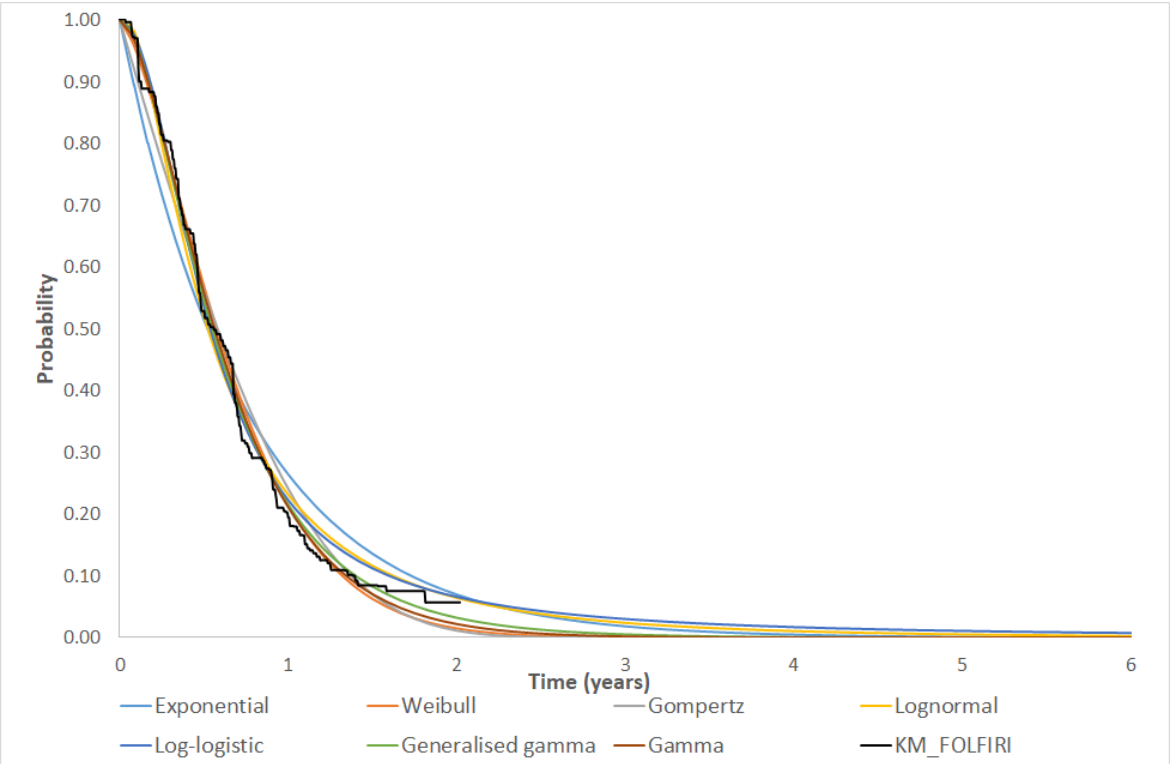
The best-fitting model us indicated by the lowest AIC or BIC value. Models that are the best fitting or within 5 points of the best-fitting are highlighted in bold.

Figure 17: Observed and model-predicted PFS, bevacizumab plus FOLFIRI, first-line setting



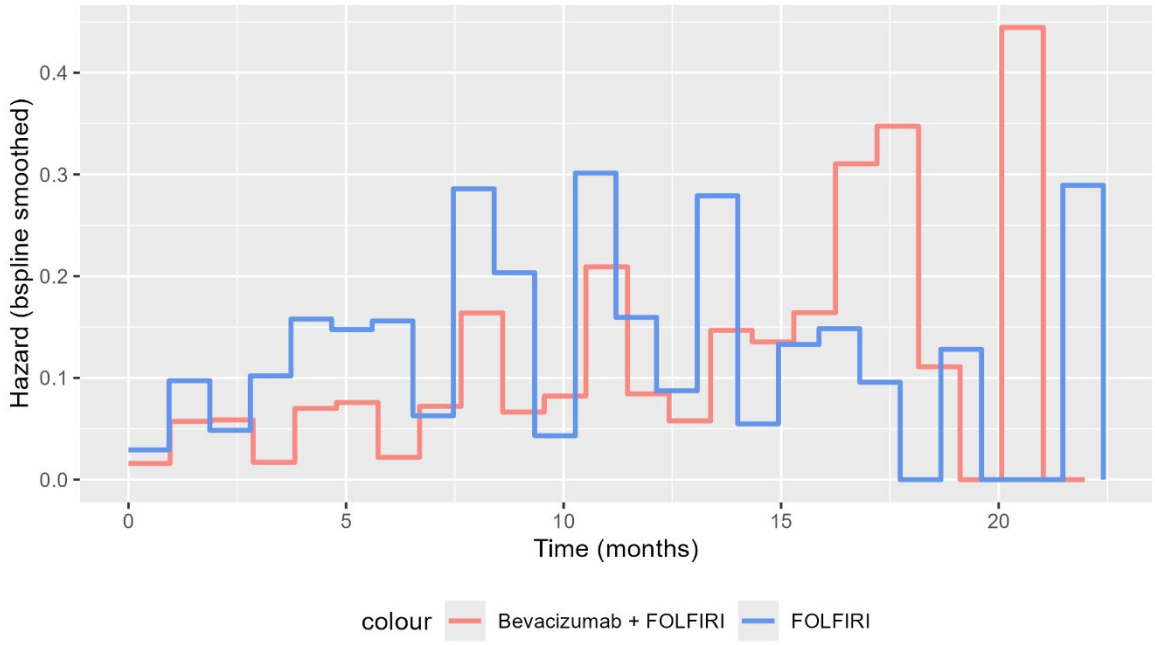
PFS: progression-free survival; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; KM: Kaplan-Meier

Figure 18: Observed and model-predicted PFS, FOLFIRI alone, first-line setting



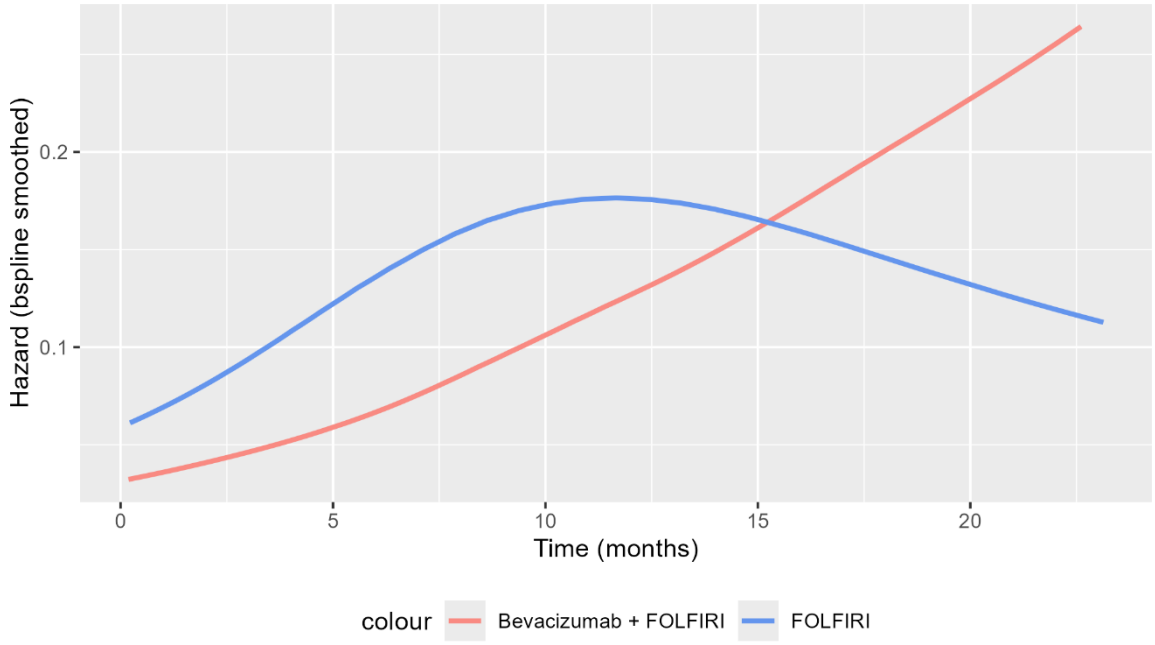
PFS: progression-free survival; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; KM: Kaplan-Meier

Figure 19: Empirical hazard plot for PFS (generated by the EAG), first-line setting



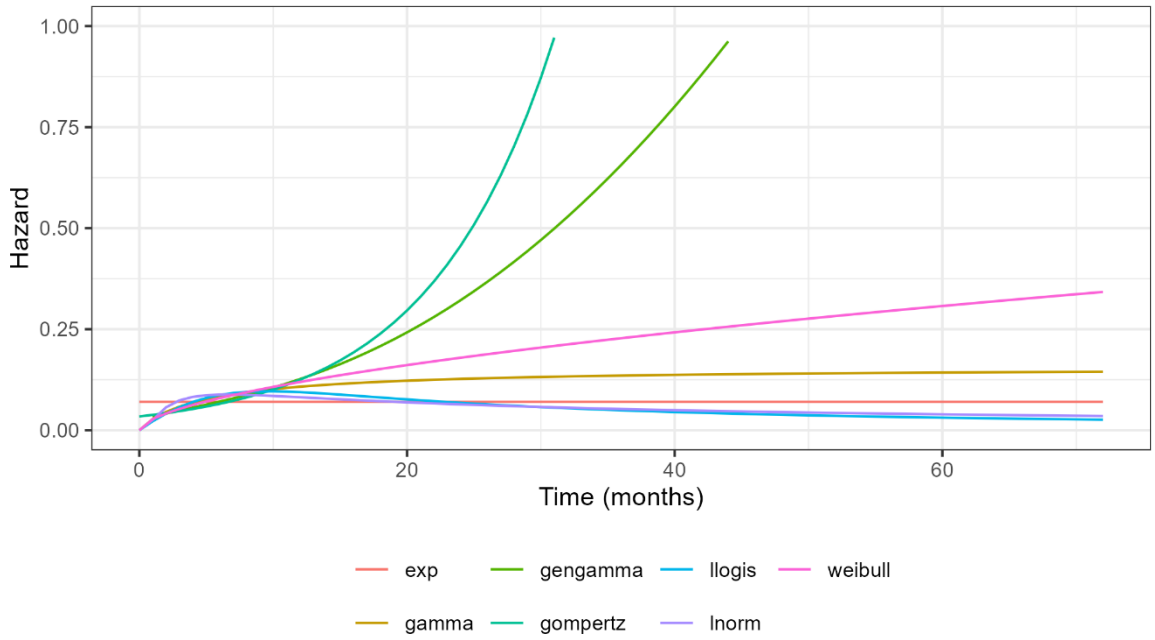
FOLFIRI: folinic acid plus fluorouracil plus irinotecan

Figure 20: Smoothed hazard plot for PFS (generated by the EAG), first-line setting



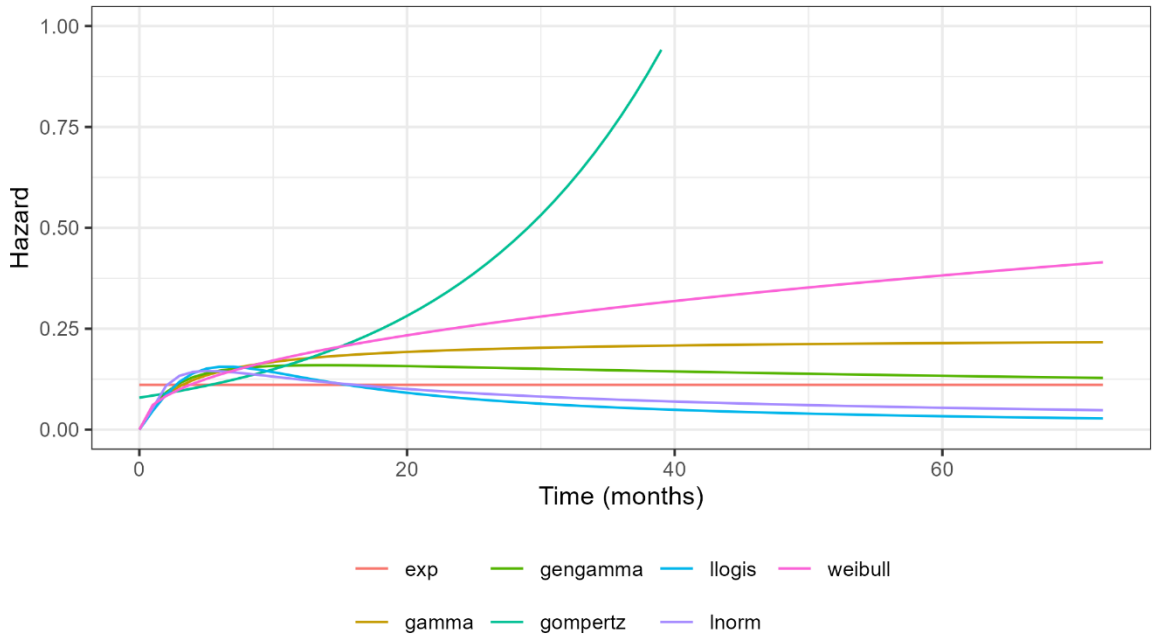
FOLFIRI: folinic acid plus fluorouracil plus irinotecan

Figure 21: Modelled hazard plots from standard parametric survival models for PFS, bevacizumab plus FOLFIRI (generated by the EAG), first-line setting



Exp: exponential; gengamma: generalised gamma; llogis: log-logistic; lnorm: log-normal

Figure 22: Modelled hazard plots from standard parametric survival models for PFS, FOLFIRI alone (generated by the EAG), first-line setting



Exp: exponential; gengamma: generalised gamma; llogis: log-logistic; lnorm: log-normal

5.4.3.2.2. Overall survival

5.4.3.2.2.1. OS for bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone

OS was modelled independently for the bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone groups using pseudo-IPD from Study NO16966,[5] based on the assumptions preferred by the Appraisal Committee in TA212.

Table 13 summarises AIC and BIC values for the fitted models, and Figure 23 and Figure 24 present the comparison of model-predicted versus observed OS for bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone, respectively. Empirical and smoothed hazard plots are shown in Figure 25 and Figure 26. Parametric model-based hazard plots for each group are presented in Figure 27 (bevacizumab plus FOLFOX/CAPOX) and Figure 28 (FOLFOX/CAPOX alone).

Table 13: AIC and BIC statistics, OS, bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone, first-line setting

Distribution	Bevacizumab plus FOLFOX/CAPOX		FOLFOX/CAPOX alone	
	AIC	BIC	AIC	BIC
Exponential	2813.47	2817.75	2806.36	2810.62
Weibull	**2732.90**	**2741.46**	**2711.40**	**2719.93**
Gamma	**2737.20**	**2745.76**	**2707.00**	**2715.53**
Gompertz	2743.71	2752.27	2740.80	2749.33
Log-logistic	2741.68	2750.24	**2707.41**	**2715.94**
Lognormal	2771.83	2780.39	2716.74	2725.27
Generalised gamma	**2734.55**	2747.40	**2708.68**	2721.47

AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion
The best-fitting model us indicated by the lowest AIC or BIC value. Models that are the best fitting or within 5 points of the best-fitting are highlighted in bold.

Figure 23: Observed and model-predicted OS, bevacizumab plus FOLFOX/CAPOX, first-line setting

OS: overall survival; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CAPOX: capecitabine plus oxaliplatin; KM: Kaplan-Meier

Figure 24: Observed and model-predicted OS, FOLFOX/CAPOX alone, first-line setting

OS: overall survival; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CAPOX: capecitabine plus oxaliplatin; KM: Kaplan-Meier

Figure 25: Empirical hazard plot for OS (generated by the EAG), first-line setting

FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CAPOX: capecitabine plus oxaliplatin

Figure 26: Smoothed hazard plots for OS (generated by the EAG), first-line setting

FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CAPOX: capecitabine plus oxaliplatin

Figure 27: Modelled hazard plots from standard parametric survival models for OS, bevacizumab plus FOLFOX/CAPOX (generated by the EAG), first-line setting

Exp: exponential; gengamma: generalised gamma; llogis: log-logistic; lnorm: log-normal

Figure 28: Modelled hazard plots from standard parametric survival models for OS, FOLFOX/CAPOX alone (generated by the EAG), first-line setting

Exp: exponential; gengamma: generalised gamma; llogis: log-logistic; lnorm: log-normal

5.4.3.2.2.2. OS for bevacizumab plus FOFLFIRI and FOLFIRI alone

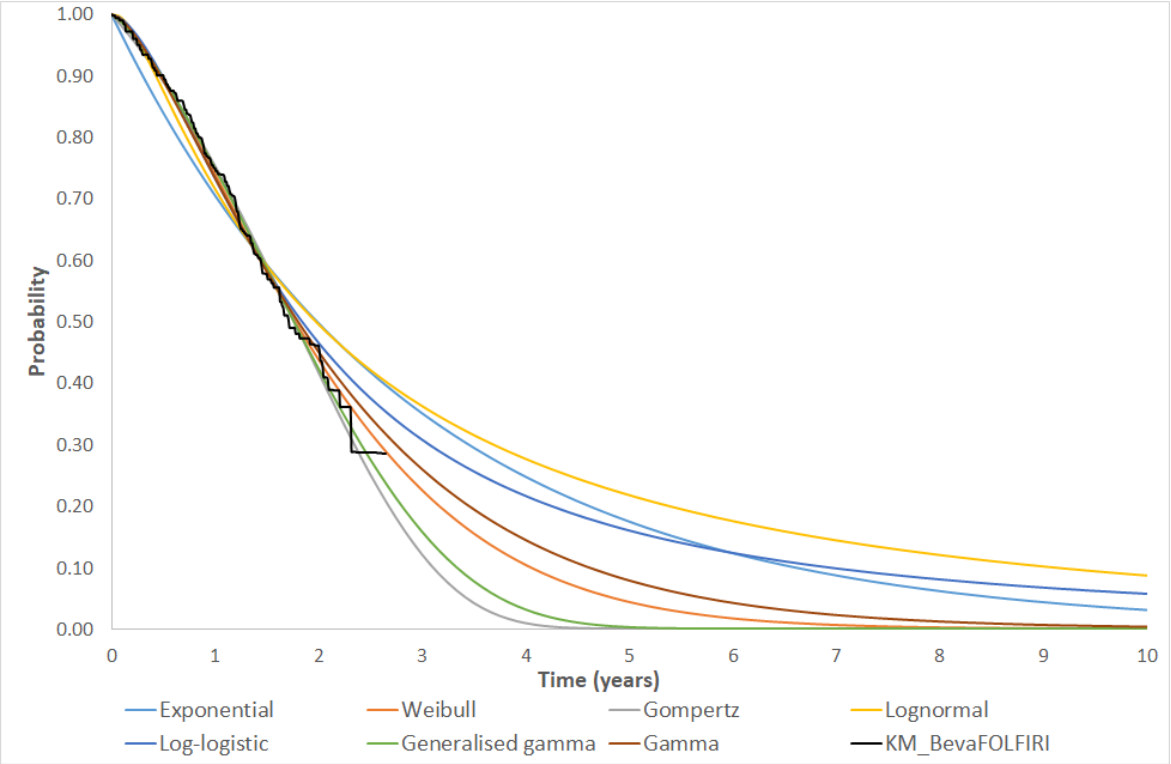
OS was modelled independently for the bevacizumab plus FOLFIRI and FOLFIRI alone groups using the pseudo-IPD derived from Hurwitz *et al.*[7]. Table 14 summarises the AIC and BIC values for the fitted models, and Figure 30 present the comparison of the model-predicted versus observed OS for bevacizumab plus FOLFIRI and FOLFIRI alone groups respectively. Empirical and smoothed hazard plots for the observed period are shown in Figure 31 (bevacizumab plus FOLFIRI) and Figure 32 (FOLFIRI alone) and the corresponding parametric model-based hazard plots for each group are presented in Figure 33 and Figure 34.

Table 14: AIC and BIC statistics, OS, bevacizumab plus FOLFIRI and FOLFIRI alone, first-line setting

Distribution	Bevacizumab plus FOLFIRI		FOLFIRI alone	
	AIC	BIC	AIC	BIC
Exponential	1535.473	1539.469	1826.109	1830.127
Weibull	**1511.575**	**1519.568**	**1795.097**	**1803.134**
Gamma	**1513.894**	**1521.887**	**1798.537**	**1806.574**
Gompertz	**1511.332**	**1519.325**	**1797.284**	**1805.321**
Log-logistic	1517.576	1525.569	1804.364	1812.401
Lognormal	1535.627	1543.62	1829.201	1837.239
Generalised gamma	**1511.819**	**1523.808**	**1795.735**	**1807.791**

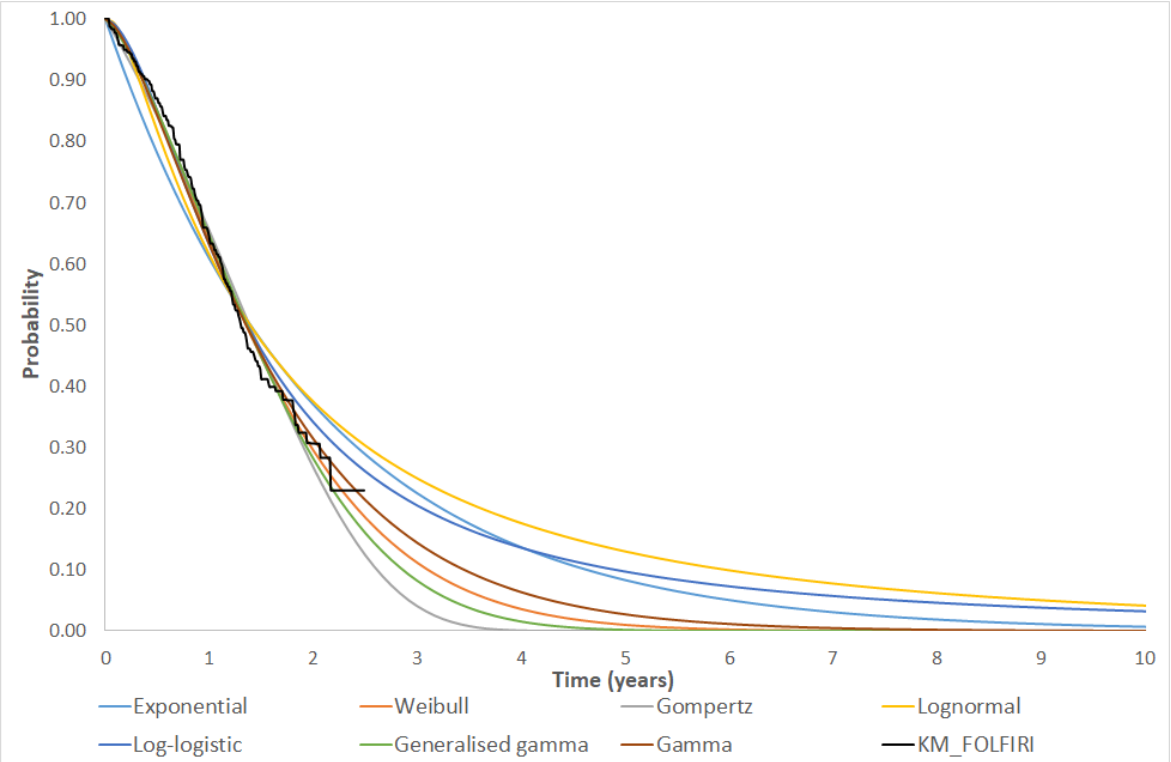
AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion
The best-fitting model us indicated by the lowest AIC or BIC value. Models that are the best fitting or within 5 points of the best-fitting are highlighted in bold.

Figure 29: Observed and model-predicted OS, bevacizumab plus FOLFIRI, first-line setting



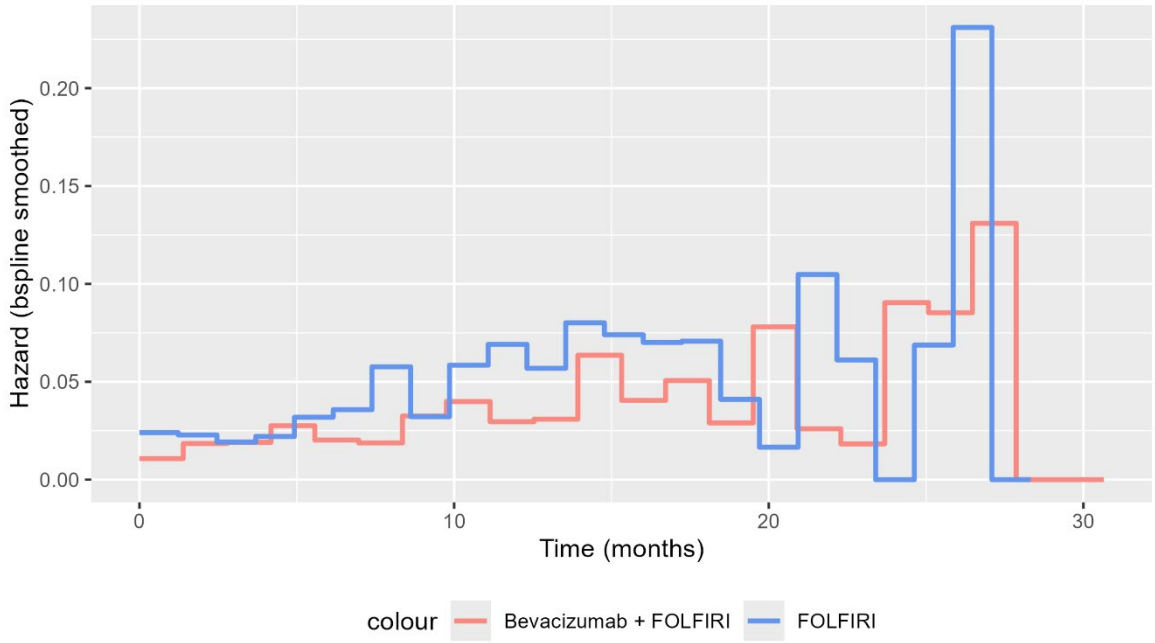
OS: overall survival; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; KM: Kaplan-Meier; BevaFOLFIRI: bevacizumab plus FOLFIRI

Figure 30: Observed and model-predicted OS, FOLFIRI alone, first-line setting



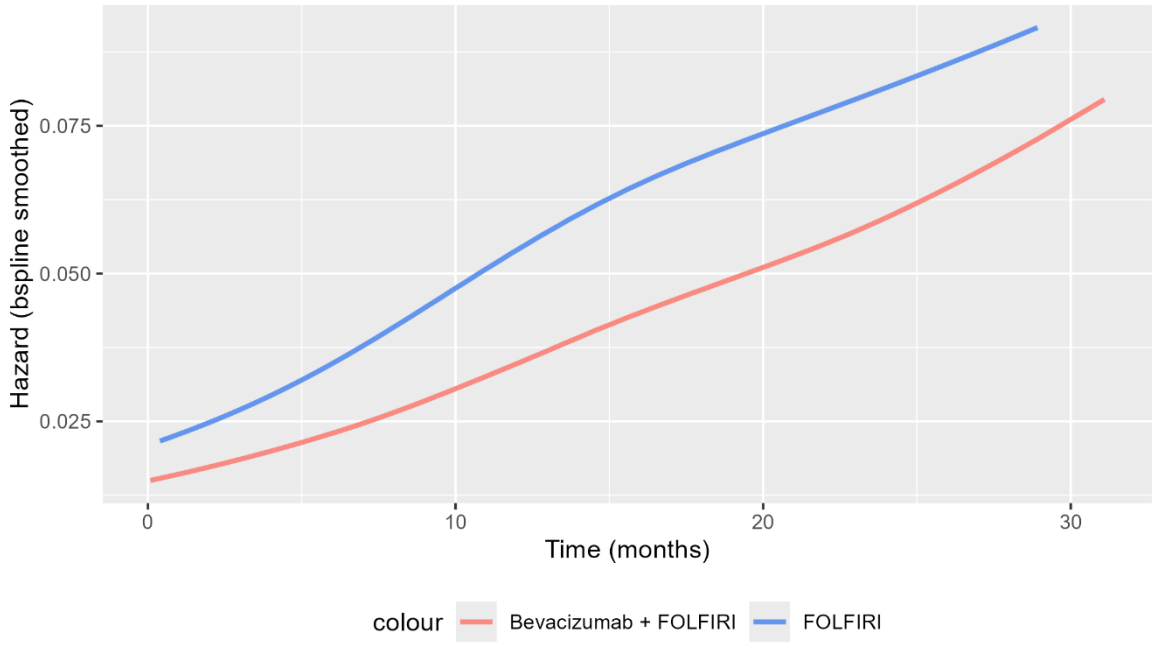
OS: overall survival; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; KM: Kaplan-Meier

Figure 31: Empirical hazard plot for OS (generated by the EAG), first-line setting



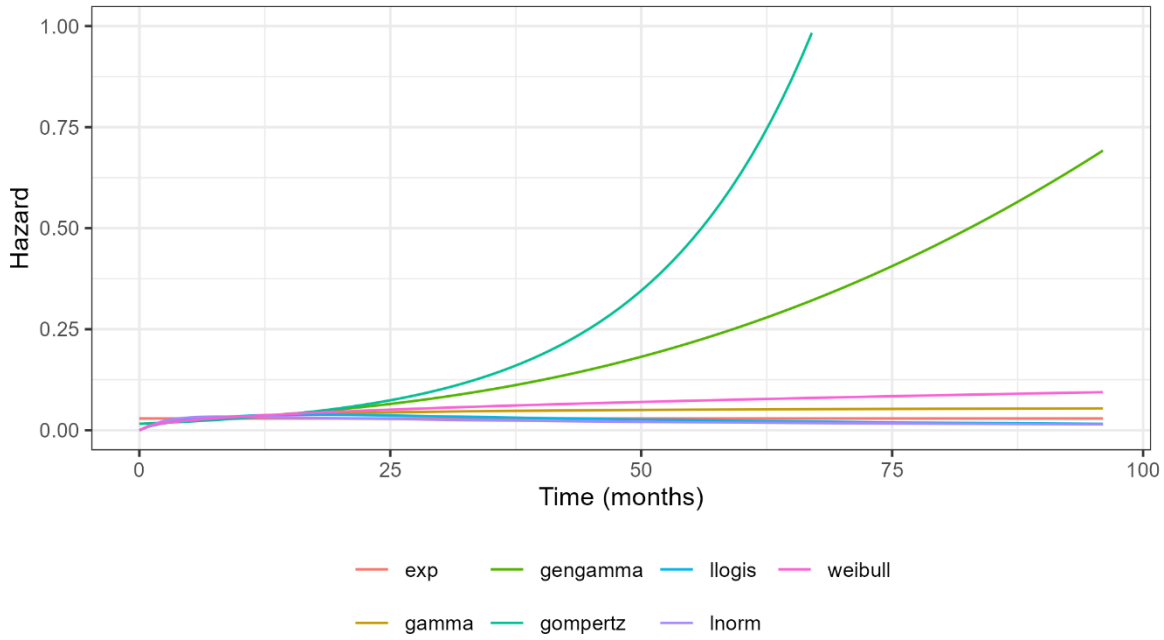
FOLFIRI: folinic acid plus fluorouracil plus irinotecan

Figure 32: Smoothed hazard plots for OS (generated by the EAG), first-line setting



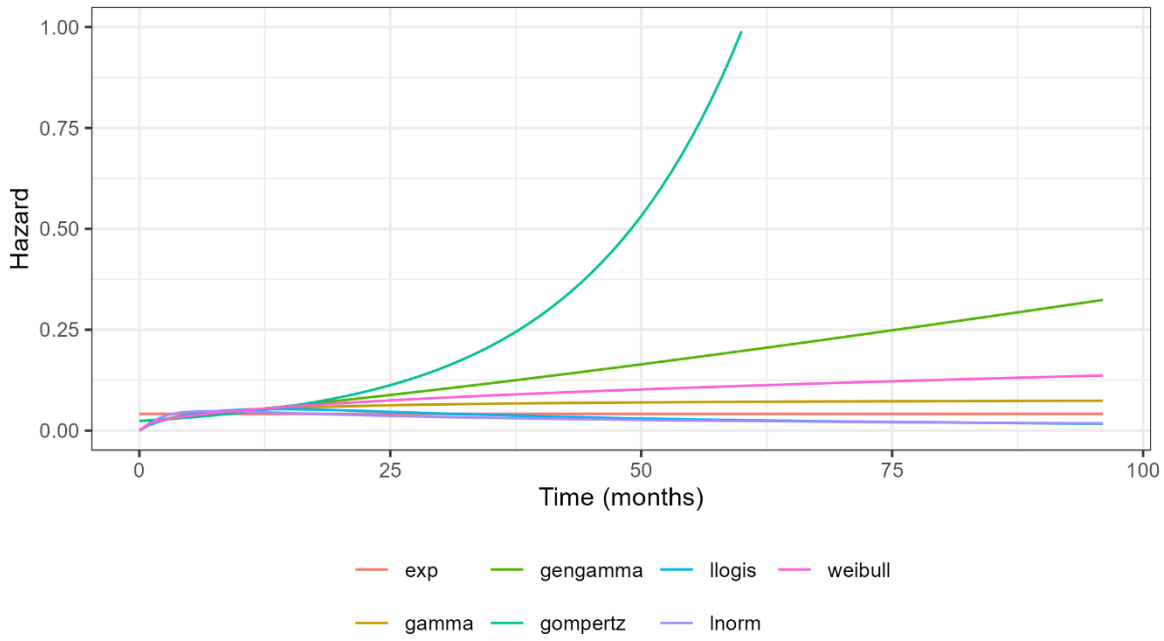
FOLFIRI: folinic acid plus fluorouracil plus irinotecan

Figure 33: Modelled hazard plots from standard parametric survival models for OS, bevacizumab plus FOLFIRI (generated by the EAG), first-line setting



Exp: exponential; gengamma: generalised gamma; llogis: log-logistic; lnorm: log-normal

Figure 34: Modelled hazard plots from standard parametric survival models for OS, FOLFIRI (generated by the EAG), first-line setting



Exp: exponential; gengamma: generalised gamma; llogis: log-logistic; lnorm: log-normal

5.4.3.2.3. Survival model selection for first-line treatment

The EAG has used a pragmatic approach to model selection, balancing between providing sufficient information for the Appraisal Committee to make an informed decision and limiting the number of analyses run.

In some cases, the hazard plots generated by the EAG using the reconstructed pseudo-IPD, appeared to have a turning point. This was evident in the PFS hazard functions in the bevacizumab plus FOLFOX/CAPOX, FOLFOX/CAPOX alone and FOLFIRI alone groups. However, clinical experts consulted by the EAG expressed their belief that the hazard trend would likely continue to increase for both PFS and OS. Therefore, the EAG prioritised the use of models with monotonically increasing hazard trends in the base case and explored the use of alternative models in scenario analyses. Based on NICE Decision Support Unit (DSU) Technical Support Document (TSD) 14,[39] the EAG additionally prioritised selecting the same type of models across treatment arms. The selected base case and sensitivity analyses are deemed to provide a plausible range in the ICER.

5.4.3.2.3.1. Distributions selected to model progression-free survival for bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone

The AIC and BIC statistics for PFS for the bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone groups are shown in Table 11. The log-logistic model has the lowest AIC and BIC values for both the bevacizumab plus FOLFOX/CAPOX and the FOLFOX/CAPOX arms with no other model being within 5 points of the log-logistic. This model has an increasing hazard until it reaches a turning point after which the hazard is decreasing; this pattern can be seen in Figure 14. However, clinical advice to the EAG suggests that the hazard should be monotonically increasing across time, which would indicate that the gamma, or the generalised gamma model, would be more appropriate (see Figure 15 and Figure 16). The EAG has followed clinical advice and has used gamma distributions for both arms in the base case and log-logistic distributions for both arms in a sensitivity analysis. Whilst there is little difference in the goodness-of-fit statistics for the gamma and generalised gamma models, the gamma was selected as it provides a bigger contrast (in terms of long-term hazards) than the log-logistic.

5.4.3.2.3.2. Distributions selected to model progression-free survival for bevacizumab plus FOLFIRI and FOLFIRI alone

The AIC and BIC statistics for the parametric model fits to the PFS data for the bevacizumab plus FOLFIRI and FOLFIRI alone groups are shown in Table 12. Three models in the bevacizumab plus FOLFIRI PFS analysis showed similar statistical fits, which were the Weibull, Gompertz and generalised gamma distributions. In the FOLFIRI alone PFS analysis, the gamma, log-logistic and

generalised gamma distributions provided similar statistical fits. These models all provided similar visual fits to the observed data.

Having examined the totality of the evidence, the EAG marginally preferred Weibull distributions for the base case analysis over generalised gamma distributions which was used in a sensitivity analysis. The summed BIC values for the two arms are very similar between the Weibull and the generalised gamma for PFS, however the Weibull was a better fit to the OS data (see Table 14) and the EAG preferred to use the same distribution for PFS and OS.

5.4.3.2.3.3. Distributions selected to model overall survival for bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone

The AIC and BIC for OS are shown in Table 13. The best-fitting model differs between the bevacizumab plus FOLFOX/CAPOX arm and the FOLFOX/CAPOX arm being the Weibull and gamma, respectively. However, both models have a monotonically increasing hazard (see Figure 28) which aligns with clinical opinion provided to the EAG.

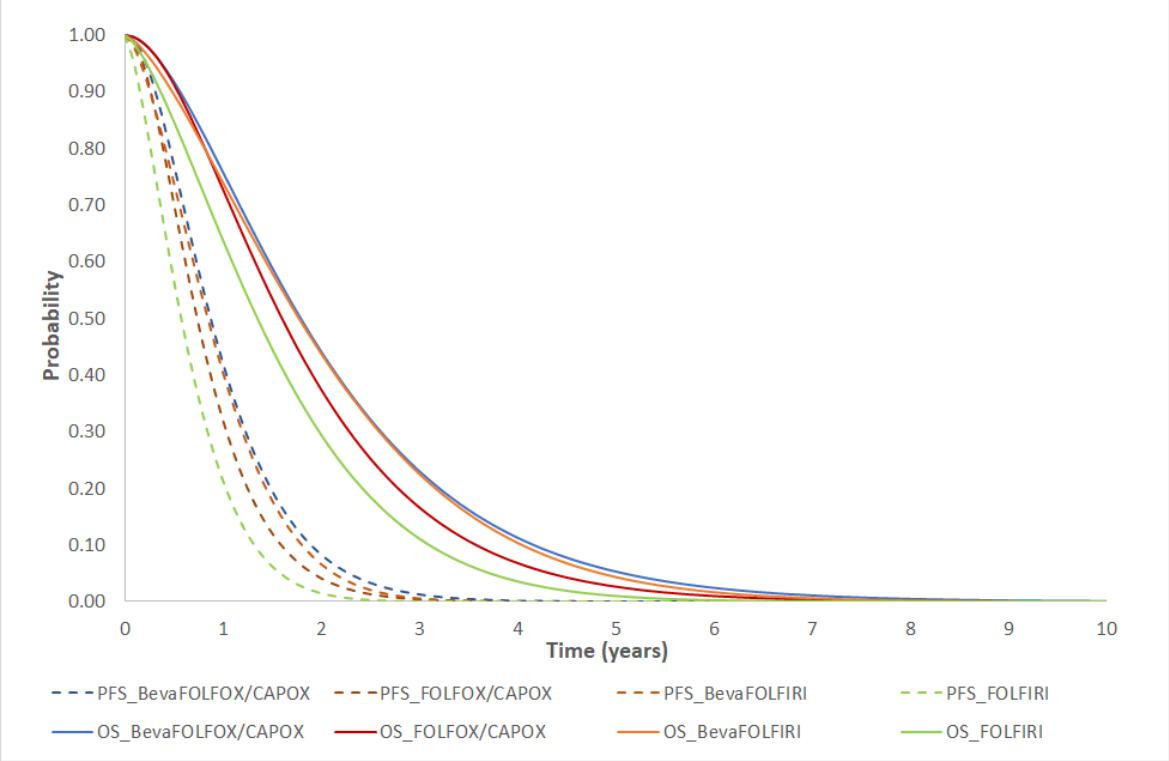
For consistency with the PFS analyses, the gamma distribution has been used in the base case, with the log-logistic, which provides a good fit to the FOLFOX/CAPOX arm and is not an overly-poor fit to the bevacizumab plus FOLFOX/CAPOX arm, used in sensitivity analyses.

5.4.3.2.3.4. Distributions selected to model overall survival for bevacizumab plus FOLFIRI and FOLFIRI alone

The AIC and BIC statistics for the parametric model fits to the OS data for the bevacizumab plus FOLFIRI and FOLFIRI alone groups are shown in Table 14. Four models had AIC and BIC values within 5 points of the minimum AIC/BIC for both groups, which were the Weibull, gamma, Gompertz and generalised gamma. All four models provided adequate visual fitting to the observed data in both groups. For consistency with the PFS analyses of the bevacizumab plus FOLFIRI and FOLFIRI alone groups, the Weibull distribution has been used in the base case, with the generalised gamma distribution as a scenario analysis. Both model choices provide good statistical and visual fit to the observed data.

Figure 35 summarises the overall model predictions for PFS and OS for each treatment group in the base case.

Figure 35: Base case PFS and OS model predictions, all treatment groups, first-line setting



BevaFOLFOX/CAPOX: bevacizumab plus FOLFOX/CAPOX; BevaFOLFIRI: bevacizumab plus FOLFIRI; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CAPOX: capecitabine plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; PFS: progression-free survival; OS: overall survival

5.4.3.3. Time-to-event data for the second-line treatment: progression-free survival and overall survival

PFS and OS were modelled independently for the bevacizumab plus FOLFOX and FOLFOX alone groups using the data from Study E3200. As the EAG did not have access to the IPD, the KM curves from Giantonio *et al*. [12] were digitised, with pseudo-IPD for PFS and OS data generated using the algorithm reported by Guyot *et al*.[38] The EAG fitted parametric survival models as described for the time-to-event data in first-line.

In the absence of clinical studies evaluating the clinical effectiveness of bevacizumab plus CAPOX versus CAPOX alone in the second-line setting, the EAG assumed equivalent efficacy between CAPOX- and FOLFOX-containing regimens. This assumption is in line with the assumptions used in the first-line setting.

No clinical evidence was found for the comparison of bevacizumab plus FOLFIRI versus FOLFIRI alone in the second-line setting. The EAG therefore made inferences on the likely cost-effectiveness of this comparison based on the ICERs produced in first-line.

5.4.3.3.1. Progression-free survival for bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone in second-line treatment

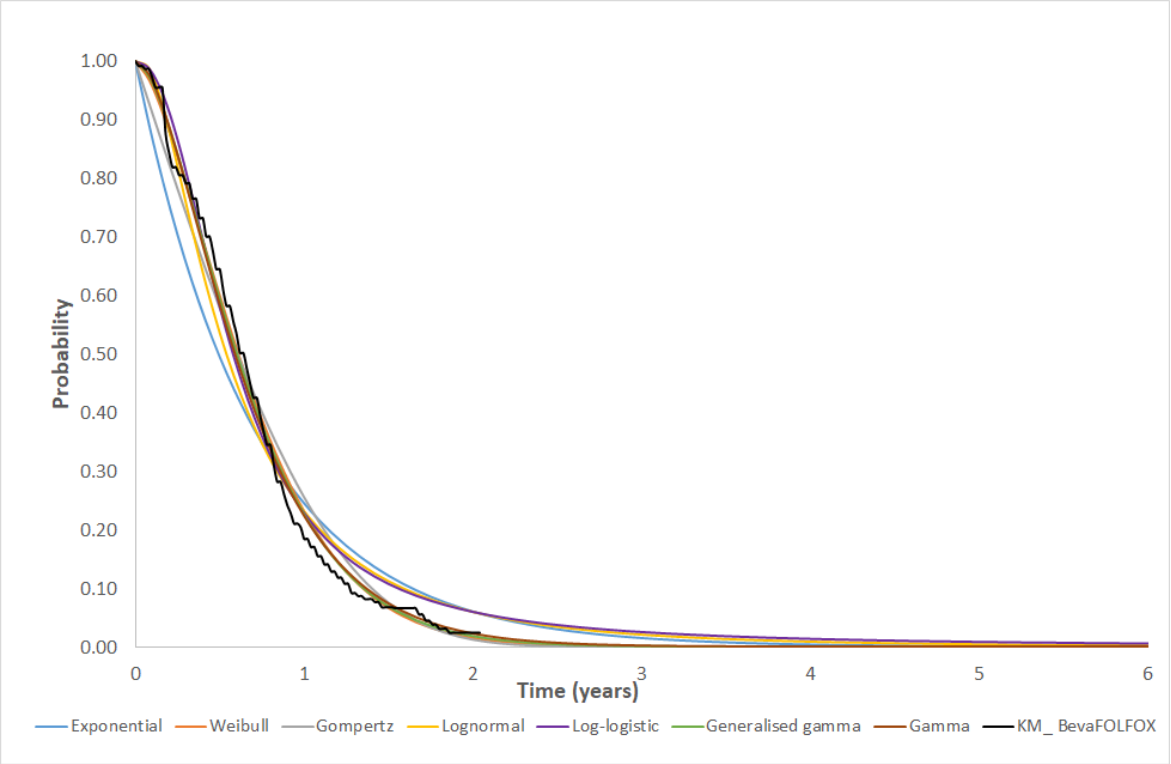
Table 15 summarises AIC and BIC values for the fitted models, Figure 36 and Figure 37 present the comparison of model-predicted versus observed PFS for bevacizumab plus FOLFOX/CAPOX versus FOLFOX/CAPOX alone, respectively. Empirical and smoothed hazard plots are shown in Figure 38 and Figure 39, respectively. Parametric model-based hazard plots for each group are presented separately in Figure 40 (bevacizumab plus FOLFOX/CAPOX) and Figure 41 (FOLFOX/CAPOX alone).

Table 15: AIC and BIC statistics, PFS, bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone, second-line setting

Distribution	**Bevacizumab plus FOLFOX/CAPOX**		**FOLFOX/CAPOX alone**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	1718.65	1722.29	1543.05	1546.68
Weibull	**1657.31**	**1664.58**	1489.56	1496.82
Gamma	**1657.20**	**1664.47**	1474.11	1481.37
Gompertz	1682.09	1689.36	1529.65	1536.91
Log-logistic	1675.11	1682.38	**1461.08**	**1468.34**
Lognormal	1697.92	1705.19	1481.00	1488.26
Generalised gamma	**1658.19**	**1669.09**	1469.95	1480.84

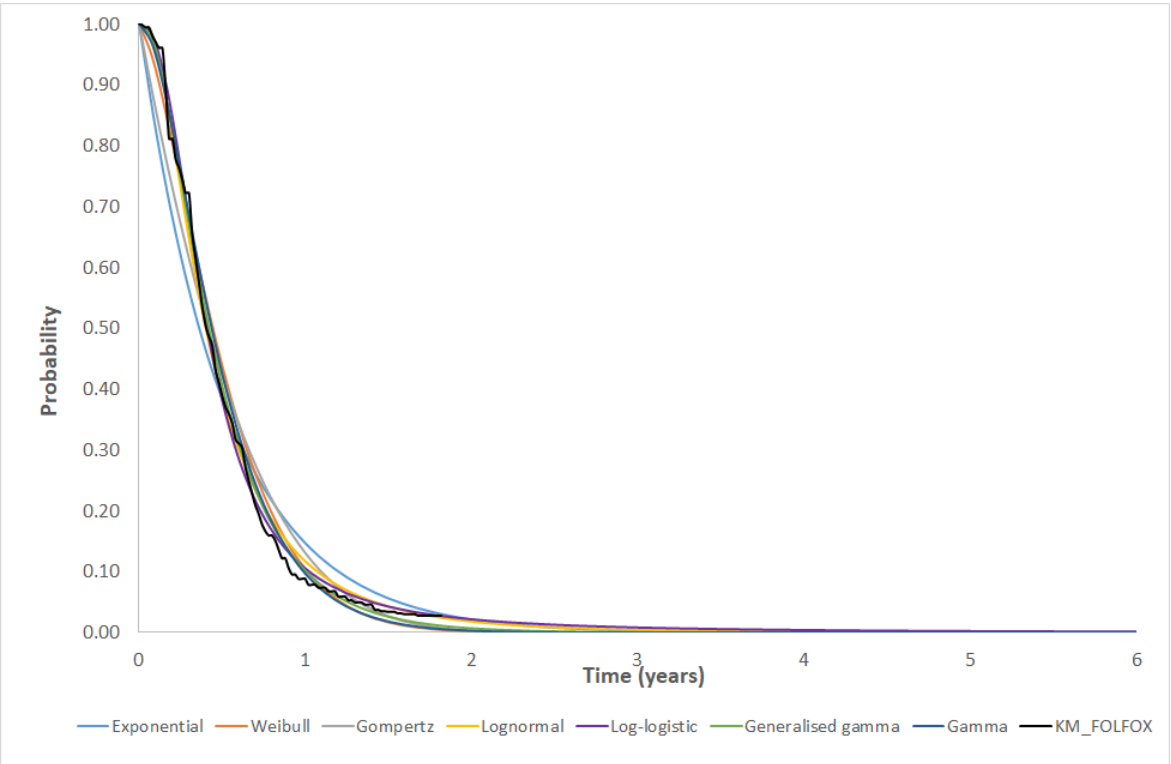
AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CAPOX: capecitabine plus oxaliplatin
The best-fitting model is indicated by the lowest AIC or BIC value. Models that are the best fitting or within 5 points of the best-fitting are highlighted in bold.

Figure 36: Observed and model-predicted PFS, bevacizumab plus FOLFOX/CAPOX, second-line setting



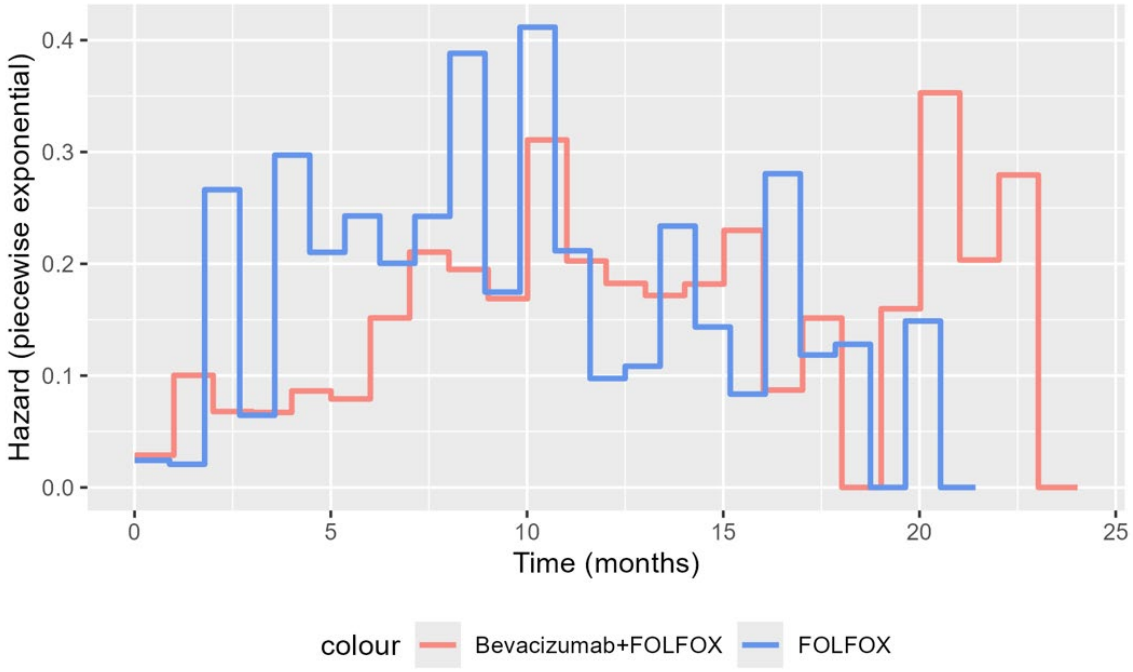
PFS: progression-free survival; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CAPOX: capecitabine plus oxaliplatin; KM: Kaplan-Meier

Figure 37: Observed and model-predicted PFS, FOLFOX/CAPOX alone, second-line setting



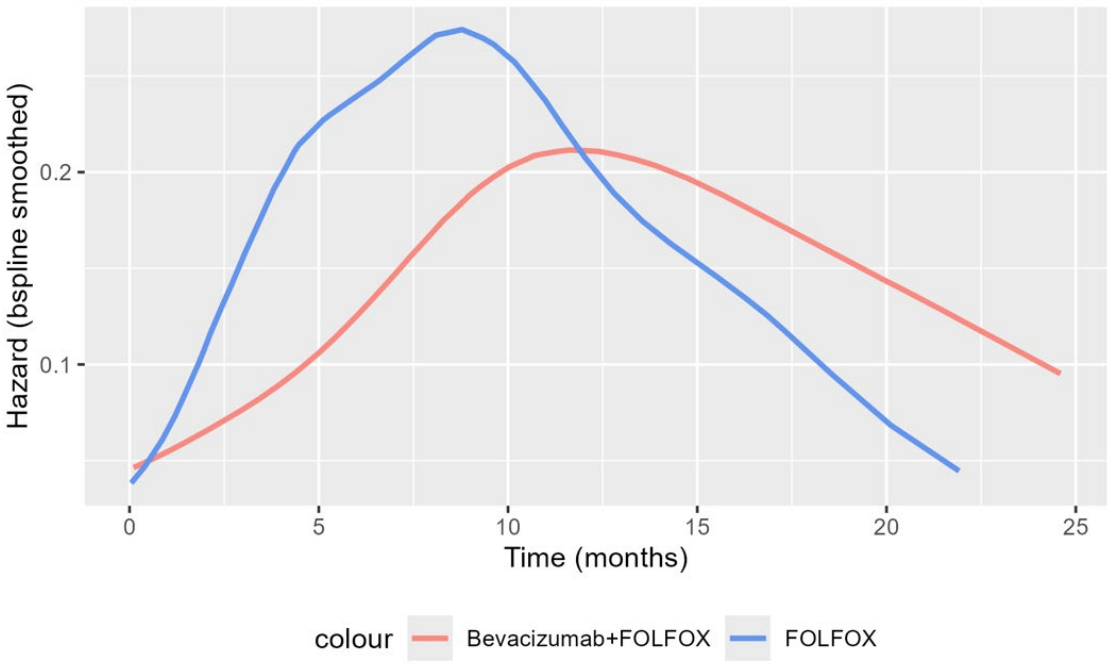
PFS: progression-free survival; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CAPOX: capecitabine plus oxaliplatin; KM: Kaplan-Meier

Figure 38: Empirical hazard plot for PFS (generated by the EAG), second-line setting



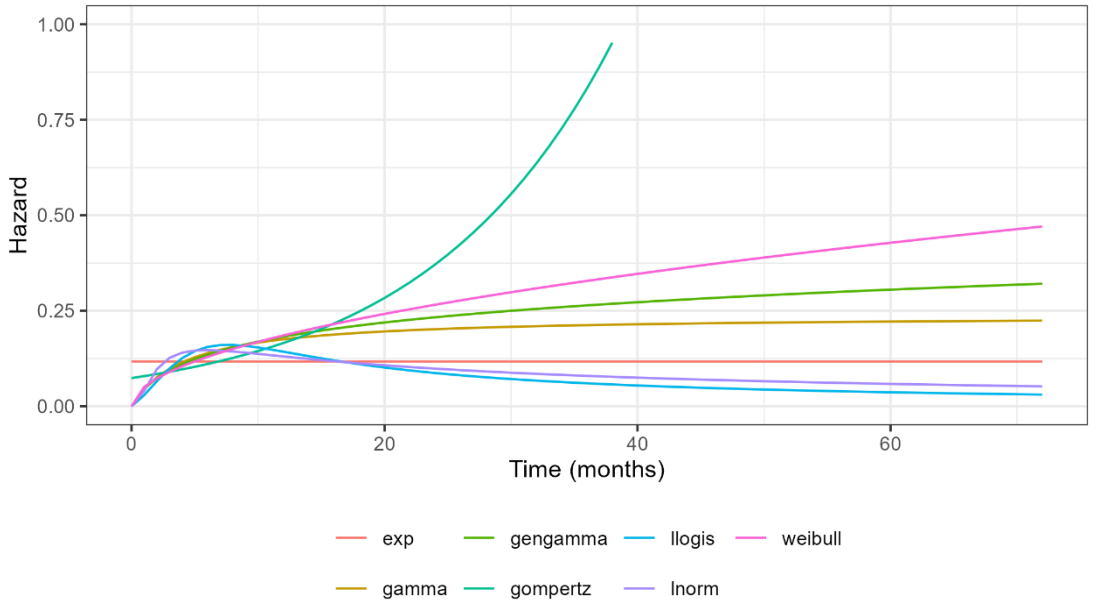
FOLFOX: folinic acid plus fluorouracil plus oxaliplatin

Figure 39: Smoothed hazard plot for PFS (generated by the EAG), second-line setting



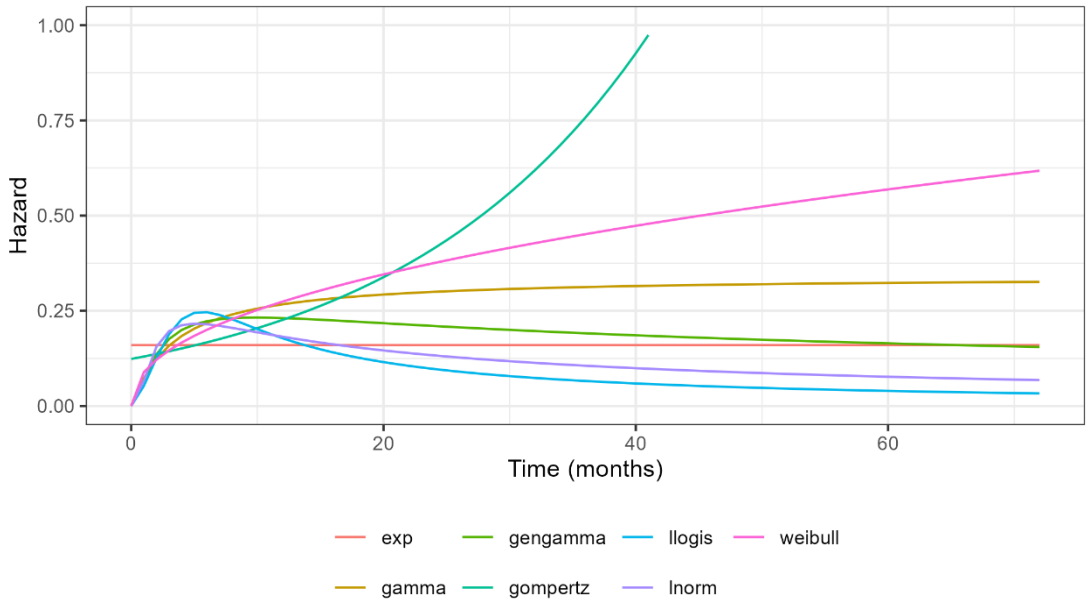
FOLFOX: folinic acid plus fluorouracil plus oxaliplatin

Figure 40: Hazard plots from standard parametric survival models for PFS, bevacizumab plus FOLFOX/CAPOX (generated by the EAG), second-line setting



Exp: exponential; gengamma: generalised gamma; llogis: log-logistic; lnorm: log-normal

Figure 41: Modelled hazard plots from standard parametric survival models for PFS, FOLFOX/CAPOX alone (generated by the EAG), second-line setting



Exp: exponential; gengamma: generalised gamma; llogis: log-logistic; lnorm: log-normal

5.4.3.3.2. Overall survival for bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone in second-line treatment

Table 16 summarises AIC and BIC values for the fitted models, Figure 42 and Figure 43 present the comparison of model-predicted versus observed OS for bevacizumab plus FOLFOX/CAPOX versus FOLFOX/CAPOX alone, respectively. Empirical and smoothed hazard plots are shown in Figure 44 and Figure 45, respectively. Parametric model-based hazard plots for each group are presented separately in Figure 46 (bevacizumab plus FOLFOX/CAPOX) and Figure 47 (FOLFOX/CAPOX alone).

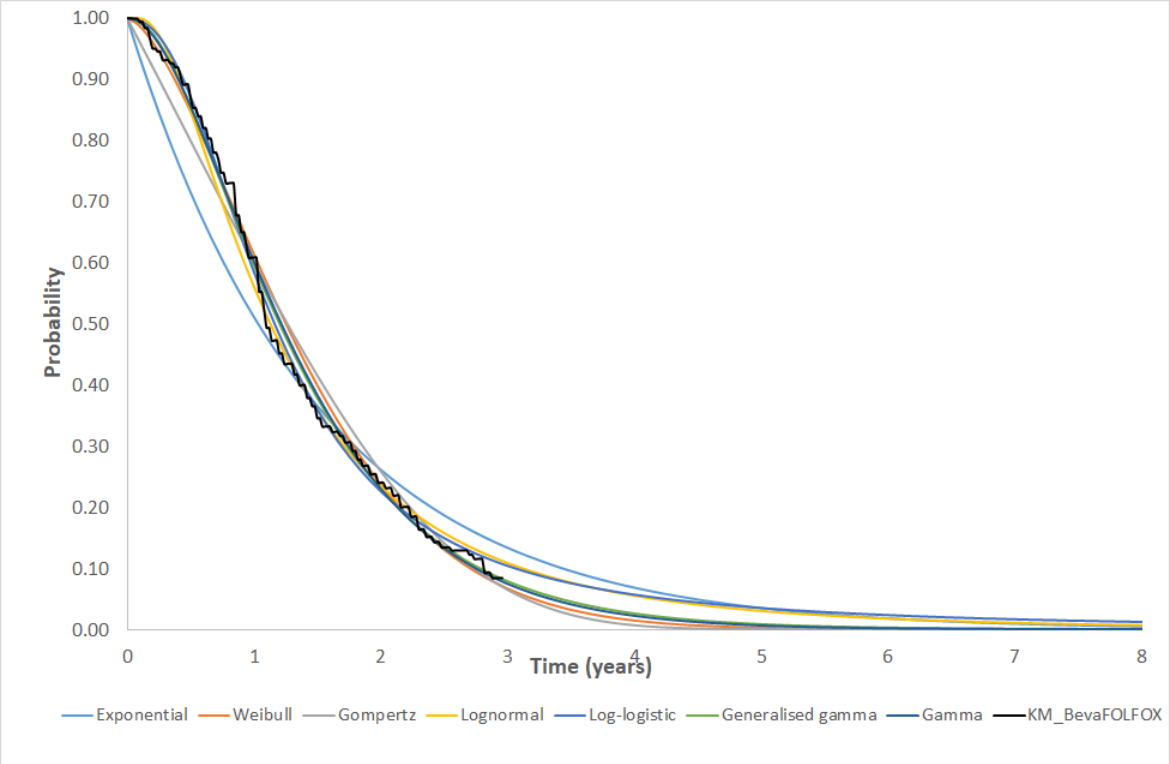
Table 16: AIC and BIC statistics, OS, bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone, second-line setting

Distribution	**Bevacizumab plus FOLFOX/CAPOX**		**FOLFOX/CAPOX alone**	
	AIC	**BIC**	**AIC**	**BIC**
Exponential	2036.95	2040.61	2036.47	2040.15
Weibull	1974.16	1981.47	1968.81	1976.16
Gamma	**1969.06**	**1976.37**	1954.54	1961.89
Gompertz	1999.58	2006.90	2006.19	2013.54
Log-logistic	**1971.80**	**1979.11**	**1946.95**	**1954.30**
Lognormal	1981.37	1988.68	**1946.36**	**1953.70**
Generalised gamma	**1970.70**	1981.67	**1947.36**	**1958.38**

AIC: Akaike Information Criterion; BIC: Bayesian Information Criterion; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CAPOX: capecitabine plus oxaliplatin

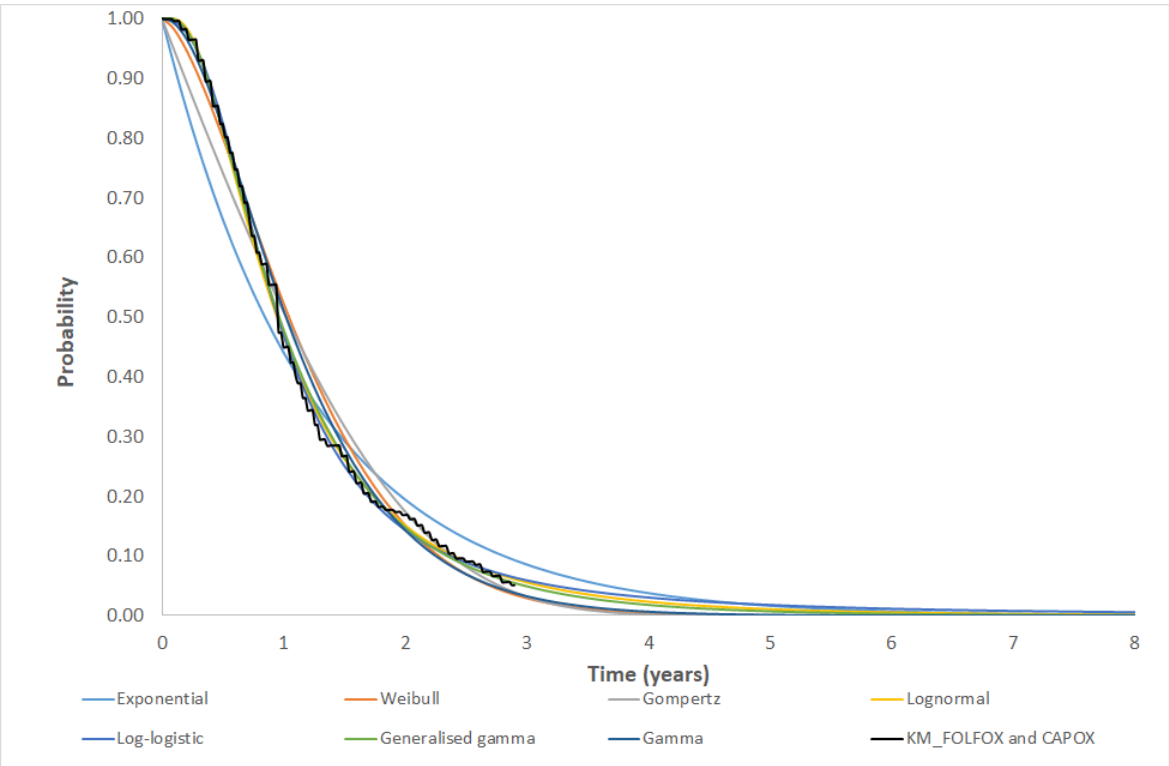
The best-fitting model is indicated by the lowest AIC or BIC value. Models that are the best fitting or within 5 points of the best-fitting are highlighted in bold.

Figure 42: Observed and model-predicted OS, bevacizumab plus FOLFOX/CAPOX, second-line setting



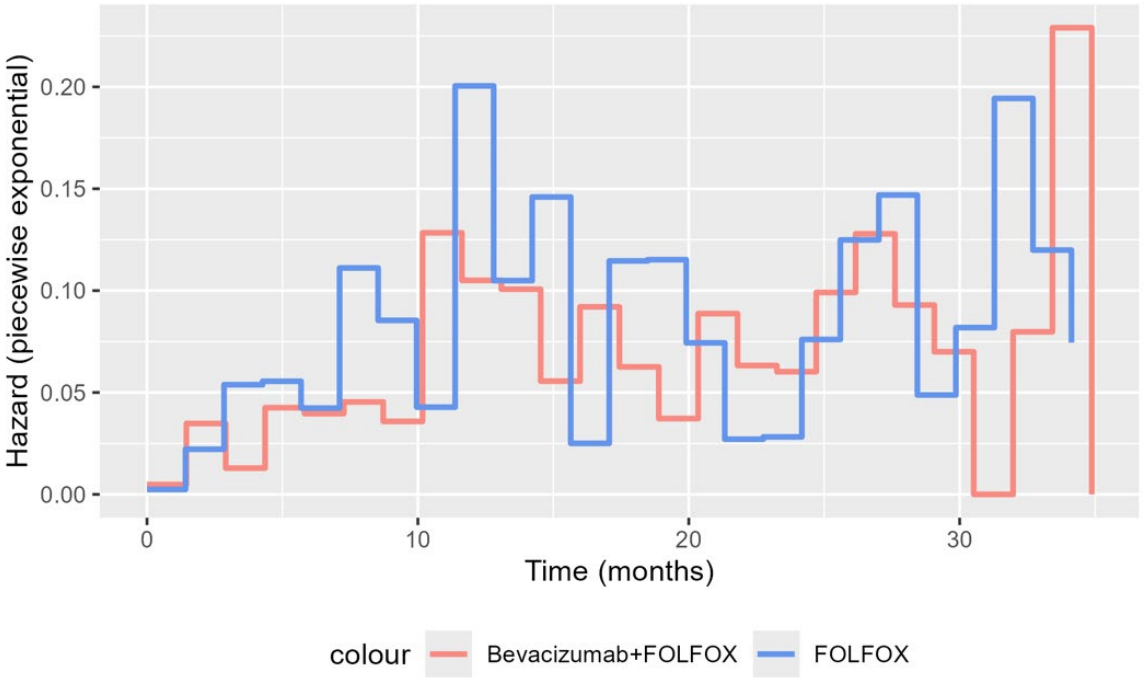
OS: overall survival; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CAPOX: capecitabine plus oxaliplatin; KM: Kaplan-Meier

Figure 43: Observed and model-predicted OS, FOLFOX/CAPOX alone, second-line setting



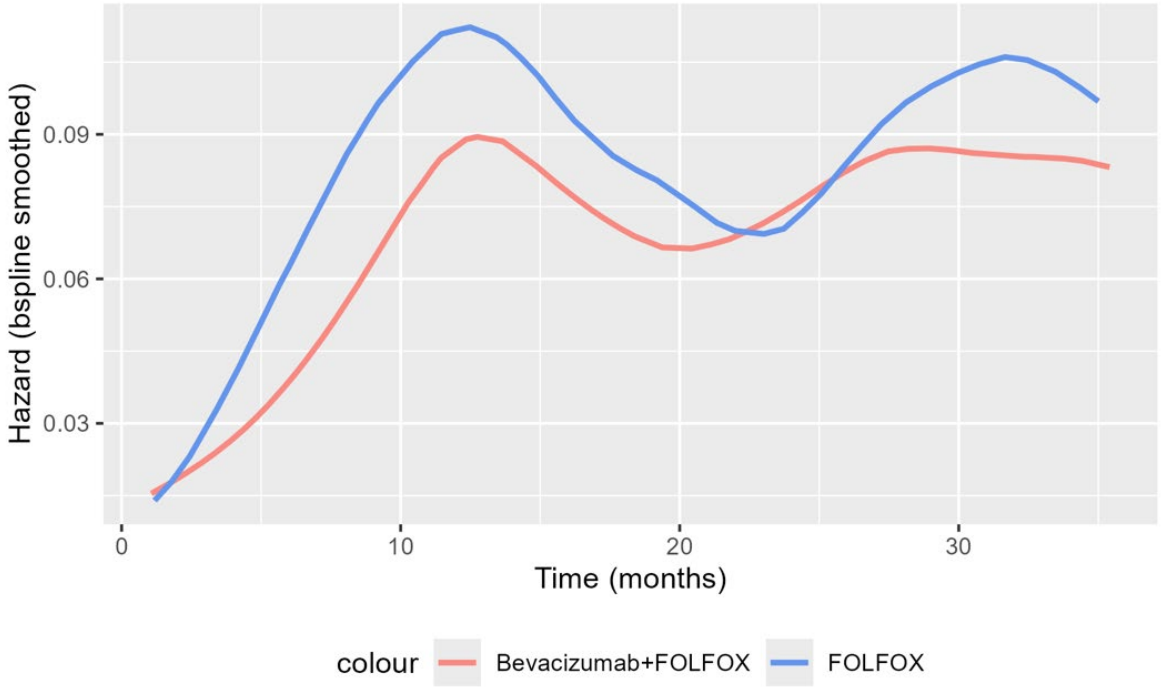
OS: overall survival; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CAPOX: capecitabine plus oxaliplatin; KM: Kaplan-Meier

Figure 44: Empirical hazard plot for OS (generated by the EAG), second-line setting



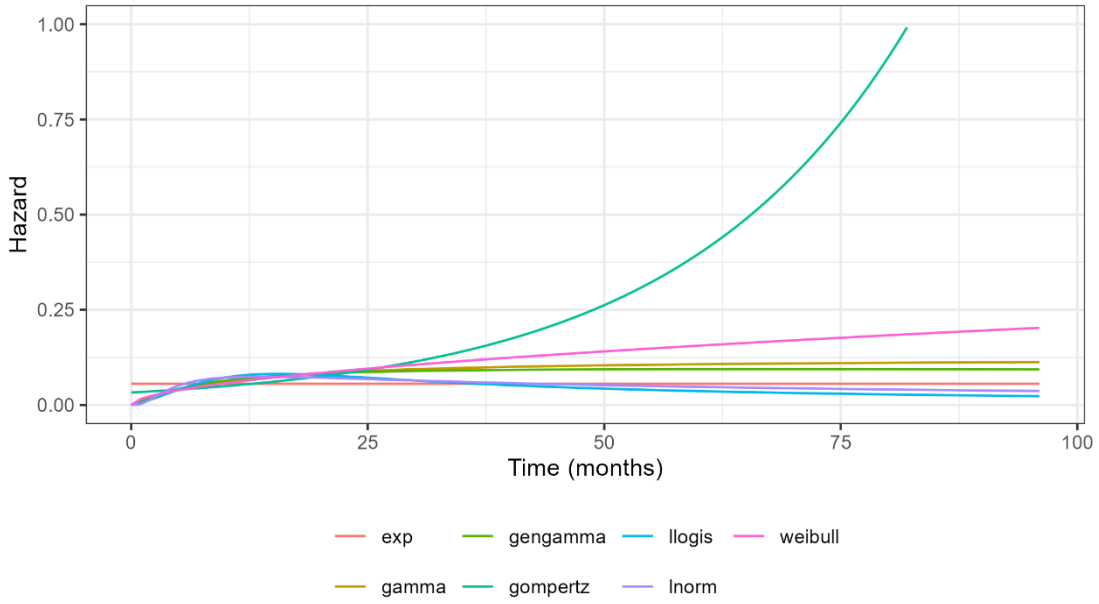
FOLFOX: folinic acid plus fluorouracil plus oxaliplatin

Figure 45: Smoothed hazard plots for OS (generated by the EAG), second-line setting



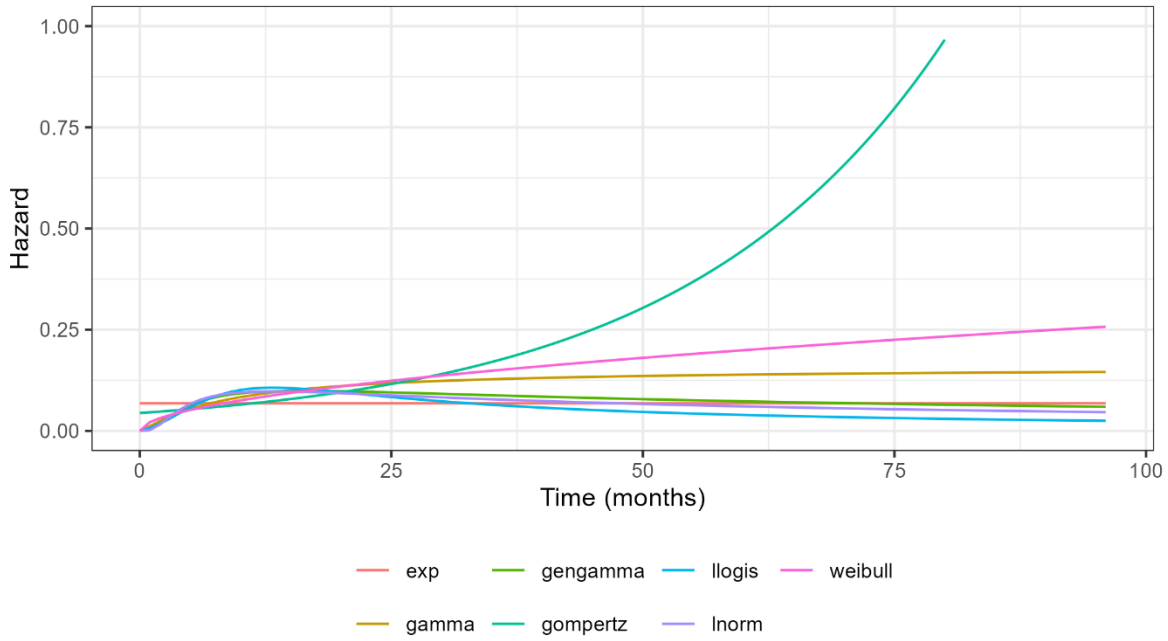
FOLFOX: folinic acid plus fluorouracil plus oxaliplatin

Figure 46: Hazard plots from standard parametric survival models for OS, bevacizumab plus FOLFOX/CAPOX (generated by the EAG), second-line setting



Exp: exponential; gengamma: generalised gamma; llogis: log-logistic; lnorm: log-normal

Figure 47: Modelled hazard plots from standard parametric survival models for OS, FOLFOX/CAPOX alone (generated by the EAG), second-line setting



Exp: exponential; gengamma: generalised gamma; llogis: log-logistic; lnorm: log-normal

5.4.3.3.3. Survival data for bevacizumab plus FOLFIRI and FOLFIRI alone

As described in Section 4.5, due to the absence of relevant clinical studies to the UK setting comparing bevacizumab plus FOLFIRI versus FOLFIRI alone, the potential cost-effectiveness of bevacizumab plus FOLFIRI versus FOLFIRI alone was estimated by using the results of bevacizumab plus FOLFOX/CAPOX versus FOLFOX/CAPOX as a proxy (see details in Sections 5.4.6.2.1 and 6.2.2).

5.4.3.3.4. Survival model selection for second-line treatment

The EAG has used a pragmatic approach to model selection balancing between providing sufficient information for the Appraisal Committee to make an informed decision and limiting the number of analyses run. The selected base case and sensitivity analyses are deemed to provide a plausible range in the ICER.

5.4.3.3.4.1. Distributions selected to model progression-free survival for bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone

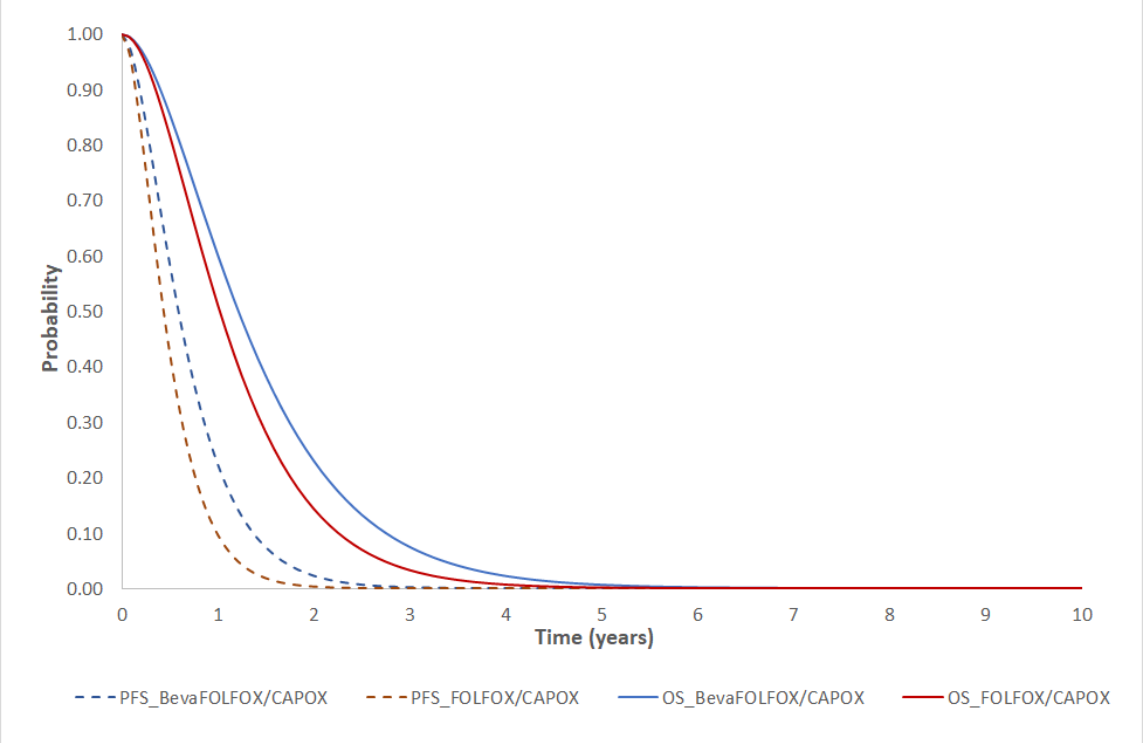
The AIC and BIC for PFS are shown in Table 15. The best fitting models differ in terms of long-term hazard projection between arms, with the bevacizumab plus FOLFOX/CAPOX arm best fitted by models with a monotonically increasing hazard, as expected by the clinicians providing advice to the EAG, whereas the FOLFOX/CAPOX arm was best fitted by a log-logistic model which has an increasing hazard until it reaches a turning point after which the hazard is decreasing. The EAG has followed clinical advice and has used the gamma distribution for PFS in the base case and log-logistic in sensitivity analyses. Whilst there is little difference in the goodness-of-fit statistics for the gamma and generalised gamma models, the gamma was selected for both treatment groups, with the log-logistic distribution used in sensitivity analyses to be consistent with the first-line analysis.

5.4.3.3.4.2. Distributions selected to model overall survival for bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone

The AIC and BIC for OS are shown in Table 16. The best-fitting models again differ in terms of long-term hazard projection between the bevacizumab plus FOLFOX/CAPOX arm and the FOLFOX/CAPOX arm, being the gamma and the lognormal the best fitting models respectively, however other models provide a good fit to the data.

For consistency with the PFS analyses, the gamma distribution has been used for both treatment groups in the base case, with the log-logistic used in sensitivity analyses. Figure 48 summarises the overall model predictions for PFS and OS for each treatment group in the base case.

Figure 48: Base case PFS and OS model predictions, second-line setting



BevaFOLFOX/CAPOX: bevacizumab plus FOLFOX/CAPOX; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CAPOX: capecitabine plus oxaliplatin, PFS: progression-free survival; OS: overall survival

5.4.3.4. Health-related quality of life for the first-line setting

5.4.3.4.1. Utility values associated with model health states

In TA118,[8] the ERG models assumed a utility value of 0.80 for the progression-free health state, based on the utility score (Health Utilities Index Mark 3) for chemotherapy patients reported by Ramsey *et al.*[40] For the post-progression health state, a utility value of 0.60 was used, derived by assuming a multiplier of 0.75 between progressed and stable disease states. The committee concluded that the utility values remained subject to considerable uncertainty.

In TA212,[6] the company used a utility value of 0.77 for the progression-free health state, based on the EQ-5D data collected in the Crystal study,[41] which compared cetuximab plus FOLFIRI versus FOLFIRI alone as the first-line treatment of mCRC. However, only 37 patients (who had KRAS wild-type mutation) completed the questionnaire, and the ERG considered this value was an overestimate. For the progressed state, a value of 0.68 was used in the company's model, based on the data from the best supportive care arm of Study 20020408[42] which assessed panitumumab in the third-line CRC treatment. The ERG explored the impact of decreasing the utility values by 10% in scenario analyses.

In this economic analysis, the EAG followed the ERG's model assumptions from TA212 by assuming a utility value of 0.77 for the progression-free health state and 0.68 for the progressed heath state in the base case. To inform the committee the EAG explored uncertainty in these values by arbitrarily increasing utility values by 5%, and by reducing utility values by 5% in scenario analyses. All heath state utility values were adjusted for aging using Hernandez Alava *et al*.[30]

5.4.3.4.2. Disutilities associated with treatment-related AEs

The previous economic models from TA118 and TA212 did not incorporate QALY losses associated with AEs. The EAG applied AE-related disutilities in the model to estimate the reduction in health-related quality-of-life for the duration of AEs. The frequencies of AEs for bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone were based on Study NO16966 while AE data for bevacizumab plus FOLFIRI and FOLFIRI alone were taken from the Study AVF2107g.

The model incorporates the expected AE-related QALY losses by multiplying the estimated disutility of each AE by its respective duration and frequency. For simplicity, it was assumed that each AE lasts 14 days based on clinical opinion. The EAG conducted a targeted literature search for disutility values , and the values used in the model were taken from Freeman *et al*.,[23] Tabberer *et al*.,[25] TA1049[29] and assumptions related to proxy conditions. The QALY losses for all AEs were summed to estimate a one-off QALY loss which was applied in the first model cycle. AE frequencies, utility decrements and the expected QALY losses are summarised in Table 17.

Table 17: Summary of AE frequencies and their utility decrements used in the economic model (first-line setting)

AEs	Frequency of AEs						Disutility	Source of disutility
	Bevacizumab plus FOLFOX	FOLFOX alone	Bevacizumab plus FOLFIRI	FOLFIRI alone	Bevacizumab plus CAPOX	CAPOX alone		
Diarrhoea	12.87%	11.42%	32.40%	24.70%	21.81%	20.31%	0.0900	Freeman *et al.*[23]
Febrile neutropenia	4.39%	4.78%	0.00%	0.00%	1.13%	0.92%	0.0900	TA1049,[29] Nafees *et al.*[26]
Hypertension	0.00%	0.00%	11.00%	2.30%	0.00%	0.00%	0.0700	TA1049[29]
Neurotoxicity	17.84%	16.51%	0.00%	0.00%	18.13%	17.40%	0.1500	Tabberer 2006[25]
Neutropenia/ granulocytopenia	40.35%	43.52%	37.00%	31.10%	7.08%	7.02%	0.0610	Freeman *et al.*[23]
Palmar-plantar Erythrodysaesthesia syndrome (Hand and foot)	1.75%	1.23%	0.00%	0.00%	11.90%	6.11%	0.1030	Freeman *et al.*[23]
Stomatitis	3.51%	2.01%	0.00%	0.00%	1.98%	1.22%	0.0380	Freeman *et al.*[23]
Venous thromboembolism	0.00%	0.00%	19.40%	16.20%	0.00%	0.00%	0.0180	Assumed to be the same as pulmonary embolism used in TA937[28] (EAG analysis)
Deep thrombophlebitis	0.00%	0.00%	8.90%	6.30%	0.00%	0.00%	0.0180	
Pulmonary embolus	0.00%	0.00%	3.60%	5.10%	0.00%	0.00%	0.0180	
Vomiting/Nausea	7.31%	7.25%	0.00%	0.00%	10.76%	7.94%	0.0790	Freeman *et al.*[23]
Grade 3 or 4 bleeding	0.00%	0.00%	3.10%	2.50%	0.00%	0.00%	0.0500	Assumed to be the same as platelet count decreased disutility used in TA653[27]
Gastrointestinal perforation	0.00%	0.00%	1.50%	0.00%	0.00%	0.00%	0.0098	Thomas *et al.*[24] based on the data from Dorian *et al.*[43]
Proteinuria	0.00%	0.00%	0.80%	0.80%	0.00%	0.00%	0.0600	Disutility for renal impairment used in TA937 (EAG analysis)
Expected QALY loss (one-off) *	**0.0029**	**0.0028**	**0.0026**	**0.0019**	**0.0028**	**0.0024**		

AE: adverse event; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; CAPOX: capecitabine plus oxaliplatin; QALY: quality-adjusted life-year; TA: technology appraisal
*based on 14-day duration

5.4.3.4.3. Caregiver disutilities

In the EAG's economic analysis, caregiver disutilities (indirect benefits to caregivers of bevacizumab plus fluoropyrimidine-based chemotherapy group) were not included in the model. This decision was made because caregiver disutilities were not included in previous TAs of first- and second-line and the EAG did not consider these to be of exceptional magnitude.

5.4.3.5. Health-related quality of life for the second-line setting

5.4.3.5.1. Utility values associated with model health states

In TA1008,[22] trifluridine-tipiracil with bevacizumab for treating mCRC after 2 systematic treatments, the EAG used the pooled utility values from the SUNLIGHT study[44] in the base case: 0.76 for the progression-free state and 0.68 for the post-progression state. A range of values was explored in the scenario analysis: from 0.72 to 0.76 for the progression-free health state and from 0.59 to 0.68 for the progressed health state. The Appraisal Committee concluded that, in the absence of pooled utility value based on all available evidence, the values from the TA405 guidance[34] (which evaluated trifluridine-tipiracil for previously treated mCRC) were likely to approximate the expected pooled utility estimates: 0.73 for the progression-free state and 0.64 for the post-progression state.

In this economic analysis for the second-line setting, the EAG followed the Appraisal Committee's preferences from TA1008[22] by assuming a utility value of 0.73 for the progression-free health state and 0.64 for the progressed heath state in the base case and explored the impact of increasing, or reducing, utility values by 5% in the scenario analyses. All heath state utility values were adjusted for aging using Hernandez Alava *et al*.[30]

5.4.3.5.2. Disutilities associated with treatment-related AEs

As in the first-line setting, the model incorporates the expected AE-related QALY losses by multiplying the disutility of each AE by its respective duration and frequency. It was assumed that each AE lasts 14 days based on the clinical opinion. The frequencies of AEs were taken from Study 3200[12] and the disutility values (based on the EAG's targeted literature search) from Freeman *et al*.,[23] Tabberer *et al*.,[25] NICE TAs (TA653,[27] TA937[28] and TA1049[29]) and assumptions relating to proxy conditions. The individual QALY losses for all AEs were added to estimate the one-off QALY loss which was then applied in the first model cycle. AE frequencies, utility decrements and the expected QALY losses are summarised in Table 26. As there was uncertainty around the impact of AEs a scenario analysis was run where the QALY losses due to AEs in the base case were multiplied by ten.

Table 18: Summary of AE frequencies and their utility decrements used in the economic model (second-line setting)

AEs	Frequency of AEs		Disutility	Source of disutility
	Bevacizumab plus FOLFOX/CAPOX	FOLFOX/CAPOX alone		
Hypertension	6.20%	1.80%	0.070	TA1049[29]
Bleeding	3.40%	0.40%	0.050	Assumed to be the same as platelet count decreased disutility used in TA653[27]
Vomiting	10.10%	3.20%	0.079	Freeman *et al*.[23]
Proteinuria	0.70%	0.00%	0.060	Disutility for renal impairment used in TA937[28] (EAG analysis)
Neuropathy	16.30%	9.20%	0.150	Tabberer *et al*.[25]
Thromboembolism	3.40%	2.50%	0.018	Assumed to be the same as pulmonary embolism used in TA937[28] (EAG analysis)
Cardiac ischaemia	0.60%	0.40%	0.070	Assumed to be the same as hypertension.
Cerebrovascular ischaemia	0.30%	0.00%	0.150	Tabberer *et al*.[25]
Expected QALY loss (one-off) *	**0.0015**	**0.0007**		

AE: adverse event; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; CAPOX: capecitabine plus oxaliplatin; QALY: quality-adjusted life-years; TA: technology appraisal
*based on 14-day duration

5.4.3.5.3. Caregiver disutilities

In the EAG's economic analysis, caregiver disutilities (indirect benefits to caregivers of bevacizumab plus fluoropyrimidine-based chemotherapy) were not included in the model. This decision was made because caregiver disutilities were not included in previous TAs of first- and second-line and the EAG did not consider these to be of exceptional magnitude.

5.4.3.6. Resource use and costs in the first-line setting

5.4.3.6.1. Overview of resource costs

The model included the costs associated with: (i) drug acquisition, administration, and monitoring; (ii) management of AEs; (iii) disease management (including best supportive care); and (iv) terminal care. Expected costs are summarised in Table 19 and further details are described in subsequent text.

Table 19: Summary of expected costs per model cycle applied in the economic model, first-line setting

Cost component per month	Bevacizumab plus FOLFOX	FOLFOX	Bevacizumab plus FOLFIRI	FOLFIRI	Bevacizumab plus CAPOX	CAPOX
Drug acquisition	[redacted]	£109	[redacted]	[redacted]	[redacted]	£26
Drug administration	£1,527	£1,470	£1,275	£1,087	£859	£819
CVAD costs (once-only costs)*	£739					
Disease management costs	Progression free health state = £133 Post-progression health state = £273					
AE management cost (once-only cost)	£529	£520	£658	£484	£440	£375
Terminal care cost (once-only cost)	£6,264					

FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; CAPOX: capecitabine plus oxaliplatin, AE: adverse events; CVAD: central venous access device

* Calculated as the unit cost of CVAD multiplied by the proportion of patients (100%) requiring CVAD.

5.4.3.6.2. Drug acquisition costs

Drug acquisition costs for bevacizumab and individual chemotherapy components are summarised in Table 22 (per treatment cycle) and Table 23 (per model cycle). All drugs were costed based on a monthly cycle duration in the economic model with monthly costs calculated as treatment cycle costs multiplied by the average number of treatment cycles per month as observed in respective studies.

The dosing schedules for bevacizumab, FOLFOX, and CAPOX were based on the Study NO16966[5] protocol, while the FOLFIRI dosing schedule followed the Study AVF2107g[7] protocol. The unit cost of bevacizumab and each chemotherapy component were taken from the British National Formulary (BNF) 2025[32] and electronic market information tool (eMIT) 2024.[31] The mean tender prices for bevacizumab 100 mg/4 ml and 400 mg/16 ml infusion vials, as provided by NICE, are [redacted] and [redacted], respectively. There is a significant range in tender prices with a low of [redacted] and a high of [redacted] for 100 mg/4 ml vial and with a low of [redacted] and [redacted] for 400 mg/16 ml vial.

5.4.3.6.2.1. Time to treatment discontinuation

Within the economic model, the expected drug acquisitions costs were estimated by multiplying the patients on treatment at the start of the model cycle (using the KM curve for TTD), the RDI and the acquisition costs per model cycle. The KM for TTD and RDI data of each drug from Study NO16966[5] (2x2 factorial design) were used for FOLFOX/CAPOX-containing regimens. The KM TTD for each drug are presented in Appendix (see Figure 51 to Figure 54). The N016966 protocol specified that if one of the regimen components was discontinued due to toxicity, treatment could be continued with the remaining components. The mean duration of each component of the regimen is presented in Table 20.

For FOLFIRI-containing regimens, as the TTD data were unavailable, the treatment duration of each component of the regimen was estimated based on the mean doses of each drug observed in Study AVF2107g. The detail calculations are summarised in Table 21.

Table 20: Mean treatment duration for each drug based on Study NO16966 (generated by the EAG from KM TTD data)

	Observed mean duration on treatment (months)
Bevacizumab plus FOLFOX-4 arm	
Bevacizumab	[redacted]
Fluorouracil	[redacted]
Folinic Acid	[redacted]
Oxaliplatin*	[redacted]
FOLFOX alone arm	
Fluorouracil	[redacted]
Folinic Acid	[redacted]
Oxaliplatin	[redacted]
Bevacizumab plus CAPOX arm	
Bevacizumab	[redacted]
Oxaliplatin†	[redacted]
Capecitabine	[redacted]
CAPOX alone arm	
Oxaliplatin	[redacted]
Capecitabine	[redacted]

FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CAPOX: capecitabine plus oxaliplatin; KM: Kaplan-Meier; TTD: time to treatment discontinuation

* As data from bevacizumab plus FOLFOX arm are unavailable, KM TTD of FOLFOX alone arm was used.

† As data from bevacizumab plus CAPOX arm are unavailable, KM TTD of CAPOX alone arm was used.

Table 21: Mean treatment duration for each drug based on Study AVF2107g (reproduced from the ERG's model in TA118)

	Observed mean doses	Dosing schedule (weeks)	Total duration (months)
Bevacizumab plus FOLFIRI arm			
Bevacizumab	[redacted]	[redacted]	[redacted]
Fluorouracil (Injection)	[redacted]	[redacted]	[redacted]
Folinic Acid	[redacted]	[redacted]	[redacted]
Irinotecan	[redacted]	[redacted]	[redacted]
FOLFIRI alone arm			
Fluorouracil (Injection)	[redacted]	[redacted]	[redacted]
Folinic Acid	[redacted]	[redacted]	[redacted]
Irinotecan	[redacted]	[redacted]	[redacted]

FOLFIRI: folinic acid plus fluorouracil plus irinotecan

5.4.3.6.2.2. Drug wastage

In the economic model, vial sharing was not assumed. To calculate weight-based (or BSA-based) doses, the EAG assumed a normal distribution using the mean body weight (or BSA) and the appropriate standard error. Based on these distributions, the EAG estimated the proportions of the population falling into four weight (or BSA) categories, with the cut-points determined by changes in the number of vials required (See details in Appendix, Table 48 and Table 49). For each category, the required doses, number of vials and the expected drug cost were calculated. These costs were then weighted according to the proportion of individuals in each category to derive an average unit drug cost for the population. This approach accounts for expected drug wastage due to variability in weight or BSA and the use of non-divisible vial sizes.

Table 22: Drug acquisition costs per treatment cycle, first-line setting

Regimen	Drugs	Dosing schedule	Total dose per treatment cycle (per protocol) (mg)*	Costs per treatment cycle†	RDI	Expected costs per treatment cycle	Source
Bevacizumab plus FOLFOX	Bevacizumab	5 mg/kg IV	375	[redacted]	[redacted]	[redacted]	NO16966 Trial Protocol,[5] clinical inputs, RDI from Bevacizumab plus arm
	Fluorouracil (Injection)	400 mg/m^2, day 1 and 2	1400	£24	[redacted]	[redacted]	
	Fluorouracil (Infusion)	600 mg/m^2, day 1 and 2	2100	£12	[redacted]	[redacted]	
	Folinic Acid	200 mg/m^2, day 1 and 2	700	£16	[redacted]	[redacted]	
	Oxaliplatin	85 mg/m^2	149	£11	[redacted]	[redacted]	
FOLFOX	Fluorouracil (Injection)	400 mg/m^2, day 1 and 2	1400	£24	[redacted]	[redacted]	NO16966 Trial Protocol, clinical inputs, RDI from FOLFOX arm
	Fluorouracil (Infusion)	600 mg/m^2, day 1 and 2	2100	£12	[redacted]	[redacted]	
	Folinic Acid	200 mg/m^2, day 1 and 2	700	£16	[redacted]	[redacted]	
	Oxaliplatin	85 mg/m^2	149	£11	[redacted]	[redacted]	
Bevacizumab plus CAPOX	Bevacizumab	7.5 mg/kg	563	[redacted]	[redacted]	[redacted]	NO16966 Trial Protocol, clinical inputs, RDI from Bevacizumab plus arm
	Oxaliplatin	130 mg/m^2	228	£21	[redacted]	[redacted]	
	Capecitabine	1000 mg/m^{2,} twice daily for 14 days	49000	£1	[redacted]	[redacted]	
CAPOX	Oxaliplatin	130 mg/m^2	228	£21	[redacted]	[redacted]	NO16966 Trial Protocol, clinical inputs, RDI from CAPOX arm
	Capecitabine	1000 mg/m^{2,} twice daily for 14 days	49000	£1	[redacted]	[redacted]	
Bevacizumab plus FOLFIRI	Bevacizumab	5 mg/kg, every 2 weeks for 6 weeks	1125	[redacted]	[redacted]	[redacted]	

Regimen	Drugs	Dosing schedule	Total dose per treatment cycle (per protocol) (mg)*	Costs per treatment cycle†	RDI	Expected costs per treatment cycle	Source
	Fluorouracil (Injection)	500 mg/m^2 , once a week for 4 weeks	3500	£52	[redacted]	[redacted]	AVF2107g Trial Protocol,[7] RDI from Bevacizumab plus arm
	Folinic Acid	20 mg/m^2, once a week for 4 weeks	140	£66	[redacted]	[redacted]	
	Irinotecan	125 mg/m^2, once a week for 4 weeks	875	£96	[redacted]	[redacted]	
FOLFIRI	Fluorouracil (Injection)	500 mg/m^2, once a week for 4 weeks	3500	£52	[redacted]	[redacted]	AVF2107g Trial Protocol, RDI from FOLFIRI alone arm
	Folinic Acid	20 mg/m^2, once a week for 4 weeks	140	£66	[redacted]	[redacted]	
	Irinotecan	125 mg/m^2, once a week for 4 weeks	875	£96	[redacted]	[redacted]	

FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; CAPOX: capecitabine plus oxaliplatin, RDI: relative dose intensity; IV: intravenous
*based on a mean body weight of 70 kg, a mean BSA of 1.75 m^2
†weighted average cost based on the body weight (or BSA)-based distribution

Table 23: Drug acquisition costs per model cycle (per month), first-line setting

Treatment regimen	Drugs	Treatment cycles per month*	Costs per treatment cycle	Expected costs per month	Total costs per regimen	Source
Bevacizumab plus FOLFOX	Bevacizumab	1.84	[redacted]	[redacted]	[redacted]	BNF 2025,[32] eMIT 2024,[31] Study NO16966[5]
	Fluorouracil		[redacted]	[redacted]		
	Folinic Acid		[redacted]	[redacted]		
	Oxaliplatin		[redacted]	[redacted]		
FOLFOX	Fluorouracil	1.84	[redacted]	[redacted]	[redacted]	BNF 2025, eMIT 2024, Study NO16966
	Folinic Acid		[redacted]	[redacted]		
	Oxaliplatin		[redacted]	[redacted]		
Bevacizumab plus CAPOX	Bevacizumab	1.31	[redacted]	[redacted]	[redacted]	BNF 2025, eMIT 2024, Study NO16966
	Oxaliplatin		[redacted]	[redacted]		
	Capecitabine		[redacted]	[redacted]		
CAPOX	Oxaliplatin	1.31	[redacted]	[redacted]	[redacted]	BNF 2025, eMIT 2024, Study NO16966
	Capecitabine		[redacted]	[redacted]		
Bevacizumab plus FOLFIRI	Bevacizumab	0.67	[redacted]	[redacted]	[redacted]	BNF 2025, eMIT 2024, Study AVF2107g
	Fluorouracil		[redacted]	[redacted]		
	Folinic Acid		[redacted]	[redacted]		
	Irinotecan		[redacted]	[redacted]		
FOLFIRI	Fluorouracil	0.67	[redacted]	[redacted]	[redacted]	BNF 2025, eMIT 2024, Study AVF2107g
	Folinic Acid		[redacted]	[redacted]		
	Irinotecan		[redacted]	[redacted]		

FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; CAPOX: capecitabine plus oxaliplatin, eMIT: electronic market information tool; BNF: British National Formulary

*Treatment cycles per month are based on pooled data of 5-FU-based regimens (Study NO16966) for bevacizumab plus FOLFOX and FOLFOX, and capecitabine-based regimens (Study NO16966) for bevacizumab plus CAPOX and CAPOX. Treatment cycles per month for FOLFIRI containing regimens are based on the trial protocol of Study AVF2107g (6-week cycle).

5.4.3.6.3. Drug administration and monitoring costs

Unit costs and resource use associated with the administration of each treatment, based on the regimens used in the pivotal studies, are described in Table 24. Unit costs were sourced from published literature and NHS Reference Costs 2023/34.[33] Resource use data for bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone were based on the respective arms of the 2x2 factorial design of the Study NO16966.[5] For FOLFIRI-containing regimens, resource use was assumed to be equivalent to that of the corresponding bevacizumab plus FOLFOX or FOLFOX arms, respectively, in Study NO16966,[5] apart from resource use for delivering chemotherapy (day case) and district nurse visit. As 5-FU was delivered via bolus injections for FOLFIRI-containing treatments (Saltz regimen) in Study AVF2107g,[7] it was assumed that a 6-week cycle required 5 days of hospital attendance for bevacizumab plus FOLFIRI and 4 days for FOLFIRI alone, based on the assumptions in TA118.[8] Accordingly, the district nurse visit was not required to flush CVAD at the end of infusion.

The EAG is aware that there have been adaptations to the regimens used in the pivotal studies that form standard treatment in England. This is the use of the modified de Gramont regiment for 5FU-containing regimens and the early cessation of oxaliplatin treatment (at 6 months) due to toxicity concerns. The implications of these adaptations have been explored in sensitivity analyses (assuming the same efficacy as in the base case) and the generated ICERs may be more representative of current English practice.

Table 24: Drug administration and monitoring costs

Types of administration	Unit cost	Frequency of resource use per treatment cycle						Source of unit cost
		Bevacizumab plus FOLFOX	FOLFOX	Bevacizumab plus FOLFIRI	FOLFIRI	Bevacizumab plus CAPOX	CAPOX	
Administration costs per treatment cycle								
Pharmacy dispensing Complex IV infusion	£55	3.00	3.00	0.00	0.00	1.00	1.00	PSSRU 2024,[45] Hospital-based Band 6 pharmacist cost, assumed to last for an hour
Pharmacy dispensing Simple IV infusion	£28	1.00	1.00	4.00	4.00	1.00	1.00	PSSRU 2024, Hospital-based Band 6 pharmacist cost, assumed to last for 30 min
Hospital-based pharmacist costs	£50	0.32	0.00	0.32	0.00	0.32	0.00	PSSRU 2024, Hospital-based Band 6 staff cost per hour
Patient transport*	£19	0.30	0.30	0.30	0.30	0.30	0.30	TA212[6]
Ambulatory pump†	£56	1.00	1.00	1.00	1.00	0.00	0.00	Baxterhealthcare[46]
District nurse visit‡	£58	1.00	1.00	0.00	0.00	0.00	0.00	NHS reference costs 2023/24,[33] District nurse, adult, face to face (Code N02AF)
Hospital-based nurse costs	£58	0.26	0.00	0.26	0.00	0.26	0.00	PSSRU 2024, average of hospital-based band 5-7 nurse costs
Delivering chemotherapy (first attendance)_outpatient	£352	1.00	1.00	1.00	1.00	1.00	1.00	NHS Reference Costs 2023/24, deliver complex chemotherapy, including prolonged infusional treatment, at first attendance (code SB14Z)
Delivering chemotherapy (subsequent visit) _outpatient	£251	0.00	0.00	4.00	3.00	0.00	0.00	NHS Reference Costs 2023/24, deliver complex chemotherapy, including prolonged infusional treatment, at first attendance (code SB15Z)

Types of administration	Unit cost	Frequency of resource use per treatment cycle						Source of unit cost
		Bevacizumab plus FOLFOX	FOLFOX	Bevacizumab plus FOLFIRI	FOLFIRI	Bevacizumab plus CAPOX	CAPOX	
Expected administration costs per treatment cycle	-	£696	£665	£1,559	£1,277	£472	£440	
Expected administration costs per monthly model cycle	-	£1,281	£1,224	£1,039	£851	£618	£577	
Monitoring costs (during treatment) per month								
Consultation at OPD	£193	1.00	1.00	1.00	1.00	1.00	1.00	NHS Reference Costs 2023/24, Consultant-led medical oncology service, Service code 370, non-admitted face-to-face attendance, follow-up (Code WF01A)
Blood tests	£9	1.84	1.84	0.67	0.67	1.31	1.31	NHS Reference Costs 2023/24, service code 303, phlebotomy (code DAPS0)
CT scan	£111	0.33	0.33	0.33	0.33	0.33	0.33	NHS Reference Costs 2023/24, computerised tomography scan of one area to more than three areas, with or without contrast, outpatient (code RD20A-RD27Z)
Expected monitoring costs per monthly cycle	-	£246	£246	£236	£236	£242	£242	
Expected total costs per monthly model cycle	-	**£1,527**	**£1,470**	**£1,275**	**£1,087**	**£859**	**£819**	

FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; CAPOX: capecitabine plus oxaliplatin, OPD: outpatient department, IV: intravenous, CT: computerised tomography; PSSRU: Personal Social Services Research Unit; TA: technology appraisal

*30% of patients are assumed to require hospital-funded transport (one-way): £45 in the TA212 (2009 prices) was inflated to 2022/23 price year.

†FOLFusor SV2 normal flow rate 2ml/hr single pack, product code 2C4702K

‡ to flush CVAD at the end of each 5FU infusion and assumed an hour time of a nurse visit.

5.4.3.6.4. Management costs of AEs

The economic model includes the costs of managing AEs of Grade 3 or greater associated with first-line treatment based on the frequencies from Study NO16966[5] (see details in Table 17). Unit costs were taken from NHS Reference Costs 2023/34,[33] and published literature. Unit costs used in the economic model are presented in Table 25. The costs for managing AEs were expected to be £529 for bevacizumab plus FOLFOX, £520 for FOLFOX, £658 for bevacizumab plus FOLFIRI, £484 for FOLFIRI, £440 for bevacizumab plus CAPOX and £375 for CAPOX. The expected costs were applied as once-only costs in the first model cycle.

Table 25: Management costs of Grade ≥3 adverse events

Adverse events	Unit cost	Source of unit costs (NHS Reference Costs 2023/34,[33] unless otherwise stated)
Diarrhoea	£564.22	Weighted mean cost of non-malignant gastrointestinal tract disorders without interventions, with CC Score 0-11+, non-elective short-stay, code FD10J-M
Febrile neutropenia	£560.68	Weighted mean cost of other haematological or splenic disorders, with CC Score 0-6+, non-elective short-stay, code SA08G-J
Hypertension	£404.67	Weighted mean cost of hypertension, non-elective short-stay, code EBO4Z
Neurotoxicity/Neuropathy	£768.33	Weighted mean cost of cerebrovascular accident, nervous system infections or encephalopathy, with CC Score 0-14+, non-elective short-stay, code AA22C-G
Neutropenia/granulocytopenia/ Grade 3 or 4 bleeding	£560.68	Weighted mean cost of other haematological or splenic disorders, with CC Score 0-6+, non-elective short-stay, code SA08G-J
Palmar-plantar Erythrodysaesthesia (Hand and foot syndrome)	£511.89	Weighted mean cost of skin disorders (without intervention, with single intervention, with interventions), with CC Score 0-12+, non-elective short-stay, code JD07A-K
Stomatitis	£519.16	Weighted mean cost of non-malignant, ear, nose, mouth, throat or neck disorders, (with or without interventions) with CC Score 0-5+, non-elective short-stay, code CB02A-2F
Venous thromboembolism	£477.36	Weighted mean cost of deep vein thrombosis with CC Score 0-12+, non-elective short-stay, code YQ51A-E
Vomiting/Nausea	£564.22	Weighted mean cost of non-malignant gastrointestinal tract disorders without interventions, with CC Score 0-11+, non-elective short-stay, code FD10J-M
Deep thrombophlebitis	£477.36	Weighted mean cost of deep vein thrombosis with CC Score 0-12+, non-elective short-stay, code YQ51A-E
Pulmonary embolus	£663.63	Weighted mean cost of pulmonary embolus with or without interventions, non-elective short-stay, with CC Score 0-12+, code DZ09J-Q
Gastrointestinal perforation	£2,771.99	Weighted mean cost of major large intestine procedures, 19 years and over, non-elective short-stay, with CC Score 0-3+, code FF34A-C
Proteinuria	£675.20	Weighted mean cost of acute kidney injury with or without interventions, non-elective short-stay, with CC Score 0-11+, code LA07H-P

Cardiac ischaemia	£702.43	Weighted mean cost of other acquired cardiac conditions with CC Score 0-13+, non-elective short-stay, code EB14A-E
Cerebrovascular ischaemia	£963.43	Weighted mean cost of stroke with CC Score 0-16+, non-elective short-stay, code AA35A-F

5.4.3.6.5. Disease management costs

Table 26 summarises the resource use and unit costs per model cycle for the progression-free and post-progression heath states in the model. These costs are assumed independent of initial treatment. Resource use estimates for the progression-free state were derived from the pooled data of Study NO16966.[5] Unit costs for each resource use item were based on the NHS Reference Costs 2023/24[33] and PSSRU 2024.[45] For simplicity, it was assumed that patients in the post-progression health state received best supportive care. The resource use associated with best supportive care was informed by the assumptions used in the most recent NICE TA for bevacizumab in the third-line treatment of mCRC, TA1008,[22] which in turn was based on TA405,[34] TA668[35] and TA866[36]. The expected costs for managing progression-free and post-progression patients were £133 and £273, respectively.

Table 26: Monthly management costs of progression-free health state

Types of resource use	**Unit cost**	**Resource use per month (Study NO16966)[5]**		**Source of unit cost**
		Progression-free	**Post-progression (Best supportive care)**	
Consultation at OPD	£192.95	0.50	0.00	NHS Reference Costs 2023/24,[33] Consultant-led medical oncology service, Service code 370, non-admitted face-to-face attendance, follow-up (Code WF01A)
Blood tests	£9.20	0.00	0.00	NHS Reference Costs 2023/24, service code 303, phlebotomy (code DAPS0)
CT scan	£110.73	0.33	0.00	NHS Reference Costs 2023/24, computerised tomography scan of one area to more than three areas, with or without contrast, outpatient (code RD20A-RD27Z)
GP home consultation	£134.10	0.00	0.25	PSSRU 2024,[45] per min cost patient contact, GP with qualifications, assuming each consultation lasts for 30 min
Community nurse specialist visit	£64.00	0.00	1.00	PSSRU 2024, per hour cost with qualifications, Band 6 nurse, assuming each consultation lasts for 1 hour
Health home visitor	£27.00	0.00	1.00	PSSRU 2024, per hour cost of home care worker, face to face visit for social services, assumed to last for one hour

District nurse visitor	£53.00	0.00	1.00	PSSRU 2024, per hour cost with qualifications, Band 5 nurse, assuming each consultation lasts for 1 hour
GP surgery visit	£45.00	0.00	1.00	PSSRU 2024, per surgery GP consultation lasting 10 min (with qualifications)
Concomitant medication costs	£50.00	0.00	1.00	TA1008[22] (EAG scenario)
Estimated costs per model cycle		£133	£273	

OPD: outpatient department; CT: computerised tomography; GP: general practitioner; PSSRU: personal social services research unit, TA: technology appraisal, EAG: External Assessment Group

5.4.3.6.6. Terminal care costs

The cost of end-of-life care was applied as a once-only cost of £6265 to patients at the point of death. This value was based on Round *et al*.[37] (as used in TA709[47]). Round *et al*. estimated mean costs per patient for four types of cancer (breast, colorectal, lung and prostate), with costs reported separately by resource use category: health care, social care, charity care, and informal care. The EAG used the health care cost estimates in the model, which we believe reflects the approach used in TA709. The terminal care cost for the CRC was reported as £4854 and was inflated from 2013/14 to 2023/24 prices.

5.4.3.6.7. Central Venous Access Device costs

Based on the clinical advice received by the EAG, the base case model assumed that every patient would receive CVAD before they started treatment. Replacement costs of CVADs were not considered for model simplicity, and the EAG considers that the exclusion of these costs is unlikely to have a significant impact on the ICERs.

5.4.3.7. Resource use and costs in the second-line setting

5.4.3.7.1. Overview of resource costs

As in the first-line setting, the model included the costs associated with: (i) drug acquisition, administration, and monitoring; (ii) management of AEs; (iii) disease management including best supportive care; and (iv) terminal care. Expected costs are summarised in Table 27.

Table 27: Summary of expected costs per model cycle applied in the economic model , second-line setting

Cost component per month	Bevacizumab plus FOLFOX	FOLFOX	Bevacizumab plus CAPOX	CAPOX
Drug acquisition	[redacted]	£72	[redacted]	£26
Drug administration	£1,527	£1,470	£859	£819
CVAD costs (once-only costs) *	£739			
Disease management costs	Progression free health state = £133 Post-progression health state = £273			
AE management cost (once-only cost)	£254	£113	£254	£113
Terminal care cost (once-only cost)	£6,264			

FOLFOX: folinic acid plus fluorouracil plus oxaliplatin, CAPOX: capecitabine plus oxaliplatin, AE: adverse event; CVAD: central venous access device

* Calculated as the unit cost of CVAD multiplied by the proportion of patients (100%) requiring CVAD.

5.4.3.7.2. Drug acquisition costs

Table 28 and Figure 26 present the excepted drug acquisition costs per treatment cycle and per model cycle, respectively. As in the first-line setting, costs were calculated based on a monthly cycle duration in the economic model with monthly costs calculated as treatment cycle costs multiplied by the average number of treatment cycles per month as observed in Study E3200.[12] The dosing schedules for bevacizumab and FOLFOX were based on the Study E3200 protocol, whereas the CAPOX schedule followed the Study NO16966 protocol[5] as the CAPOX regimen was not evaluated in the Study E3200.

No data were identified for the dosage level for bevacizumab plus CAPOX in second-line treatment. The EAG assumed a dose of 15mg/kg, as in first-line the dose was 10mg/kg, and it was noted that for bevacizumab plus FOLFOX the dosage was 50% higher in second-line than in first-line (7.5mg/kg (Study NO16966) compared with 5mg/kg (Study E3200)). A dose of 15 mg/kg every three weeks for CAPOX-containing regimens is included in the bevacizumab Summary of Product Characteristics,[48].

Unit costs were taken from BNF 2025[32] and eMIT 2024.[31] As described in Section 5.4.3.6.2, bevacizumab prices remain the same at [redacted] and [redacted] for 100 mg/4 ml and 400 mg/16 ml infusion vials, respectively. As KM curves for TTD were not available in Study E3200, it was assumed that each treatment component would be discontinued at 5 months for bevacizumab plus FOLFOX/CAPOX group and at 4 months for FOLFOX/CAPOX alone group based on the observed median treatment cycles in Study E3200 (10 cycles for bevacizumab plus FOLFOX arm and 7 cycles for FOLFOX alone arm, under a 2-week treatment cycle protocol). As in the first-line setting, no vial sharing was assumed in the base case and the drug wastage was calculated as described in Section 5.4.3.6.2.2.

Table 28: Drug acquisition costs per treatment cycle, second-line setting

Regimen	Drugs	Dosing schedule	Total dose per treatment cycle (per protocol) (mg)*	Costs per treatment cycle†	RDI	Expected costs per treatment cycle	Source
Bevacizumab plus FOLFOX	Bevacizumab	10 mg/kg IV	750	[redacted]	[redacted]	[redacted]	Dosing schedule from E3200,[12] RDI from bevacizumab plus arm from Study NO16966[5]
	Fluorouracil (Injection)	400 mg/m^2, bolus injection	700	£12	[redacted]	[redacted]	
	Fluorouracil (Infusion)	1200 mg/m^2 infusion over 46 hours	2100	£4	[redacted]	[redacted]	
	Folinic Acid	400 mg/m^2, infusion over 2 hours	700	£14	[redacted]	[redacted]	
	Oxaliplatin	85 mg/m^2, infusion over 2 hours	149	£11	[redacted]	[redacted]	
FOLFOX	Fluorouracil (Injection)	400 mg/m^2, bolus injection	700	£12	[redacted]	[redacted]	Dosing schedule from E3200, RDI from bevacizumab plus arm from Study NO16966
	Fluorouracil (Infusion)	1200 mg/m^2 infusion over 46 hours	2100	£4	[redacted]	[redacted]	
	Folinic Acid	400 mg/m^2, infusion over 2 hours	700	£14	[redacted]	[redacted]	
	Oxaliplatin	85 mg/m^2, infusion over 2 hours	149	£11	[redacted]	[redacted]	
Bevacizumab plus CAPOX	Bevacizumab	15 mg/kg IV	1125	[redacted]	[redacted]	[redacted]	Assumption
	Oxaliplatin	130 mg/m^2	228	£21	[redacted]	[redacted]	NO16966 Trial Protocol, clinical inputs, RDI from Bevacizumab plus arm
	Capecitabine	1000 mg/m^2	49000	£1	[redacted]	[redacted]	
CAPOX	Oxaliplatin	130 mg/m^2	228	£21	[redacted]	[redacted]	

	Capecitabine	1000 mg/m^2	49000	£1	[redacted]	[redacted]	NO16966 Trial Protocol, clinical inputs, RDI from CAPOX arm

FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CAPOX: capecitabine plus oxaliplatin, RDI: relative dose intensity, IV; intravenous
*based on a mean body weight of 70 kg, a mean BSA of 1.75 m^2
†weighted average cost based on the body weight (or BSA)-based distribution

Table 29: Drug acquisition costs per model cycle (per month), second-line setting

Treatment regimen	Drugs	Treatment cycles per month*	Costs per treatment cycle	Expected costs per month	Total costs per regimen	Source
Bevacizumab plus FOLFOX	Bevacizumab	1.84	[redacted]	[redacted]	[redacted]	BNF 2025,[32] eMIT 2024,[31] Study E3200[12]
	Fluorouracil		[redacted]	[redacted]		
	Folinic Acid		[redacted]	[redacted]		
	Oxaliplatin		[redacted]	[redacted]		
FOLFOX	Fluorouracil	1.84	[redacted]	[redacted]	[redacted]	BNF 2025, eMIT 2024, Study E3200
	Folinic Acid		[redacted]	[redacted]		
	Oxaliplatin		[redacted]	[redacted]		
Bevacizumab plus CAPOX	Bevacizumab	1.31	[redacted]	[redacted]	[redacted]	BNF 2025, eMIT 2024, Study NO16966
	Oxaliplatin		[redacted]	[redacted]		
	Capecitabine		[redacted]	[redacted]		
CAPOX	Oxaliplatin	1.31	[redacted]	[redacted]	[redacted]	BNF 2025, eMIT 2024, Study NO16966
	Capecitabine		[redacted]	[redacted]		

FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; CAPOX: capecitabine plus oxaliplatin, eMIT: electronic market information tool; BNF: British National Formulary

5.4.3.7.3. Drug administration and monitoring costs

For model simplicity, the resource use requirements for delivering bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone in the second-line setting were assumed to be the same as those used in the first-line setting (see Section 5.4.3.6.3).

5.4.3.7.4. Management costs of AEs

The model includes the costs of managing AEs of Grade 3 or greater associated with second-line treatment using bevacizumab plus FOLFOX and FOLFOX alone, based on the frequencies from Study E3200[12] (see details in Table 18). Due to the lack of data for CAPOX-containing regimens, it was assumed that AE frequencies were the same between FOLFOX-and CAPOX-containing treatments. The costs for managing AEs were estimated to be £254 for bevacizumab plus FOLFOX/CAPOX and £113 for FOLFOX/CAPOX alone.

5.4.3.7.5. Disease management costs, terminal care costs, and Central Venous Access Device costs

The disease management costs for progression-free and post-progression health state (best supportive care) were assumed to be the same as those in the first-line setting, £133 and £273, respectively. Similarly, the terminal care costs were estimated to be £6265, and the CVAD device usage was assumed to remain the same.

5.4.4. Methods for model evaluation

The health outcomes and costs were estimated for three comparisons of intervention versus comparator in both first- and second-line settings: (i) bevacizumab plus FOLFOX versus FOLFOX alone, (ii) bevacizumab plus FOLFIRI versus FOLFIRI alone and (iii) bevacizumab plus CAPOX versus CAPOX alone. The ICER was presented for each pair-wise comparison, based on the point estimates of the model parameters. Uncertainty was evaluated using probabilistic sensitivity analysis (PSA) and deterministic sensitivity analyses (DSAs). PSA was undertaken using 1,000 iterations. The distributions used within the PSA are provided within the Appendix in Table 52 to Table 58.

The EAG conducted a range of DSAs to explore the impact of alternative assumptions on the ICERs for each comparison in both first-and second-line settings.

5.4.4.1. First-line setting

- DSA1: This analysis selected the log-logistic distribution for both PFS and OS in the bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone groups and the generalised gamma distribution for PFS and OS in the bevacizumab plus FOLFIRI and FOLFIRI alone groups.
- DSA2: This analysis explored the use of mdG regimen for FOLFIRI-containing regimens (see Table 2 for the dosing schedule and Table 50 and Table 51 for detailed calculations of drug acquisition

costs). The clinical efficacy of mdG was assumed to be equivalent to that of the Saltz regimen used in Study AVF2107g.[7] Regarding the RDI, TTD, monitoring requirements and AE frequencies, it was assumed that these parameters were comparable between mdG regimen and the FOLFOLX-4-containing regimens from Study NO16966,[5] due to the similarity in dosing schedules. This latter assumption is consistent with that made by both the company and the EAG in TA212.[6]

- DSA3: Based on the EAG's experts' opinions and the ERG's clinical advisors in TA212,[6] it was assumed that oxaliplatin would be discontinued at 6 months due to toxicity while patients can continue treatment with non-oxaliplatin chemotherapy components. This scenario is not applicable to FOLFIRI-containing regimens.
- DSA4: The utility values for progression-free and post-progression health states were assumed to be equal to the base case estimates plus 5%.
- DSA5: The utility values for progression-free and post-progression health states were assumed to be equal to the base case estimates minus 5%.
- DSA6: Disutility values associated with AEs were increased by ten times.
- DSA7: This analysis applied the median price of bevacizumab ([redacted] for 100 mg/4 ml infusion vial [redacted] for 400 mg/16 ml infusion vial).
- DSA8: This analysis explored the impact of assuming vial sharing across patients, thereby reducing drug wastage.

5.4.4.2. Second-line setting

- DSA1: This analysis selected the log-logistic distribution for both PFS and OS in the bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone groups.
- DSA2: This analysis applied the HRs based on Mocellin *et al*. to the modelled OS and PFS functions for the FOLFOX alone group to generate OS and PFS curves for bevacizumab plus FOLFOX. The HRs of bevacizumab plus chemotherapy versus chemotherapy alone were reported as 0.67 for PFS and 0.79 for OS.
- DSA3: The utility values for progression-free and post-progression health states were assumed to be equal to the base case estimates plus 5%.
- DSA4: The utility values for progression-free and post-progression health states were assumed to be equal to the base case estimates minus 5%.
- DSA5: Disutility values associated with AEs were increased by ten times.
- DSA6: This analysis applied the median price of bevacizumab ([redacted] for 100 mg/4 ml infusion vial [redacted] for 400 mg/16 ml infusion vial).
- DSA7: This analysis explored the assumption of vial sharing of drugs across patients, thereby reducing drug wastage.

5.4.5.Model verification and validation

The EAG undertook the following measures to ensure the validity of the model.

- Model testing using sensitivity and use of extreme parameter values.
- Comparing the estimated model results with the health outcomes from TA118[8] and TA212[6] models
- Comparison of mean of all probabilistic parameter samples against point estimates of parameters

5.4.6.Results of the EAG's economic analysis

The results of the EAG's economic analysis are presented separately for the first- and second-line treatment settings in Sections 5.4.6.1 and 5.4.6.2, respectively.

5.4.6.1. Results of the EAG's economic analysis in the first-line setting

5.4.6.1.1. Central estimates of cost-effectiveness

The pair-wise results of the deterministic and probabilistic versions of the EAG's base case model are presented in Table 30 and Table 31, respectively. The model appears to be linear with the deterministic and probabilistic results being similar.

For all pair-wise comparisons, the model indicates that the addition of bevacizumab to fluoropyrimidine-based chemotherapy increases QALY, and increases costs, resulting in ICERs of less than [redacted] per QALY gained. As shown in Table 32, the costs of drug acquisition and administration costs (due to longer survival) are greater when bevacizumab is provided.

Cost-effectiveness planes and cost-effectiveness acceptability curves (CEACs) for each pair-wise comparison are provided in the Appendix (Figure 55 to Figure 60). The CEACs indicate that the probabilities that bevacizumab in addition to fluoropyrimidine-based chemotherapy generates more net benefit than fluoropyrimidine-based chemotherapy alone are approximately [redacted] for bevacizumab plus FOLFOX, [redacted] for bevacizumab plus FOLFIRI and [redacted] for bevacizumab plus CAPOX assuming a willingness-to-pay threshold of £20,000 per QALY gained. When the willingness-to-pay threshold is increased to £30,000 per QALY gained the probabilities are [redacted] for bevacizumab plus FOLFOX, [redacted] for bevacizumab plus FOLFIRI and [redacted] for bevacizumab plus CAPOX.

Table 30: Base case results – bevacizumab plus fluoropyrimidine-based chemotherapy versus fluoropyrimidine-based chemotherapy alone, deterministic, including bevacizumab mean tender price, first-line setting

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Model 1							
Bevacizumab plus FOLFOX	2.139	1.458	[redacted]	0.260	0.169	[redacted]	[redacted]
FOLFOX	1.880	1.289	£22,102				
Model 2							
Bevacizumab plus FOLFIRI	2.068	1.411	[redacted]	0.488	0.324	[redacted]	[redacted]
FOLFIRI	1.580	1.087	£18,119				
Model 3							
Bevacizumab plus CAPOX	2.139	1.458	[redacted]	0.260	0.169	[redacted]	[redacted]
CAPOX	1.880	1.289	£16,313				

LYG: life-year gained; QALY: quality-adjusted life-year; Inc: incremental; ICER: incremental cost-effectiveness ratio; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; CAPOX: capecitabine plus oxaliplatin
*Undiscounted

Table 31: Base case results – bevacizumab plus fluoropyrimidine-based chemotherapy versus fluoropyrimidine-based chemotherapy alone, probabilistic, including bevacizumab mean tender price, first-line setting

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Model 1							
Bevacizumab plus FOLFOX	2.138	1.455	[redacted]	0.260	0.169	[redacted]	[redacted]
FOLFOX	1.878	1.286	£22,081				
Model 2							
Bevacizumab plus FOLFIRI	2.071	1.410	[redacted]	0.484	0.320	[redacted]	[redacted]
FOLFIRI	1.587	1.090	£18,109				
Model 3							
Bevacizumab plus CAPOX	2.138	1.455	[redacted]	0.260	0.169	[redacted]	[redacted]
CAPOX	1.878	1.286	£16,293				

LYG: life-year gained; QALY: quality-adjusted life-year; Inc: incremental; ICER: incremental cost-effectiveness ratio; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; CAPOX: capecitabine plus oxaliplatin
*Undiscounted

Table 32: Detailed breakdown of model-predicted costs (discounted), deterministic, first-line setting

	Bevacizumab plus FOLFOX	FOLFOX alone	Bevacizumab plus FOLFIRI	FOLFIRI alone	Bevacizumab plus CAPOX	CAPOX alone
Progression-free						
Acquisition costs	[redacted]	£780	[redacted]	£780	[redacted]	£160
Administration costs	£11,322	£10,629	£10,672	£7,011	£6,002	£5,543
Health state costs	£660	£440	£568	£382	£717	£501
AE costs	£527	£518	£656	£482	£439	£374
CVAD costs	£737	£737	£737	£737	£737	£737
Post-progression costs	£3,386	£3,129	£3,358	£2,798	£3,386	£3,129
Terminal care costs	£5,819	£5,869	£5,833	£5,929	£5,819	£5,869
Total costs	[redacted]	£22,102	[redacted]	£18,119	[redacted]	£16,313

FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; CAPOX: capecitabine plus oxaliplatin; AE: adverse events; CVAD: central venous access device

5.4.6.1.2. Deterministic sensitivity analysis results

The results of DSAs are presented in Table 33 (bevacizumab plus FOLFOX versus FOLFOX alone), Table 34 (bevacizumab plus FOLFIRI versus FOLFIRI alone) and Table 35 (bevacizumab plus CAPOX versus CAPOX alone).

The DSAs did not markedly change the ICERs for bevacizumab plus FOLFOX or bevacizumab plus CAPOX. For the comparison of bevacizumab plus FOLFIRI versus FOLFIRI alone, one DSA stands out. The use of generalised gamma distributions for PFS and OS rather than the Weibull distribution (DSA1) increased the ICER to approximately [redacted].

The EAG explored the impact of using the median tender price in sensitivity analysis (DSA7) which suggested that this does not have a significant impact on the ICER. However, the EAG believes that using the mean or median of all available tender prices without accounting for the weighted distribution across NHS trusts would likely overestimate the price of bevacizumab resulting in unfavourable cost-effectiveness results for bevacizumab. The level of overestimation would be affected by the level of price variation which is considerable in this case study. Therefore, the EAG conducted additional sensitivity analyses generating ICERs when using each of the 8 tender prices for bevacizumab. These confidential ICERs are shown in Figure 49. Except for when using the highest tender price, all ICERs were estimated to be below [redacted] per QALY gained.

Table 33: Deterministic sensitivity analysis results – bevacizumab plus FOLFOX versus FOLFOX alone, first-line setting

No.	Scenario	Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
-	Base-case (deterministic)	Bevacizumab plus FOLFOX	2.139	1.458	[redacted]	0.260	0.169	[redacted]	[redacted]
		FOLFOX alone	1.880	1.289	£22,102				
1	PFS and OS models: log-logistic	Bevacizumab plus FOLFOX	2.713	1.735	[redacted]	0.429	0.246	[redacted]	[redacted]
		FOLFOX alone	2.284	1.489	£22,936				
3	Oxaliplatin stopped at 6 month	Bevacizumab plus FOLFOX	2.139	1.458	[redacted]	0.260	0.169	[redacted]	[redacted]
		FOLFOX alone	1.880	1.289	£22,075				
4	Utility values for health states increased by 5%	Bevacizumab plus FOLFOX	2.139	1.531	[redacted]	0.260	0.178	[redacted]	[redacted]
		FOLFOX alone	1.880	1.353	£22,102				
5	Utility values for health states decreased by 5%	Bevacizumab plus FOLFOX	2.139	1.385	[redacted]	0.260	0.161	[redacted]	[redacted]
		FOLFOX alone	1.880	1.224	£22,102				
6	AE disutilities increased by 10 times	Bevacizumab plus FOLFOX	2.139	1.456	[redacted]	0.260	0.169	[redacted]	[redacted]
		FOLFOX alone	1.880	1.287	£22,102				
7	Median price of bevacizumab used	Bevacizumab plus FOLFOX	2.139	1.458	[redacted]	0.260	0.169	[redacted]	[redacted]
		FOLFOX alone	1.880	1.289	£22,102				
8	Vial sharing is assumed	Bevacizumab plus FOLFOX	2.139	1.458	[redacted]	0.260	0.169	[redacted]	[redacted]
		FOLFOX alone	1.880	1.289	£21,853				

LYG: life-year gained; QALY: quality-adjusted life-year; Inc: incremental; ICER: incremental cost-effectiveness ratio; WTP: willingness-to-pay; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; CAPOX: capecitabine plus oxaliplatin, AE: adverse events, PFS: progression-free survival; OS: overall survival
*Undiscounted

Table 34: Deterministic sensitivity analysis results – bevacizumab plus FOLFIRI versus FOLFIRI alone, first-line setting

No.	Scenario	Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
-	Base-case	Bevacizumab plus FOLFIRI	2.068	1.411	[redacted]	0.488	0.324	[redacted]	[redacted]
		FOLFIRI alone	1.580	1.087	£18,119				
1	PFS and OS models: generalised gamma	Bevacizumab plus FOLFIRI	1.853	1.283	[redacted]	0.342	0.236	[redacted]	[redacted]
		FOLFIRI alone	1.510	1.047	£17,903				
2	Using mdG regimen for FOLFIRI-containing regimens	Bevacizumab plus FOLFIRI	2.068	1.411	[redacted]	0.488	0.324	[redacted]	[redacted]
		FOLFIRI alone	1.580	1.087	£21,332				
4	Utility values for health states increased by 5%	Bevacizumab plus FOLFIRI	2.068	1.482	[redacted]	0.488	0.340	[redacted]	[redacted]
		FOLFIRI alone	1.580	1.141	£18,119				
5	Utility values for health states decreased by 5%	Bevacizumab plus FOLFIRI	2.068	1.340	[redacted]	0.488	0.308	[redacted]	[redacted]
		FOLFIRI alone	1.580	1.033	£18,119				
6	AE disutilities increased by 10 times	Bevacizumab plus FOLFIRI	2.068	1.409	[redacted]	0.488	0.323	[redacted]	[redacted]
		FOLFIRI alone	1.580	1.086	£18,119				
7	Median price of bevacizumab used	Bevacizumab plus FOLFIRI	2.068	1.411	[redacted]	0.488	0.324	[redacted]	[redacted]
		FOLFIRI alone	1.580	1.087	£18,119				
8	Vial sharing is assumed	Bevacizumab plus FOLFIRI	2.068	1.411	[redacted]	0.488	0.324	[redacted]	[redacted]
		FOLFIRI alone	1.580	1.087	£17,791				

LYG: life-year gained; QALY: quality-adjusted life-year; Inc: incremental; ICER: incremental cost-effectiveness ratio; WTP: willingness-to-pay; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; CAPOX: capecitabine plus oxaliplatin; mdG: modified de Gramont, PFS: progression-free survival; OS: overall survival, AE: adverse event
*Undiscounted

Table 35: Deterministic sensitivity analysis results – bevacizumab plus CAPOX versus CAPOX alone, first-line setting

No.	Scenario	Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
-	Base-case (deterministic)	Bevacizumab plus CAPOX	2.139	1.458	[redacted]	0.260	0.169	[redacted]	[redacted]
		CAPOX alone	1.880	1.289	£16,313				
1	PFS and OS models: log-logistic	Bevacizumab plus CAPOX	2.713	1.735	[redacted]	0.429	0.246	[redacted]	[redacted]
		CAPOX alone	2.284	1.489	£17,146				
3	Oxaliplatin stopped at 6 month	Bevacizumab plus CAPOX	2.139	1.458	[redacted]	0.260	0.169	[redacted]	[redacted]
		CAPOX alone	1.880	1.289	£16,283				
4	Utility values for health states increased by 5%	Bevacizumab plus CAPOX	2.139	1.531	[redacted]	0.260	0.178	[redacted]	[redacted]
		CAPOX alone	1.880	1.353	£16,313				
5	Utility values for health states decreased by 5%	Bevacizumab plus CAPOX	2.139	1.385	[redacted]	0.260	0.161	[redacted]	[redacted]
		CAPOX alone	1.880	1.224	£16,313				
6	AE disutilities increased by 10 times	Bevacizumab plus CAPOX	2.139	1.456	[redacted]	0.260	0.169	[redacted]	[redacted]
		CAPOX alone	1.880	1.287	£16,313				
7	Median price of bevacizumab used	Bevacizumab plus CAPOX	2.139	1.458	[redacted]	0.260	0.169	[redacted]	[redacted]
		CAPOX alone	1.880	1.289	£16,313				
8	Vial sharing is assumed	Bevacizumab plus CAPOX	2.139	1.458	[redacted]	0.260	0.169	[redacted]	[redacted]
		CAPOX alone	1.880	1.289	£16,259				

LYG: life-year gained; QALY: quality-adjusted life-year; Inc: incremental; ICER: incremental cost-effectiveness ratio; WTP: willingness-to-pay; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; CAPOX: capecitabine plus oxaliplatin; PFS: progression-free survival; OS: overall survival; AE: adverse event
*Undiscounted

Figure 49: ICERs for bevacizumab plus fluoropyrimidine-based chemotherapy versus fluoropyrimidine-based chemotherapy alone at each provided bevacizumab price, first-line setting

ICER: incremental cost-effectiveness ratio; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; CAPOX: capecitabine plus oxaliplatin

5.4.6.2. Results of the EAG's economic analysis in the second-line setting

5.4.6.2.1. Central estimates of cost-effectiveness

The pair-wise results of the deterministic and probabilistic versions of the EAG's base case model are presented in Table 36 and Table 37, respectively. The model appears to be linear with the probabilistic and deterministic results being similar.

The cost-effectiveness planes and CEACs for each pair-wise comparison are provided in Appendix (see Figure 61 to Figure 64)

For all pair wise comparisons, the model indicates that the addition of bevacizumab to the FOLFOX/CAPOX is expected to increase QALYs and increase costs compared with FOLFOX/CAPOX alone, with deterministic ICERs of [redacted], and [redacted], respectively, when the decision severity modifier is set to unity. Assuming a decision severity modifier of 1.2, these ICERs become [redacted] and [redacted], respectively. As shown in Table 38, the drug acquisition costs (due to bevacizumab use) and administration costs (due to extended survival) are the key drivers of the increase in cost.

The CEACs indicate that the probabilities of bevacizumab in combination with fluoropyrimidine-based chemotherapy generate more net benefit than fluoropyrimidine-based chemotherapy alone when assuming a disease severity modifier of 1, are approximately [redacted] for bevacizumab plus FOLFOX and [redacted] for bevacizumab plus CAPOX at a willingness-to-pay threshold of £20,000 per QALY gained. Using a willingness-to-pay threshold of £30,000 per QALY gained, the probabilities are [redacted] for bevacizumab plus FOLFOX and [redacted] for bevacizumab plus CAPOX. When applying a disease severity modifier of 1.2, the probabilities become [redacted] (bevacizumab plus FOLFOX) and [redacted] (bevacizumab plus CAPOX) at the £20,000 per QALY threshold, and [redacted] and [redacted] respectively at the £30,000 per QALY threshold.

In the second-line setting, no results were generated for the comparison of bevacizumab plus FOLFIRI compared with FOLFIRI alone. However, as the base case ICER for bevacizumab plus FOLFIRI versus FOLFIRI alone in the first-line was [redacted] higher than that for bevacizumab plus FOLFOX versus FOLFOX alone, it is estimated that the ICER would be approximately [redacted] (with a disease severity modifier of 1) and [redacted] (with a disease severity modifier of 1.2) if this ratio continued into second-line.

Table 36: Base case results – bevacizumab plus fluoropyrimidine-based chemotherapy versus fluoropyrimidine-based chemotherapy alone, deterministic, including bevacizumab mean tender price, second-line setting

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER without severity modifier	ICER with severity modifier of 1.2
Model 1								
Bevacizumab plus FOLFOX	1.433	0.943	[redacted]	0.241	0.159	[redacted]	[redacted]	[redacted]
FOLFOX	1.192	0.784	£15,546					
Model 3								
Bevacizumab plus CAPOX	1.433	0.943	[redacted]	0.241	0.159	[redacted]	[redacted]	[redacted]
CAPOX	1.192	0.784	£12,757					

LYG: life-year gained; QALY: quality-adjusted life-year; Inc: incremental; ICER: incremental cost-effectiveness ratio; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; CAPOX: capecitabine plus oxaliplatin
*Undiscounted

Table 37: Base case results – bevacizumab plus fluoropyrimidine-based chemotherapy versus fluoropyrimidine-based chemotherapy alone, probabilistic, including bevacizumab mean tender price, second-line setting

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER without severity modifier	ICER with severity modifier of 1.2
Model 1								
Bevacizumab plus FOLFOX	1.432	0.942	[redacted]	0.241	0.159	[redacted]	[redacted]	[redacted]
FOLFOX	1.191	0.782	£15,518					
Model 3								
Bevacizumab plus CAPOX	1.432	0.942	[redacted]	0.241	0.159	[redacted]	[redacted]	[redacted]
CAPOX	1.191	0.782	£12,735					

LYG: life-year gained; QALY: quality-adjusted life-year; Inc: incremental; ICER: incremental cost-effectiveness ratio; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; CAPOX: capecitabine plus oxaliplatin
*Undiscounted

Table 38: Detailed breakdown of model-predicted costs (discounted), deterministic, second-line setting

	Bevacizumab plus FOLFOX	FOLFOX alone	Bevacizumab plus CAPOX	CAPOX alone
Progression-free				
Acquisition costs	[redacted]	£287	[redacted]	£105
Administration costs	£7,637	£5,880	£4,297	£3,274
Health state costs	£575	£402	£575	£402
AE costs	£254	£113	£254	£113
CVAD costs	£737	£737	£737	£737
Post-progression costs	£2,260	£2,121	£2,260	£2,121
Terminal care costs	£5,958	£6,006	£5,958	£6,006
Total costs	[redacted]	£15,546	[redacted]	£12,757

FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; CAPOX: capecitabine plus oxaliplatin; AE: adverse events; CVAD: central venous access device

5.4.6.2.2. Deterministic sensitivity analysis results

The results of DSAs are presented in Table 39 (bevacizumab plus FOLFOX versus FOLFOX alone) and Table 40 (bevacizumab plus CAPOX versus CAPOX alone).

Regarding the comparison of bevacizumab plus FOLFOX versus FOLFOX alone, all scenarios, except DSA1 and DSA2, produced ICERs similar to the base case, ranging between [redacted] and [redacted] (with severity modifier: [redacted] to [redacted]). In DSA1, where the log-logistic distribution was applied to both PFS and OS instead of gamma distribution, the ICER decreased to below [redacted] (with severity modifier: approximately [redacted]). In DSA2, where the HR from Mocellin *et al*. was used, the ICER increased to approximately [redacted] (with severity modifier: approximately [redacted]).

Similarly, for the comparison of bevacizumab plus CAPOX versus CAPOX alone, all scenarios, except DSA1 and DSA2, produced ICERs similar to the base case, ranging between [redacted] and [redacted] (with severity modifier: [redacted] to [redacted]). In DSA1, where the log-logistic distribution was applied to both PFS and OS instead of gamma distribution, the ICER decreased to around [redacted] (with severity modifier: [redacted]). In DSA2, where the HR from Mocellin *et al.* was used, the ICER increased to approximately [redacted] (with severity modifier: approximately [redacted]).

As in the first-line setting, the EAG conducted additional sensitivity analyses exploring the impact of each tender price of bevacizumab on the ICER. (Figure 50). Assuming a disease severity modifier of 1.2, the ICERs were estimated to fall below [redacted] per QALY gained in all but the two highest tender prices.

Table 39: Deterministic sensitivity analysis results – bevacizumab plus FOLFOX versus FOLFOX alone, second-line setting

No.	Scenario	Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER without severity modifier	ICER with severity modifier of 1.2
-	Base-case (deterministic)	Bevacizumab plus FOLFOX	1.433	0.943	[redacted]	0.241	0.159	[redacted]	[redacted]	[redacted]
		FOLFOX alone	1.192	0.784	£15,546					
1	PFS and OS models: log-logistic	Bevacizumab plus FOLFOX	1.625	1.043	[redacted]	0.340	0.213	[redacted]	[redacted]	[redacted]
		FOLFOX alone	1.285	0.830	£15,697					
2	HR based on Mocellin *et al.* was used	Bevacizumab plus FOLFOX	1.395	0.919	[redacted]	0.203	0.135	[redacted]	[redacted]	[redacted]
		FOLFOX alone	1.192	0.784	£15,546					
3	Utility values for health states increased by 5%	Bevacizumab plus FOLFOX	1.433	1.038	[redacted]	0.241	0.175	[redacted]	[redacted]	[redacted]
		FOLFOX alone	1.192	0.862	£15,546					
4	Utility values for health states decreased by 5%	Bevacizumab plus FOLFOX	1.433	0.849	[redacted]	0.241	0.143	[redacted]	[redacted]	[redacted]
		FOLFOX alone	1.192	0.705	£15,546					
5	AE disutilities increased by 10 times	Bevacizumab plus FOLFOX	1.433	0.942	[redacted]	0.241	0.159	[redacted]	[redacted]	[redacted]
		FOLFOX alone	1.192	0.783	£15,546					
6	Median price of bevacizumab used	Bevacizumab plus FOLFOX	1.433	0.943	[redacted]	0.241	0.159	[redacted]	[redacted]	[redacted]
		FOLFOX alone	1.192	0.784	£15,546					
7	Vial sharing is assumed	Bevacizumab plus FOLFOX	1.433	0.943	[redacted]	0.241	0.159	[redacted]	[redacted]	[redacted]
		FOLFOX alone	1.192	0.784	£15,493					

LYG: life-year gained; QALY: quality-adjusted life-year; Inc: incremental; ICER: incremental cost-effectiveness ratio; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; CAPOX: capecitabine plus oxaliplatin; PFS: progression-free survival; OS: overall survival; HR: hazard ratio, AE: adverse event
*Undiscounted

Table 40: Deterministic sensitivity analysis results – bevacizumab plus CAPOX versus CAPOX alone, second-line setting

No.	Scenario	Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER without severity modifier	ICER with severity modifier of 1.2
-	Base-case (deterministic)	Bevacizumab plus CAPOX	1.433	0.943	[redacted]	0.241	0.159	[redacted]	[redacted]	[redacted]
		CAPOX alone	1.192	0.784	£12,757					
1	PFS and OS models: log-logistic	Bevacizumab plus CAPOX	1.625	1.043	[redacted]	0.340	0.213	[redacted]	[redacted]	[redacted]
		CAPOX alone	1.285	0.830	£12,908					
2	HR based on Mocellin *et al.* was used	Bevacizumab plus CAPOX	1.395	0.919	[redacted]	0.203	0.135	[redacted]	[redacted]	[redacted]
		CAPOX alone	1.192	0.784	£12,757					
3	Utility values for health states increased by 5%	Bevacizumab plus CAPOX	1.433	1.038	[redacted]	0.241	0.175	[redacted]	[redacted]	[redacted]
		CAPOX alone	1.192	0.862	£12,757					
4	Utility values for health states decreased by 5%	Bevacizumab plus CAPOX	1.433	0.849	[redacted]	0.241	0.143	[redacted]	[redacted]	[redacted]
		CAPOX alone	1.192	0.705	£12,757					
5	AE disutilities increased by 10 times	Bevacizumab plus CAPOX	1.433	0.942	[redacted]	0.241	0.159	[redacted]	[redacted]	[redacted]
		CAPOX alone	1.192	0.783	£12,757					
6	Median price of bevacizumab used	Bevacizumab plus CAPOX	1.433	0.943	[redacted]	0.241	0.159	[redacted]	[redacted]	[redacted]
		CAPOX alone	1.192	0.784	£12,757					
7	Vial sharing is assumed	Bevacizumab plus CAPOX	1.433	0.943	[redacted]	0.241	0.159	[redacted]	[redacted]	[redacted]
		CAPOX alone	1.192	0.784	£12,721					

LYG: life-year gained; QALY: quality-adjusted life-year; Inc: incremental; ICER: incremental cost-effectiveness ratio; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; CAPOX: capecitabine plus oxaliplatin, PFS: progression-free survival; OS: overall survival; HR: hazard ratio; AE: adverse event
*Undiscounted

Figure 50: ICERs for bevacizumab plus fluoropyrimidine-based chemotherapy versus fluoropyrimidine-based chemotherapy alone at different tender prices of bevacizumab, second-line setting, with the disease severity modifier assumed to be 1.2

ICER: incremental cost-effectiveness ratio; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CAPOX: capecitabine plus oxaliplatin;

5.5. Disease severity modifier

As described in the NICE methods manual,[49] the severity of a condition is defined as the anticipated future health lost by people living with the condition under standard of care in the NHS. The severity of the disease is assessed using both absolute and proportional QALY shortfalls applying discounting of QALYs at 3.5% per annum. The absolute QALY shortfall was calculated as the difference between the expected total QALYs for the general population with the same age and sex distribution and the expected total QALYs for people living with mCRC under current treatment in the NHS over their remaining lifetime. The proportional QALY shortfall was estimated by dividing the absolute QALY shortfall by the expected total QALYs for the general population with the same age and sex distribution over their remaining lifetime. The NICE-recommend QALY weightings for severity are summarised in Table 41.

Table 41: Summary of QALY weightings for disease severity

QALY weight	Proportional QALY shortfall	Absolute QALY shortfall
1.0	Less than 0.85	Less than 12
1.2	0.85 to 0.95	12 to 18
1.7	At least 0.95	At least 18

QALY: quality-adjusted life-year

As the simplified model deliberately considered only one line of treatment the expected total QALYs gained across multiple treatments will be underestimated. To address this limitation, the EAG applied the following adjustments to the expected total QALYs for patients.

- In the first-line setting: the expected total QALYs were estimated as the sum of total QALYs from the comparator group in the first-and the second-line model and the reported QALYs for trifluridine-tipiracil plus bevacizumab group reported in TA1008.[22]
- In the second-line setting: the expected total QALYs were estimated as the sum of total QALYs from the comparator group in the second-line model and the trifluridine-tipiracil plus bevacizumab group in TA1008.

However, this approach has the limitations that it assumes i) that there is no doubling counting of QALYs accrued during the period from progression to death (whereas, in reality, there will be QALYs associated with both initial treatment where the patient is in the progressed disease state and the subsequent treatment where the patient would be in the progression-free state), and ii) that all patients progress and receive subsequent-lines of treatment rather than the PFS event being death.

Both limitations are likely to over-estimate the QALYs gained under current care and could be unfavourable to bevacizumab were the proportional or absolute QALY shortfall marginally falling short of an increased QALY weight.

The absolute and proportional QALY shortfalls were estimated using the University of York QALY shortfall calculator[50] assuming that patients receiving first-line treatment had a mean age of 60 years with 40% of the cohort being female, and patients receiving second-line treatment had a mean age of 61 years with 39.5% of the cohort being female (Section 5.4.3.1). The estimated disease severity modifier for both first-and second-line settings are summarised in Table 42; it is estimated that in second-line treatment a disease severity modifier of 1.2 would apply, but that this would remain at 1.0 for first-line treatment.

Table 42: Summary of QALY shortfall analysis

Treatment	Estimated total QALYs for patients who would be expected to have standard of care	Total QALYs for the general population	Absolute Shortfall	Proportional Shortfall	Disease severity modifier
First-line setting†					
FOLFOX/CAPOX alone	2.99 (1.29 +1.70)‡	12.68	9.69	76.41%	1.0
FOLFIRI alone	2.79 (1.09 +1.70)‡		9.89	77.99%	1.0
Second-line setting†					
FOLFOX/CAPOX alone	1.70 (0.78 + 0.92)§	12.33	10.63	86.21%	1.2

†assuming that patients progressed before death and that every progressed patient would receive subsequent lines of treatment

‡ 1.29 QALYs and 1.09 QALYs were generated from the EAG's model for the FOLFOX/CAPOX and FOLFIRI groups, respectively. The additional 1.70 QALYs was based on FOLFOX / CAPOX being used as second-line treatment.

§ 0.78 QALYs were generated from the EAG's model for FOLFOX and CAPOX, 0.92 QALYs was taken from the trifluridine-tipiracil plus bevacizumab arm in TA1008[22])

6. DISCUSSION

6.1. Clinical effectiveness findings

6.1.1.Clinical effectiveness principal findings in the first-line setting

6.1.1.1. Number and types of studies included in the review

Based on the pragmatic approach to reviewing clinical effectiveness evidence in the first-line setting, the EAG identified two relevant clinical studies to inform the EAG's economic analysis. Study NO16966[5] evaluated bevacizumab in combination with FOLFOX/CAPOX compared with FOLFOX/CAPOX alone, and Study AVF2107g[7] evaluated bevacizumab in combination with FOLFIRI versus FOLFIRI alone.

In Study NO16966, the available data were based on pooled results from the FOLFOX-and CAPOX-containing arms within the 2x2 factorial design by assuming comparable efficacy between these two regimens, an assumption that our clinical advisors were comfortable with. In Study AVF2107g, there is potential confounding of the OS data to a certain degree due to continued use of bevacizumab in the bevacizumab plus FOLFIRI arm beyond progression. Additionally, the study used the Saltz regimen as opposed to the mdG regimen, which is more commonly used within NHS.

6.1.1.2. Impact on the progression-free survival

Within Study NO16966, the addition of bevacizumab 5 mg/kg or 7.5mg/kg to FOLFOX/CAPOX resulted in a statistically significant increase in median progression-free survival of 1.4 months (HR = 0.83, $P = 0.0023$).

Within Study AVF2107g, the addition of bevacizumab 5 mg/kg to FOLFIRI results in a statistically significant increase in median progression-free survival of 4.4 months (HR = 0.54, $P < 0.001$).

6.1.1.3. Impact on the overall survival

Within Study NO16966, the addition of bevacizumab 5 mg/kg or 7.5 mg/kg to FOLFOX/CAPOX resulted in a statistically significant increase in median overall survival of 1.4 months (HR = 0.89, $P = 0.0769$).

Within Study AVF2107g, the addition of bevacizumab 5 mg/kg to FOLFIRI results in a statistically significant increase in median overall survival of 4.7 months (HR = 0.66, $P < 0.001$).

6.1.2. Clinical effectiveness principal findings in the second-line setting

6.1.2.1. Number and types of studies included in the review

The EAG identified a single clinical study relevant to inform the EAG's economic analysis in the second-line setting. Study E3200[12] evaluated the use of bevacizumab in combination with FOLFOX compared with FOLFOX alone. Although patients previously treated with oxaliplatin or bevacizumab were excluded from the study, the EAG considers that unlikely to have a significant impact on the economic analysis, as the economic model for the second-line setting does not consider prior treatments. In addition, data reported by

Masi *et al.*[16] suggested that prior bevacizumab use in the first-line setting may not influence the efficacy of bevacizumab plus chemotherapy in the second-line of treatment.

6.1.2.2. Impact on the progression-free survival
Within Study E3200, the addition of bevacizumab 10 mg/kg to FOLFOX resulted in a statistically significant increase in median progression-free survival of 2.6 months (HR = 0.61, P <0.0001).

6.1.2.3. Impact on the overall survival
Within Study E3200, the addition of bevacizumab 10 mg/kg to FOLFOX resulted in a statistically significant increase in median overall survival of 2.1 months (HR = 0.75, P = 0.0011).

6.2. Cost-effectiveness findings

6.2.1.First-line setting
For the first-line treatment of mCRC, the EAG's base case model suggests that bevacizumab in combination with fluoropyrimidine-based chemotherapy (FOLFOX, FOLFIRI or CAPOX) is expected to generate more QALYs gained and incur higher costs than fluoropyrimidine-based chemotherapy alone (FOLFOX, FOLFIRI or CAPOX alone). The main reasons underpinning these findings are: (i) extended PFS and OS, (ii) increased drug acquisition and administration costs associated with the addition of bevacizumab, (iii) higher overall disease management costs due to extended OS, and (iv) a slight increase in AE management costs.

The EAG's cost-effectiveness deterministic model suggests that bevacizumab plus FOLFOX costs approximately [redacted] more and generates 0.169 more QALYs than FOLFOX alone whilst bevacizumab plus CAPOX is expected to cost approximately [redacted] and generate 0.169 QALYs than CAPOX alone. For both comparisons, the deterministic and probabilistic ICERs are similar and fall below [redacted] per QALY gained. For bevacizumab plus FOLFIRI versus FOLFIRI alone, incremental costs are approximately [redacted] and incremental QALYs 0.324, resulting in an ICER of approximately [redacted]. Most of the scenarios show ICERs similar to the base case and consistently below [redacted] per QALY gained. The ICERs were sensitive to the choice of distribution for PFS and OS: applying the log-logistic model resulted in ICERs below [redacted] for comparisons of bevacizumab plus FOLFOX/CAPOX versus FOLFOX/CAPOX alone, while the use of generalised gamma model increased the ICER to approximately [redacted] for bevacizumab plus FOLFIRI versus FOLFIRI alone.

The EAG believes that the analyses requested by NICE using the mean and median prices will overestimate the ICER as these assume the drug usage is largely independent of price. Given the wide variation in tender prices this is unlikely to be correct and so the EAG has provided the ICERs at each of the 8 tender prices to further inform the committee. The base case ICER only exceeded [redacted] per QALY gained when the highest tender price was used.

6.2.2.Second-line setting

For the second-line treatment of mCRC, the EAG's base case model suggests that bevacizumab in combination with fluoropyrimidine-based chemotherapy (FOLFOX or CAPOX) is expected to generate more QALYs and incur higher costs than fluoropyrimidine-based chemotherapy alone (FOLFOX or CAPOX alone) for the reasons described in Section 6.2.1.

The EAG's cost-effectiveness deterministic model suggests that bevacizumab plus FOLFOX costs approximately [redacted] more and generates 0.159 more QALYs than FOLFOX alone whilst bevacizumab plus CAPOX is expected to cost approximately [redacted] more and generate 0.159 more QALYs than CAPOX alone. The deterministic ICERs are approximately [redacted] (FOLFOX) and [redacted] (CAPOX), when the severity modifier was assumed to be 1. With a severity modifier of 1.2, the deterministic ICERs decreased to approximately [redacted] and [redacted], respectively.

As no results were generated by the model for the comparison of bevacizumab plus FOLFIRI versus FOLFIRI alone, ICERs were estimated based on the assumption that they would be [redacted] higher than those for bevacizumab plus FOLFOX versus FOLFOX alone as observed in the first-line (see Section 5.4.6.2.1). Therefore, the resulting ICERs for bevacizumab plus FOLFIRI versus FOLFIRI alone were around [redacted] with a severity modifier of 1 and [redacted] with a severity modifier of 1.2.

As for first-line treatment the EAG has provided ICERs using each of the 8 tender prices. Assuming a disease severity modifier of 1.2, the base case ICER only exceeded [redacted] per QALY gained when the two highest tender prices were used.

6.3. Strengths and limitations of the assessment

Strengths

This work has produced revised estimates of the cost-effectiveness of bevacizumab in the first-line and the second-line treatment of mCRC following price reductions after the loss of exclusivity. One strength was the methodology applied, which we are unaware of being applied elsewhere, which deliberately avoided modelling sequential treatments allowing the resources required for a more complex MTA to be significantly reduced. The EAG was cognisant that an STA would be unlikely given that there are multiple manufacturers of bevacizumab and no clear incentive for a single company to fund an STA. The approach we have taken (along with the assumptions used) may guide further evaluations of biosimilar or generic products where it is anticipated that these have a high probability of being cost-effective.

For the clinical effectiveness data in both first-and second-line settings, the EAG either digitised KM curves from study publications or used provided KM estimates and generated pseudo-IPD for PFS and OS using the algorithm reported by Guyot *et al*., in accordance with TSD 14 and NICE health technology evaluations manual. This allows robust survival modelling and comparative effectiveness analysis when the actual IPD are not available. In addition, uncertainty around survival parameters was explicitly incorporated in the probabilistic economic model by using the variance-covariance matrix derived from the parametric models fitted to the reconstructed pseudo-IPD.

The economic analysis is consistent with the NICE Reference Case and aligns with the NICE final scope. The life years gained, and QALYs predicted by the model, are similar to the values estimated by the models in TA118[8] and TA212[6]. A range of sensitivity analyses were conducted to explore key areas of uncertainty.

Limitations

The pragmatic approach relied on several strong assumptions (more details are provided in Section 5.1). Key assumptions were that: (i) subsequent NICE-recommended treatments following disease progression are cost-effective, (ii) there is no interaction in efficacy between prior use of bevacizumab and subsequent treatments and (iii) economic models include only a single line of treatment, excluding the outcomes of active subsequent treatments and a simple partition survival model was appropriate. Whilst these appeared to not present a large problem in this appraisal, this may not be the case in other evaluations.

There is an underestimation of LYG (and QALYs) associated with standard of care as all progressed patients were modelled to receive best supportive care instead of active subsequent treatments which affects absolute and proportional QALY losses used in the disease severity modifier calculations. The EAG attempted to adjust for this by adding QALYs associated with later lines of treatments although this will overestimate QALYs. (see Section 5.5).

The reviews of clinical and cost-effectiveness were based on the previous NICE TAs given the intentional pragmatic approach. The EAG considers it unlikely that this approach omitted any relevant evidence that would significantly change the ICER.

Only the numbers at risk at time zero were available when generating the IPD for PFS and OS from Study E3200. Censoring patterns later within the follow-up period may therefore differ slightly from that observed within the trial.

REFERENCES

1. National Institute for Health and Care Excellence. Bevacizumab (originator and biosimilars) with fluoropyrimidine-based chemotherapy for metastatic colorectal cancer [ID6465]. Final scope. London; 2025.
2. Cancer Research UK. Bowel cancer statistics. Available from: https://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/bowel-cancer (Accessed 15/06/2025).
3. Cancer Research UK. Early Cancer Diagnosis Data Hub. Available from: https://crukcancerintelligence.shinyapps.io/EarlyDiagnosis/ (Accessed 15/06/2025).
4. National Institute for Health and Care Excellence. Colorectal cancer NICE guideline [NG151]. *Journal* 2020. https://www.nice.org.uk/guidance/NG15116/04/25
5. Cassidy J, Clarke S, Díaz-Rubio E, Scheithauer W, Figer A, Wong R, *et al.* XELOX vs FOLFOX-4 as first-line therapy for metastatic colorectal cancer: NO16966 updated results. *Br J Cancer* 2011;105:58-64.
6. National Institute for Health and Care Excellence. Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of metastatic colorectal cancer [TA212]. *Journal* 2010. https://www.nice.org.uk/guidance/ta21216/04/25
7. Hurwitz H, Fehrenbacher L, Novotny W, Cartwright T, Hainsworth J, Heim W, *et al.* Bevacizumab plus Irinotecan, Fluorouracil, and Leucovorin for Metastatic Colorectal Cancer. *New England Journal of Medicine* 2004;350:2335-42.
8. National Institute for Health and Care Excellence. Bevacizumab and cetuximab for the treatment of metastatic colorectal cancer [TA118]. *Journal* 2007. https://www.nice.org.uk/guidance/ta11816/04/25
9. National Institute for Health and Care Excellence. Cetuximab, bevacizumab and panitumumab for the treatment of metastatic colorectal cancer after first-line chemotherapyr [TA242]. *Journal* 2012. https://www.nice.org.uk/guidance/ta24216/04/25
10. Golfinopoulos V, Salanti G, Pavlidis N, Ioannidis JP. Survival and disease-progression benefits with treatment regimens for advanced colorectal cancer: a meta-analysis. *Lancet Oncol* 2007;8:898-911.
11. Mocellin S, Baretta Z, Roqué i Figuls M, Solà I, Martin-Richard M, Hallum S, *et al.* Second-line systemic therapy for metastatic colorectal cancer. *Cochrane Database of Systematic Reviews* 2017; 10.1002/14651858.CD006875.pub3.
12. Giantonio BJ, Catalano PJ, Meropol NJ, O'Dwyer PJ, Mitchell EP, Alberts SR, *et al.* Bevacizumab in combination with oxaliplatin, fluorouracil, and leucovorin (FOLFOX4) for previously treated metastatic colorectal cancer: results from the Eastern Cooperative Oncology Group Study E3200. *J Clin Oncol* 2007;25:1539-44.
13. Tournigand C, André T, Achille E, Lledo G, Flesh M, Mery-Mignard D, *et al.* FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. *J Clin Oncol* 2004;22:229-37.
14. Bennouna J, Sastre J, Arnold D, Österlund P, Greil R, Van Cutsem E, *et al.* Continuation of bevacizumab after first progression in metastatic colorectal cancer (ML18147): a randomised phase 3 trial. *Lancet Oncol* 2013;14:29-37.
15. Cao R, Zhang S, Ma D, Hu L. A multi-center randomized phase II clinical study of bevacizumab plus irinotecan, 5-fluorouracil, and leucovorin (FOLFIRI) compared with FOLFIRI alone as second-line treatment for Chinese patients with metastatic colorectal cancer. *Med Oncol* 2015;32:325.
16. Masi G, Salvatore L, Boni L, Loupakis F, Cremolini C, Fornaro L, *et al.* Continuation or reintroduction of bevacizumab beyond progression to first-line therapy in metastatic colorectal cancer: final results of the randomized BEBYP trial. *Annals of Oncology* 2015;26:724-30.
17. Smith RD, Hall J, Gurney H, Harnett PR. A cost-utility approach to the use of 5-fluorouracil and levamisole as adjuvant chemotherapy for Dukes' C colonic carcinoma. *Med J Aust* 1993;158:319-22.
18. Brown ML, Nayfield SG, Shibley LM. Adjuvant therapy for stage III colon cancer: economics returns to research and cost-effectiveness of treatment. *J Natl Cancer Inst* 1994;86:424-30.

19. Wilke H, Glynne-Jones R, Thaler J, Adenis A, Preusser P, Aguilar EA, *et al.* Cetuximab Plus Irinotecan in Heavily Pretreated Metastatic Colorectal Cancer Progressing on Irinotecan: MABEL Study. *Journal of Clinical Oncology* 2008;26:5335-43.
20. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual. *Journal* 2022. https://www.nice.org.uk/process/pmg3606/03/24
21. Office for National Statistics. National life tables: England. Available from: https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/lifeexpectancies/datasets/nationallifetablesenglandreferencetables/current. London, UK; 2024.
22. National Institute for Health and Care Excellence. Trifluridine–tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments [TA1008]. *Journal* 2024. https://www.nice.org.uk/guidance/ta100816/04/25
23. Freeman K, Connock M, Cummins E, Gurung T, Taylor-Phillips S, Court R, *et al.* Fluorouracil plasma monitoring: the My5-FU assay for guiding dose adjustment in patients receiving fluorouracil chemotherapy by continuous infusion. Diagnostic Assessment Report commissioned by the NIHR HTA Programme on behalf of the National Institute for Health and Care Excellence.; 2014.
24. Thomas C, Mandrik O, Saunders CL, Thompson D, Whyte S, Griffin S, *et al.* The Costs and Benefits of Risk Stratification for Colorectal Cancer Screening Based On Phenotypic and Genetic Risk: A Health Economic Analysis. *Cancer Prev Res (Phila)* 2021;14:811-22.
25. Tabberer M, Stamuli E, Walker M, Summerhayes M, Lees M. PCN74 utilities associated with non-small cell lung cancer (NSCLC): a community study. *Value in Health* 2006;9:A298.
26. Nafees B, Stafford M, Gavriel S, Bhalla S, Watkins J. Health state utilities for non small cell lung cancer. *Health Qual Life Outcomes* 2008;6:84.
27. National Institute for Health and Care Excellence. Osimertinib for treating EGFR T790M mutation-positive advanced non-small-cell lung cancer [TA653]. *Journal* 2020. https://www.nice.org.uk/guidance/ta65316/04/25
28. National Institute for Health and Care Excellence. Targeted-release budesonide for treating primary IgA nephropathy[TA937]. *Journal* 2023. https://www.nice.org.uk/guidance/ta93716/04/25
29. National Institute for Health and Care Excellence. Blinatumomab with chemotherapy for consolidation treatment of Philadelphia-chromosome-negative CD19-positive minimal residual disease-negative B-cell precursor acute lymphoblastic leukaemia [TA1049]. *Journal* 2025. https://www.nice.org.uk/guidance/ta104927/05/2025
30. Hernández Alava M, Pudney S, Wailoo A. Estimating EQ-5D by age and sex for the UK. Sheffield, UK; 2022.
31. Department of Health and Social Care. Drugs and pharmaceutical electronic market information tool (eMIT). 2024. https://www.gov.uk/government/publications/drugs-and-pharmaceutical-electronic-market-information-emit (Accessed 10 November 2023).
32. National Institute for Health and Care Excellence. British National Formulary (BNF). *Journal* 2025. https://bnf.nice.org.uk01/052025
33. NHS England. National Schedule of NHS Costs 2023/24. Available from: https://www.england.nhs.uk/costing-in-the-nhs/national-cost-collection/; 2024.
34. National Institute for Health and Care Excellence. Trifluridine–tipiracil for previously treated metastatic colorectal cancer [TA405]. *Journal* 2016. https://www.nice.org.uk/guidance/ta40516/04/25
35. National Institute for Health and Care Excellence. Encorafenib plus cetuximab for previously treated BRAF V600E mutation-positive metastatic colorectal cancer [TA668]. *Journal* 2021. https://www.nice.org.uk/guidance/ta66816/04/25
36. National Institute for Health and Care Excellence. Regorafenib for previously treated metastatic colorectal cancer [TA866]. *Journal* 2023. https://www.nice.org.uk/guidance/ta86616/04/25
37. Round J, Jones L, Morris S. Estimating the cost of caring for people with cancer at the end of life: A modelling study. *Palliat Med* 2015;29:899-907.
38. Guyot P, Ades AE, Ouwens MJ, Welton NJ. Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. *BMC Med Res Methodol* 2012;12:9.

39. Latimer N. NICE DSU Technical Support Document 14: Undertaking survival analysis for economic evaluations alongside clinical trials - extrapolation with patient-level data. 2011. Available from http://www.nicedsu.org.uk/.
40. Ramsey SD, Andersen MR, Etzioni R, Moinpour C, Peacock S, Potosky A*, et al.* Quality of life in survivors of colorectal carcinoma. *Cancer* 2000;88:1294-303.
41. Cutsem EV, Nowacki M, Lang I, Cascinu S, Shchepotin I, Maurel J*, et al.* Randomized phase III study of irinotecan and 5-FU/FA with or without cetuximab in the first-line treatment of patients with metastatic colorectal cancer (mCRC): The CRYSTAL trial. *Journal of Clinical Oncology* 2007;25:4000-.
42. Van Cutsem E, Peeters M, Siena S, Humblet Y, Hendlisz A, Neyns B*, et al.* Open-label phase III trial of panitumumab plus best supportive care compared with best supportive care alone in patients with chemotherapy-refractory metastatic colorectal cancer. *J Clin Oncol* 2007;25:1658-64.
43. Dorian P, Kongnakorn T, Phatak H, Rublee DA, Kuznik A, Lanitis T*, et al.* Cost-effectiveness of apixaban vs. current standard of care for stroke prevention in patients with atrial fibrillation. *Eur Heart J* 2014;35:1897-906.
44. Taieb J, Fakih M, Tabernero J, Ciardiello F, Van Cutsem E, Soler G*, et al.* Impact of Treatment With Trifluridine/Tipiracil in Combination With Bevacizumab on Health-Related Quality of Life and Performance Status in Refractory Metastatic Colorectal Cancer: An Analysis of the Phase III SUNLIGHT Trial. *Clinical Colorectal Cancer* 2025;24:180-7.e4.
45. Personal Social Services Research U. Unit Costs of Health and Social Care. *Journal* 2024. https://www.pssru.ac.uk/unitcostsreport/14/06/25
46. Baxter healthcare. Baxter Healthcare Ltd: List Price. 2022. https://www.baxterhealthcare.co.uk/sites/g/files/ebysai1286/files/2022-02/Baxter%20UK%20List%20Prices%201st%20April%202022.pdf (Accessed 30/06/2025).
47. National Institute for Health and Care Excellence. Pembrolizumab for untreated metastatic colorectal cancer with high microsatellite instability or mismatch repair deficiency [TA709]. *Journal* 2021. https://www.nice.org.uk/guidance/ta70916/04/25
48. European Medicines Agency. Summary of Product Characteristics - Avastin (bevacizumab). Amsterdam, Netherlands; 2025.
49. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual; 2025.
50. Schneider P MS, Love-Koh J, Doran T, Gutacker N. QALY Shortfall Calculator. https://shiny.york.ac.uk/shortfall/ (Accessed 18th July 2025).

APPENDIX

Table 43: Current NICE recommendations for the systemic treatment of metastatic colorectal cancer with no known mutations

NICE TA	NICE recommendations
First-line treatment (no specific mutation)	
TA61 - Guidance on the use of capecitabine and tegafur with uracil for mCRC (2003)	Oral therapy with capecitabine is recommended as an option for the first-line treatment of mCRC.
TA118 - Bevacizumab and cetuximab for the treatment of mCRC (2007)	Not recommended. The appraisal was replaced by TA242.
TA212 - Bevacizumab in combination with oxaliplatin and either fluorouracil plus folinic acid or capecitabine for the treatment of mCRC (2010)	Not recommended.
Second-line/third-line treatment (no specific mutation)	
TA242 - Cetuximab, bevacizumab and panitumumab for the treatment of mCRC after first-line chemotherapy (2012)	Not recommended.
TA307- Aflibercept in combination with irinotecan and fluorouracil-based therapy for treating mCRC that has progressed following prior oxaliplatin-based chemotherapy (2014)	Not recommended.
TA405 – Trifluridine-tipiracil for previously treated mCRC (2016)	Trifluridine–tipiracil is recommended, within its marketing authorisation, as an option for treating mCRC, that is: • in adults who have had previous treatment with available therapies including fluoropyrimidine-, oxaliplatin- or irinotecan-based chemotherapies, anti-vascular endothelial growth factor (VEGF) agents and anti-epidermal growth factor receptor (EGFR) agents, or when these therapies are not suitable, and • only when the company provides trifluridine–tipiracil with the discount agreed in the patient access scheme.
TA866 – Regorafenib for previously treated mCRC (2023)	Regorafenib is recommended, within its marketing authorisation, as an option for mCRC in adults who have had previous treatment (including fluoropyrimidine-based chemotherapy, anti-VEGF therapy, and anti-EGFR therapy) or when these treatments are unsuitable. Regorafenib is only recommended if the company provides it according to the commercial arrangement.
TA1008 – Trifluridine–tipiracil with bevacizumab for treating metastatic colorectal cancer after 2 systemic treatments (2024)	Trifluridine–tipiracil with bevacizumab is recommended, within its marketing authorisation, for treating metastatic colorectal cancer in adults who have had 2 lines of treatment (including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-vascular endothelial growth factor, or anti-epidermal growth factor receptor treatments).

	Trifluridine–tipiracil with bevacizumab is only recommended if the company provides trifluridine–tipiracil according to the commercial arrangement.

mCRC: metastatic colorectal cancer; NICE: National Institute for Health and Care Excellence; TA: technology appraisal

Table 44: Population characteristics of Study NO16966 (generated from the CS, TA212)

	Treatment allocation					
	FOLFOX (N=317)	**Placebo plus FOLFOX (N=351)**	**Bevacizumab plus FOLFOX (N=349)**	**CAPOX (N=317)**	**Placebo plus CAPOX (N=350)**	**Bevacizumab plus CAPOX (N=350)**
Demographics						
Gender						
Male	204 (64%)	186 (53%)	205 (59%)	194 (61%)	205 (59%)	213 (61%)
Female	113 (36%)	165 (47%)	144 (41%)	123 (39%)	145 (41%)	137 (39%)
Race						
Caucasian	236 (74%)	312 (89%)	300 (86%)	237 (75%)	312 (89%)	313 (89%)
Black	4 (18%)	7 (2%)	11 (3%)	8 (3%)	5 (1%)	5 (1%)
Oriental	-	0	-	-	-	-
Other	77 (24%)	32 (9%)	38 (11%)	72 (23%)	33 (9%)	32 (9%)
Age						
Mean (years)	60.6	58.8	59.7	60.3	59.1	59.7
Range (years)	24-83	26-83	19-82	24-84	18-83	18-86
ECOG PS (baseline)						
0	163 (51%)	211 (60%)	198 (57%)	160 (50%)	207 (59%)	207 (59%)
1	154 (49%)	138 (40%)	147 (43%)	157 50%)	143 (41%)	142 (41%)
2	-	-	-	-	-	1 (<1%)
Alkaline Phosphatase (baseline)						
Abnormal	135 (43%)	147 (42%)	146 (42%)	132 (42%)	149 (43%)	156 (45%)
Normal	182 (57%)	201 (58%)	199 (58%)	183 (58%)	200 (57%)	191 (55%)
Disease characteristics						
Time from diagnosis with mCRC to randomization						
Mean (days)	104.6	95.9	88.0	76.5	83.0	90.7
Range (days)	1-2868	1-1571	0-1401	0-899	0-2437	2-2813
Number of metastatic sites						
= 1	118 (37.2%)	142 (40.5%)	150 (43.0%)	127 (40.1%)	155 (44.3%)	134 (38.3%)
>1	198 (62.5%)	208 (59.3%)	198 (56.7%)	190 (59.9%)	195 (55.7%)	216 (61.7%)
Liver metastases?						
Yes	238 (76.3%)	269 (76.7%)	266 (76.0%)	241 (76.0%)	261 (74.6%)	272 (77.7%)
No	75 (23.6%)	82 (23.4%)	84 (24.0%)	76 (24.0%)	89 (25.4%)	78 (22.3%)
Treatment history						
Prior adjuvant therapy?						
Yes	83 (26%)	85 (24%)	88 (25%)	58 (28%)	91 (26%)	76 (22%)
No	234 (74%)	266 (76%)	261 (75%	229 (77%)	259 (71%)	274 (78%)

Treatment for metastatic disease						
First	296 (93%)	333 (95%)	332 (95%)	301 (95%)	334 (95%)	333 (95%)
Second	21 (7%)	18 (5%)	16 (5%)	16 (5%)	16 (5%)	17 (5%)

FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; CAPOX: capecitabine plus oxaliplatin; mCRC: metastatic colorectal cancer; ECOG PS: Eastern Cooperative Oncology Group Performance Status

Table 45: Population characteristics of Study AVF2107g (generated from EAG report, TA118)

Patient characteristics	**AVF2107g***
Median age years, (range)	Arm 1: 60 (21-83) Arm 2: 60 (23-86) Arm 3: 61.5 (29-88)
Mean age years	Arm 1: 59.2 Arm 2: 59.5 Arm 3: -
Male (%)	Arm 1: 60 Arm 2: 59 Arm 3: 63
ECOG PS	Arm 1: 0 (55%) 1 (44%) 2 (<1%) Arm 2: 0 (58%) 1 (41%) 2 (<1%) Arm 3: -
Site of primary tumour	Arm 1: Colon 81%; Rectum 19% Arm 2: Colon 77%; Rectum 23% Arm 3: -
Number of metastatic sites	Arm 1: 1, 39%; >1, 61% Arm 2: 1, 37%; >1, 63% Arm 3: -
Site(s) of metastases	Not reported

ECOG PS: Eastern Cooperative Oncology Group Performance Status
*Arm 1: bevacizumab plus FOLFIRI, Arm 2: placebo plus FOLFIRI; Arm 3: bevacizumab plus 5-FU/FA

Table 46: Population characteristics of Study E3200

Characteristic	**Bevacizumab plus FOLFOX-4 (n =286)**	**FOLFOX-4 (n=291)**	**Bevacizumab (n=243)**
Age, years			
Median	62.0	60.8	59.6
Range	21-85	25-84	23-82
Female sex, %	39.5	39.2	40.7
Performance status, %			
0	48.9	51.2	48.6
1	46.9	43.0	43.6
2	4.2	5.8	7.8
Prior radiation therapy, %	25.9	24.7	25.9
Disease site			
Liver	73.4	75.9	70.8
Lung	55.5	51.2	59.7

FOLFOX: folinic acid plus fluorouracil plus oxaliplatin

Table 47: Population characteristics of Study GERCOR

Parameter	Arm A: FOLFIRI/FOLFOX-6		Arm B: FOLFOX6/FOLFIRI	
	No. of patients	%	No. of patients	%
Demographic characteristics				
No. of patients	109	100	111	100
Male	62	57	80	72
Female	47	43	31	28
Age, years				
Median	61		65	
Range	29-75		40-75	
WHO performance status				
0	49	45	52	47
1	42	39	52	47
2	18	17	7	6
Primary site				
Colon	73	67	80	72
Rectum	36	33	29	26
Multiple	0	0	2	2
Metastases				
Synchronous	83	76	85	77
Metachronous	26	24	26	23
Metastatic site				
Liver	95	87	89	80
Lung	34	31	33	30
Other	43	39	55	50
No. of sites				
1	64	59	66	59
≥2	45	41	45	41
CEA				
<10 ng/ml	28	26	37	33
≥10 ng/ml	76	70	66	59
Unknown	5	5	8	7
Alkaline phosphatase				
Normal	48	44	59	51
Increased	52	49	33	40
Unknown	9	8	9	9
Adjuvant chemotherapy				
Yes	19	17	23	21
No	90	83	88	79

FOLFIRI: folinic acid plus fluorouracil plus irinotecan; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CEA: carcinoembryonic antigen

Figure 51: KM TTD of bevacizumab plus FOLFOX arm

KM: Kaplan-Meier, TTD: time to treatment discontinuation; 5FU: 5 fluorouracil or folinic acid; PFS: progression-free survival; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin

Figure 52: KM TTD of FOLFOX alone arm

KM: Kaplan-Meier, TTD: time to treatment discontinuation; 5FU/FA: 5 fluorouracil or folinic acid; PFS: progression-free survival; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin

Figure 53: KM TTD of bevacizumab plus CAPOX arm

KM: Kaplan-Meier, TTD: time to treatment discontinuation; PFS: progression-free survival; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CAPOX: capecitabine plus oxaliplatin

Figure 54: KM TTD of CAPOX alone arm

KM: Kaplan-Meier, TTD: time to treatment discontinuation; PFS: progression-free survival; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CAPOX: capecitabine plus oxaliplatin

Table 48: Proportions of patients in each category

Category	Proportion of patients	Source
Body weight		
<60 kg	2.28%	Based on the normal distribution of mean body weight (75 kg) and its SE (7.5)
60 kg to 80 kg	72.48%	
80 kg to 100 kg	25.21%	
100 kg and over	0.04%	
Body Surface Area (BSA)		
< 1.5 m^2	7.66%	Based on the normal distribution of mean BSA (1.75 m^2) and its SE (0.175)
1.50 - 1.7 m^2	31.10%	
1.7 - 2.00 m^2	53.59%	
> 2.00 m^2	7.66%	

SE: standard error

Table 49: Detailed calculation of weighted average cost per treatment cycle

	Weighted average cost per treatment cycle	Category	Costs	*Notes*
Bevacizumab, 5 mg/kg	[redacted]	<60 kg	[redacted]	300mg (3*100mg)
		60 to 80	[redacted]	400mg (1*400mg)
		80 to 100	[redacted]	500mg (1*400mg+1*100 mg)
		100+	[redacted]	600mg (1*400mg+2*100mg)
Bevacizumab, 7.5 mg/kg	[redacted]	<60 kg	[redacted]	450mg (1*400mg+1*100mg)
		60 to 80	[redacted]	600mg (1*400mg+2*100mg)
		80 to 100	[redacted]	750mg (2*400mg)
		100+	[redacted]	900mg (2*400mg+1*100mg)
Bevacizumab, 10 mg/kg	[redacted]	<60 kg	[redacted]	600mg (2*100 mg+ 1*400mg)
		60 to 80		800mg (2*400mg)
		80 to 100		1000mg (2*400mg+2*100mg)
		100+	[redacted]	1200mg (3*400mg)
Bevacizumab, 15 mg/kg	[redacted]	<60 kg	[redacted]	900mg (2*400mg+1*100mg)
		60 to 80	[redacted]	1200mg (3*400mg)
		80 to 100	[redacted]	1500mg (4*400mg)
		100+	[redacted]	1800mg (4*400mg + 2*100mg)
Fluorouracil (Injection), 400 mg/m^2	£12.16	< 1.5 m^2	£12.16	600mg (1*1000mg)
		1.50- 1.7 m^2	£12.16	680mg (1*1000mg)
		1.7 - 2.00 m^2	£12.16	800mg (1*1000mg)
		> 2.00 m^2	£12.16	880mg (1*1000mg)
Fluorouracil (Injection), 500 mg/m^2	£13.09	< 1.5 m^2	£12.16	750mg (1*1000mg)
		1.50- 1.7 m^2	£12.16	850mg (1*1000mg)
		1.7 - 2.00 m^2	£12.16	1000mg (1*1000mg)

		> 2.00 m^2	£24.32	1100mg (2*1000mg)
Fluorouracil (Infusion), 600 mg/m^2	£6.21	< 1.5 m^2	£3.20	900mg (1*1000mg)
		1.50- 1.7 m^2	£6.46	1020mg (1*1000mg + 1*500mg)
		1.7 - 2.00 m^2	£6.46	1200mg (1*1000mg + 1*500mg)
		> 2.00 m^2	£6.46	1320mg (1*1000mg + 1*500mg)
Folinic acid, 200 mg/m^2	£7.79	< 1.5 m^2	£6.10	300mg (1*350mg)
		1.50- 1.7 m^2	£6.10	340mg (1*350mg)
		1.7 - 2.00 m^2	£8.86	400mg (1*350mg + 1*100mg)
		> 2.00 m^2	£8.86	440mg (1*350mg + 1*100mg)
Folinic acid, 20 mg/m^2	£16.58	< 1.5 m^2	£16.58	30mg (1*100mg)
		1.50- 1.7 m^2	£16.58	34mg (1*100mg)
		1.7 - 2.00 m^2	£16.58	40mg (1*100mg)
		> 2.00 m^2	£16.58	44mg (1*100mg)
Oxaliplatin, 85 mg/m^2	£11.31	< 1.5 m^2	£11.31	127.5mg (1*200mg)
		1.50- 1.7 m^2	£11.31	144.5mg (1*200mg)
		1.7 - 2.00 m^2	£11.31	170mg (1*200mg)
		> 2.00 m^2	£11.31	187mg (1*200mg)
Oxaliplatin, 130 mg/m^2	£21.26	< 1.5 m^2	£11.31	1195mg (1*200mg)
		1.50- 1.7 m^2	£17.79	221mg (1*200mg + 1*50mg)
		1.7 - 2.00 m^2	£24.27	260mg (1*200mg + 2*50mg)
		> 2.00 m^2	£24.27	286mg (1*200mg + 2*50mg)
Capecitabine, 1000 mg/m^2	£0.67	< 1.5 m^2	£0.50	1500mg (3*500mg)
		1.50- 1.7 m^2	£0.67	1700mg (4*500mg)
		1.7 - 2.00 m^2	£0.67	2000mg (4*500mg)
		> 2.00 m^2	£0.84	2200mg (5*500mg)
Irinotecan, 125 mg/m^2	£24.10	< 1.5 m^2	£26.13	187.5mg (2*100mg)
		1.50- 1.7 m^2	£17.97	212.5mg (2*100mg + 1*40mg)
		1.7 - 2.00 m^2	£26.96	250mg (3*100mg)
		> 2.00 m^2	£26.96	275mg (3*100mg)

Table 50: Drug acquisition costs per treatment cycle of FOLFIRI-containing regimens, based on mdG

Regimen	Drugs	Dosing schedule	Total dose per treatment cycle (per protocol) (mg)*	Costs per treatment cycle†	RDI	Expected costs per treatment cycle	Source
Bevacizumab plus FOLFIRI	Bevacizumab	5 mg/kg IV over 30-90 min	375	[redacted]	96.53%	[redacted]	EAG's clinical inputs
	Fluorouracil (Injection)	400 mg/m^2, bolus injection	700	£12	92.00%	£11	
	Fluorouracil (Injection)	2400 mg/m^2 infusion over 46 hr	4200	£7	92.00%	£6	
	Folinic Acid	400 mg/m^2, infusion over 120 min	700	£14	94.00%	£13	
	Irinotecan	180 mg/m^2 IV infusion	315	£35	87.00%	£30	
FOLFIRI	Fluorouracil (Injection)	400 mg/m^2, bolus injection	700	£12	93.00%	£11	EAG's clinical inputs
		2400 mg/m^2 infusion over 46 hr	4200	£7	93.00%	£6	
	Folinic Acid	400 mg/m^2, infusion over 120 min	700	£14	96.00%	£13	
	Irinotecan	180 mg/m^2 IV infusion	315	£35	89.00%	£31	

FOLFIRI: folinic acid plus fluorouracil plus irinotecan; RDI: relative dose intensity; IV: intravenous

*based on a mean body weight of 70 kg, a mean BSA of 1.75 m^2

†weighted average cost based on the body weight (or BSA)-based distribution

Table 51: Drug acquisition costs per model cycle of FOLFIRI-containing regimens, based on mdG

Treatment regimen	Drugs	Treatment cycles per month*	Costs per treatment cycle	Expected costs per month	Total costs per regimen	Source
Bevacizumab plus FOLFIRI	Bevacizumab	2	[redacted]	[redacted]	[redacted]	BNF 2025, eMIT 2024
	Fluorouracil		£17	£34		
	Folinic Acid		£13	£26		
	Irinotecan		£30	£61		
FOLFIRI	Fluorouracil	2	£17	£35	£124	BNF 2025, eMIT 2024
	Folinic Acid		£13	£27		
	Irinotecan		£31	£62		

FOLFIRI: folinic acid plus fluorouracil plus irinotecan; eMIT: electronic market information tool; BNF: British National Formulary
*Treatment cycles per month are based on the clinical inputs (every 2 weeks cycle was assumed).

Table 52: Distributions used in the EAG's probabilistic analyses for all treatments, both first-and second-line settings

Model parameter (first-and second-line settings, unless stated otherwise)	Distribution	Mean	SD	Parameter 1*	Parameter 2*
Patient characteristics					
Initial age_ first-line setting	Uniform	60.00	-	58.00	62.00
Initial age_ second-line setting	Uniform	61.00	-	59.00	63.00
Proportion of females	Beta	0.40	-	59.60	89.42
Body weight(kg)	Fixed	75.00	-	-	-
Body surface area (m^2)	Fixed	1.75	-	-	-
Health state utility values			-		
Progression-free state _first-line setting	Uniform	0.77	-	0.75	0.79
Progression-free state_ second-line setting	Uniform	0.73	-	0.71	0.75
Utility decrement between progression-free and post-progression state	Normal	0.09	0.009	-	-
Disutility due to AEs					
Diarrhoea	Beta	0.09	-	90.91	919.20
Febrile neutropenia	Beta	0.09	-	90.91	919.20
Hypertension	Beta	0.07	-	92.93	1234.64
Neurotoxicity	Beta	0.15	-	84.85	480.82
Neutropenia/ granulocytopenia	Beta	0.06	-	93.84	1444.51
Palmar-plantar Erythrodysaesthesia syndrome (Hand and foot)	Beta	0.10	-	89.60	780.28
Stomatitis	Beta	0.04	-	96.16	2434.42
Venous thromboembolism	Beta	0.02	-	98.18	5356.37
Deep thrombophlebitis	Beta	0.02	-	98.18	5356.37
Pulmonary embolus	Beta	0.02	-	98.18	5356.37
Vomiting/Nausea	Beta	0.08	-	92.02	1072.80
Grade 3 or 4 bleeding	Beta	0.05	-	94.95	1804.05
Gastrointestinal perforation	Beta	0.01	-	99.01	9972.93
Proteinuria	Beta	0.06	-	93.94	1471.73
Cardiac ischaemia	Beta	0.07	-	92.93	1234.64
Cerebrovascular ischaemia	Beta	0.15	-	84.85	480.82
Duration of all AEs	Beta	0.04	-	96.13	2411.80
Unit costs for drug administration and monitoring					
Pharmacy dispensing_ Complex IV infusion	Fixed	£55.00	-	-	-
Pharmacy dispensing_ Simple IV infusion	Fixed	£27.50	-	-	-
Hospital-based pharmacist costs (for bevacizumab) to update registry for bevacizumab	Fixed	£50.00	-	-	-
Patient transport	Gamma	£18.84	-	100.00	0.19
Ambulatory pump	Fixed	£56.48	-	-	-

District nurse visit	Fixed	£58.11	-	-	-
Consultation at OPD	Fixed	£192.95	-	-	-
Blood tests	Fixed	£9.20	-	-	-
CT scan	Fixed	£110.73	-	-	-
Hospital-based nurse costs (for bevacizumab)	Fixed	£58.33	-	-	-
Delivering chemotherapy (first attendance) _ outpatient	Fixed	£352.31	-	-	-
Delivering chemotherapy (subsequent visit) _ outpatient	Fixed	£250.77	-	-	-
Unit costs for disease management					
Consultation at OPD	Fixed	£192.95	-	-	-
Blood tests	Fixed	£9.20	-	-	-
CT scan	Fixed	£110.73	-	-	-
GP home consultation	Fixed	£134.10	-	-	-
Community nurse specialist visit	Fixed	£64.00	-	-	-
Health home visitor	Fixed	£27.00	-	-	-
District nurse visitor	Fixed	£53.00	-	-	-
GP surgery visit	Fixed	£45.00	-	-	-
Concomitant medication costs	Gamma	£50.00	-	100.00	0.50
Costs of CVAD	Fixed	£738.64	-	-	-
Proportion requiring CVAD	Fixed	1.00	-	-	-
Terminal care costs_ one-off costs	Gamma	£6264.49	-	100.00	62.64
Unit costs for drug acquisition					
Fluorouracil (injection)	Fixed	£12.16	-	-	-
Fluorouracil (infusion)_ 1g/20ml	Fixed	£3.20	-	-	-
Fluorouracil (infusion)_ 2.5g/100ml	Fixed	£4.08	-	-	-
Fluorouracil (infusion)_500mg/10ml	Fixed	£3.26	-	-	-
Fluorouracil (infusion)_5g/100ml	Fixed	£6.27	-	-	-
Folinic acid_ 100mg/10ml	Fixed	£27.63	-	-	-
Folinic acid_ 350mg/35ml	Fixed	£60.97	-	-	-
Oxaliplatin_ 200mg/40ml	Fixed	£11.31	-	-	-
Oxaliplatin_50mg/10ml	Fixed	£6.48	-	-	-
Irinotecan_ 100mg/5ml	Fixed	£8.99	-	-	-
Irinotecan_ 40mg/2ml	Fixed	£8.16	-	-	-
Capecitabine	Fixed	£20.13	-	-	-
Unit costs for managing AEs					
Cardiac disorders	Fixed	£702.43	-	-	-
Diarrhoea	Fixed	£564.22	-	-	-
Febrile neutropenia	Fixed	£560.68	-	-	-
Hypertension	Fixed	£404.67	-	-	-
Infections excluding febrile neutropenia	Fixed	£549.10	-	-	-
Neurotoxicity	Fixed	£768.33	-	-	-
Neutropenia/granulocytopenia	Fixed	£560.68	-	-	-

Palmar-plantar Erythrodysaesthesia syndrome (Hand and foot)	Fixed	£511.89	-	-	-
Stomatitis	Fixed	£519.16	-	-	-
Venous thromboembolism	Fixed	£477.36	-	-	-
Vomiting/Nausea	Fixed	£564.22	-	-	-
Deep thrombophlebitis	Fixed	£477.36	-	-	-
Pulmonary embolus	Fixed	£663.63	-	-	-
Grade 3 or 4 bleeding	Fixed	£560.68	-	-	-
Gastrointestinal perforation	Fixed	£2771.99	-	-	-
Proteinuria	Fixed	£675.20	-	-	-
Cardiac ischaemia	Fixed	£702.43			
Cerebrovascular ischaemia	Fixed	£963.43			
Resource use for disease management (progression-free)					
Consultation at OPD	Normal	0.50	0.05	-	-
Blood tests	Normal	0.00	0.00	-	-
CT scan	Normal	0.33	0.03	-	-
Resource use for best supportive care					
GP home consultation	Normal	0.25	0.03	-	-
Community nurse specialist visit	Normal	1.00	0.10	-	-
Health home visitor	Normal	1.00	0.10	-	-
District nurse visitor	Normal	1.00	0.10	-	-
GP surgery visit	Normal	1.00	0.10	-	-
Concomitant medication costs	Normal	1.00	0.10	-	-

SD: standard deviation; AE: adverse event; IV: intravenous; OPD: outpatient department; CT: computed tomography; GP: general practitioner; CVAD: central venous access device

*Alpha and beta parameters for beta and gamma distributions, minimum and maximum values for uniform distribution

Table 53: Distributions used in the EAG's probabilistic analyses for bevacizumab plus FOLFOX, both first- and second-line settings

Model parameter (first-and second-line settings, unless stated otherwise)	Distribution	Mean	SD	Parameter 1*	Parameter 2*
Survival parameters_ first-line setting					
OS_ gamma_ shape	Multivariate normal	[redacted]	-	[redacted]	[redacted]
OS_ gamma_ rate	Multivariate normal	[redacted]	-	[redacted]	[redacted]
PFS_ gamma_ shape	Multivariate normal	[redacted]	-	[redacted]	[redacted]
PFS_ gamma_ rate	Multivariate normal	[redacted]	-	[redacted]	[redacted]
Survival parameters_ second-line setting					
OS_ gamma_ shape	Multivariate normal	0.7539	-	0.0067	0.0070
OS_ gamma_ rate	Multivariate normal	-2.0909	-	0.0070	0.0090
PFS_ gamma_ shape	Multivariate normal	0.6955	-	0.0064	0.0064
PFS_ gamma_ rate	Multivariate normal	-1.4376	-	0.0064	0.0083
Frequency of AEs_ first-line setting					
Diarrhoea	Beta	12.87%	-	44.00	298.00
Febrile neutropenia	Beta	4.39%	-	15.00	327.00
Hypertension	Beta	0.00%	-	0.00	342.00
Neurotoxicity	Beta	17.84%	-	61.00	281.00
Neutropenia/ granulocytopenia	Beta	40.35%	-	138.00	204.00
Palmar-plantar Erythrodysaesthesia syndrome (Hand and foot)	Beta	1.75%	-	6.00	336.00
Stomatitis	Beta	3.51%	-	12.00	330.00
Venous thromboembolism	Beta	0.00%	-	0.00	342.00
Deep thrombophlebitis	Beta	0.00%	-	0.00	342.00
Pulmonary embolus	Beta	0.00%	-	0.00	342.00
Vomiting/Nausea	Beta	7.31%	-	25.00	317.00
Grade 3 or 4 bleeding	Beta	0.00%	-	0.00	342.00
Gastrointestinal perforation	Beta	0.00%	-	0.00	342.00
Proteinuria	Beta	0.00%	-	0.00	342.00
Frequency of AEs_ second-line setting					
Hypertension	Beta	6.20%	-	93.74	1418.17
Bleeding	Beta	3.40%	-	96.57	2743.61
Vomiting	Beta	10.10%	-	89.80	799.30
Proteinuria	Beta	0.70%	-	99.29	14085.42
Neuropathy	Beta	16.30%	-	83.54	428.96
Thromboembolism	Beta	3.40%	-	96.57	2743.61

Cardiac ischaemia	Beta	0.60%	-	99.39	16466.27
Cerebrovascular ischaemia	Beta	0.30%	-	99.70	33132.64
Frequency of resource use (during treatment)					
Pharmacy dispensing_ Complex IV infusion	Normal	3.00	0.30	-	-
Pharmacy dispensing_ Simple IV infusion	Normal	1.00	0.10	-	-
Hospital-based pharmacist costs (for bevacizumab) to update registry for bevacizumab	Normal	0.32	0.03	-	-
Patient transport	Normal	0.30	0.03	-	-
Ambulatory pump	Normal	1.00	0.10	-	-
District nurse visit	Normal	1.00	0.10	-	-
Hospital-based nurse costs (for bevacizumab)	Normal	0.26	0.03	-	-
Delivering chemotherapy (first attendance) _ outpatient	Normal	1.00	0.10	-	-
Delivering chemotherapy (subsequent visit) _ outpatient	Normal	0.00	0.00	-	-
Consultation at OPD	Normal	1.00	0.10	-	-
Blood tests	Normal	1.84	0.18	-	-
CT scan	Normal	0.33	0.03	-	-

OS: overall survival; PFS: progression-free survival; SD: standard deviation; AE: adverse event; IV: intravenous; OPD: outpatient department; CT: computed tomography

*Alpha and beta parameters for beta and gamma distributions, variance-covariance matrix for multivariate normal distribution

Table 54: Distributions used in the EAG's probabilistic analyses for FOLFOX alone, both first-and second-line settings

Model parameter (first-and second-line settings, unless stated otherwise)	Distribution	Mean	SD	Parameter 1*	Parameter 2*
Survival parameters_ first-line setting					
OS_ gamma_ shape	Multivariate normal	[redacted]	-	[redacted]	[redacted]
OS_ gamma_ rate	Multivariate normal	[redacted]	-	[redacted]	[redacted]
PFS_ gamma_ shape	Multivariate normal	[redacted]	-	[redacted]	[redacted]
PFS_ gamma_ rate	Multivariate normal	[redacted]	-	[redacted]	[redacted]
Survival parameters_ second-line setting					
OS_ gamma_ shape	Multivariate normal	0.8149	-	0.0064	0.0066
OS_ gamma_ rate	Multivariate normal	-1.8456	-	0.0066	0.0083
PFS_ gamma_ shape	Multivariate normal	0.7446	-	0.0064	0.0065
PFS_ gamma_ rate	Multivariate normal	-1.0764	-	0.0065	0.0083
Frequency of AEs_ first-line setting					
Diarrhoea	Beta	11.42%	-	74.00	574.00
Febrile neutropenia	Beta	4.78%	-	31.00	617.00
Hypertension	Beta	0.00%	-	0.00	648.00
Neurotoxicity	Beta	16.51%	-	107.00	541.00
Neutropenia/ granulocytopenia	Beta	43.52%	-	282.00	366.00
Palmar-plantar Erythrodysaesthesia syndrome (Hand and foot)	Beta	1.23%	-	8.00	640.00
Stomatitis	Beta	2.01%	-	13.00	635.00
Venous thromboembolism	Beta	0.00%	-	0.00	648.00
Deep thrombophlebitis	Beta	0.00%	-	0.00	648.00
Pulmonary embolus	Beta	0.00%	-	0.00	648.00
Vomiting/Nausea	Beta	7.25%	-	47.00	601.00
Grade 3 or 4 bleeding	Beta	0.00%	-	0.00	648.00
Gastrointestinal perforation	Beta	0.00%	-	0.00	648.00
Proteinuria	Beta	0.00%	-	0.00	648.00
Frequency of AEs_ second-line setting					
Hypertension	Beta	1.80%	-	98.18	5356.37
Bleeding	Beta	0.40%	-	99.60	24799.40
Vomiting	Beta	3.20%	-	96.77	2927.23
Proteinuria	Beta	0.00%	-	0.00	0.00
Neuropathy	Beta	9.20%	-	90.71	895.25

Thromboembolism	Beta	2.50%	-	97.48	3801.53
Cardiac ischaemia	Beta	0.40%	-	99.60	24799.40
Cerebrovascular ischaemia	Beta	0.00%	-	0.00	0.00
Frequency of resource use (during treatment)					
Pharmacy dispensing_ Complex IV infusion	Normal	3.00	0.30	-	-
Pharmacy dispensing_ Simple IV infusion	Normal	1.00	0.10	-	-
Hospital-based pharmacist costs (for bevacizumab) to update registry for bevacizumab	Normal	0.00	0.00	-	-
Patient transport	Normal	0.30	0.03	-	-
Ambulatory pump	Normal	1.00	0.10	-	-
District nurse visit	Normal	1.00	0.10	-	-
Hospital-based nurse costs (for bevacizumab)	Normal	0.00		-	-
Delivering chemotherapy (first attendance) _ outpatient	Normal	1.00	0.10	-	-
Delivering chemotherapy (subsequent visit) _ outpatient	Normal	0.00	0.00	-	-
Consultation at OPD	Normal	1.00	0.10	-	-
Blood tests	Normal	1.84	0.18	-	-
CT scan	Normal	0.33	0.03	-	-

OS: overall survival; PFS: progression-free survival; SD: standard deviation; AE: adverse event; IV: intravenous; OPD: outpatient department; CT: computed tomography

*Alpha and beta parameters for beta and gamma distributions, variance-covariance matrix for multivariate normal distribution

Table 55: Distributions used in the EAG's probabilistic analyses for bevacizumab plus FOLFIRI, first-line setting

Model parameter	Distribution	Mean	SD	Parameter 1*	Parameter 2*
Survival parameters					
OS_ Weibull_ shape	Multivariate normal	0.3760	-	0.0047	-0.0022
OS_ Weibull_ scale	Multivariate normal	3.3101	-	-0.0022	0.0038
PFS_ Weibull_ shape	Multivariate normal	0.4622	-	0.0030	-0.0003
PFS_ Weibull_ scale	Multivariate normal	2.5494	-	-0.0003	0.0018
Frequency of AEs					
Diarrhoea	Beta	32.40%	-	67.28	140.37
Febrile neutropenia	Beta	0.00%	-	0.00	0.00
Hypertension	Beta	11.00%	-	88.89	719.20
Neurotoxicity	Beta	0.00%	-	0.00	0.00
Neutropenia/ granulocytopenia	Beta	37.00%	-	62.63	106.64
Palmar-plantar Erythrodysaesthesia syndrome (Hand and foot)	Beta	0.00%	-	0.00	0.00
Stomatitis	Beta	0.00%	-	0.00	0.00
Venous thromboembolism	Beta	19.40%	-	80.41	334.06
Deep thrombophlebitis	Beta	8.90%	-	91.01	931.58
Pulmonary embolus	Beta	3.60%	-	96.36	2580.41
Vomiting/Nausea	Beta	0.00%	-	0.00	0.00
Grade 3 or 4 bleeding	Beta	3.10%	-	96.87	3027.94
Gastrointestinal perforation	Beta	1.50%	-	98.49	6467.18
Proteinuria	Beta	0.80%	-	99.19	12299.81
Frequency of resource use (during treatment)					
Pharmacy dispensing_ Complex IV infusion	Normal	0.00	0.00	-	-
Pharmacy dispensing_ Simple IV infusion	Normal	4.00	0.40	-	-
Hospital-based pharmacist costs (for bevacizumab) to update registry for bevacizumab	Normal	0.32	0.03	-	-
Patient transport	Normal	0.30	0.03	-	-
Ambulatory pump	Normal	1.00	0.10	-	-
District nurse visit	Normal	0.00	0.00	-	-
Hospital-based nurse costs (for bevacizumab)	Normal	0.26	0.03	-	-
Delivering chemotherapy (first attendance) _ outpatient	Normal	1.00	0.10	-	-

Delivering chemotherapy (subsequent visit) _ outpatient	Normal	4.00	0.40	-	-
Consultation at OPD	Normal	1.00	0.10	-	-
Blood tests	Normal	0.67	0.07	-	-
CT scan	Normal	0.33	0.03	-	-

OS: overall survival; PFS: progression-free survival; SD: standard deviation; AE: adverse event; IV: intravenous; OPD: outpatient department; CT: computed tomography

*Alpha and beta parameters for beta and gamma distributions, variance-covariance matrix for multivariate normal distribution

Table 56: Distributions used in the EAG's probabilistic analyses for FOLFIRI alone, first-line setting

Model parameter	Distribution	Mean	SD	Parameter 1*	Parameter 2*
Survival parameters					
OS_ gamma_ shape	Multivariate normal	0.3688	-	0.0035	-0.0010
OS_ gamma_ rate	Multivariate normal	3.0401	-	-0.0010	0.0025
PFS_ gamma_ shape	Multivariate normal	0.3700	-	0.0021	0.0001
PFS_ gamma_ rate	Multivariate normal	2.1863	-	0.0001	0.0017
Frequency of AEs					
Diarrhoea	Beta	24.70%	-	75.05	228.81
Febrile neutropenia	Beta	0.00%	-	0.00	0.00
Hypertension	Beta	2.30%	-	97.68	4149.15
Neurotoxicity	Beta	0.00%	-	0.00	0.00
Neutropenia/ granulocytopenia	Beta	31.10%	-	68.59	151.95
Palmar-plantar Erythrodysaesthesia syndrome (Hand and foot)	Beta	0.00%	-	0.00	0.00
Stomatitis	Beta	0.00%	-	0.00	0.00
Venous thromboembolism	Beta	16.20%	-	83.64	432.65
Deep thrombophlebitis	Beta	6.30%	-	93.64	1392.66
Pulmonary embolus	Beta	5.10%	-	94.85	1764.94
Vomiting/Nausea	Beta	0.00%	-	0.00	0.00
Grade 3 or 4 bleeding	Beta	2.50%	-	97.48	3801.53
Gastrointestinal perforation	Beta	0.00%	-	0.00	0.00
Proteinuria	Beta	0.80%	-	99.19	12299.81
Frequency of resource use (during treatment)					
Pharmacy dispensing_ Complex IV infusion	Normal	0.00	0.00	-	-
Pharmacy dispensing_ Simple IV infusion	Normal	4.00	0.40	-	-
Hospital-based pharmacist costs (for bevacizumab) to update registry for bevacizumab	Normal	0.00	0.00	-	-
Patient transport	Normal	0.30	0.03	-	-
Ambulatory pump	Normal	1.00	0.10	-	-
District nurse visit	Normal	0.00	0.00	-	-
Hospital-based nurse costs (for bevacizumab)	Normal	0.00	0.00	-	-
Delivering chemotherapy (first	Normal	1.00	0.10	-	-

attendance) _ outpatient					
Delivering chemotherapy (subsequent visit) _ outpatient	Normal	3.00	0.30	-	-
Consultation at OPD	Normal	1.00	0.10	-	-
Blood tests	Normal	0.67	0.07	-	-
CT scan	Normal	0.33	0.03	-	-

OS: overall survival; PFS: progression-free survival; SD: standard deviation; AE: adverse event; IV: intravenous; OPD: outpatient department; CT: computed tomography

*Alpha and beta parameters for beta and gamma distributions, variance-covariance matrix for multivariate normal distribution

Table 57: Distributions used in the EAG's probabilistic analyses for bevacizumab plus CAPOX, both first- and second-line settings

Model parameter (first-and second-line settings, unless stated otherwise)	Distribution	Mean	SD	Parameter 1*	Parameter 2*
Survival parameters_ first-line setting					
OS_ gamma_ shape	Multivariate normal	[redacted]	-	[redacted]	[redacted]
OS_ gamma_ rate	Multivariate normal	[redacted]	-	[redacted]	[redacted]
PFS_ gamma_ shape	Multivariate normal	[redacted]	-	[redacted]	[redacted]
PFS_ gamma_ rate	Multivariate normal	[redacted]	-	[redacted]	[redacted]
Survival parameters_ second-line setting					
OS_ gamma_ shape	Multivariate normal	0.7539	-	0.0067	0.0070
OS_ gamma_ rate	Multivariate normal	-2.0909	-	0.0070	0.0090
PFS_ gamma_ shape	Multivariate normal	0.6955	-	0.0064	0.0064
PFS_ gamma_ rate	Multivariate normal	-1.4376	-	0.0064	0.0083
Frequency of AEs_ first-line setting					
Diarrhoea	Beta	21.81%	-	77.00	276.00
Febrile neutropenia	Beta	1.13%	-	4.00	349.00
Hypertension	Beta	0.00%	-	0.00	353.00
Neurotoxicity	Beta	18.13%	-	64.00	289.00
Neutropenia/ granulocytopenia	Beta	7.08%	-	25.00	328.00
Palmar-plantar Erythrodysaesthesia syndrome (Hand and foot)	Beta	11.90%	-	42.00	311.00
Stomatitis	Beta	1.98%	-	7.00	346.00
Venous thromboembolism	Beta	0.00%	-	0.00	353.00
Deep thrombophlebitis	Beta	0.00%	-	0.00	353.00
Pulmonary embolus	Beta	0.00%	-	0.00	353.00
Vomiting/Nausea	Beta	10.76%	-	38.00	315.00
Grade 3 or 4 bleeding	Beta	0.00%	-	0.00	353.00
Gastrointestinal perforation	Beta	0.00%	-	0.00	353.00
Proteinuria	Beta	0.00%	-	0.00	353.00
Frequency of AEs_ second-line setting					
Hypertension	Beta	6.20%	-	93.74	1418.17
Bleeding	Beta	3.40%	-	96.57	2743.61
Vomiting	Beta	10.10%	-	89.80	799.30
Proteinuria	Beta	0.70%	-	99.29	14085.42
Neuropathy	Beta	16.30%	-	83.54	428.96

Thromboembolism	Beta	3.40%	-	96.57	2743.61
Cardiac ischaemia	Beta	0.60%	-	99.39	16466.27
Cerebrovascular ischaemia	Beta	0.30%	-	99.70	33132.64
Frequency of resource use (during treatment)					
Pharmacy dispensing_ Complex IV infusion	Normal	1.00	0.10	-	-
Pharmacy dispensing_ Simple IV infusion	Normal	1.00	0.10	-	-
Hospital-based pharmacist costs (for bevacizumab) to update registry for bevacizumab	Normal	0.32	0.03	-	-
Patient transport	Normal	0.30	0.03	-	-
Ambulatory pump	Normal	0.00	0.00	-	-
District nurse visit	Normal	0.00	0.00	-	-
Hospital-based nurse costs (for bevacizumab)	Normal	0.26	0.03	-	-
Delivering chemotherapy (first attendance) _ outpatient	Normal	1.00	0.10	-	-
Delivering chemotherapy (subsequent visit) _ outpatient	Normal	0.00	0.00	-	-
Consultation at OPD	Normal	1.00	0.10	-	-
Blood tests	Normal	1.31	0.13	-	-
CT scan	Normal	0.33	0.03	-	-

OS: overall survival; PFS: progression-free survival; SD: standard deviation; AE: adverse event; IV: intravenous; OPD: outpatient department; CT: computed tomography

*Alpha and beta parameters for beta and gamma distributions, variance-covariance matrix for multivariate normal distribution

Table 58: Distributions used in the EAG's probabilistic analyses for CAPOX alone, both first-and second-line settings

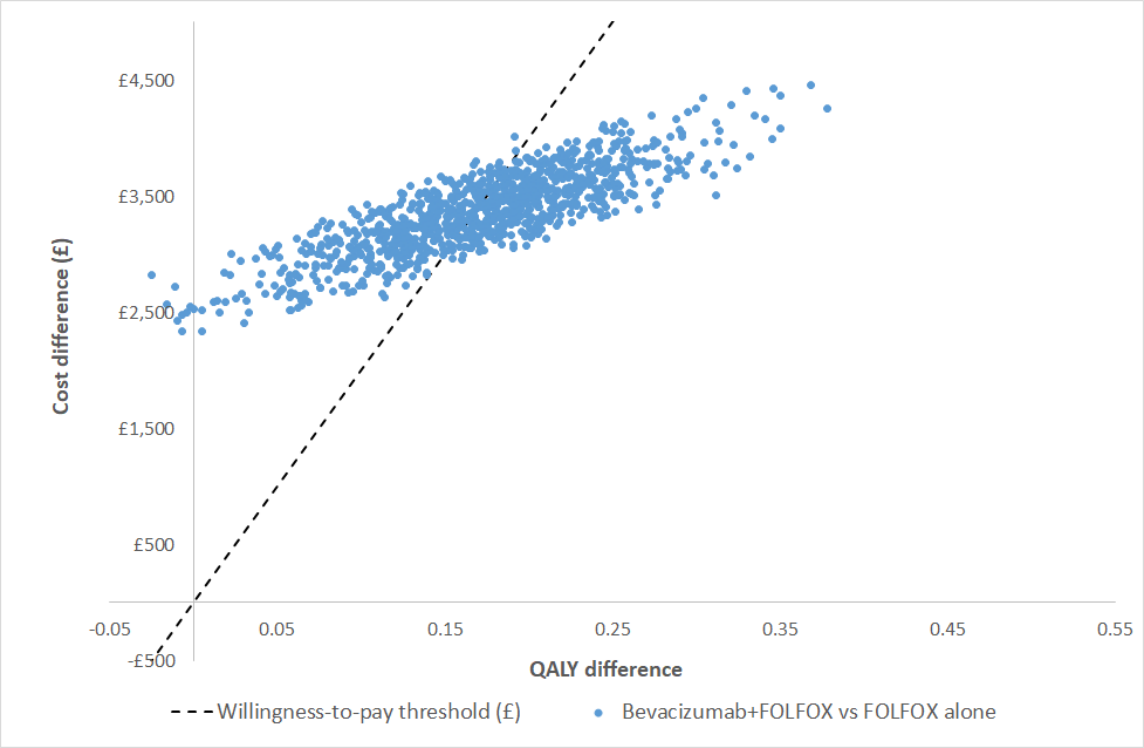
Model parameter (first-and second-line settings, unless stated otherwise)	Distribution	Mean	SD	Parameter 1*	Parameter 2*
Survival parameters_ first-line setting					
OS_ gamma_ shape	Multivariate normal	[redacted]	-	[redacted]	[redacted]
OS_ gamma_ rate	Multivariate normal	[redacted]	-	[redacted]	[redacted]
PFS_ gamma_ shape	Multivariate normal	[redacted]	-	[redacted]	[redacted]
PFS_ gamma_ rate	Multivariate normal	[redacted]	-	[redacted]	[redacted]
Survival parameters_ first-line setting					
OS_ gamma_ shape	Multivariate normal	0.8149	-	0.0064	0.0066
OS_ gamma_ rate	Multivariate normal	-1.8456	-	0.0066	0.0083
PFS_ gamma_ shape	Multivariate normal	0.7446	-	0.0064	0.0065
PFS_ gamma_ rate	Multivariate normal	-1.0764	-	0.0065	0.0083
Frequency of AEs_ first-line setting					
Diarrhoea	Beta	20.31%	-	133.00	522.00
Febrile neutropenia	Beta	0.92%	-	6.00	649.00
Hypertension	Beta	0.00%	-	0.00	655.00
Neurotoxicity	Beta	17.40%	-	114.00	541.00
Neutropenia/ granulocytopenia	Beta	7.02%	-	46.00	609.00
Palmar-plantar Erythrodysaesthesia syndrome (Hand and foot)	Beta	6.11%	-	40.00	615.00
Stomatitis	Beta	1.22%	-	8.00	647.00
Venous thromboembolism	Beta	0.00%	-	0.00	655.00
Deep thrombophlebitis	Beta	0.00%	-	0.00	655.00
Pulmonary embolus	Beta	0.00%	-	0.00	655.00
Vomiting/Nausea	Beta	7.94%	-	52.00	603.00
Grade 3 or 4 bleeding	Beta	0.00%	-	0.00	655.00
Gastrointestinal perforation	Beta	0.00%	-	0.00	655.00
Proteinuria	Beta	0.00%	-	0.00	655.00
Frequency of AEs_ second-line setting					
Hypertension	Beta	1.80%	-	98.18	5356.37
Bleeding	Beta	0.40%	-	99.60	24799.40
Vomiting	Beta	3.20%	-	96.77	2927.23
Proteinuria	Beta	0.00%	-	0.00	0.00
Neuropathy	Beta	9.20%	-	90.71	895.25

Thromboembolism	Beta	2.50%	-	97.48	3801.53
Cardiac ischaemia	Beta	0.40%	-	99.60	24799.40
Cerebrovascular ischaemia	Beta	0.00%	-	0.00	0.00
Frequency of resource use (during treatment)					
Pharmacy dispensing_ Complex IV infusion	Normal	1.00	0.10	-	-
Pharmacy dispensing_ Simple IV infusion	Normal	1.00	0.10	-	-
Hospital-based pharmacist costs (for bevacizumab) to update registry for bevacizumab	Normal	0.00	0.00	-	-
Patient transport	Normal	0.30	0.03	-	-
Ambulatory pump	Normal	0.00	0.00	-	-
District nurse visit	Normal	0.00	0.00	-	-
Hospital-based nurse costs (for bevacizumab)	Normal	0.00	0.00	-	-
Delivering chemotherapy (first attendance) _ outpatient	Normal	1.00	0.10	-	-
Delivering chemotherapy (subsequent visit) _ outpatient	Normal	0.00	0.00	-	-
Consultation at OPD	Normal	1.00	0.10	-	-
Blood tests	Normal	1.31	0.13	-	-
CT scan	Normal	0.33	0.03	-	-

OS: overall survival; PFS: progression-free survival; SD: standard deviation; AE: adverse event; IV: intravenous; OPD: outpatient department; CT: computed tomography

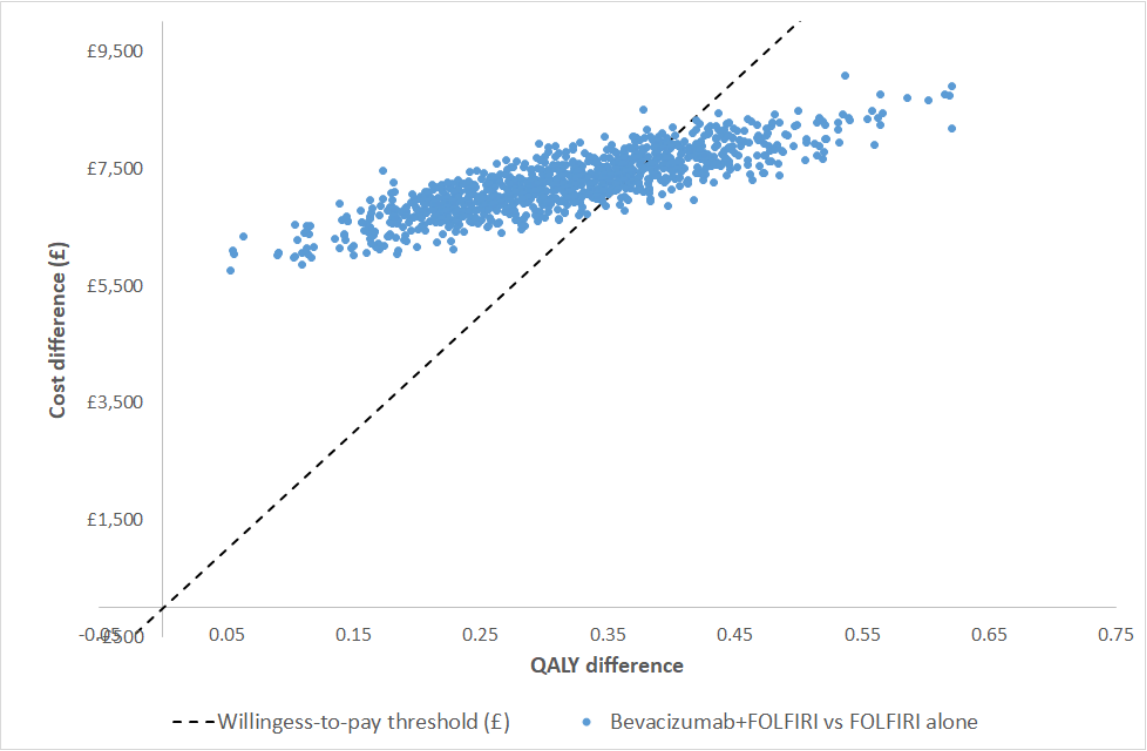
*Alpha and beta parameters for beta and gamma distributions, variance-covariance matrix for multivariate normal distribution

Figure 55: Cost-effectiveness plane for bevacizumab plus FOLFOX versus FOLFOX alone, first-line setting



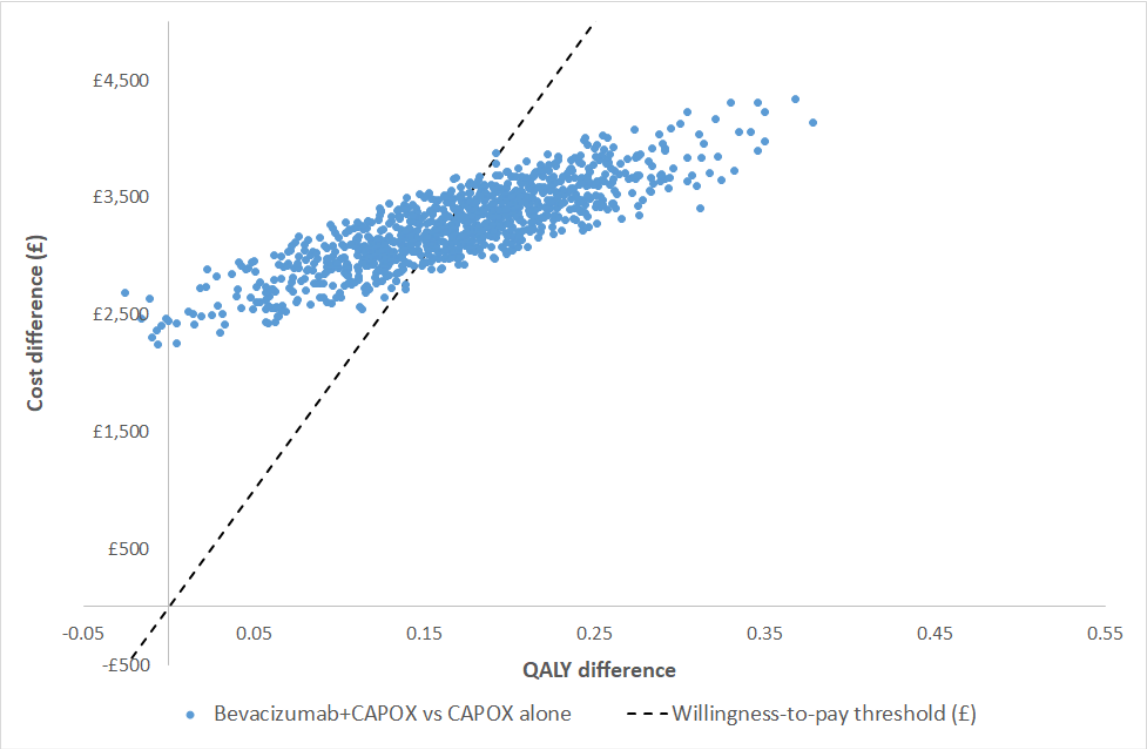
FOLFOX: folinic acid plus fluorouracil plus oxaliplatin

Figure 56: Cost-effectiveness plane for bevacizumab plus FOLFIRI versus FOLFIRI alone, first-line setting



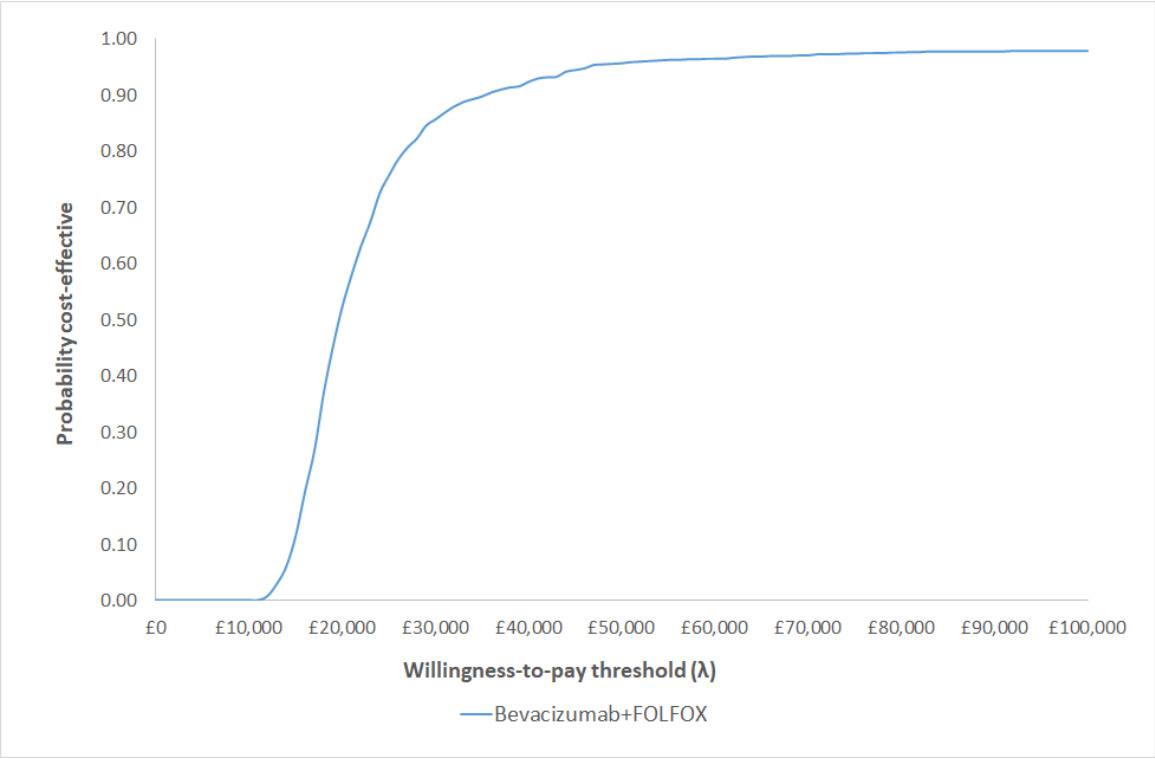
FOLFOX: folinic acid plus fluorouracil plus irinotecan

Figure 57: Cost-effectiveness plane for bevacizumab plus CAPOX versus CAPOX alone, first-line setting



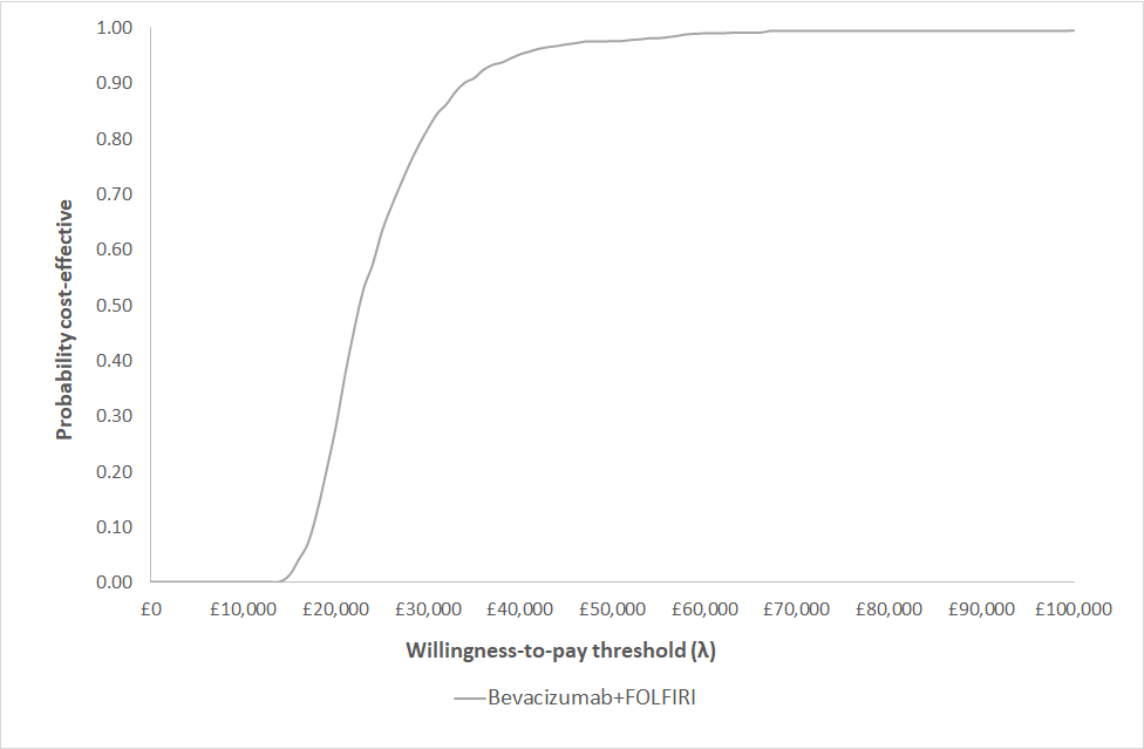
CAPOX: capecitabine plus oxaliplatin

Figure 58: CEAC for bevacizumab plus FOLFOX versus FOLFOX alone, first-line setting



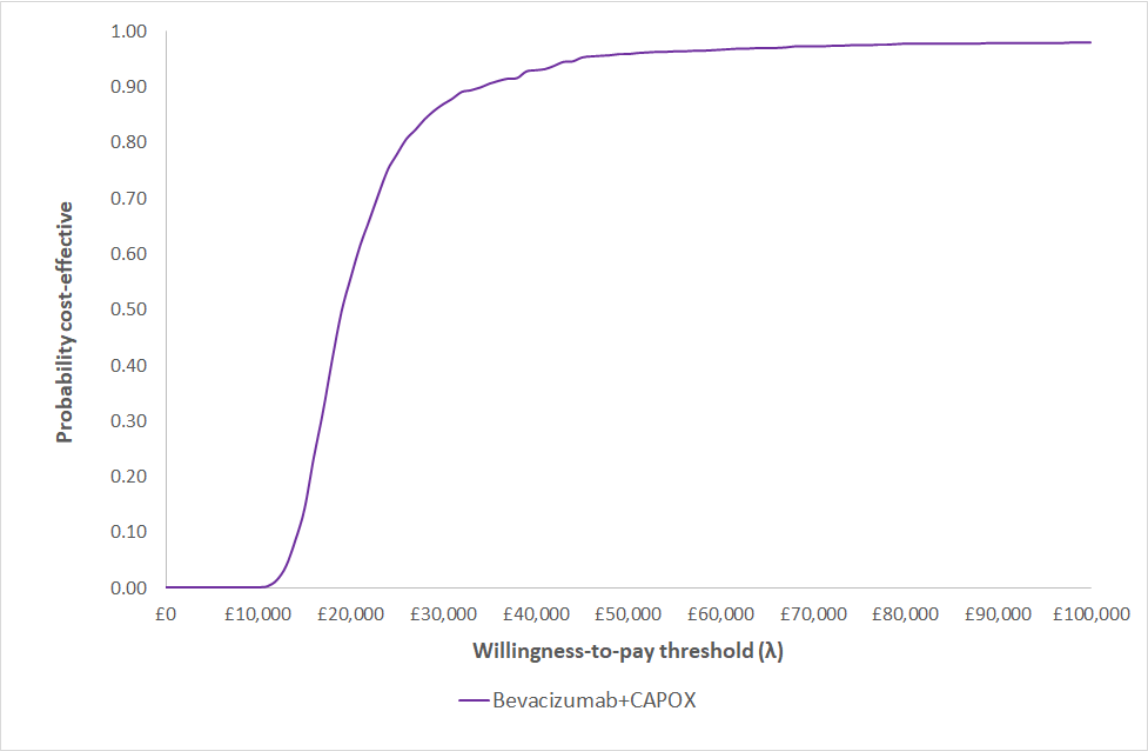
FOLFOX: folinic acid plus fluorouracil plus oxaliplatin

Figure 59: CEAC for bevacizumab plus FOLFIRI versus FOLFIRI alone, first-line setting



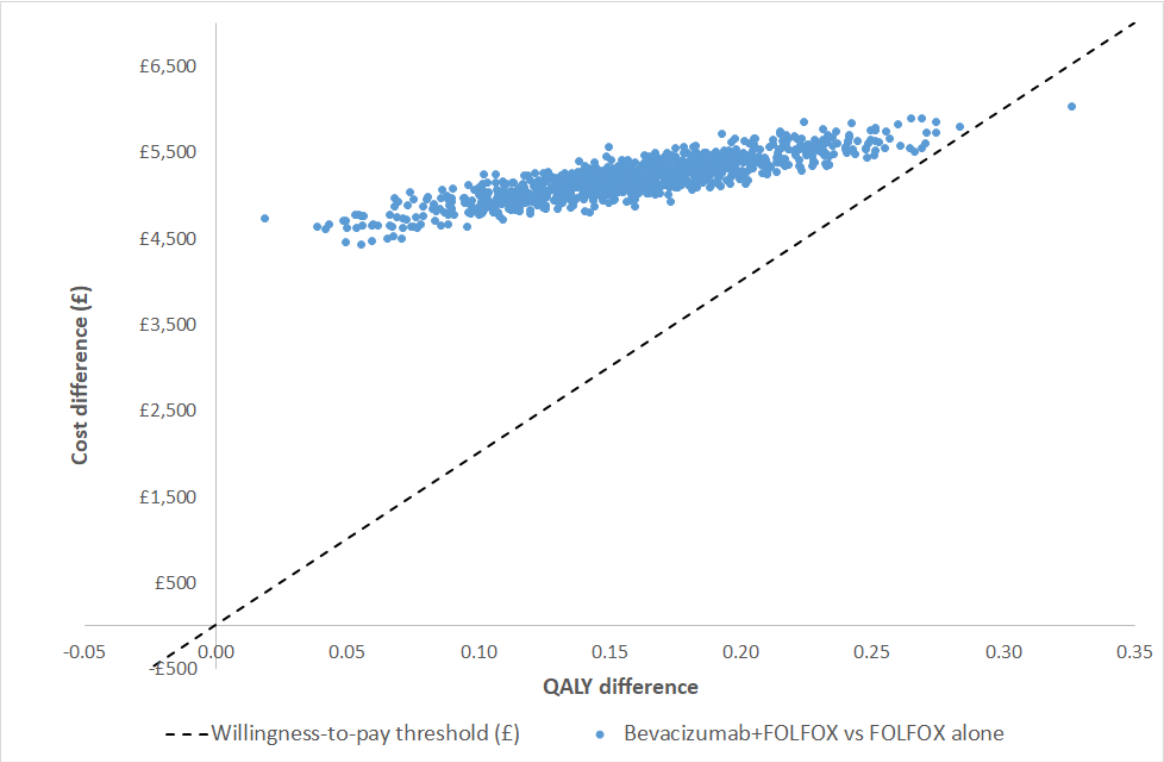
FOLFIRI: folinic acid plus fluorouracil plus irinotecan

Figure 60: CEAC for bevacizumab plus CAPOX versus CAPOX alone, first-line setting



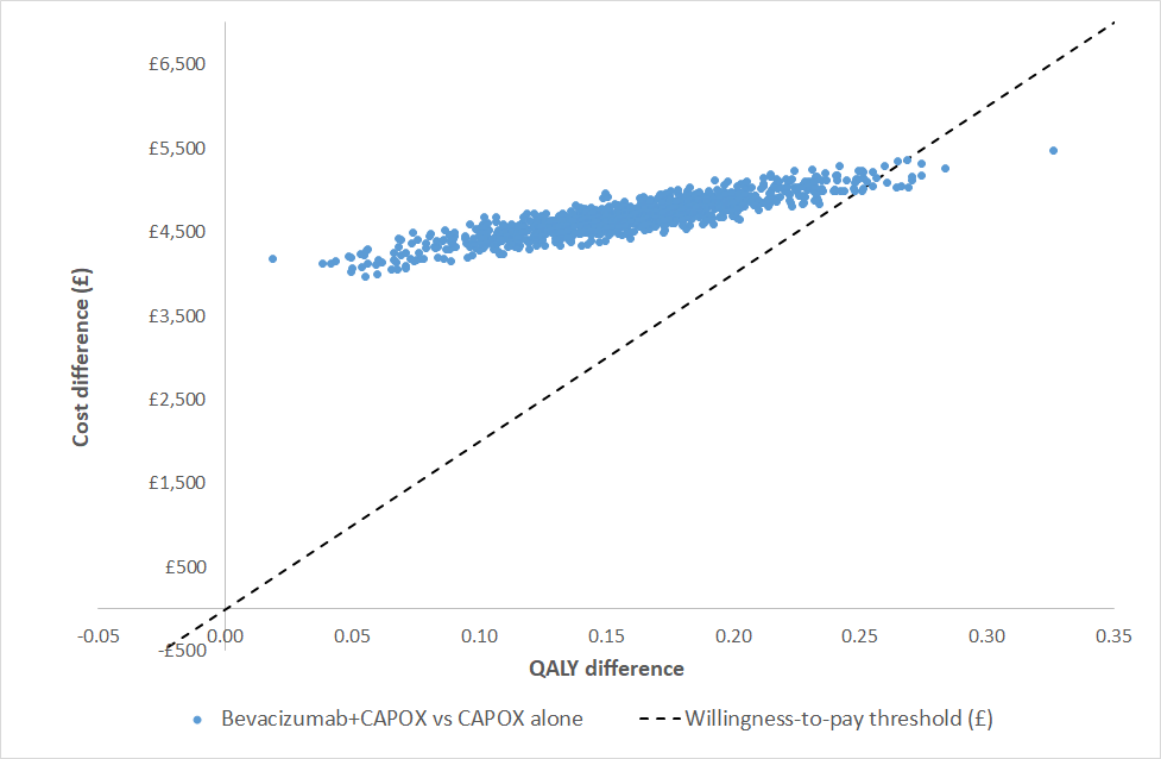
CAPOX: capecitabine plus oxaliplatin

Figure 61: Cost-effectiveness plane for bevacizumab plus FOLFOX versus FOLFOX alone, second-line setting



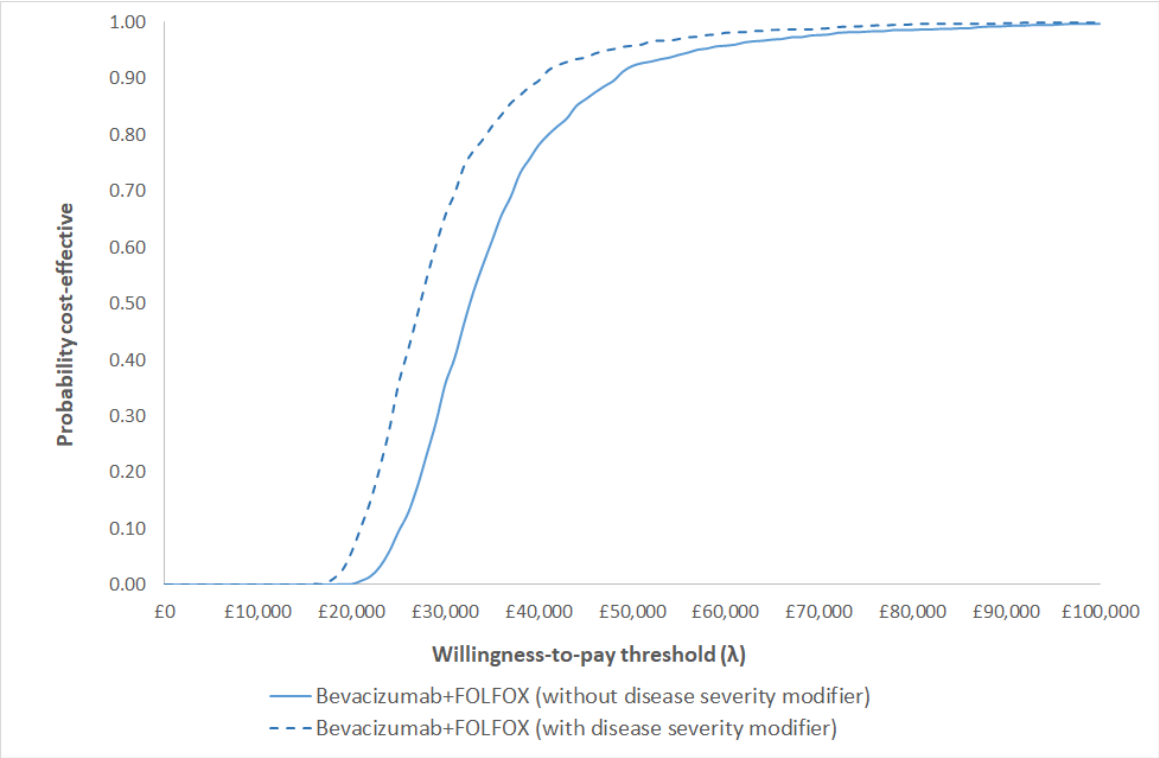
FOLFOX: folinic acid plus fluorouracil plus oxaliplatin

Figure 62: Cost-effectiveness plane for bevacizumab plus CAPOX versus CAPOX alone, second-line setting



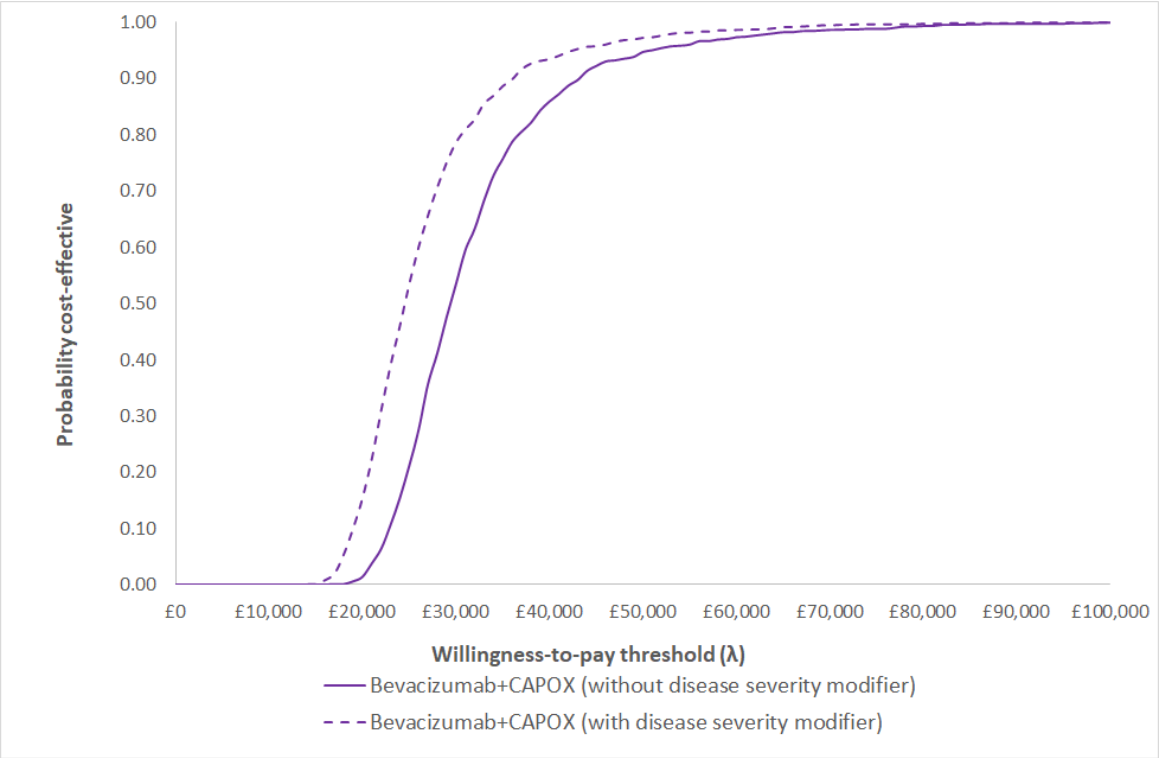
CAPOX: capecitabine plus oxaliplatin

Figure 63: CEAC for bevacizumab plus FOLFOX versus FOLFOX alone, second-line setting



FOLFOX: folinic acid plus fluorouracil plus oxaliplatin

Figure 64: CEAC for bevacizumab plus CAPOX versus CAPOX alone, second-line setting



CAPOX: capecitabine plus oxaliplatin

Bevacizumab (originator and biosimilars) with fluoropyrimidine-based chemotherapy for metastatic colorectal cancer (including review of TA212) [ID6465]

A Pragmatic Multiple Technology Appraisal

Addendum: Additional economic analyses undertaken using the updated prices of bevacizumab

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Declared competing interests of the authors

No author has any competing interests to declare.

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1. INTRODUCTION

This addendum provides the results of additional analyses in both first-and second-line settings, conducted in response to a request made by NICE following the pre-meeting briefing (PMB) in advance of the first Appraisal Committee Meeting (ACM). The EAG was advised that "*the mean MPSC price weighted by market share should be used for the intervention*" rather than the mean of individual prices previously stipulated. The weighted mean prices for bevacizumab 100 mg/4 ml and 400 mg/16 ml infusion vials, as provided by NICE, are [redacted] and [redacted], respectively. Further information related to the calculation of these prices is contained in the discussion (Section 3). The updated results of the EAG's economic analysis are presented separately for the first-and second-line treatment settings in Sections 2.1 and 2.2, respectively.

During the preparation of the addendum, the EAG identified programming errors in two scenario analyses that had been presented in the main report: (i) DSA2 for bevacizumab plus FOLFIRI vs FOLFIRI (first-line setting) where the times on treatment had not been updated to those associated with the modified de Gramont (mdG) regimen, and (ii) DSA3 and DSA4 (second-line setting) where the change in utility was run at 10% rather than 5%. These errors have been corrected in this addendum.

Additionally, in the scenario exploring the use of median price of bevacizumab, the EAG has also updated the cost to reflect the median cost weighted by the market share [redacted] for 100 mg/4 ml vials and [redacted] for 400 mg/16 ml vials) which is DSA7 in the first-line setting and DSA6 in the second-line setting.

2. RESULTS

2.1. Results of the EAG's economic analysis in the first-line setting

2.1.1. Central estimates of cost-effectiveness

The pair-wise results of the deterministic and probabilistic versions of the EAG's base case model are presented in Table 1 and Table 2, respectively. The detailed breakdown of model-predicted costs is summarised in Table 3.

For all pair-wise comparisons, the ICERs for bevacizumab plus fluoropyrimidine-based chemotherapy versus fluoropyrimidine-based chemotherapy alone are less than [redacted] per QALY gained. The model appears to be linear with the deterministic and probabilistic results being similar.

Cost-effectiveness planes and cost-effectiveness curves (CEACs) for each pair-wise comparison are presented in the Appendix (Figure 1 to Figure 6). The CEACs indicate that the probabilities that bevacizumab in addition to fluoropyrimidine-based chemotherapy generates more net benefit, assuming a willingness-to-pay threshold of £20,000 per QALY gained, than fluoropyrimidine-based chemotherapy alone are [redacted] for bevacizumab plus FOLFOX, [redacted] for bevacizumab plus FOLFIRI and [redacted] for bevacizumab plus CAPOX. When the willingness-to-pay threshold is increased to £30,000 per QALY gained the probabilities are [redacted] for bevacizumab plus FOLFOX, [redacted] for bevacizumab plus FOLFIRI and [redacted] for bevacizumab plus CAPOX.

Table 1: Base case results – bevacizumab plus fluoropyrimidine-based chemotherapy versus fluoropyrimidine-based chemotherapy alone, deterministic, including bevacizumab weighted mean tender price, first-line setting

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Model 1							
Bevacizumab plus FOLFOX	2.139	1.458	[redacted]	0.260	0.169	[redacted]	[redacted]
FOLFOX	1.880	1.289	£22,102				
Model 2							
Bevacizumab plus FOLFIRI	2.068	1.411	[redacted]	0.488	0.324	[redacted]	[redacted]
FOLFIRI	1.580	1.087	£18,119				
Model 3							
Bevacizumab plus CAPOX	2.139	1.458	[redacted]	0.260	0.169	[redacted]	[redacted]
CAPOX	1.880	1.289	£16,313				

LYG: life-year gained; QALY: quality-adjusted life-year; Inc: incremental; ICER: incremental cost-effectiveness ratio; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; CAPOX: capecitabine plus oxaliplatin
*Undiscounted

Table 2: Base case results – bevacizumab plus fluoropyrimidine-based chemotherapy versus fluoropyrimidine-based chemotherapy alone, probabilistic, including bevacizumab weighted mean tender price, first-line setting

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
Model 1							
Bevacizumab plus FOLFOX	2.138	1.455	[redacted]	0.260	0.169	[redacted]	[redacted]
FOLFOX	1.878	1.286	£22,079				
Model 2							
Bevacizumab plus FOLFIRI	2.071	1.410	[redacted]	0.484	0.320	[redacted]	[redacted]
FOLFIRI	1.587	1.090	£18,109				
Model 3							
Bevacizumab plus CAPOX	2.138	1.455	[redacted]	0.260	0.169	[redacted]	[redacted]
CAPOX	1.878	1.286	£16,291				

LYG: life-year gained; QALY: quality-adjusted life-year; Inc: incremental; ICER: incremental cost-effectiveness ratio; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; CAPOX: capecitabine plus oxaliplatin
*Undiscounted

Table 3: Detailed breakdown of model-predicted costs (discounted), deterministic, first-line setting

	Bevacizumab plus FOLFOX	FOLFOX alone	Bevacizumab plus FOLFIRI	FOLFIRI alone	Bevacizumab plus CAPOX	CAPOX alone
Progression-free						
Acquisition costs	[redacted]	£780	[redacted]	£780	[redacted]	£160
Administration costs	£11,322	£10,629	£10,672	£7,011	£6,002	£5,543
Health state costs	£660	£440	£568	£382	£717	£501
AE costs	£527	£518	£656	£482	£439	£374
CVAD costs	£737	£737	£737	£737	£737	£737
Post-progression costs	£3,386	£3,129	£3,358	£2,798	£3,386	£3,129
Terminal care costs	£5,819	£5,869	£5,833	£5,929	£5,819	£5,869
Total costs	[redacted]	£22,102	[redacted]	£18,119	[redacted]	£16,313

FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; CAPOX: capecitabine plus oxaliplatin; AE: adverse events; CVAD: central venous access device

2.1.2. Deterministic sensitivity analysis results

The results of deterministic sensitivity analyses (DSAs) are presented in Table 4 (bevacizumab plus FOLFOX versus FOLFOX alone), Table 5 (bevacizumab plus FOLFIRI versus FOLFIRI alone) and Table 6 (bevacizumab plus CAPOX versus CAPOX alone).

The ICERs for bevacizumab plus FOLFOX or bevacizumab plus CAPOX are less than [redacted] per QALY gained across all scenarios. For the comparison of bevacizumab plus FOLFIRI versus FOLFIRI alone, two DSAs stand out. The use of generalised gamma distributions for PFS and OS, rather than Weibull distributions (DSA1), increased the ICER to approximately [redacted] per QALY gained, whilst the use of an mdG regimen for FOLFIRI-containing regimens reduced the ICER to approximately [redacted] per QALY gained.

Table 4: Deterministic sensitivity analysis results – bevacizumab plus FOLFOX versus FOLFOX alone, first-line setting

No.	Scenario	Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
-	Base-case (deterministic)	Bevacizumab plus FOLFOX	2.139	1.458	[redacted]	0.260	0.169	[redacted]	[redacted]
		FOLFOX alone	1.880	1.289	£22,102				
1	PFS and OS models: log-logistic	Bevacizumab plus FOLFOX	2.713	1.735	[redacted]	0.429	0.246	[redacted]	[redacted]
		FOLFOX alone	2.284	1.489	£22,936				
3	Oxaliplatin stopped at 6 month	Bevacizumab plus FOLFOX	2.139	1.458	[redacted]	0.260	0.169	[redacted]	[redacted]
		FOLFOX alone	1.880	1.289	£22,075				
4	Utility values for health states increased by 5%	Bevacizumab plus FOLFOX	2.139	1.531	[redacted]	0.260	0.178	[redacted]	[redacted]
		FOLFOX alone	1.880	1.353	£22,102				
5	Utility values for health states decreased by 5%	Bevacizumab plus FOLFOX	2.139	1.385	[redacted]	0.260	0.161	[redacted]	[redacted]
		FOLFOX alone	1.880	1.224	£22,102				
6	AE disutilities increased by 10 times	Bevacizumab plus FOLFOX	2.139	1.456	[redacted]	0.260	0.169	[redacted]	[redacted]
		FOLFOX alone	1.880	1.287	£22,102				
7	Median price of bevacizumab used†	Bevacizumab plus FOLFOX	2.139	1.458	[redacted]	0.260	0.169	[redacted]	[redacted]
		FOLFOX alone	1.880	1.289	£22,102				
8	Vial sharing is assumed	Bevacizumab plus FOLFOX	2.139	1.458	[redacted]	0.260	0.169	[redacted]	[redacted]
		FOLFOX alone	1.880	1.289	£21,853				

LYG: life-year gained; QALY: quality-adjusted life-year; Inc: incremental; ICER: incremental cost-effectiveness ratio; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; AE: adverse events, PFS: progression-free survival; OS: overall survival

*Undiscounted

†Median price weighted by the market share was used [redacted] for 100 mg/4 ml vials and [redacted] for 400 mg/16 ml vials).

Table 5: Deterministic sensitivity analysis results – bevacizumab plus FOLFIRI versus FOLFIRI alone, first-line setting

No.	Scenario	Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
-	Base-case	Bevacizumab plus FOLFIRI	2.068	1.411	[redacted]	0.488	0.324	[redacted]	[redacted]
		FOLFIRI alone	1.580	1.087	£18,119				
1	PFS and OS models: generalised gamma	Bevacizumab plus FOLFIRI	1.853	1.283	[redacted]	0.342	0.236	[redacted]	[redacted]
		FOLFIRI alone	1.510	1.047	£17,903				
2	Using mdG regimen for FOLFIRI-containing regimens‡	Bevacizumab plus FOLFIRI	2.068	1.411	[redacted]	0.488	0.324	[redacted]	[redacted]
		FOLFIRI alone	1.580	1.087	[redacted]				
4	Utility values for health states increased by 5%	Bevacizumab plus FOLFIRI	2.068	1.482	[redacted]	0.488	0.340	[redacted]	[redacted]
		FOLFIRI alone	1.580	1.141	£18,119				
5	Utility values for health states decreased by 5%	Bevacizumab plus FOLFIRI	2.068	1.340	[redacted]	0.488	0.308	[redacted]	[redacted]
		FOLFIRI alone	1.580	1.033	£18,119				
6	AE disutilities increased by 10 times	Bevacizumab plus FOLFIRI	2.068	1.409	[redacted]	0.488	0.323	[redacted]	[redacted]
		FOLFIRI alone	1.580	1.086	£18,119				
7	Median price of bevacizumab used†	Bevacizumab plus FOLFIRI	2.068	1.411	[redacted]	0.488	0.324	[redacted]	[redacted]
		FOLFIRI alone	1.580	1.087	£18,119				
8	Vial sharing is assumed	Bevacizumab plus FOLFIRI	2.068	1.411	[redacted]	0.488	0.324	[redacted]	[redacted]
		FOLFIRI alone	1.580	1.087	£17,791				

LYG: life-year gained; QALY: quality-adjusted life-year; Inc: incremental; ICER: incremental cost-effectiveness ratio; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; mdG: modified de Gramont, PFS: progression-free survival; OS: overall survival, AE: adverse event

*Undiscounted

†Median price weighted by the market share was used [redacted] for 100 mg/4 ml vials and [redacted] for 400 mg/16 ml vials).

‡Includes the correction of a programming error contained in the main report.

Table 6: Deterministic sensitivity analysis results – bevacizumab plus CAPOX versus CAPOX alone, first-line setting

No.	Scenario	Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER
-	Base-case (deterministic)	Bevacizumab plus CAPOX	2.139	1.458	[redacted]	0.260	0.169	[redacted]	[redacted]
		CAPOX alone	1.880	1.289	£16,313				
1	PFS and OS models: log-logistic	Bevacizumab plus CAPOX	2.713	1.735	[redacted]	0.429	0.246	[redacted]	[redacted]
		CAPOX alone	2.284	1.489	£17,146				
3	Oxaliplatin stopped at 6 month	Bevacizumab plus CAPOX	2.139	1.458	[redacted]	0.260	0.169	[redacted]	[redacted]
		CAPOX alone	1.880	1.289	£16,283				
4	Utility values for health states increased by 5%	Bevacizumab plus CAPOX	2.139	1.531	[redacted]	0.260	0.178	[redacted]	[redacted]
		CAPOX alone	1.880	1.353	£16,313				
5	Utility values for health states decreased by 5%	Bevacizumab plus CAPOX	2.139	1.385	[redacted]	0.260	0.161	[redacted]	[redacted]
		CAPOX alone	1.880	1.224	£16,313				
6	AE disutilities increased by 10 times	Bevacizumab plus CAPOX	2.139	1.456	[redacted]	0.260	0.169	[redacted]	[redacted]
		CAPOX alone	1.880	1.287	£16,313				
7	Median price of bevacizumab used†	Bevacizumab plus CAPOX	2.139	1.458	[redacted]	0.260	0.169	[redacted]	[redacted]
		CAPOX alone	1.880	1.289	£16,313				
8	Vial sharing is assumed	Bevacizumab plus CAPOX	2.139	1.458	[redacted]	0.260	0.169	[redacted]	[redacted]
		CAPOX alone	1.880	1.289	£16,259				

LYG: life-year gained; QALY: quality-adjusted life-year; Inc: incremental; ICER: incremental cost-effectiveness ratio; WTP: willingness-to-pay; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CAPOX: capecitabine plus oxaliplatin; PFS: progression-free survival; OS: overall survival; AE: adverse event

*Undiscounted

†Median price weighted by the market share was used [redacted] for 100 mg/4 ml vials and [redacted] for 400 mg/16 ml vials).

2.2. Results of the EAG's economic analysis in the second-line setting

2.2.1. Central estimates of cost-effectiveness

The pair-wise results of the deterministic and probabilistic versions of the EAG's base case model are presented in Table 7 and Table 8, respectively. The detailed breakdown of model-predicted costs is summarised in Table 9.

When assuming a disease severity modifier of 1, the deterministic ICER for bevacizumab when added to FOLFOX is [redacted], when bevacizumab is added to CAPOX this value is [redacted]. Assuming a severity modifier of 1.2, these ICERs become [redacted] and [redacted], respectively. For both comparisons, the deterministic and probabilistic ICERs are similar.

Cost-effectiveness planes and cost-effectiveness curves (CEACs) for each pair-wise comparison are presented in the Appendix (Figure 7 to Figure 10). When assuming a disease severity modifier of 1, the CEACs indicate that the probabilities of bevacizumab in combination with fluoropyrimidine-based chemotherapy generating more net benefit (at a willingness-to-pay threshold of £20,000 per QALY gained) than fluoropyrimidine-based chemotherapy alone, are [redacted] for bevacizumab plus FOLFOX and [redacted] for bevacizumab plus CAPOX. Using a willingness-to-pay threshold of £30,000 per QALY gained, the probabilities are [redacted] for bevacizumab plus FOLFOX and [redacted] for bevacizumab plus CAPOX. When applying a disease severity modifier of 1.2, the probabilities become [redacted] (bevacizumab plus FOLFOX) and [redacted] (bevacizumab plus CAPOX) at the £20,000 per QALY threshold, and [redacted] and [redacted] respectively at the £30,000 per QALY threshold.

Table 7: Base case results – bevacizumab plus fluoropyrimidine-based chemotherapy versus fluoropyrimidine-based chemotherapy alone, deterministic, including bevacizumab weighted mean tender price, second-line setting

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER without severity modifier	ICER with severity modifier of 1.2
Model 1								
Bevacizumab plus FOLFOX	1.433	0.943	[redacted]	0.241	0.159	[redacted]	[redacted]	[redacted]
FOLFOX	1.192	0.784	£15,546					
Model 3								
Bevacizumab plus CAPOX	1.433	0.943	[redacted]	0.241	0.159	[redacted]	[redacted]	[redacted]
CAPOX	1.192	0.784	£12,757					

LYG: life-year gained; QALY: quality-adjusted life-year; Inc: incremental; ICER: incremental cost-effectiveness ratio; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CAPOX: capecitabine plus oxaliplatin
*Undiscounted

Table 8: Base case results – bevacizumab plus fluoropyrimidine-based chemotherapy versus fluoropyrimidine-based chemotherapy alone, probabilistic, including bevacizumab weighted mean tender price, second-line setting

Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER without severity modifier	ICER with severity modifier of 1.2
Model 1								
Bevacizumab plus FOLFOX	1.432	0.942	[redacted]	0.241	0.159	[redacted]	[redacted]	[redacted]
FOLFOX	1.191	0.782	£15,518					
Model 3								
Bevacizumab plus CAPOX	1.432	0.942	[redacted]	0.241	0.159	[redacted]	[redacted]	[redacted]
CAPOX	1.191	0.782	£12,735					

LYG: life-year gained; QALY: quality-adjusted life-year; Inc: incremental; ICER: incremental cost-effectiveness ratio; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; CAPOX: capecitabine plus oxaliplatin
*Undiscounted

Table 9: Detailed breakdown of model-predicted costs (discounted), deterministic, second-line setting

	Bevacizumab plus FOLFOX	FOLFOX alone	Bevacizumab plus CAPOX	CAPOX alone
Progression-free				
Acquisition costs	[redacted]	£287	[redacted]	£105
Administration costs	£7,637	£5,880	£4,297	£3,274
Health state costs	£575	£402	£575	£402
AE costs	£254	£113	£254	£113
CVAD costs	£737	£737	£737	£737
Post-progression costs	£2,260	£2,121	£2,260	£2,121
Terminal care costs	£5,958	£6,006	£5,958	£6,006
Total costs	[redacted]	£15,546	[redacted]	£12,757

FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; FOLFIRI: folinic acid plus fluorouracil plus irinotecan; CAPOX: capecitabine plus oxaliplatin; AE: adverse events; CVAD: central venous access device

2.2.2. Deterministic sensitivity analysis results

The results of DSAs are presented in Table 10 (bevacizumab plus FOLFOX versus FOLFOX alone) and Table 11 (bevacizumab plus CAPOX versus CAPOX alone).

For the comparison of bevacizumab plus FOLFOX versus FOLFOX alone, all scenarios, except DSA1 and DSA2, produced ICERs similar to the base case, ranging between [redacted] and [redacted] (with a severity modifier equal to 1.2: [redacted] to [redacted]). In DSA1, where the log-logistic distribution was applied to both PFS and OS instead of gamma distribution, the ICER decreased to below [redacted] (with severity modifier: approximately [redacted]). In DSA2, where the HR from Mocellin *et al*.[1] was used, the ICER increased to approximately [redacted] (with severity modifier: approximately [redacted]).

Similarly, for the comparison of bevacizumab plus CAPOX versus CAPOX alone, all scenarios, except DSA1 and DSA2, produced ICERs similar to the base case, ranging between [redacted] and [redacted] (with severity modifier equal to 1.2: [redacted] to [redacted]). In DSA1, where the log-logistic distribution was applied to both PFS and OS instead of gamma distribution, the ICER decreased to around [redacted] (with severity modifier: [redacted]). In DSA2, where the HR from Mocellin *et al.* was used, the ICER increased to approximately [redacted] (with severity modifier: approximately [redacted]).

Table 10: Deterministic sensitivity analysis results – bevacizumab plus FOLFOX versus FOLFOX alone, second-line setting

No.	Scenario	Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER without severity modifier	ICER with severity modifier of 1.2
-	Base-case (deterministic)	Bevacizumab plus FOLFOX	1.433	0.943	[redacted]	0.241	0.159	[redacted]	[redacted]	[redacted]
		FOLFOX alone	1.192	0.784	£15,546					
1	PFS and OS models: log-logistic	Bevacizumab plus FOLFOX	1.625	1.043	[redacted]	0.340	0.213	[redacted]	[redacted]	[redacted]
		FOLFOX alone	1.285	0.830	£15,697					
2	HR based on Mocellin *et al.* was used	Bevacizumab plus FOLFOX	1.395	0.919	[redacted]	0.203	0.135	[redacted]	[redacted]	[redacted]
		FOLFOX alone	1.192	0.784	£15,546					
3	Utility values for health states increased by 5%†	Bevacizumab plus FOLFOX	1.433	0.990	[redacted]	0.241	0.167	[redacted]	[redacted]	[redacted]
		FOLFOX alone	1.192	0.823	£15,546					
4	Utility values for health states decreased by 5%†	Bevacizumab plus FOLFOX	1.433	0.896	[redacted]	0.241	0.151	[redacted]	[redacted]	[redacted]
		FOLFOX alone	1.192	0.745	£15,546					
5	AE disutilities increased by 10 times	Bevacizumab plus FOLFOX	1.433	0.942	[redacted]	0.241	0.159	[redacted]	[redacted]	[redacted]
		FOLFOX alone	1.192	0.783	£15,546					
6	Median price of bevacizumab used‡	Bevacizumab plus FOLFOX	1.433	0.943	[redacted]	0.241	0.159	[redacted]	[redacted]	[redacted]
		FOLFOX alone	1.192	0.784	£15,546					
7	Vial sharing is assumed	Bevacizumab plus FOLFOX	1.433	0.943	[redacted]	0.241	0.159	[redacted]	[redacted]	[redacted]
		FOLFOX alone	1.192	0.784	£15,493					

LYG: life-year gained; QALY: quality-adjusted life-year; Inc: incremental; ICER: incremental cost-effectiveness ratio; FOLFOX: folinic acid plus fluorouracil plus oxaliplatin; PFS: progression-free survival; OS: overall survival; HR: hazard ratio, AE: adverse event

*Undiscounted

†Includes the correction of minor programming error contained in the main report.

‡Median price weighted by the market share was used [redacted] for 100 mg/4 ml vials and [redacted] for 400 mg/16 ml vials).

Table 11: Deterministic sensitivity analysis results – bevacizumab plus CAPOX versus CAPOX alone, second-line setting

No.	Scenario	Option	LYGs*	QALYs	Costs	Inc. LYGs*	Inc. QALYs	Inc. costs	ICER without severity modifier	ICER with severity modifier of 1.2
-	Base-case (deterministic)	Bevacizumab plus CAPOX	1.433	0.943	[redacted]	0.241	0.159	[redacted]	[redacted]	[redacted]
		CAPOX alone	1.192	0.784	£12,757					
1	PFS and OS models: log-logistic	Bevacizumab plus CAPOX	1.625	1.043	[redacted]	0.340	0.213	[redacted]	[redacted]	[redacted]
		CAPOX alone	1.285	0.830	£12,908					
2	HR based on Mocellin *et al.* was used	Bevacizumab plus CAPOX	1.395	0.919	[redacted]	0.203	0.135	[redacted]	[redacted]	[redacted]
		CAPOX alone	1.192	0.784	£12,757					
3	Utility values for health states increased by 5%†	Bevacizumab plus CAPOX	1.433	0.990	[redacted]	0.241	0.167	[redacted]	[redacted]	[redacted]
		CAPOX alone	1.192	0.823	£12,757					
4	Utility values for health states decreased by 5%†	Bevacizumab plus CAPOX	1.433	0.896	[redacted]	0.241	0.151	[redacted]	[redacted]	[redacted]
		CAPOX alone	1.192	0.745	£12,757					
5	AE disutilities increased by 10 times	Bevacizumab plus CAPOX	1.433	0.942	[redacted]	0.241	0.159	[redacted]	[redacted]	[redacted]
		CAPOX alone	1.192	0.783	£12,757					
6	Median price of bevacizumab used‡	Bevacizumab plus CAPOX	1.433	0.943	[redacted]	0.241	0.159	[redacted]	[redacted]	[redacted]
		CAPOX alone	1.192	0.784	£12,757					
7	Vial sharing is assumed	Bevacizumab plus CAPOX	1.433	0.943	[redacted]	0.241	0.159	[redacted]	[redacted]	[redacted]
		CAPOX alone	1.192	0.784	£12,721					

LYG: life-year gained; QALY: quality-adjusted life-year; Inc: incremental; ICER: incremental cost-effectiveness ratio; CAPOX: capecitabine plus oxaliplatin, PFS: progression-free survival; OS: overall survival; HR: hazard ratio; AE: adverse event

*Undiscounted

†Includes the correction of minor programming error contained in the main report.

‡Median price weighted by the market share was used [redacted] for 100 mg/4 ml vials and [redacted] for 400 mg/16 ml vials).

3. DISCUSSION OF THE ASSUMED PRICE OF BEVACIZUMAB

Following the PMB meeting prior to the first ACM, the EAG was provided with the following additional information from the NICE Commercial Liaison Team: "

- *The market share was calculated using the NHS define dataset in RxInfo. We used a sample size of the last 12 months, taken on 21/10/2025. The share is of total sales of Bevacizumab and isn't indication specific.*
- *Biosimilar usage is complex and isn't as simple as everyone buys the cheapest. We reached out to MPSC who gave this context when asked the question. "Decisions are then made by commissioners/NHS groups about how to direct usage based on the offers (i.e. new patients may all be put on one brand, or a decision may be made to share out usage across brands to lessen the possibility of shortages)."*
- *In this specific instance, the cheapest brand of Bevacizumab is only available in 2/4 regions which may be a contributing factor on why usage is low."*

In addition, the EAG noted that the market share of each bevacizumab biosimilar was adjusted to account for unknowns (missing data) which represented 5% for bevacizumab 100 mg/4 ml infusion vials and 6% for bevacizumab 400 mg/16 ml infusion vials. The EAG believes that the missing data are unlikely to have a significant impact on the cost-effectiveness results.

4. CONCLUSION

Using the updated prices in the first-line setting, the deterministic ICERs for bevacizumab plus fluoropyrimidine-based chemotherapy versus fluoropyrimidine-based chemotherapy alone were consistently less than [redacted] per QALY gained in the base case and across all scenarios, except for two DSAs for bevacizumab plus FOLFIRI versus FOLFIRI alone. When the generalised gamma distributions were used for PFS and OS rather than Weibull distributions in DSA1 for bevacizumab plus FOLFIRI versus FOLFIRI alone, the ICER increased to approximately [redacted] per QALY gained, whilst the use of an mdG regimen for FOLFIRI-containing regimens in DSA2 reduced the ICER to approximately [redacted] per QALY gained.

Using the updated prices in the second-line setting, the deterministic ICERs were approximately [redacted] (FOLFOX) and [redacted] (CAPOX), when the severity modifier was assumed to be 1. With a severity modifier of 1.2, the deterministic ICERs decreased to approximately [redacted] and [redacted], respectively. The ICERs across scenarios, except DSA1 and DSA2, were less than [redacted] with a severity modifier of 1.2). In DSA1, for bevacizumab plus FOLFOX, where the log-logistic distribution was applied to PFS and OS instead of gamma distribution, the ICER was below [redacted] (approximately [redacted] with a severity modifier of 1.2). The ICERs for bevacizumab plus CAPOX were [redacted] and [redacted], respectively. In DSA2, for bevacizumab plus FOLFOX, where the HR from Mocellin *et al*.[1] was used, the ICER increased to approximately [redacted] with a severity modifier of 1.2). The ICERs for bevacizumab plus CAPOX were [redacted] and [redacted], respectively.

As no results were generated by the model for the comparison of bevacizumab plus FOLFIRI versus FOLFIRI alone in the second-line setting, ICERs were estimated based on the assumption that they would be [redacted] higher than those for bevacizumab plus FOLFOX versus FOLFOX alone as observed in first-line treatment (see Section 2.1.1). Therefore, the resulting ICERs for bevacizumab plus FOLFIRI versus FOLFIRI alone were estimated to be [redacted] with a severity modifier of 1 and [redacted] with a severity modifier of 1.2.

The EAG highlights that the cost-effectiveness of bevacizumab in combination with fluoropyrimidine-based chemotherapy (FOLFOX, FOLFIRI or CAPOX) is notably influenced by three key factors: (i) the assumed acquisition price of bevacizumab in metastatic colorectal cancer; (ii) whether a decision severity modifier of 1.2 is deemed appropriate in the second-line treatment setting; and (iii) whether the Appraisal Committee's preferred assumptions equate to the EAG's base case or incorporate any of the DSAs.

REFERENCES

1. Mocellin S, Baretta Z, Roqué i Figuls M, Solà I, Martin-Richard M, Hallum S*, et al.* Second-line systemic therapy for metastatic colorectal cancer. *Cochrane Database of Systematic Reviews* 2017; 10.1002/14651858.CD006875.pub3.

APPENDIX

Figure 1: Cost-effectiveness plane for bevacizumab plus FOLFOX versus FOLFOX alone, first-line setting

FOLFOX: folinic acid plus fluorouracil plus oxaliplatin, QALY: quality-adjusted life-year

Figure 2: Cost-effectiveness plane for bevacizumab plus FOLFIRI versus FOLFIRI alone, first-line setting

FOLFIRI: folinic acid plus fluorouracil plus irinotecan, QALY: quality-adjusted life-year

Figure 3: Cost-effectiveness plane for bevacizumab plus CAPOX versus CAPOX alone, first-line setting

CAPOX: capecitabine plus oxaliplatin, QALY: quality-adjusted life-year

Figure 4: CEAC for bevacizumab plus FOLFOX versus FOLFOX alone, first-line setting

FOLFOX: folinic acid plus fluorouracil plus oxaliplatin

Figure 5: CEAC for bevacizumab plus FOLFIRI versus FOLFIRI alone, first-line setting

FOLFIRI: folinic acid plus fluorouracil plus irinotecan

Figure 6: CEAC for bevacizumab plus CAPOX versus CAPOX alone, first-line setting

CAPOX: capecitabine plus oxaliplatin

Figure 7: Cost-effectiveness plane for bevacizumab plus FOLFOX versus FOLFOX alone, second-line setting

FOLFOX: folinic acid plus fluorouracil plus oxaliplatin, QALY: quality-adjusted life-year

Figure 8: Cost-effectiveness plane for bevacizumab plus CAPOX versus CAPOX alone, second-line setting

CAPOX: capecitabine plus oxaliplatin, QALY: quality-adjusted life-year

Figure 9: CEAC for bevacizumab plus FOLFOX versus FOLFOX alone, second-line setting

FOLFOX: folinic acid plus fluorouracil plus oxaliplatin

Figure 10: CEAC for bevacizumab plus CAPOX versus CAPOX alone, second-line setting

CAPOX: capecitabine plus oxaliplatin