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

Slides for Zoom: confidential information redacted

A Health Technology Appraisal

Technology appraisal committee B [5th November 2025]

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Whole life cycle approach and biosimilar taskforce

- The 10 Year Plan empowers NICE to move from static to dynamic assessment, reviewing its guidance and helping the NHS maximise the health benefit for every pound spent → 'Whole Lifecycle Approach'

- A biosimilar taskforce is coordinating the work of MHRA, NICE and NHS England on biosimilars

- NICE methods and processes are being reviewed and optimised within the Whole Lifecycle Approach:
    - consideration of biosimilars in indications where the originator has not been recommended by NICE.
    - providing clearer advice about which treatments to use when branded and biosimilar options exist.

- Bevacizumab for treatment of metastatic colorectal cancer had not previously been recommended by NICE.
- Due to demand for a new evaluation of bevacizumab from stakeholders and entry of biosimilar competition, biosimilar bevacizumab was selected as a pilot for the evaluation of biosimilars using existing methods.

- The learnings from this evaluation will help inform the wider whole lifecycle approach as it is developed

Abbreviations: MHRA, Medicines and Healthcare products Regulatory Agency, HTA, health technology assessment

Piloting a ‘pragmatic approach’

- NICE is piloting an approach where EAG was tasked with assessing the cost effectiveness of bevacizumab in the most efficient/cost-efficient way.
    - Expedited version of multiple technology appraisal process, EAG had shorter timelines than MTA
    - No submissions from companies or stakeholders or technical engagement
    - At scoping the population was **restricted to people who are not candidates for targeted treatments or immunotherapies**
- Expedited approach necessitated the following simplifications:
    - No new systematic reviews; EAG reviewed previous TA submissions and used clinical expert advice for identifying new data
    - EAG extracted key clinical data, reduced critical appraisal than standard MTA
    - New model has been developed with simplifying assumptions including not running a sequential model that includes follow on treatment

Abbreviations: MTA, multiple technology appraisal, TA, technical appraisal

Bevacizumab costs

- There are a range of confidential prices for bevacizumab in MPSC
- During the development of the EAG report, the EAG were asked to use the unweighted mean price and was not provided with data on market share.
- Following the EAG report, NICE requested weighted mean price (based on bevacizumab market share across all indications).
- The cheapest bevacizumab product may not always be selected. MPSC stated "Decisions are made by commissioners/NHS groups about how to direct usage (i.e. new patients may all be offered one brand, or a decision may be made to share out usage across brands to lessen the possibility of shortages)."
- For bevacizumab, the weighted mean price is ~20% lower than the unweighted mean price.
- For purpose of this pilot weighted mean price is preferred approach.
- Issues around handling the pricing of biosimilars will be explored by the biosimilar taskforce in the near future.

Abbreviations: MSPC Medicines Procurement Supply Chain

Bevacizumab (originator and biosimilars) with fluoropyrimidine-based chemotherapy for treating metastatic colorectal cancer

- ✓ **Background and key issues**
- ❑ Clinical effectiveness
- ❑ Modelling and cost effectiveness
- ❑ Other considerations
- ❑ Summary

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Bevacizumab

Marketing authorisation of originator (Avastin; Roche)	Bevacizumab in combination with fluoropyrimidine-based chemotherapy is indicated for treatment of adult patients with metastatic carcinoma of the colon or rectum
Administration	IV infusion
Price	Mean weighted MPSC price of 8 products Avastin (originator), [redacted]

See appendix for further detail on bevacizumab

Abbreviations: IV, intravenous; MSPC, Medicines Procurement and Supply Chain

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Previous appraisals of originator bevacizumab (Avastin)

Technical Appraisal	Population	Committee discussion and cost effectiveness
TA118 (2007) MTA (bevacizumab + FOLFIRI, cetuximab)	Untreated mCRC	• Potential confounding of OS outcome in AVF2107g study as patients continued to get bevacizumab after disease progression. Impact of bevacizumab 1st line for mCRC uncertain • Company & EAG used different methods to model PFS and OS • No estimates suggest cost-effective use of NHS resources
TA212 (2010) STA (MA extended to include combination with fluoropyrimidine based therapy) Bevacizumab + FOLFOX/CAPOX	mCRC	• FOLFOX and CAPOX can be considered equivalent • Modest clinical benefit as 1st line treatment • Clinically beneficial as 2nd line treatment • Utilities from small study of people having cetuximab • ICERs above threshold
TA242 (2012) MTA (cetuximab, bevacizumab + chemo w/o oxaliplatin, panitumumab)	mCRC after 1st line chemo	• Not feasible to carry out a cost effectiveness evaluation of bevacizumab + non-oxaliplatin therapy because no clinical evidence at 2nd line for this population

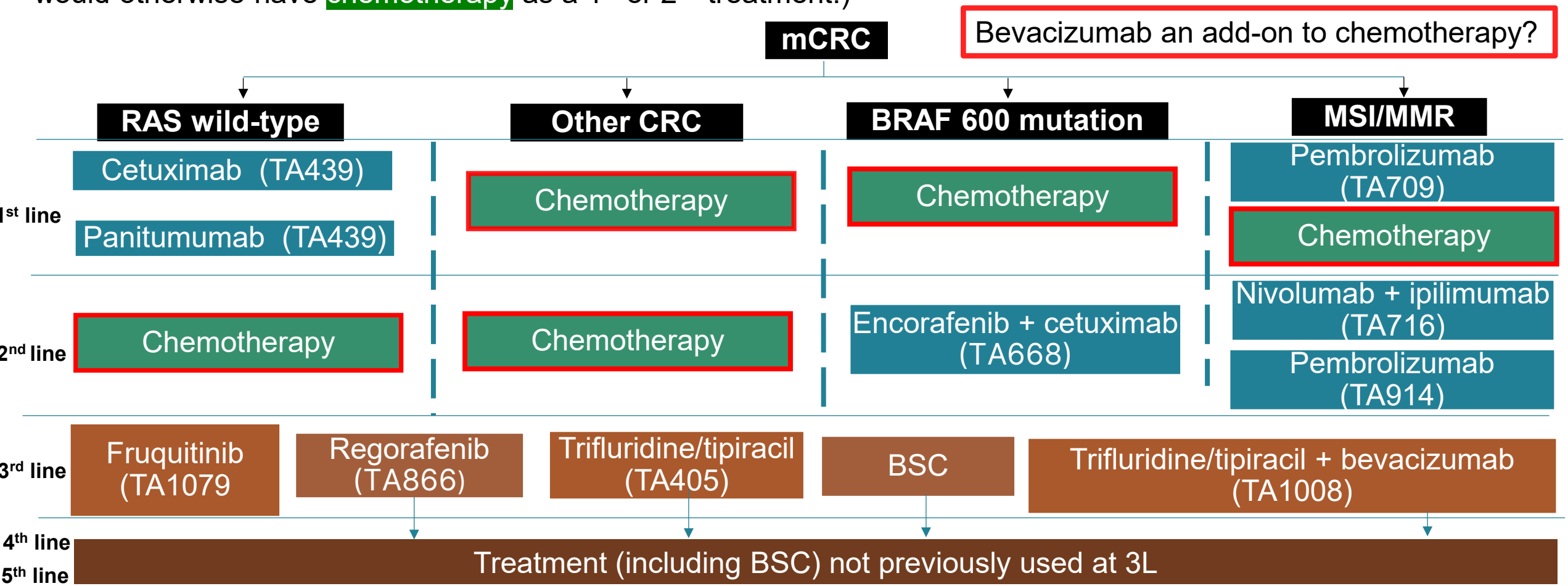
Abbreviations; mCRC, metastatic colorectal cancer; MTA, multiple technology appraisal; STA, single technology appraisal; w/o without

FOLFOX/CAPOX/FOLFIRI chemotherapy components

mCRC treatment pathway

Chemotherapy: FOLFOX, FOLFIRI, CAPOX

Metastatic colorectal cancer has different subtypes, with targeted treatment options/immunotherapy at 1st and 2nd line. This appraisal is focussed on people who are **not** candidates for targeted treatments or immunotherapy, and would otherwise have chemotherapy as a 1st or 2nd treatment.)



Where would bevacizumab be used as an add on to chemotherapy?
Would it be used for mCRC with known mutations if a targeted treatment is not available/suitable at that position?
Would these mutations affect the clinical effectiveness of chemotherapy or bevacizumab?

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Abbreviations: MSI, microsatellite instability; MMR, mismatch repair; BSC, best supportive care; EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer

Decision problem: Population and Comparators

	EAG decision problem	As per final scope?	EAG comments
Population	• People with untreated metastatic carcinoma of the colon or rectum who would receive fluoropyrimidine-based chemotherapy and • People 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	No- broader to include 2nd line population	Following final scope, the EAG broadened decision problem to include 2nd-line bevacizumab (anticipating there would be a subsequent scope by NICE to cover second-line treatment). EAG note many assumptions & parameters overlap between 1st and 2nd line treatments; combining both more efficient. Expansion to 2nd line was also driven from consultation with experts
Comparators	• FOLFOX • FOLFIRI • CAPOX	No- excludes capecitabine	Capecitabine monotherapy not a relevant comparator; lack of data comparing bevacizumab plus capecitabine vs capecitabine alone

Does the committee agree with the population and comparators?

Intervention and Outcomes

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

Key issues

Key issue	ICER impact	Slide
Use of model which only includes one line of treatment	uncertain	21
EAG modelling assumptions	**ICER impact**	**Slide**
Extrapolation of PFS	moderate	22
Extrapolation of OS		22
Utility values	small	23
Severity modifier (implications of modelling approach + whether severity modifier applicable)	moderate	24
Drug dosage and admin costs (in particular sensitivity analyses reflecting differences in dosing regimen in NHS vs clinical trials)	minimal (for B FOLFOX/CAPOX), moderate for B-FOLFIRI	appendix

Key (modelled scenarios – change from base case [+/-]):
Minimal ICER impact: < £1,000
Small ICER impact: £1,000 to £5,000
Moderate ICER impact: > £5,000 to £10,000

Abbreviations: PFS, progression-free survival; OS, overall survival

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Clinical trials: first-line treatment

As far as EAG's clinicians are aware, no new studies have been published since the original TAs

	Study NO16966 (reported by TA212)		Study AVF2107g (reported by TA118)
Design	FOLFOX vs. CAPOX trial then amended to open label 2x2 randomised trial (4 arms)		RCT
Population	Untreated metastatic colorectal cancer		
Intervention	Bevacizumab (originator) + FOLFOX	Bevacizumab (originator) + CAPOX	Bevacizumab (originator) + FOLFIRI
Comparator(s)	Placebo + FOLFOX	Placebo + CAPOX	Placebo + FOLFIRI
Primary outcome	PFS		OS
How used in model (current evaluation)	Pooled FOLFOX/CAPOX data (from 2x2) used in models assessing bevacizumab + FOLFOX; and bevacizumab + CAPOX, plus exclusion of people with prior adjuvant therapy		Used in model assessing cost-effectiveness of bevacizumab + FOLFIRI

See appendix for more detail of Study NO16966 design

Abbreviations: b-, bevacizumab plus; TA, technical appraisal; PFS, progression-free survival; OS, overall survival

1st line PFS and OS results B-FOLFOX/CAPOX vs. placebo + FOLFOX/CAPOX

- Data from 2x2 part of NO16966 comparing bevacizumab + FOLFOX/CAPOX compared with FOLFOX/CAPOX showed around a 1.4 month increase in median PFS and OS with bevacizumab +FOLFOX/CAPOX
- Excluding data from patients who had prior adjuvant therapy (committee's preference in TA212 and used in model for current appraisal) decreased the hazard ratio for PFS and OS

PFS	B-FOLFOX/CAPOX (n=699)	FOLFOX/CAPOX (n=701)
Events	513	547
Median PFS months	9.4	8.0
HR (97.5% CI)	0.83 (0.72 to 0.95)	
Excluding [redacted] patients who had prior adjuvant therapy		
HR (97.5% CI)	[redacted]	

OS	B-FOLFOX/CAPOX (n=699)	FOLFOX/CAPOX (n=701)
Events	420	455
Median OS months	21.3	19.9
HR (97.5% CI)	0.89 (0.76 to 1.03)	
Excluding [redacted] patients who had prior adjuvant therapy		
HR (97.5% CI)	[redacted]	

For EAG generated KM plots informing the model see appendix

Abbreviations: B-bevacizumab plus; PFS, progression-free survival; OS, overall survival; KM, Kaplan-Meier; HR, hazard ratio

1st line PFS and OS results B-FOLFIRI vs. FOLFIRI + placebo

Bevacizumab plus FOLFIRI improved median PFS and OS by 4.4 months and 4.7 months (respectively) compared with FOLFIRI + placebo

Data from study AVF2107g

	B-FOLFIRI (n=402)	FOLFIRI + placebo (n=411)
Median PFS months	10.6	6.2
HR	0.54 p<0.01	

	B-FOLFIRI (n=402)	FOLFIRI + placebo (n=411)
Median OS months	20.3	15.6
HR	0.66, p<0.001	

see appendix for KM curves (reproduced from Hurwitz et al.)

Abbreviations: B-, bevacizumab plus; PFS, progression-free survival; OS, overall survival; HR, hazard ratio

Clinical trials: 2nd line treatment

No previous TAs or clinical studies evaluating bevacizumab + FOLFIRI vs FOLFIRI or bevacizumab + CAPOX vs CAPOX) for second line treatment were identified

	E3200 (referred to in TA212)
Design	Open-label, randomised clinical trial
Population	Advanced/ mCRC previously treated with irinotecan and fluoropyrimidine based chemo for advanced disease (no prior bevacizumab or oxaliplatin)
Intervention	Bevacizumab + FOLFOX (n=286)
Comparator(s)	FOLFOX (n=291), Bevacizumab (n=243)
Primary outcome	OS
How used in model	Model assessing B-FOLFOX vs. FOLFOX at 2nd line • also used to inform model assessing B-CAPOX vs CAPOX at 2nd line • CAPOX assumed equivalent to FOLFOX

Abbreviations: B-FOLFOX; bevacizumab plus FOLFOX; B-CAPOX bevacizumab + CAPOX mCRC, metastatic colorectal cancer; TA, technical appraisal; OS, overall survival; PFS, progression-free survival

2nd line PFS and OS results B-FOLFOX vs. FOLFOX

bevacizumab plus FOLFOX significantly improved median PFS and OS by 2.6 months and 2.1 months (respectively) compared with FOLFOX

	B-FOLFOX	FOLFOX
Median PFS months	7.3	4.7
HR	0.61 (p<0.0001)	

	B-FOLFOX	FOLFOX
Median OS months	12.9	10.8
HR	0.75 (p=0.0011)	

see appendix for KM curves in study E3200 generated by the EAG

Abbreviations: B-FOLFOX; bevacizumab plus FOLFOX; PFS, progression-free survival; OS, overall survival; HR, hazard ratio

Meta-analysis identified by EAG- 2nd line

Hazard ratios similar between studies (broadly consistent with E3200)

- EAG identified Mocellin et al (2017), a meta-analysis of second line systemic therapies in people with mCRC that progressed, recurred or did not respond to 1st line therapy
- 4 trials compared bevacizumab + chemotherapy vs chemotherapy alone. There were differences in chemotherapy regimen, the location studies were conducted in, bevacizumab dose. In Masi et al (2015) people had bevacizumab previously
- Consistency of Masi et al (2015) results suggests previous use of bevacizumab may not affect 2nd line efficacy

Study	Chemotherapy regimen	PFS HR (95% CI)	OS HR (95% CI)
Giantonio (2007) (n = 577) (E3200 study)	FOLFOX	0.61 (0.48, 0.78)	0.75 (0.60, 0.94)
Bennouna (2013) (n = 820)	Pooled: irinotecan or oxaliplatin based	0.68 (0.58, 0.80)	0.81 (0.69,0.95)
Cao (2015) (n =142)	FOLFIRI	0.71 (0.52, 0.97)	0.78 (0.55, 1.11)
Masi (2015) (n = 184)	Pooled: irinotecan or oxaliplatin based	0.70 (0.52, 0.94)	0.77 (0.56, 1.06)
Total (n = 1,723)		0.67 (0.60, 0.75)	0.79 (0.70, 0.88)

Abbreviations: mCRC, metastatic colorectal cancer; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval

heterogeneity notes

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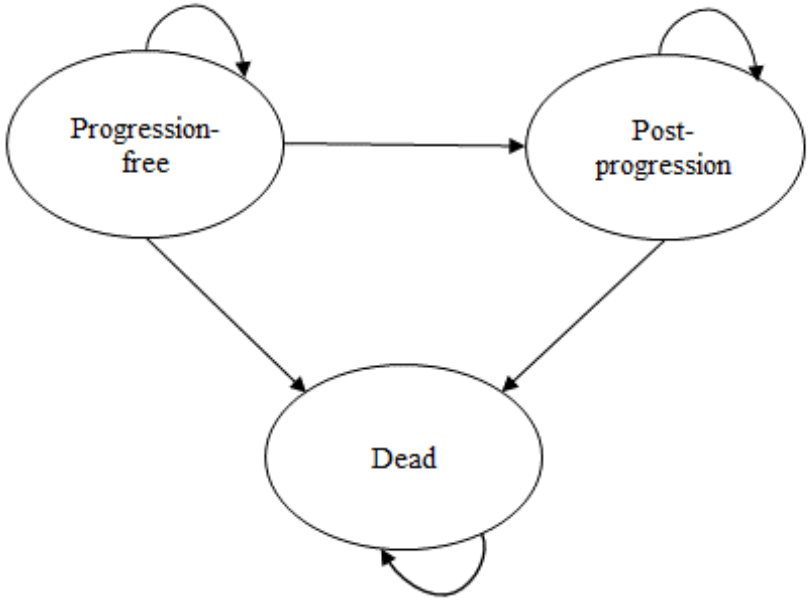
Economic model

Partitioned survival model



- **Cycle length** 4 week (with half cycle correction)
- **Time horizon** lifetime (up to 100 years)

Abbreviations: mCRC, metastatic colorectal cancer

Populations:

- **1st line:** adults with previously untreated mCRC who would normally receive chemotherapy
  - (i) Mean age 60 years, 40% female
- **2nd line**: adult patients with mCRC who would normally receive chemotherapy as a second-line treatment.
  - (i) mean age 61 years, 39.5% female

Treatment sequence: bevacizumab + chemotherapy or chemotherapy followed by best supportive care

Type of chemotherapy

Model	Treatment	Population
Model 1		
Intervention	Bevacizumab plus FOLFOX	1st and 2nd line
Comparator	FOLFOX	
Model 2		
Intervention	Bevacizumab plus FOLFIRI	1st line*
Comparator	FOLFIRI	
Model 3		
Intervention	Bevacizumab plus CAPOX	1st and 2nd line
Comparator	CAPOX	

*As no data identified at 2nd line for model 2, 2nd line ICER estimated assuming the relative difference in ICERs between model 2 and model 1 in the first line setting

Issue 1: model includes one line of treatment

Background:

- Given the expedited approach and associated time constraints, the EAG made some simplifying assumptions in its modelling approach
- In model people have bevacizumab + chemotherapy or chemotherapy alone followed by best supportive care (costs and QALYs associated with subsequent treatments not included)

EAG:

- This approach is appropriate if committee agrees with its key principles:
  - Subsequent NICE recommended treatments are cost-effective thus extending life will only improve the net monetary benefit of a strategy
  - Early treatment with bevacizumab does not affect the relative clinical efficacy of later treatments
- Consider approach is appropriate in this case but notes that
  - it may underestimate life expectancy and QALYs associated with standard care (which is important in considering whether severity modifier is applicable)
  - EAG have attempted to adjust the values accordingly for severity modifier calculations, but this will overestimate QALYs

- Does committee agree that the EAG's key principles/ assumptions have been met?
- If so, is the EAG approach reasonable?
- Given the constraints on time is the EAG's approach appropriate for decision making?

Abbreviations: QALY, quality-adjusted life year

Issue 2: Modelling assumptions: extrapolation of PFS and OS

EAG considered the following when selecting the most appropriate parametric distribution for PFS and OS:

- Statistical fit of the distribution to the KM data (AIC/BIC)
- Underlying hazards should have monotonically increasing hazards (clinical expert advice)- excludes log-logistic
- Should have a good visual fit to the data
- The distributions used for each arm and for PFS and OS within a model should be the same

- EAG consulted clinical experts on plausibility of survival model predictions
- EAG selected scenarios which could be plausible, and provided widest possible spread of plausible outcomes

	1st line distributions used for PFS/OS	2nd line distributions used for PFS/OS
B-FOLFOX vs FOLFOX	Base case: gamma Scenario: log-logistic	Base case: gamma Scenario: log-logistic
B-FOLFIRI vs FOLFIRI	Base case: Weibull Scenario: generalised gamma	
B-CAPOX vs CAPOX	Base case: gamma Scenario: log-logistic	Base case: gamma Scenario: log logistic

Are these the most appropriate distributions?

See supplementary appendix for data underpinning EAG selection 1st line, 2nd line

Abbreviations: AIC, Akaike information criterion; BIC, Bayesian information criterion; b-bevacizumab plus; PFS, progression-free survival; OS, overall survival; KM, Kaplan-Meier

Issue 3 Modelling assumptions: utility

EAG used utility values from previous appraisals and additionally applied AE-related disutilities in model

	1st line		2nd line
Previous TA	TA118	TA212	TA1008 trifluridine-tipiracil 2+
Progression-free (PF) health state	0.80 HUI3 Ramsey et al (2000)	0.77 EQ-5D in Crystal trial (cetuximab + FOLFIRI vs FOLFIRI alone)	0.73 values used in TA405 (trifluridine-tipiracil 1+ previous treatment)
Progressed-disease (PD) health stare	0.60 (PF->PD 0.75x multiplier (assumption)	0.68 BSC arm in 20020408 (trial of panitumumab 3rd line)	0.64 values used in TA405
Disutility for AEs	Not included	Not included	Not included
Uncertainty noted in original appraisal	Committee: considerable uncertainty	Crystal included 37 people (who had KRAS wt mutation)	
EAG preference for current appraisal		PF 0.77, PD 0.68 And add one-off disutility for AEs (appendix)	PF 0.73, PD: 0.64 And add one-off disutility for AEs (appendix)
Scenarios	Increase/decrease utility values by 5% (arbitrary). Increase AE disutility 10x		

Does the committee accept the utility values chosen by the EAG?

Issue 4: severity modifier (1/2)

Background:

- Given the simplified model only includes 1 line of treatment the expected QALY gains on standard care (which may include multiple lines of treatment) is likely to be underestimated
- In determining the severity modifier, the EAG attempted to address this by estimating total QALYs by adding QALYs gained through later lines of treatment noting potential limitations from assuming:
  - No double counting of QALYs accrued between progression and death
  - All patients progress and receive subsequent lines of treatment rather than die
- These limitations are likely to overestimate QALY gains of standard care

	line	Standard care regimen	QALYs
Data that is summed to generate QALYs on standard care	1st line	FOLFOX/CAPOX	1.29
		FOLFIRI	1.09
	2nd line	FOLFOX/CAPOX: 0.78 (no estimate FOLFIRI)	0.78
	3rd line	trifluridine-tipiracil + bevacizumab arm (TA1008)	0.92

Abbreviations: QALY, quality-adjusted life year; TA, technical appraisal

Issue 3: Severity modifier estimations (2/2)

A 1.2x severity modifier is estimated to be applicable in 2nd line setting because proportional shortfall is over 85%

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 +0.78+0.92)	12.68	9.69	76.41%	1.0
FOLFIRI alone	2.79 (1.09 +0.78 + 0.92)		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

Considering the potential limitations in the approach, are the committee satisfied that a severity modifier is appropriate in second-line?

Abbreviations: QALY, quality-adjusted life year

See appendix for (QALY weightings for severity)

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Equality considerations

- No potential equality issues identified during the scoping process

Are there any equality issues relevant to the potential recommendation?

Summary of cost effectiveness estimates- EAG base case

Comparison: First line	ICER (£/QALY) versus (FOLFOX, FOLFIRI, CAPOX)
Model 1: Bevacizumab plus FOLFOX versus FOLFOX	
EAG base case	**Under £20,000**
Model 2: Bevacizumab plus FOLFIRI versus FOLFIRI	
EAG base case	**between £20,000 - £30,000**
Model 3: Bevacizumab plus CAPOX versus CAPOX	
EAG base case	**Under £20,000**

Comparison: Second line	ICER (£/QALY) versus (FOLFOX, CAPOX) without severity modifier	ICER (£/QALY) versus (FOLFOX, CAPOX) with 1.2 severity modifier
Model 1: Bevacizumab plus FOLFOX versus FOLFOX		
EAG base case	**between £20,000 - £30,000**	**between £20,000 - £30,000**
Model 3: Bevacizumab plus CAPOX versus CAPOX		
EAG base case	**between £20,000 - £30,000**	**between £20,000 - £30,000**

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Supplementary appendix

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Bevacizumab

Mechanism of action	Monoclonal antibody that inhibits tumour growth and blood vessel formation, binds to and blocks activity of VEGF
Dosing schedule	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

back bevacizumab details

Abbreviations: VEGF, vascular endothelial growth factor

Background on metastatic colorectal cancer (mCRC)

Causes

- Colorectal cancer (CRC), also known as bowel cancer, is a type of cancer that starts in the tissues of the colon or rectum
- mCRC occurs when the cancer has spreads beyond the colon or rectum to other parts of the body most commonly to the liver, lungs and peritoneum
- **Epidemiology**
- CRC is the fourth most common cancer in the UK; approximately 44,100 new cases of CRC were diagnosed annually in the UK between 2017 and 2019
- Around 23% of newly diagnosed CRC cases in England in 2021 were metastatic

Symptoms and prognosis

- CRC symptoms: changes in bowel habits, blood in the stool, abdominal pain, fatigue, and unexplained weight loss; mCRC symptoms similar but depend on part of body cancer has spread to; may include fatigue, low energy and reduced appetite
- In England, CRC has 1- and 5-year survival rates of around 44% and 11%, while stage 4 disease (including mCRC) has a 5-year survival rate of around 10%

Chemotherapies

Fluoropyrimidines are anti-metabolite drugs which include 5-fluorouracil (5-FU), folinic acid, capecitabine

FOLFIRI	FOLFOX	CAPOX (aka XELOX)
Folinic acid Fluorouracil (5-FU) Irinotecan	Folinic acid Fluorouracil (5-FU) oxaliplatin	Capecitabine oxaliplatin

Study NO16966 (adapted from Cassidy *et al.*)

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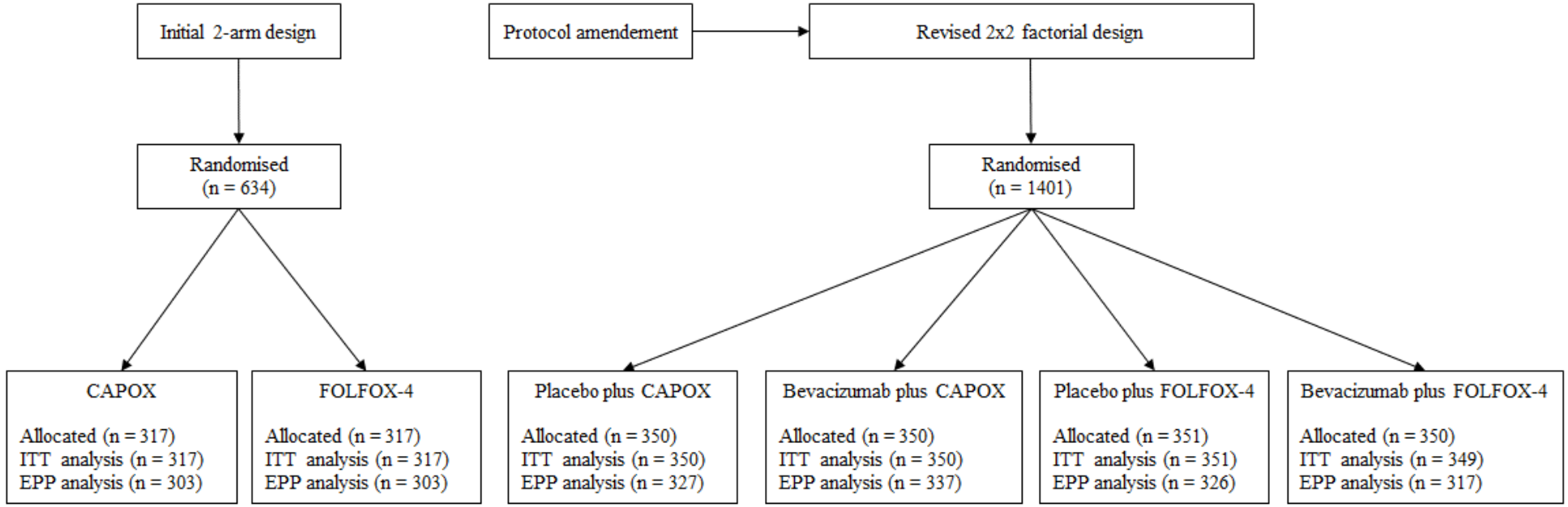

Abbreviations: ITT, intention-to-treat; EPP, eligible patient population

Decision problem: Intervention and Outcomes

	Final scope	As per final scope?	EAG comments
Intervention	Bevacizumab/ biosimilars + fluoropyrimidine based chemotherapy	As per final scope	
Outcomes	OS, PFS, response rates, AEs, HRQoL	As per final scope	

back to population and comparators

Abbreviations: OS, overall survival; PFS, progression-free survival; HRQoL, health-related quality of life; AEs, adverse events

Meta-analyses identified by EAG- 2nd line

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Hazard ratios similar between studies (broadly consistent with E3200)

Study	Chemotherapy regimen	Heterogeneity notes	PFS HR (95% CI)	OS HR (95% CI)
Giantonio 2007 (n = 577) (E3200 study)	FOLFOX		0.61 (0.48, 0.78)	0.75 (0.60, 0.94)
Bennouna 2013 (n = 820)	Pooled: either irinotecan or oxaliplatin based	Lower bevacizumab does 5mg/kg not 10mg/kg	0.68 (0.58, 0.80)	0.81 (0.69,0.95)
Cao 2015 (n =142)	FOLFIRI	Conducted in China only	0.71 (0.52, 0.97)	0.78 (0.55, 1.11)
Masi 2015 (n = 184)	Pooled: either irinotecan or oxaliplatin based	Conducted in Italy only + had bevacizumab previously	0.70 (0.52, 0.94)	0.77 (0.56, 1.06)
Total (n = 1,723)			0.67 (0.60, 0.75)	0.79 (0.70, 0.88)

Abbreviations: mCRC, metastatic colorectal cancer; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval

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PFS and OS results b-FOLFOX/CAPOX vs. placebo + FOLFOX/CAPOX

NO16966 pooled FOLFOX/CAPOX data from 2x2 part of trial. EAG provided PFS and OS KM from TA212 submission with people who had prior therapy excluded and generated pseudo IPD.

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Abbreviations: B-bevacizumab plus; PFS, progression-free survival; OS, overall survival; KM, Kaplan-Meier; HR, hazard ratio; IPD, individual patient data; ITT, intention-to-treat

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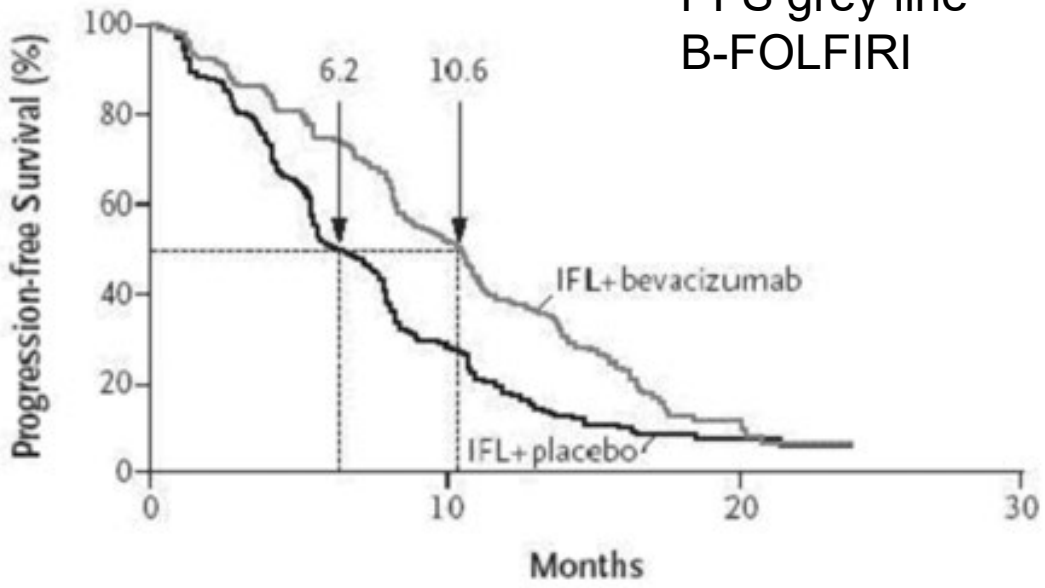
First-line

PFS and OS results B-FOLFIRI vs. FOLFIRI

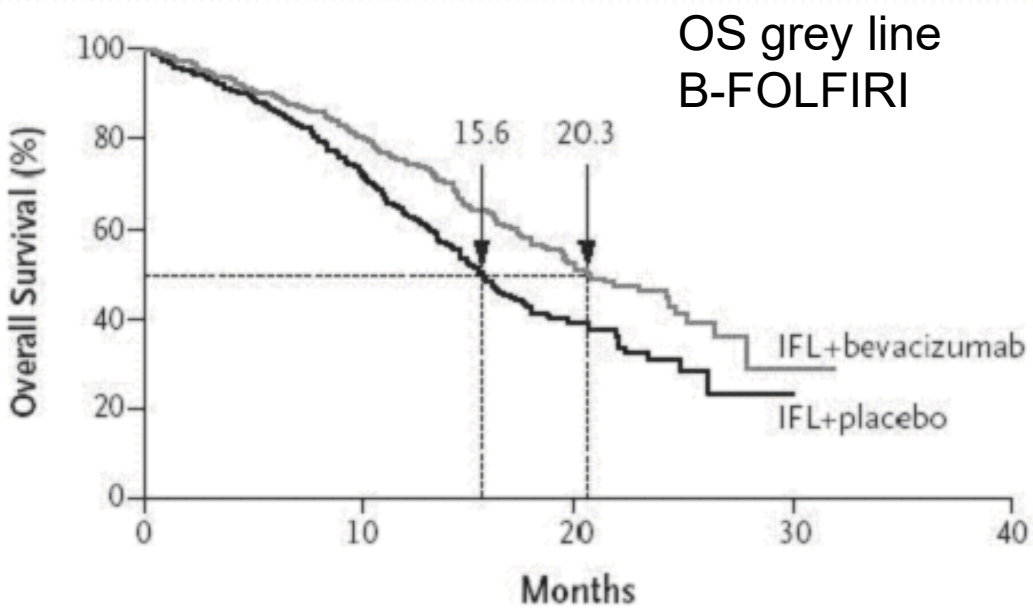
AVF2107g (reproduced from Hurwitz et al). IFL=FOLFIRI

PFS grey line
B-FOLFIRI



No. at Risk						
IFL+bevacizumab	402	269	143	36	6	0
IFL+placebo	411	225	73	17	8	0

OS grey line
B-FOLFIRI



No. at Risk								
IFL+bevacizumab	402	362	320	178	73	20	1	0
IFL+placebo	411	363	292	139	51	12	0	0

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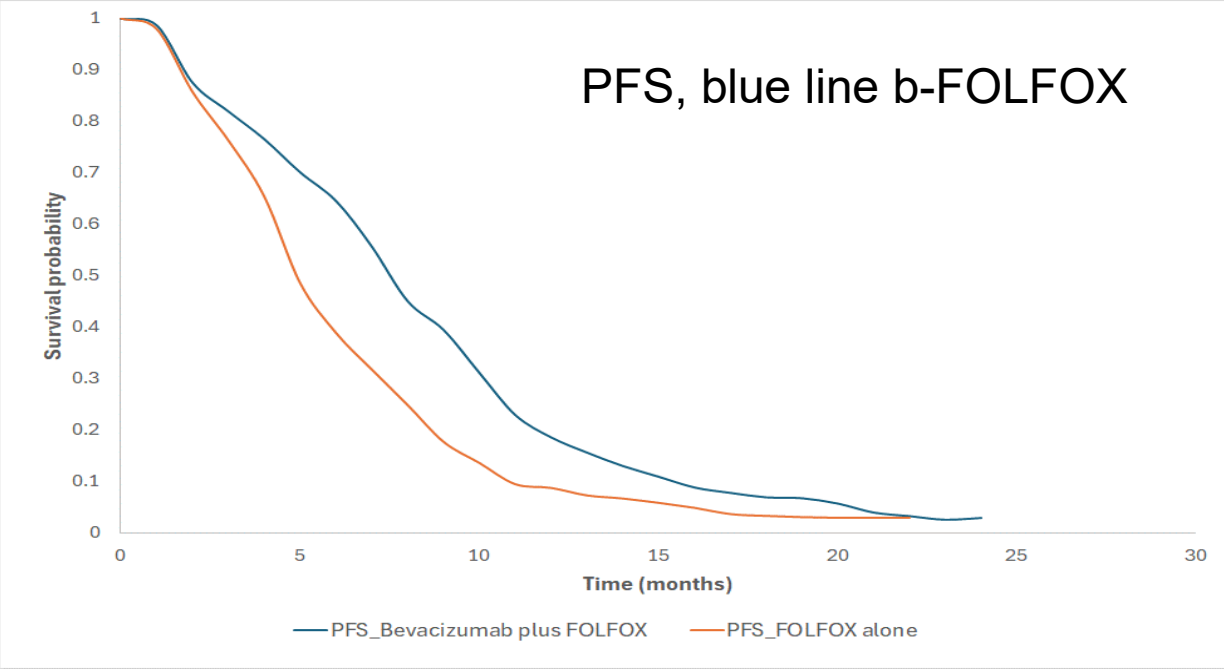
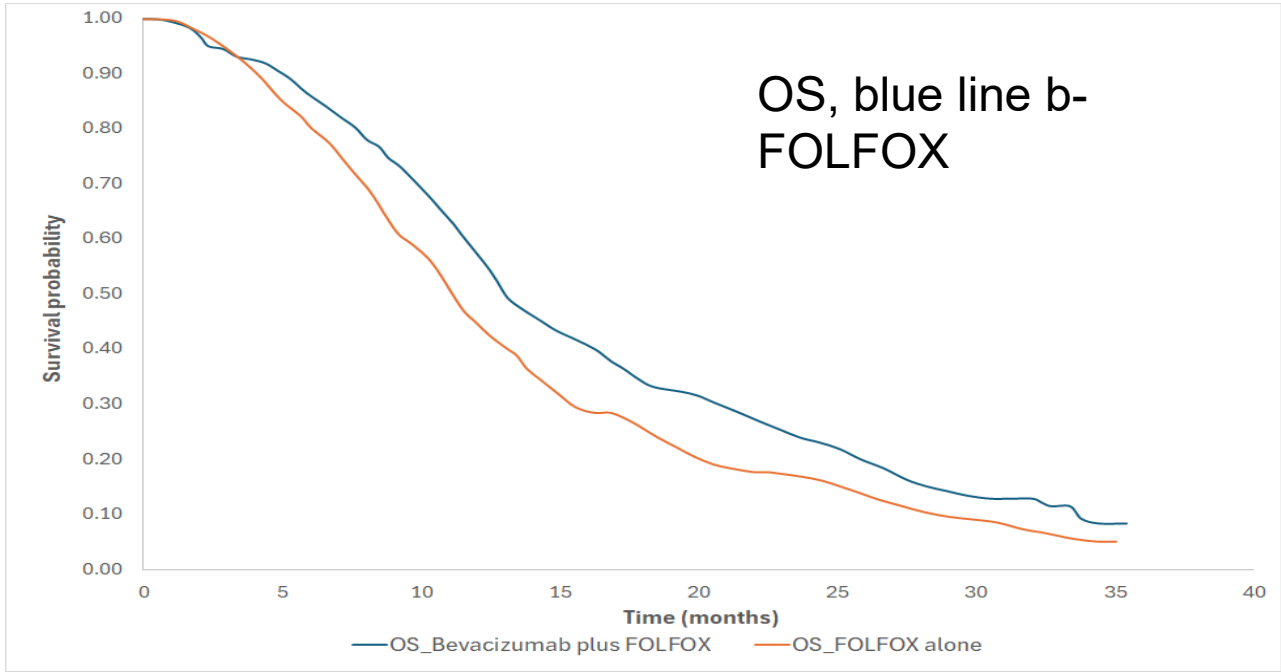
Abbreviations: B-, bevacizumab plus; PFS, progression-free survival; OS, overall survival

Second-line

PFS and OS results b-FOLFOX vs. FOLFOX

Study E3200 PFS and OS curves generated by the EAG





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NICE

Abbreviations: b-FOLFOX; bevacizumab plus FOLFOX; PFS, progression-free survival; OS, overall survival

First-line

Data informing choice of distribution

	PFS AIC/BIC best statistical fit*	PFS modelled hazard	Visual fit	PFS preferred	OS AIC/BIC best statistical fit*	OS underlying hazards	OS visual fit	OS preferred
B-FOLFOX/ CAPOX	Log-logistic	See slide	See slide	Gamma • log-logistic excluded on modelled hazard (but used in scenario). • g.gamma also had good fit, but gamma gives bigger contrast to log-logistic	Weibull	See slide	See slide	Gamma Consistency with PFS
FOLFOX/ CAPOX	Log-logistic	See slide	See slide		Gamma	See slide	See slide	
B-FOLFIRI	Weibull Gompertz g. Gamma	See slide	See slide	Weibull • AIC/BIC very similar to g.gamma, but Weibull better fit to OS data. • g.gamma used in sensitivity analysis	Weibull Gamma Gompertz g.gamma	See slide	Best AIC/BIC models had adequate visual fit See slide	Weibull. Provided adequate fit to observed OS data, enabling consistent model choice across OS and PFS
FOLFIRI	Gamma Log-logistic g. gamma	See slide	See slide			See slide		

NICE *These models have within 5 points of the best-fitting

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AIC and BIC statistics

Bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone

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

*Models that are the best fitting or within 5 points of the best-fitting are highlighted in bold

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression- free survival

Observed and model-predicted

Bevacizumab plus FOLFOX/CAPOX

FOLFOX/CAPOX, alone

EAG base case: gamma; Scenario: log-logistic (best statistical fit)

Abbreviations: PFS, progression-free survival; KM, Kaplan-Meier

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Modelled hazard plots from standard parametric survival models (generated by EAG)

Bevacizumab plus FOLFOX/CAPOX

FOLFOX/CAPOX, alone

Abbreviations: PFS, progression-free survival; exp, exponential; gengamma, generalised gamma; llogis, log-logistic; lnorm, log-normal

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AIC and BIC statistics

Bevacizumab plus FOLFIRI and FOLFIRI alone

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**

*Models that are the best fitting or within 5 points of the best-fitting are highlighted in bold

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression- free survival

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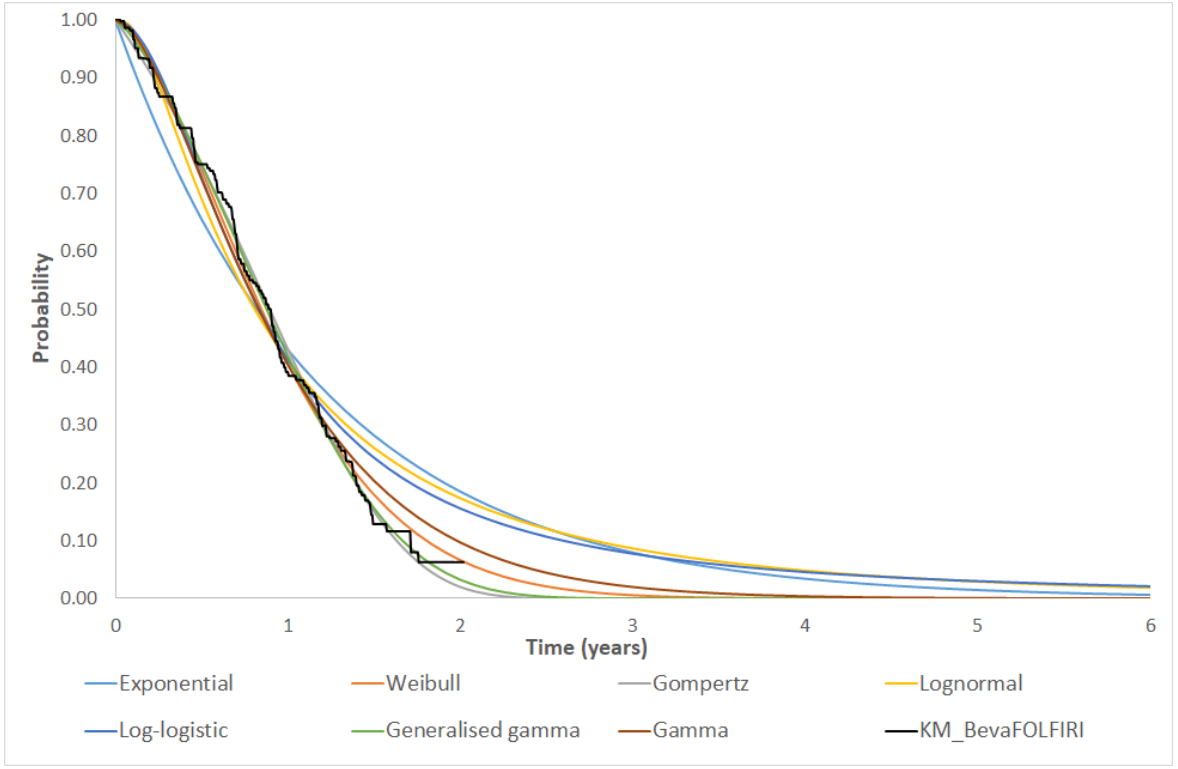
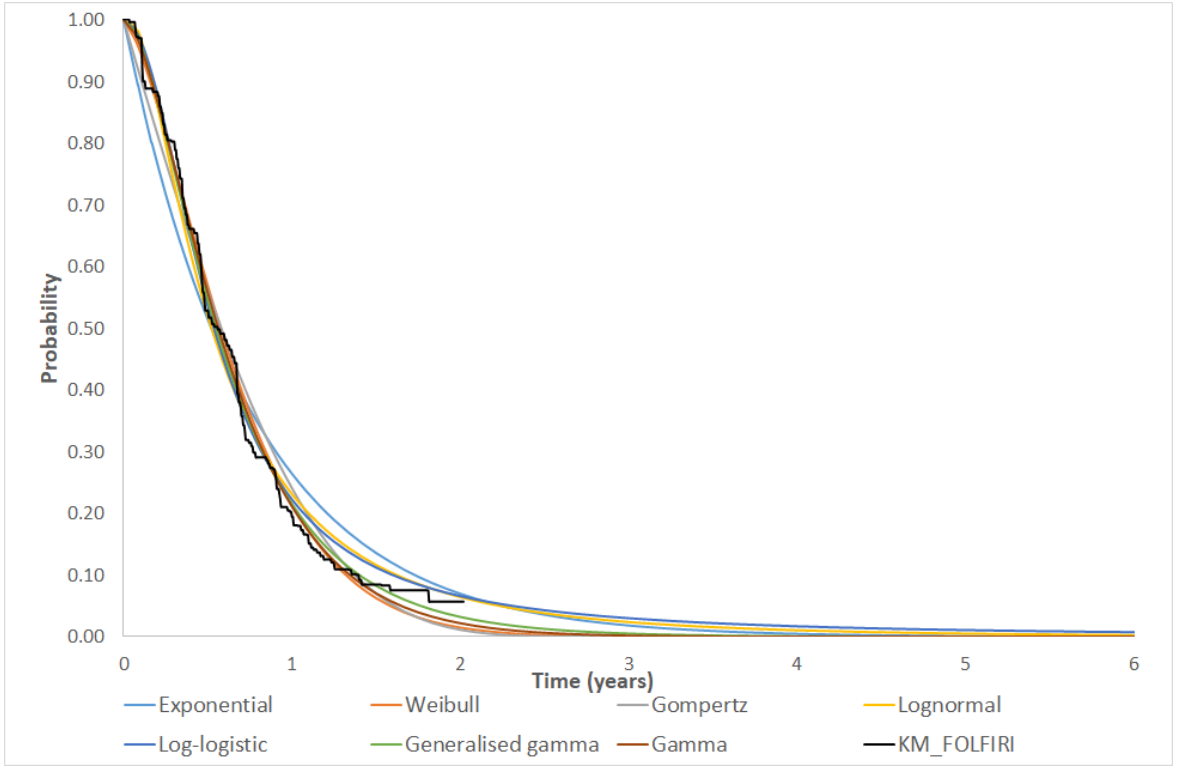
Observed and model-predicted

Bevacizumab plus FOLFIRI



FOLFIRI alone



EAG base case: Weibull; Scenario: generalised gamma

Abbreviations: PFS, progression-free survival; KM, Kaplan-Meier

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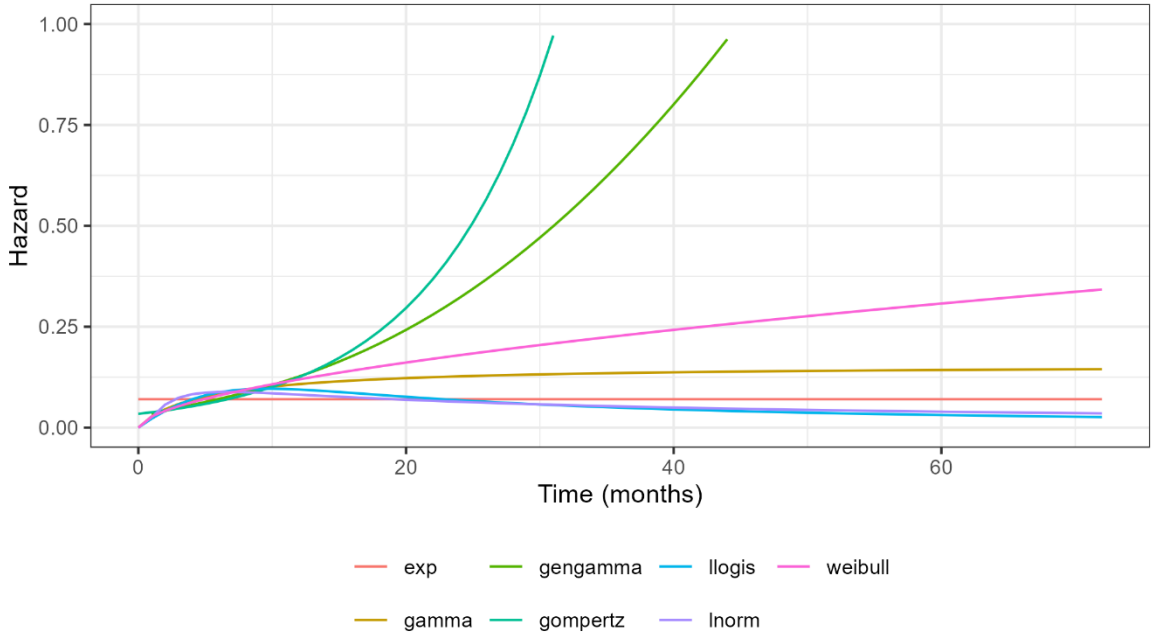
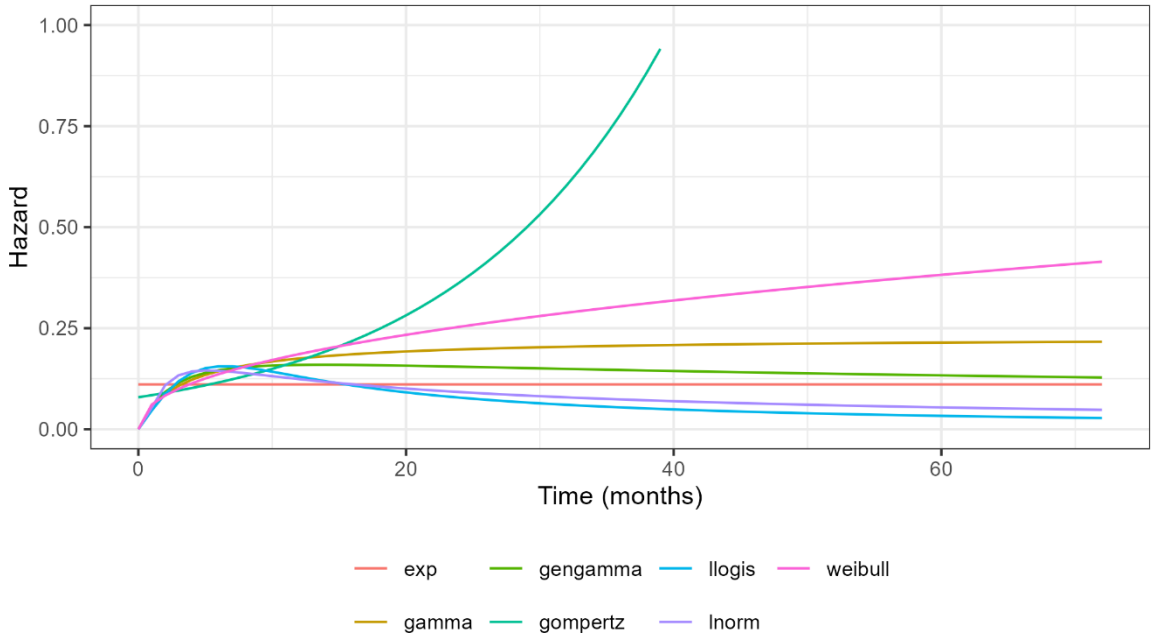
Modelled hazard plots from standard parametric survival models (generated by EAG)

Bevacizumab plus FOLFIRI



FOLFIRI alone



Abbreviations: PFS, progression-free survival; exp, exponential; gengamma, generalised gamma; llogis, log-logistic; lnorm, log-normal

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AIC and BIC statistics

Bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone

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

*Models that are the best fitting or within 5 points of the best-fitting are highlighted in bold

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; OS, overall survival

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Observed and model-predicted

Bevacizumab plus FOLFOX/CAPOX

FOLFOX/CAPOX, alone

EAG base case: gamma; Scenario: log-logistic (best statistical fit)

Abbreviations: OS, overall survival; KM, Kaplan-Meier

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Modelled hazard plots from standard parametric survival models (generated by EAG)

Bevacizumab plus FOLFOX/CAPOX

FOLFOX/CAPOX, alone

Abbreviations: OS, overall survival; exp, exponential; gengamma, generalised gamma; llogis, log-logistic; lnorm, log-normal

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AIC and BIC statistics

Bevacizumab plus FOLFIRI and FOLFIRI alone

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**

*Models that are the best fitting or within 5 points of the best-fitting are highlighted in bold

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; OS, overall survival

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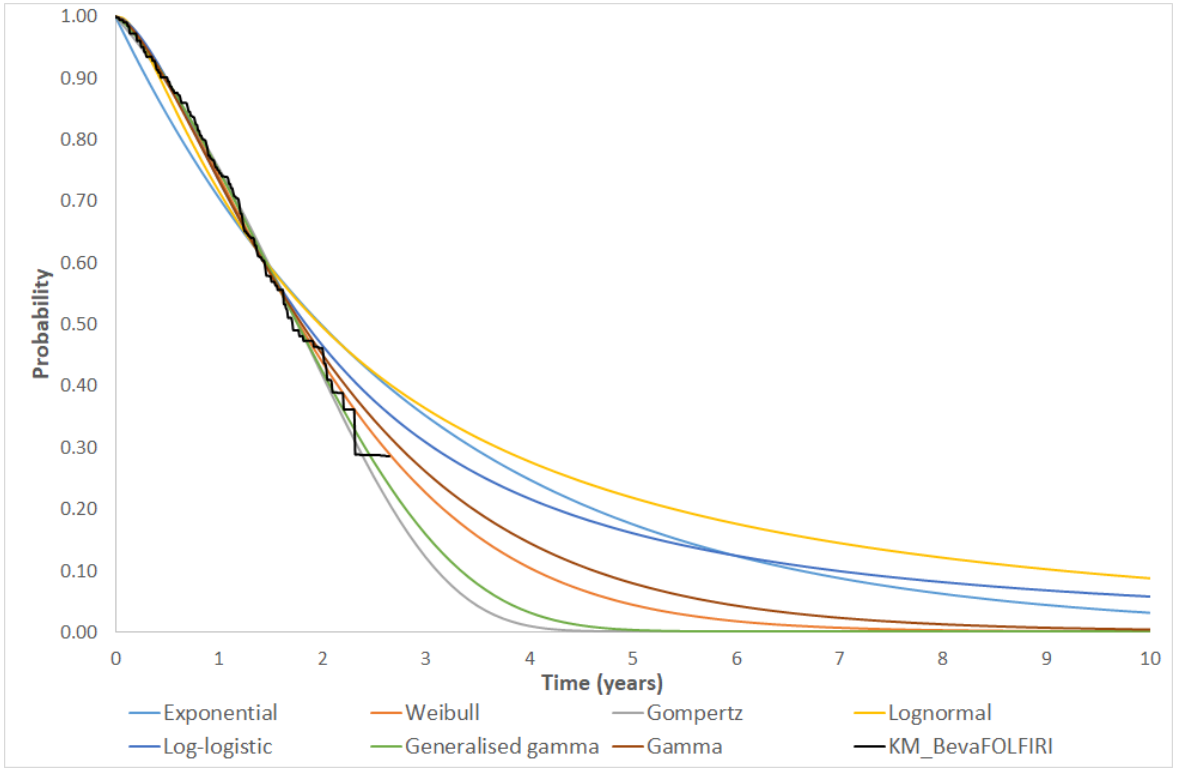
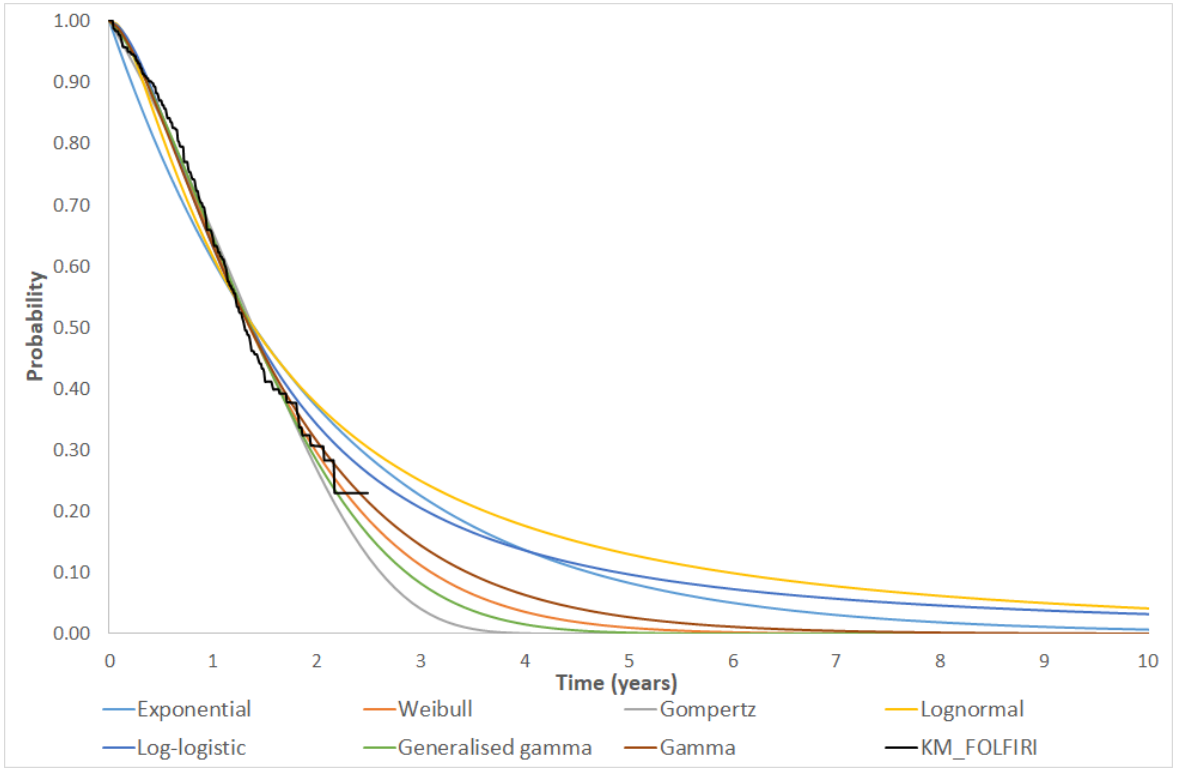
Observed and model-predicted

Bevacizumab plus FOLFIRI



FOLFIRI, alone



EAG base case: Weibull; Scenario: generalised gamma

Abbreviations: OS, overall survival; KM, Kaplan-Meier

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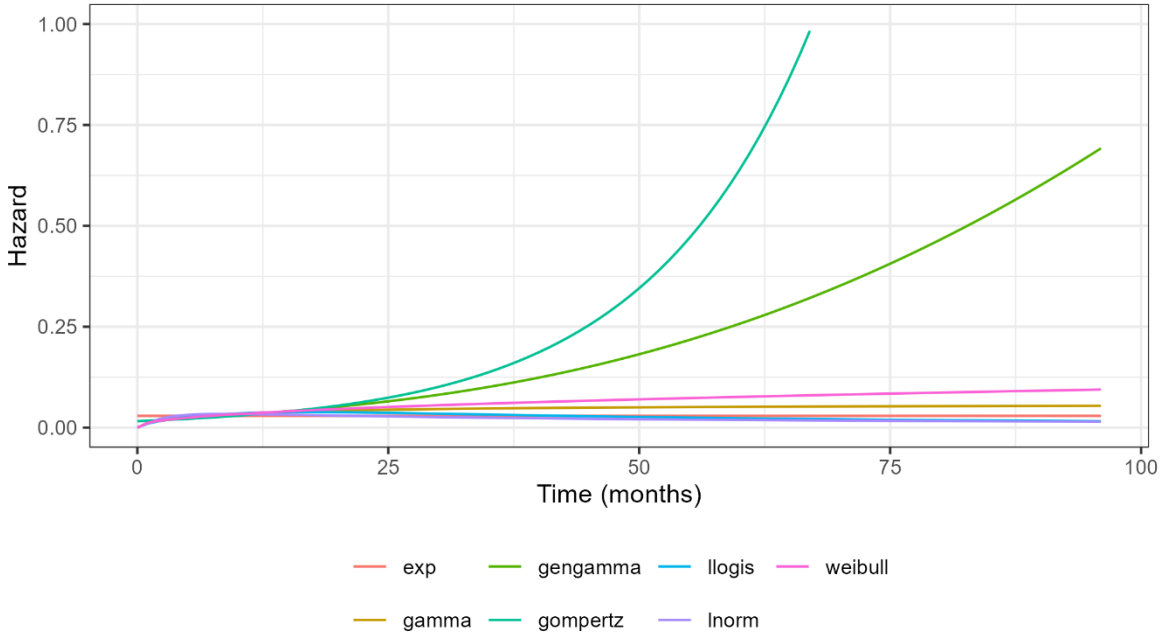
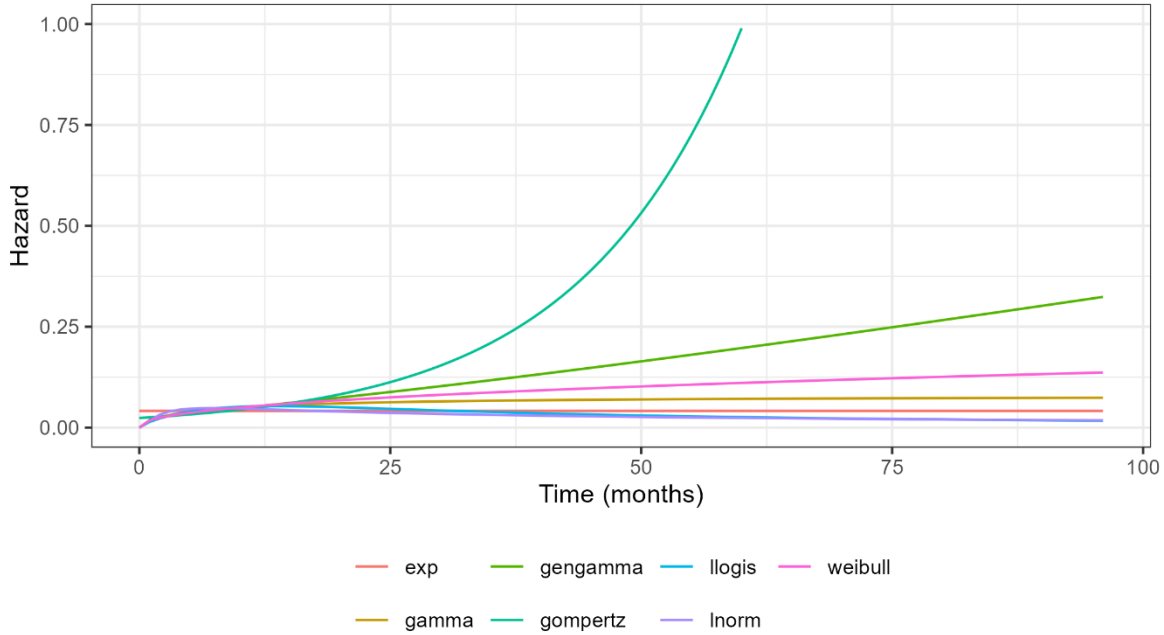
Modelled hazard plots from standard parametric survival models (generated by EAG)

Bevacizumab plus FOLFIRI



FOLFIRI alone, alone



Abbreviations: OS, overall survival; exp, exponential; gengamma, generalised gamma; llogis, log-logistic; lnorm, log-normal

Second-line data informing choice of distribution

	PFS AIC/BIC best statistical fit*	PFS modelled hazard	Visual fit	PFS preferred	OS AIC/BIC	OS underlying hazards	OS visual fit	OS preferred
B-FOLFOX/ CAPOX	Weibull Gamma g.gamma	See slide	See slide	Gamma (log-logistic in sensitivity analysis) Consistent with 1st line approach	Gamma (other models also give good fit)	See slide	See slide	Gamma (consistent with PFS) also used log-logistic in scenario
FOLFOX/ CAPOX	Log-logistic	See slide	See slide		Log normal (other models also give good fit)	See slide	See slide	

*These models have within 5 points of the best-fitting

Abbreviations: PFS, progression-free survival; OS, overall survival; AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion

AIC and BIC statistics, PFS

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Bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone

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

*Models that are the best fitting or within 5 points of the best-fitting are highlighted in bold

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; PFS, progression- free survival

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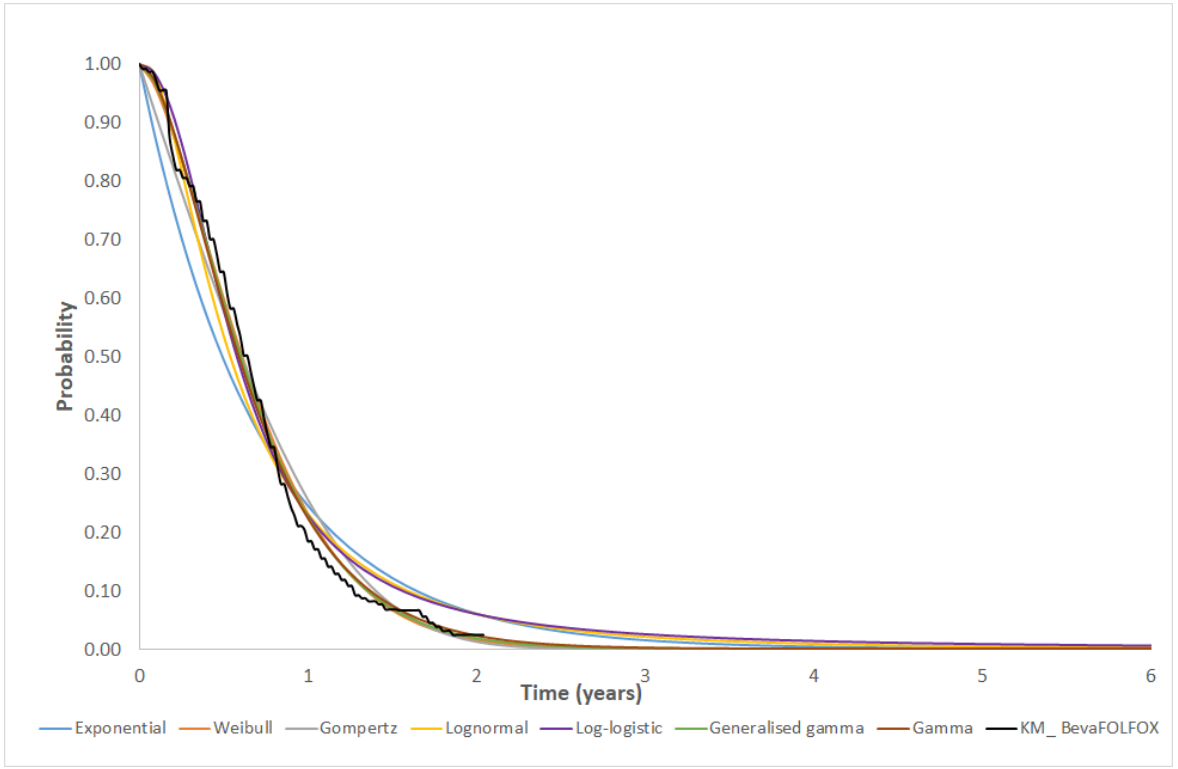
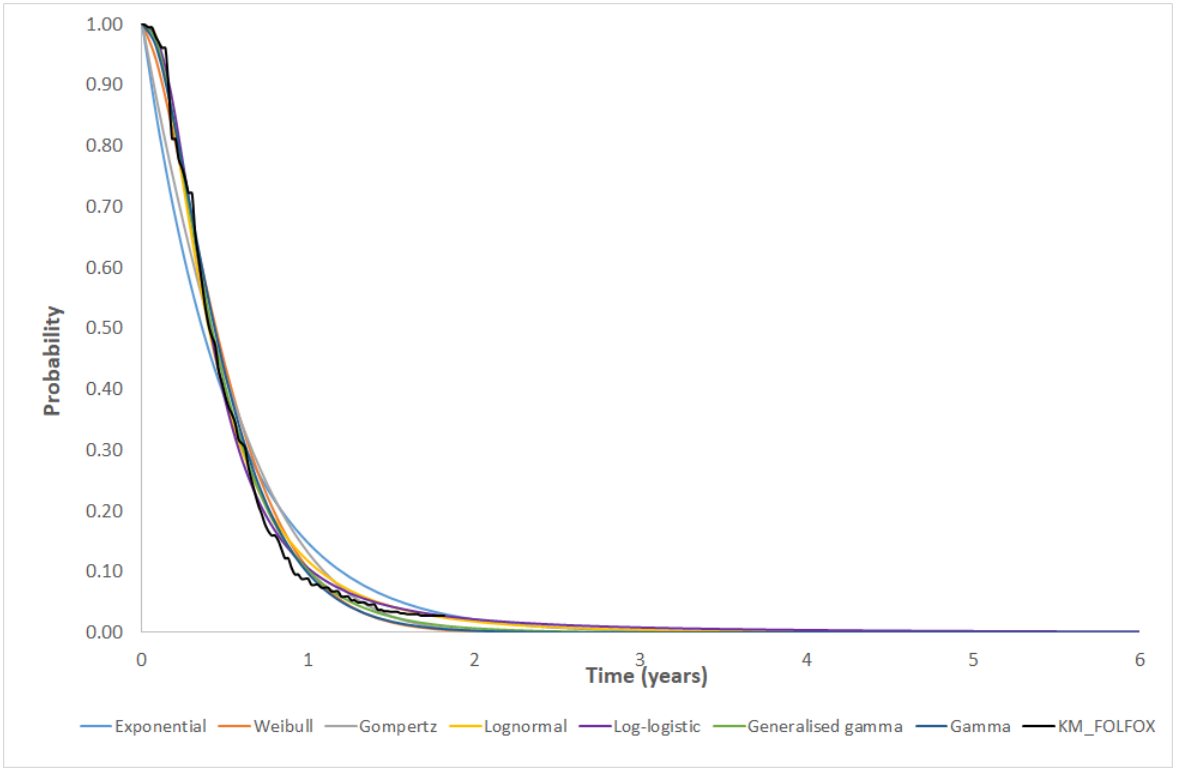
Observed and model-predicted

Bevacizumab plus FOLFOX/CAPOX



FOLFOX/CAPOX, alone



EAG base case: gamma; Scenario: log-logistic

Abbreviations: PFS, progression-free survival

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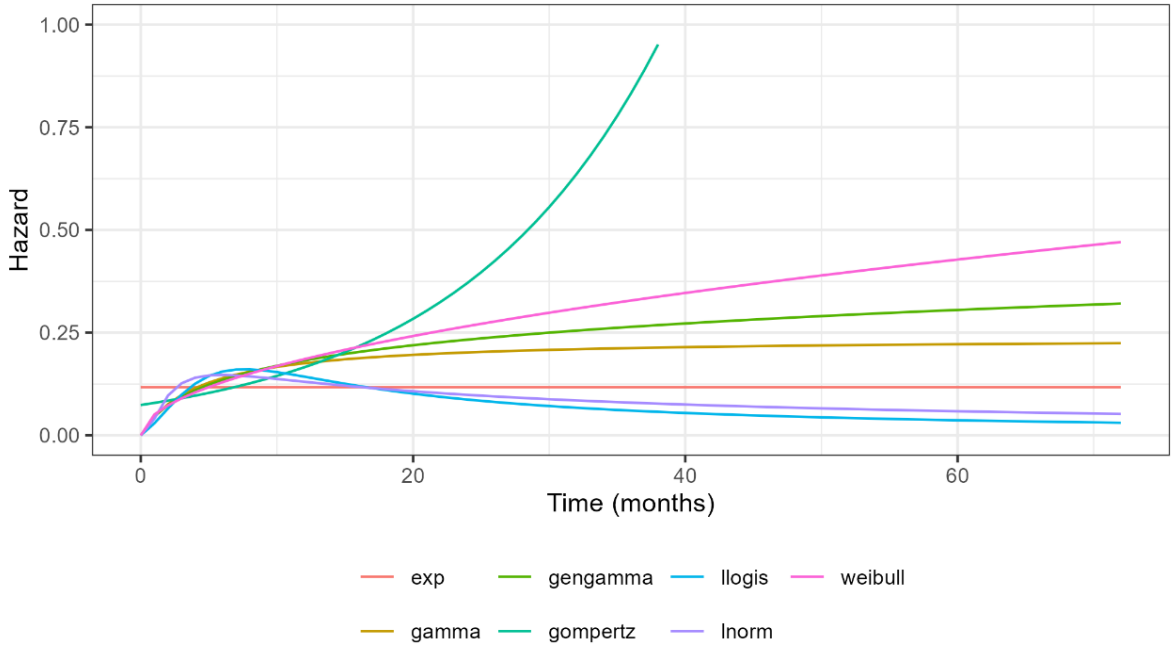
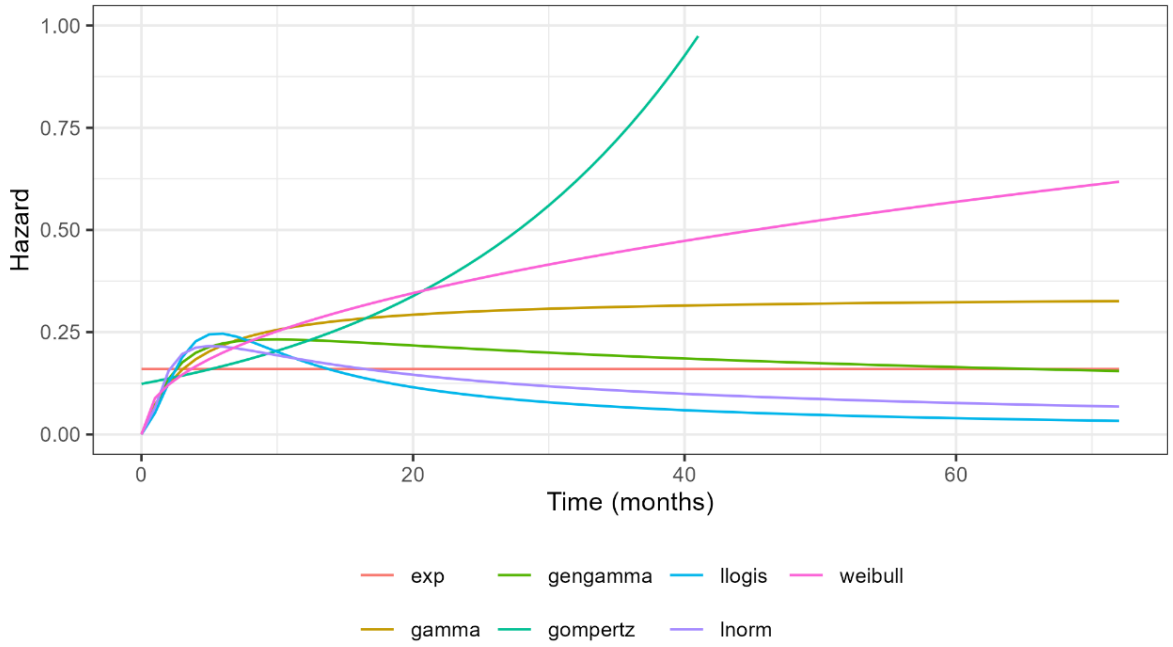
Modelled hazard plots from standard parametric survival models (generated by EAG)

Bevacizumab plus FOLFOX/CAPOX



FOLFOX/CAPOX, alone



Abbreviations: PFS, progression-free survival; exp, exponential; gengamma, generalised gamma; llogis, log-logistic; lnorm, log-normal

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AIC and BIC statistics, OS

bevacizumab plus FOLFOX/CAPOX and FOLFOX/CAPOX alone

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**

*Models that are the best fitting or within 5 points of the best-fitting are highlighted in bold

Abbreviations: AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; OS, overall survival

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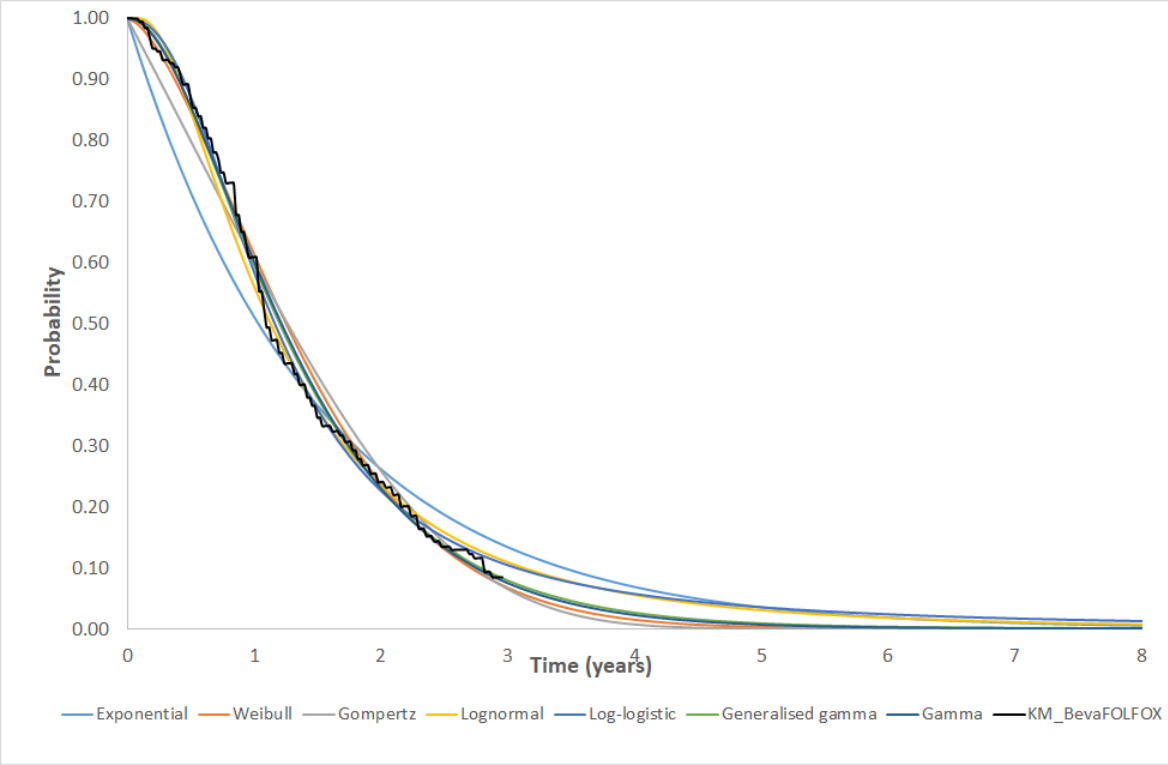
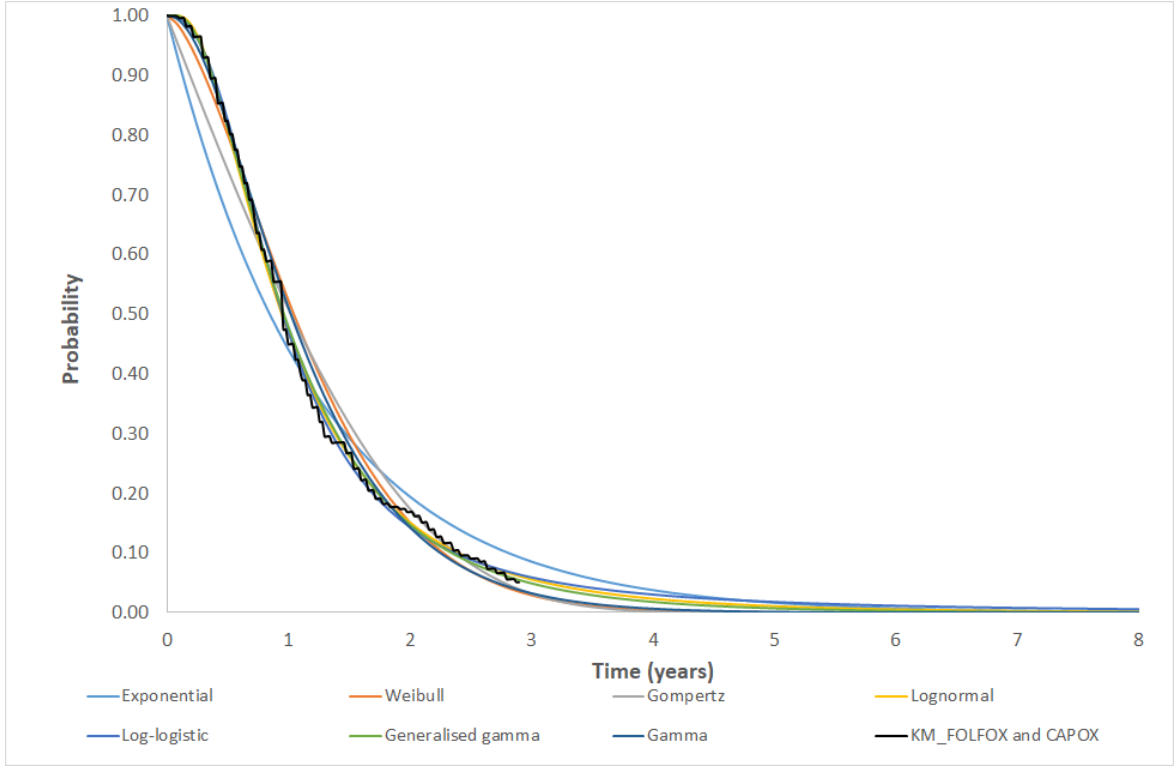
Observed and model-predicted

bevacizumab plus FOLFOX/CAPOX



FOLFOX/CAPOX, alone



EAG base case: gamma (assumed to = FOLFOX); Scenario: log-logistic

NICE

Abbreviations: OS, overall survival; KM, Kaplan-Meier

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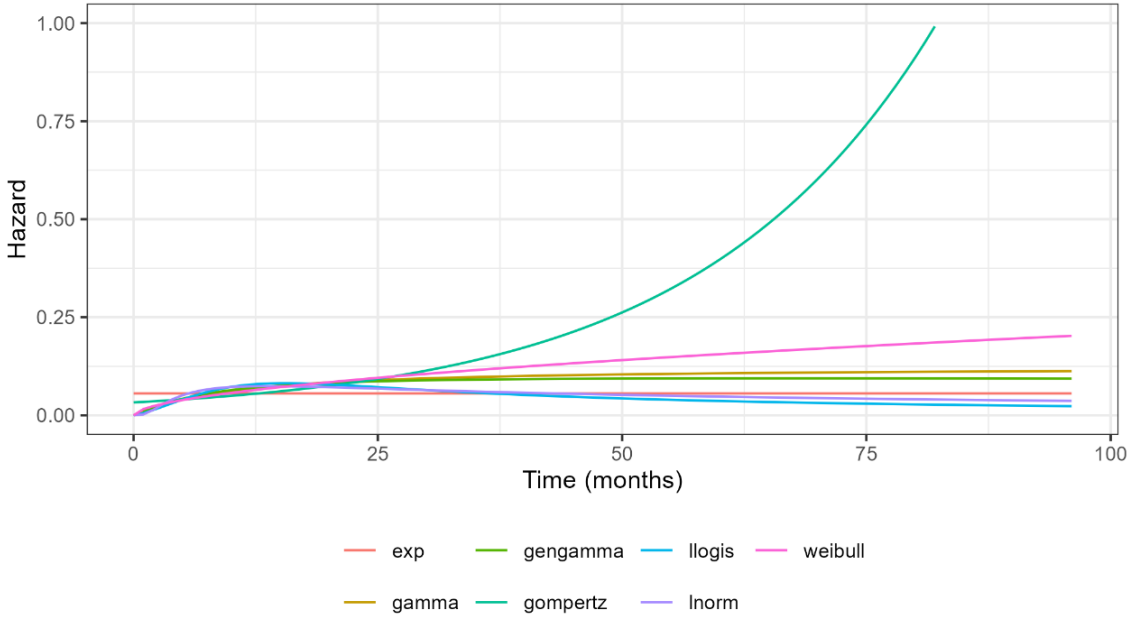
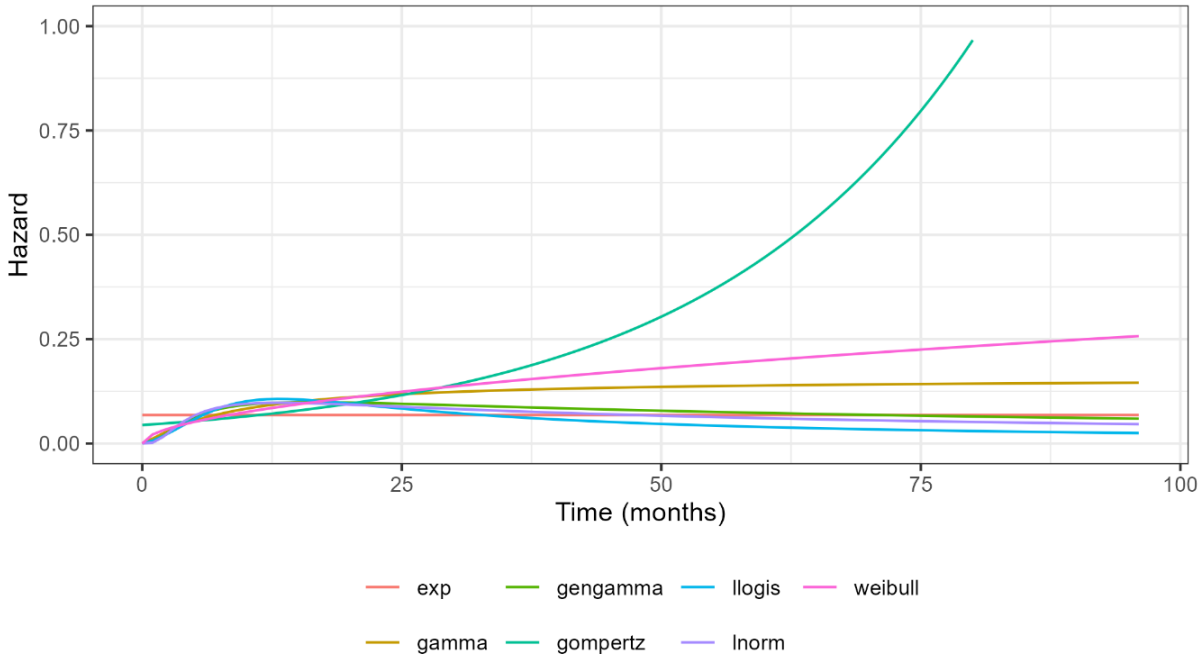
Modelled hazard plots from standard parametric survival models (generated by EAG)

Bevacizumab plus FOLFOX/CAPOX



FOLFOX/CAPOX, alone



Abbreviations: OS, overall survival; exp, exponential; gengamma, generalised gamma; llogis, log-logistic; lnorm, log-normal

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EAG modelling assumptions: utility

Additional EAG analyses to apply disutility values for adverse events

- Applied disutility values for AEs (summed to a one-off QALY loss in 1st cycle):
  - Frequency for adverse effects with b/FOLFOX/CAPOX, FOLFOX/CAPOX from NO16966; for b/FOLFIRI, FOLFIRI from AVF2107g; 2nd line from E3200
  - Duration: 14 days based on clinical opinion
  - Disutility from published studies (populations treated with 5 FU, NSCLC, acute lymphoblastic leukaemia [TA1049])

	Treatment					
	B- FOLFOX	FOLFOX	B- FOLFIRI	FOLFIRI	B- CAPOX	CAPOX
Expected QALY loss (one-off) 1st line	0.0029	0.0028	0.0026	0.0019	0.0028	0.0024
Expected QALY loss (one-off) 2nd line	0.0015	0.0007			Assumed equivalent to FOLFOX model	

Abbreviations: AE, adverse event; TA, technical appraisal; 5 FU, 5 fluorouracil; NSCLC, non-small cell lung cancer

Modelling assumptions: drug administration and monitoring (1/3)

	B-FOLFOX vs FOLFOX	B-FOLFIRI vs. FOLFIRI	B-CAPOX vs CAPOX
Dosing schedule bevacizumab	5mg/kg every 2 weeks	5mg/kg every 2 weeks	7.5mg/kg every 3 weeks
Dosing schedule comparator based on NO16966 (FOLFOX/CAPOX) and AVF2107g (FOLFIRI)	2-week cycle • IV Oxaliplatin 85mg/m2 on day 1 • Folinic acid 200mg/m2/day followed by • bolus 5FU 400mg/m2/day and a 22-hour infusion of 5-FU 600 mg/m2/day for 2 consecutive days.	6-week cycle (4 weeks treatment, 2 weeks rest) • IV irinotecan 125mg/m2 • Bolus 5-FU 500mg/m2 • Bolus folinic acid 20mg/m2	3-week cycle • IV Oxaliplatin 130mg/m2 on day 1 • Oral capecitabine 1000mg/m2 twice daily on days 1-14
Source of time to treatment discontinuation	1st line TTD KM from NO16966	Not available used mean dose of each component of regimen from AVF2107g	1st line TTD KM from NO16966
Relative dosing intensity applied?	Yes, from NO16966		Yes, from NO16966

Modelling assumptions: drug administration and monitoring (2/3)

	B-FOLFOX vs FOLFOX	B-CAPOX vs CAPOX
Dosing schedule bevacizumab	10mg/kg every 2 weeks	15mg/kg every 3 weeks
Dosing schedules for bevacizumab and FOLFOX based on Study E3200 CAPOX schedule followed Study NO16966 as CAPOX regimen not evaluated Study E3200	2-week cycle • IV Oxaliplatin 85mg/m2 over 2 hours • Folinic acid 400mg/m2/ over 2 hours • 46-hour infusion of 5-FU 1200mg/m2, • Bolus injection 5FU 400mg/m2	3-week cycle • IV Oxaliplatin 130mg/m2 • Oral capecitabine 1000mg/m2
Source of time to treatment discontinuation	Study E3200	Study E3200
Relative dosing intensity applied?	Yes, from Study E3200	Yes, from Study E3200

Drug administration and monitoring costs (3/3) (sensitivity analyses)

- Unit costs associated with drug and admin costs from published literature and NHS reference costs 2023/24
- Admin resource costs were based on dosing schedules from trial
- Differences in regimens used in NHS compared with trials explored in sensitivity analyses (which explored different costs but same efficacy) including:
    - Modified de Gramont regimen for 5-FU containing regimen (model 2 only)
    - Early cessation of oxaliplatin (at 6 months) due to toxicity concerns (minimal ICER impact for B FOLFOX/CAPOX), moderate ICER impact for B-FOLFIRI)
    - EAG considers results from these analyses may be more representative of current English practice

Have the appropriate drug administration costs been included/ assessed in sensitivity analyses?

Abbreviations: 5-FU, fluorouracil

QALY weightings for severity (1/2)

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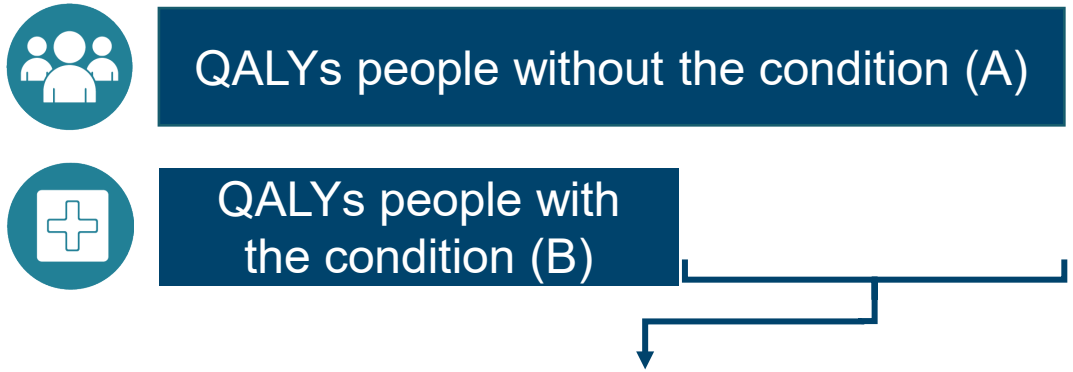
Severity modifier calculations and components:



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A
- *Note: The QALY weightings for severity are applied based on **whichever of absolute or proportional shortfall implies the greater severity**. If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply

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

Abbreviations: QALY, quality-adjusted life year