Trifluridine-tipiracil with bevacizumab for treating metastatic colorectal cancer [ID6298]

Confidential information redacted

Technology appraisal committee B [11 July 2024]

Chair: Charles Crawley

Lead team: Andrew Makin, Rhiannon Owen, Tony Wootton

External assessment group: Aberdeen HTA group

Technical team: Emma McCarthy, Michael Bell, Adam Brooke, Emily Crowe

Company: Servier Laboratories Ltd

Trifluridine-tipiracil (Lonsurf, Servier Laboratories) with bevacizumab

Marketing authorisation	"Lonsurf is indicated in combination with bevacizumab for the treatment of adult patients with metastatic colorectal cancer (CRC) who have received two prior anti-cancer regimens including fluoropyrimidine-, oxaliplatin- and irinotecan-based chemotherapies, anti-VEGF agents, and/or anti-EGFR agents"
Mechanism of action	• Trifluridine is incorporated into DNA of tumour cells and inhibits tumour proliferation. • Tipiracil hydrochloride prolongs the action of trifluridine. • Bevacizumab binds to VEGF-A to prevent interaction with VEGF receptors, preventing formation of tumour blood vessels.
Administration	• Trifluridine-tipiracil – oral tablets, twice daily (days 1 to 5 and 8 to 12 of each 28-day cycle) • Bevacizumab – intravenous infusion, once every 2 weeks
Price	• Confidential patient access scheme price available for trifluridine-tipiracil • Multiple confidential commercial medicines unit prices available for bevacizumab (biosimilars available)

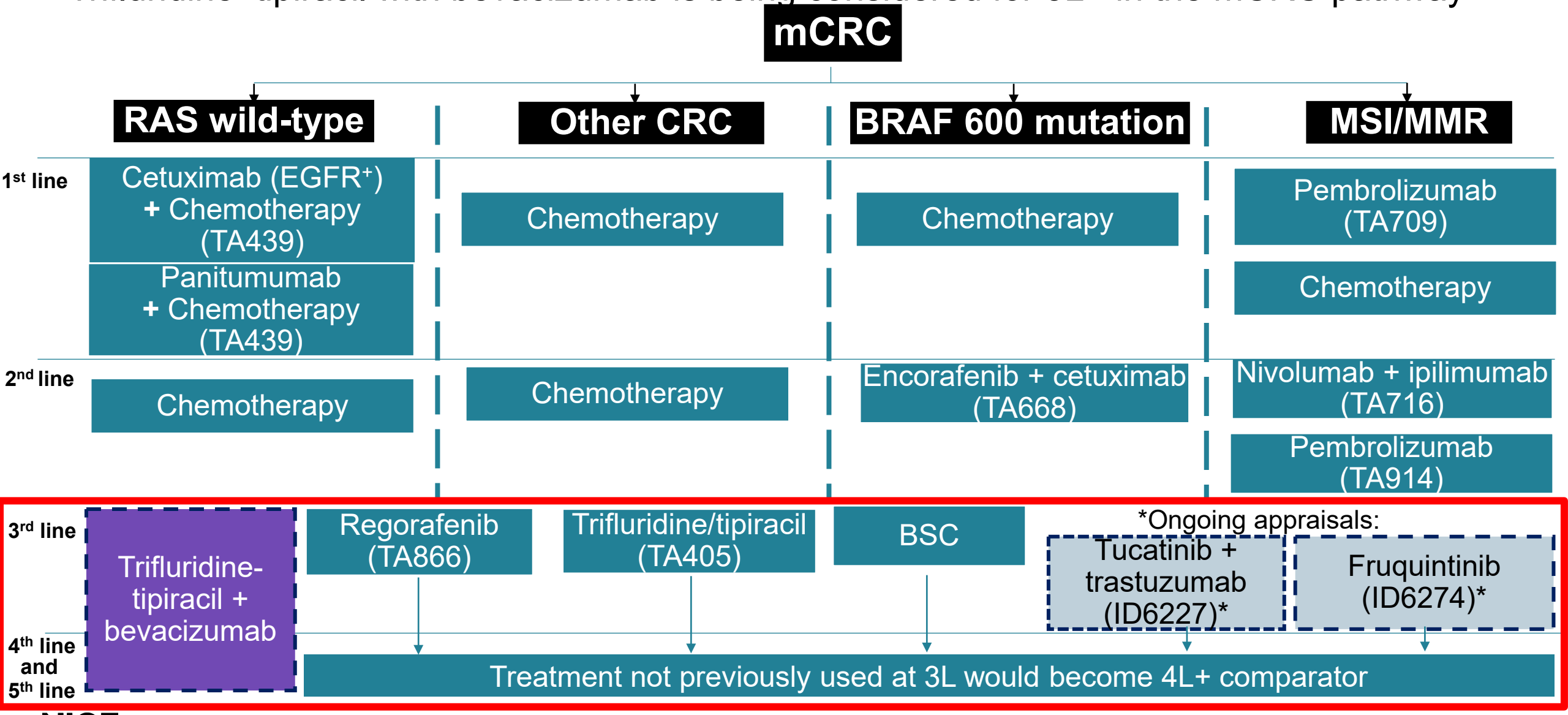
Abbreviations: VEGF, Vascular endothelial growth factor; EGFR; epidermal growth factor,

Treatment pathway

RECAP

Chemotherapy: FOLFOX, FOLFIRI, CAPOX, FOLFOXIRI (or 5-FU, oxaliplatin/irinotecan)

Trifluridine–tipiracil with bevacizumab is being considered for 3L+ in the mCRC pathway

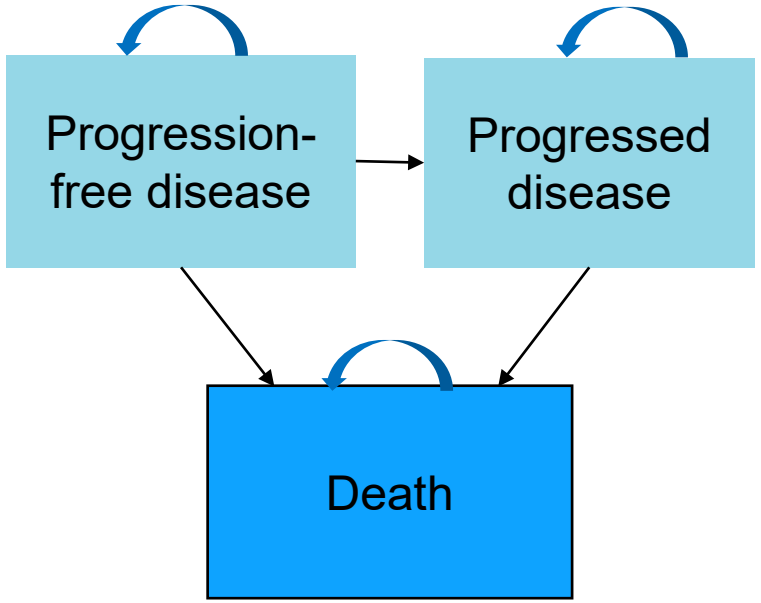


MSI, microsatellite instability; MMR, mismatch repair; 5 FU, 5-fluorouracil; FA- folinic acid; FOLFOX, folinic acid, fluorouracil and oxaliplatin; FOLFIRI, folinic acid, fluorouracil and irinotecan; CAPOX, capecitabine and oxaliplatin; BSC, best supportive care; EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer

Model overview

Cohort partitioned survival model - EAG says model structure is appropriate

Model structure:



Trifluridine-tipiracil with bevacizumab affects **QALYs** by:

- Increasing time in OS and PFS states → better survival and QoL
- Improved QoL in progression-free disease
- Improved QoL vs comparators (in progression-free and progressed states)

Trifluridine-tipiracil with bevacizumab affects **costs** by:

- Increased acquisition costs (2 treatments instead of 1)
- Additional administration costs for IV bevacizumab
- Increased treatment acquisition and administration costs due to longer time on treatment – mainly since patients spend longer progression-free)

Assumptions with greatest ICER effect:

- Modelling of long-term overall survival for trifluridine-tipiracil + bevacizumab and trifluridine-tipiracil monotherapy
- Source of data for OS, PFS and ToT for regorafenib

- OS, PFS and ToT for trifluridine-tipiracil with bevacizumab and trifluridine-tipiracil monotherapy estimated from SUNLIGHT - regorafenib and BSC health effects obtained from random-effects NMA

Abbreviations: BSC, best supportive care; ICER, incremental cost-effectiveness ratio OS, overall survival; PFS, progression free survival; QoL, quality of life; ToT, time on treatment; NMA, network meta-analysis

Draft guidance (DG) consultation

Preliminary recommendation:
"Trifluridine–tipiracil with bevacizumab is not 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)."

Consultation responses received from:

- Servier (company)
- Clinical expert
- Patient expert
- Web comment (n=1)

Consultation responses to draft guidance summary

Company (Servier):

- Provided a response to areas of uncertainty and additional analyses requested by committee (further detail in key issue slides) and updated base case
- Additional RWE from literature sources, audit data and SACT (n=6,170)

Clinical and patient expert comments

- Highlighted potential issue with administration cost of bevacizumab (IV treatment) vs existing oral treatments
- Trifluridine-tipiracil with bevacizumab well tolerated and widely used in other countries
- No quantifiable data available on patient tolerance of treatments
- Highlighted potential issue with genetic response differences between ethnic groups
- Uncertainties around age distribution of patients could underestimate increased benefit to younger patients

Web comment from patient

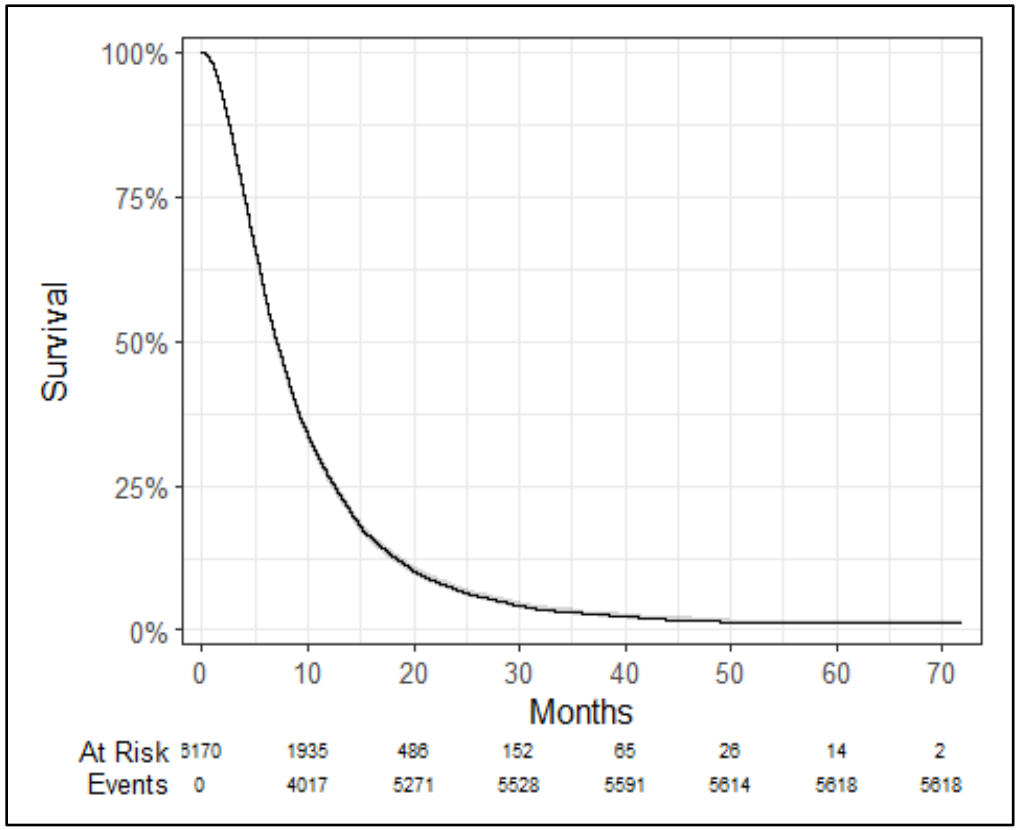
- Previous systemic treatments for stage 4 cancer have had significant side effects – trifluridine-tipiracil plus bevacizumab provides another option for controlling disease

SACT; Systemic Anti-Cancer Therapy

Additional RWE – SACT data analysis pilot

- RWE of people having trifluridine-tipiracil monotherapy in UK practice provided from Systemic Anti-Cancer Therapy (SACT) data (n=6,170)
  - Aims to address uncertainty in OS modelling and severity modifier calculations
- Pilot project – analysis from NICE Data and Analytics (collaborating with the National Disease Registration Service (NDRS)) includes:
  - KM curve of people receiving treatment with trifluridine-tipiracil monotherapy
  - Mean and median age of people starting treatment with trifluridine-tipiracil

KM curve for people having trifluridine-tipiracil:



Age at start of regimen	Mean: 65 (SD 11) Median: 66 (IQR 57-73)

KM; Kaplan-Meier, SD; standard deviation; IQR, interquartile range

Recap: ACM1 conclusions (1)

Trifluridine–tipiracil plus bevacizumab is not recommended

Issue	Committee conclusions ACM1	Resolved?
OS extrapolation of trifluridine-tipiracil plus bevacizumab and trifluridine-tipiracil monotherapy	Uncertainty in overall survival modelling – additional analyses requested	No – for discussion
Severity modifier	Uncertainty in QALY shortfall calculations, further analysis required	No, for discussion
Regorafenib time on treatment	Company's approach where time on treatment = PFS may be an overestimate – further sensitivity analysis required	No – for discussion
Regorafenib RDI	Committee preferred analysis more closely matching regorafenib use in clinical practice (i.e. likely dose reductions in line with CORRECT)	Partially – for discussion

OS, overall survival; QALY, quality-adjusted life year; PFS, progression-free survival; RDI, relative dose intensity; HR, hazard ratio; NMA, network meta-analysis

Recap: ACM1 conclusions (2)

Trifluridine–tipiracil plus bevacizumab is not recommended

Issue	Committee conclusions ACM1	Resolved?
Treatment waning	Sensitivity analyses needed in which the treatment effect on survival with the intervention and comparators wanes over time	No, for discussion
Utility values	Pooled utility values for each health state across all treatments	Partially – for discussion
Costs of subsequent treatment	Data from NHSE on the proportion of people having subsequent treatment is appropriate for decision making.	Partially
Comparators	Trifluridine-tipiracil monotherapy and regorafenib are the key comparators	Yes
Previous bevacizumab use	SUNLIGHT ITT population generalisable to NHS	Yes

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ITT, intention to treat

Key issues for discussion at ACM2

Issue	ICER impact
Overall survival extrapolation (trifluridine-tipiracil with bevacizumab and trifluridine-tipiracil monotherapy)	Large
Treatment waning	Large
Utility values	Moderate
Severity modifier	Large
Regorafenib time on treatment (regorafenib arm)	Moderate
RDI regorafenib (regorafenib arm)	Small
Ongoing administration cost of bevacizumab*	Large

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RDI, relative dose intensity

*Not discussed at ACM1 – raised at consultation

Key issue: Overall survival extrapolation (trifluridine-tipiracil with bevacizumab and trifluridine-tipiracil monotherapy)

Background: ACM1 – Committee requested RWE on OS for trifluridine–tipiracil monotherapy in UK practice, and modelling of trifluridine–tipiracil plus bevacizumab OS by applying the SUNLIGHT OS HR to this data.

Company response to consultation

- Revised base case applied NMA OS HR to SUNLIGHT tri-tip curve (with scenarios using RWE from literature, NHS audit data, SACT data and ongoing study (PROMETCO)
- In all additional analyses using RWE, projected survival of trifluridine-tipiracil plus bevacizumab similar to SUNLIGHT OS – log logistic extrapolation still preferred

EAG critique

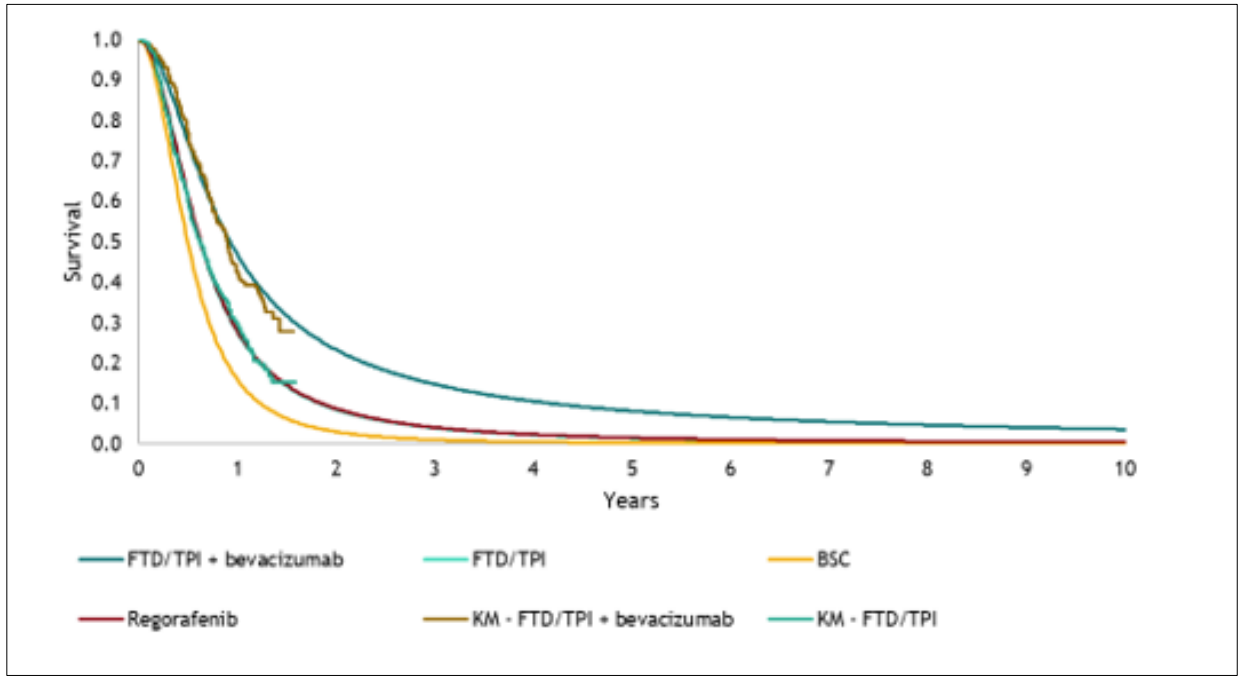
- KM curves from SUNLIGHT and SACT are similar – trifluridine-tipiracil monotherapy arm from SUNLIGHT aligned with UK clinical practice outcomes
- Revised base case applied SUNLIGHT OS HR to SACT tri-tip curve
  - Generalised gamma extrapolation still preferred - closer replication of KM curve at 2 years, more plausible projection at 5 years

Abbreviations: RWE, real world evidence; HR, hazard ratio; OS, overall survival; SACT, Systemic Anti-Cancer Therapy; PFS, progression free survival; NMA, network meta-analysis; KM, Kaplan-Meier

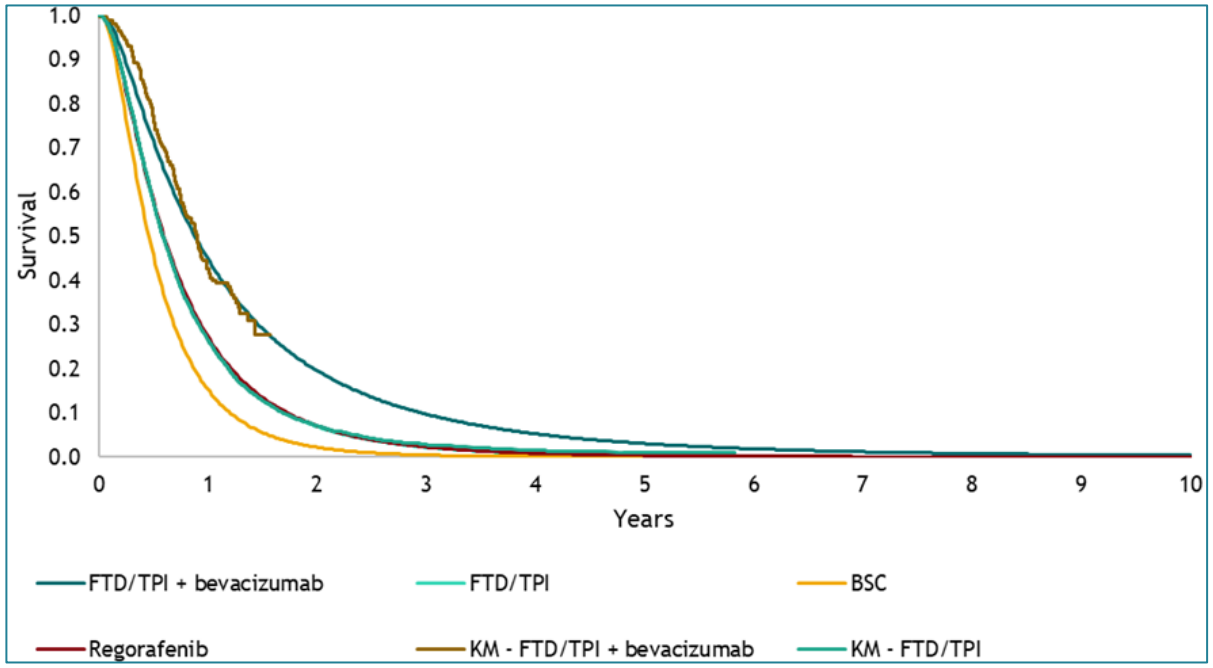
Key issue: Appropriate overall survival extrapolation

Updated OS extrapolations - trifluridine-tipiracil monotherapy as reference curve

Company base case OS curve



EAG base case OS curve



Company – Log-logistic hazard profile aligns with SUNLIGHT OS data
Generalised gamma hazards cross over after 18 months – not plausible

EAG – Log-logistic better fit at 5 years, but censoring beyond 4 years means potential underestimation of OS at 5 years in KM curve – generalised gamma more plausible

Abbreviations: FTD/TPI, trifluridine-tipiracil; OS, overall survival; KM, Kaplan-Meier

See appendix for EAG scenario with OS modelling direct from KM curve

Key issue: Appropriate overall survival extrapolation

Updated OS extrapolations - trifluridine-tipiracil monotherapy as reference curve

	Company (log logistic)		EAG (generalised gamma)	
	Tri-tip plus bevacizumab	Tri-tip monotherapy	Tri-tip plus bevacizumab	Tri-tip monotherapy
Source	HR – NMA (0.59)	SUNLIGHT	HR – SUNLIGHT (0.61)	SACT
1 year	46.9%	27.7%	44.9%	26.9%
2 years	23.1%	8.4%	19.4%	6.8%
3 years	14.6%	3.8%	9.6%	2.2%
4 years	9.9%	2.2%	5.2%	0.8%
5 years	6.6%	1.4%	3.0%	0.8%
10 years	1.6%	0.3%	0.3%	<0.1%

How should overall survival be modelled?
Which source of data should be used for overall survival?

Abbreviations: HR, hazard ratio; OS, overall survival; SACT, Systemic Anti-Cancer Therapy

Key issue: Appropriate overall survival extrapolation

EAG fitting of curves to SACT data

	AIC	BIC	Proportion alive at (Years)				
			1	2	3	5	10
KM			26.7%	7.1%	2.8%	1.1%	--
Exponential	16,568	16,575	29.7%	8.8%	**2.6%**	0.2%	0.0%
Generalised Gamma	15,587	15,607	26.9%	**6.9%**	2.2%	0.3%	0.0%
Gompertz	16,553	16,566	30.5%	8.7%	2.3%	0.1%	0.0%
Log-Logistic	**15,568**	**15,581**	25.4%	7.8%	3.6%	**1.3%**	0.3%
Log Normal	15,643	15,656	**26.6%**	7.9%	3.2%	0.8%	0.1%
Weibull	16,140	16,153	30.4%	6.0%	0.9%	0.0%	0.0%

EAG

- Small differences in curve at tail end have large effects on ICER
- GG has good statistical fit + acceptable AIC/BIC
- Log-logistic fitted to SACT extends OS benefit indefinitely for trifluridine-tipiracil + bevacizumab – not enough follow up to support this
- Log-logistic has proportion of people alive at 10 years – implausible, curve trending towards 0 preferred

How should overall survival be modelled?
What source of data should be used for overall survival?

Abbreviations: GG, generalised gamma, OS, overall survival; Systemic Anti-Cancer Therapy

See appendix for zoomed in curves at tail end

Key issue: Treatment waning

Background: ACM1 – Committee requested sensitivity analyses in which the treatment effect on survival with the intervention and comparators wanes over time.

Company response to consultation

- Revised base case with treatment waning applied between years 3-5
- No evidence from SUNLIGHT to suggest waning effect (KM curves show effect across entire observed period), and no waning assumption in previous mCRC appraisals
- Survival projection for trifluridine-tipiracil plus bevacizumab with treatment waning slightly optimistic over time horizon

EAG critique

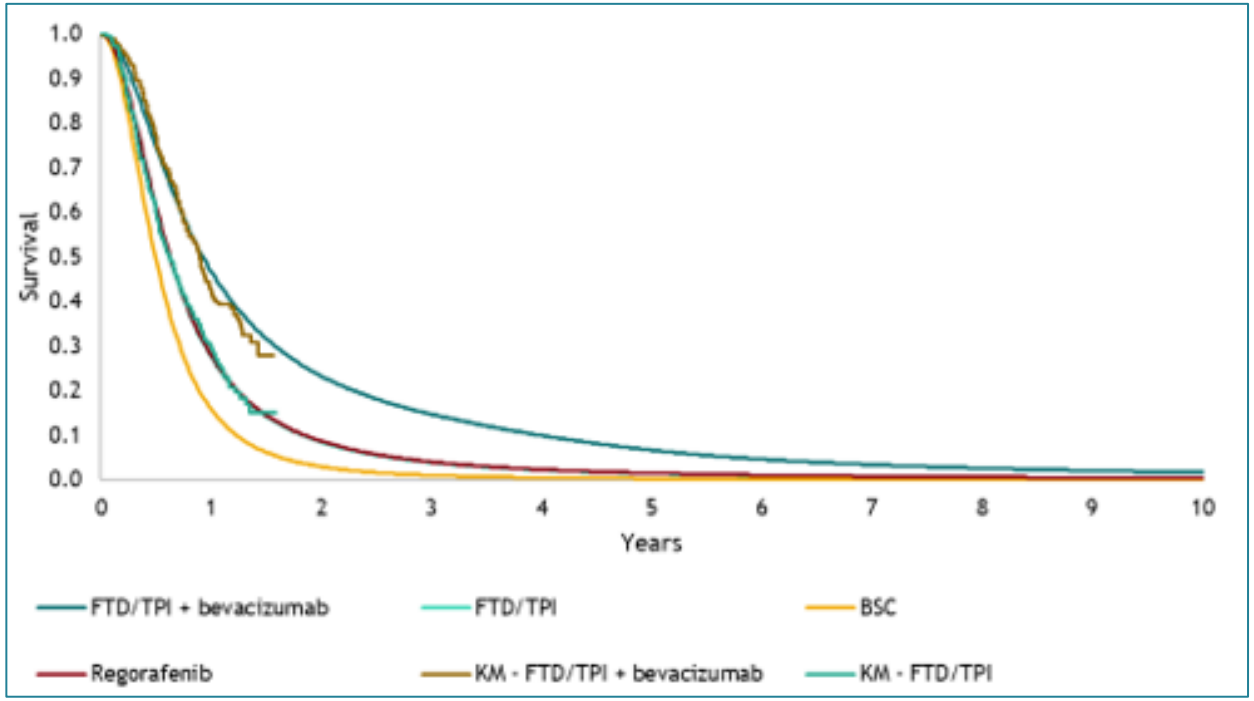
- Company's model assumes an increase in OS benefit for trifluridine-tipiracil plus bevacizumab beyond trial follow up - insufficient evidence for this, treatment waning at years 3-5 does not sufficiently account for this
- Treatment waning explored at 1-2 years in scenario – aligned with PFS curve
- Waning effect likely appropriate for log-logistic extrapolation but **not** generalised gamma

Should a treatment waning effect be applied? At what point should it be applied?

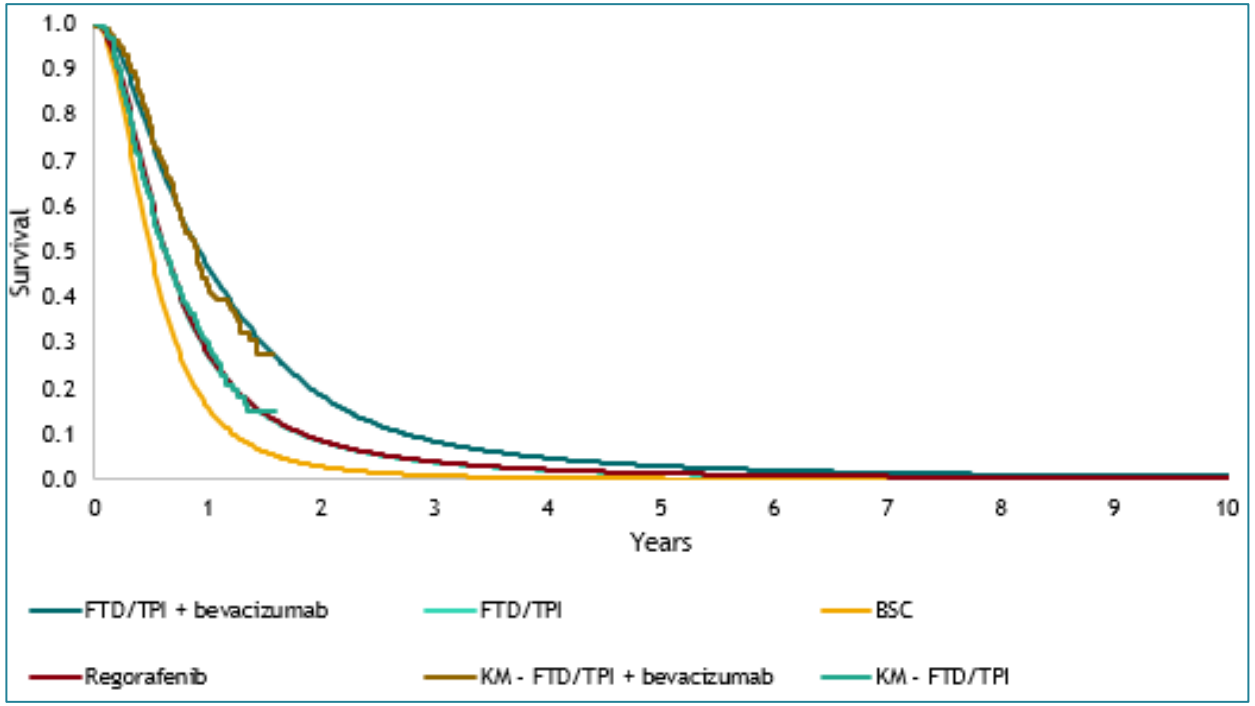
Abbreviations: HR, hazard ratio; OS, overall survival; PFS, progression free survival;.

Key issue: Treatment waning

Company - HRs applied to trifluridine-tipiracil (SUNLIGHT) – treatment waning 3-5 years:



EAG scenario - HRs applied to trifluridine-tipiracil (SUNLIGHT) – treatment waning 1-2 years (log logistic):



EAG – Treatment waning effect only necessary if log-logistic assumption applied – offsets indefinite benefit derived when using log-logistic extrapolation without treatment waning.

Should a treatment waning effect be applied? At what point should it be applied?

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Abbreviations: FTD/TPI, trifluridine-tipiracil; OS, overall survival

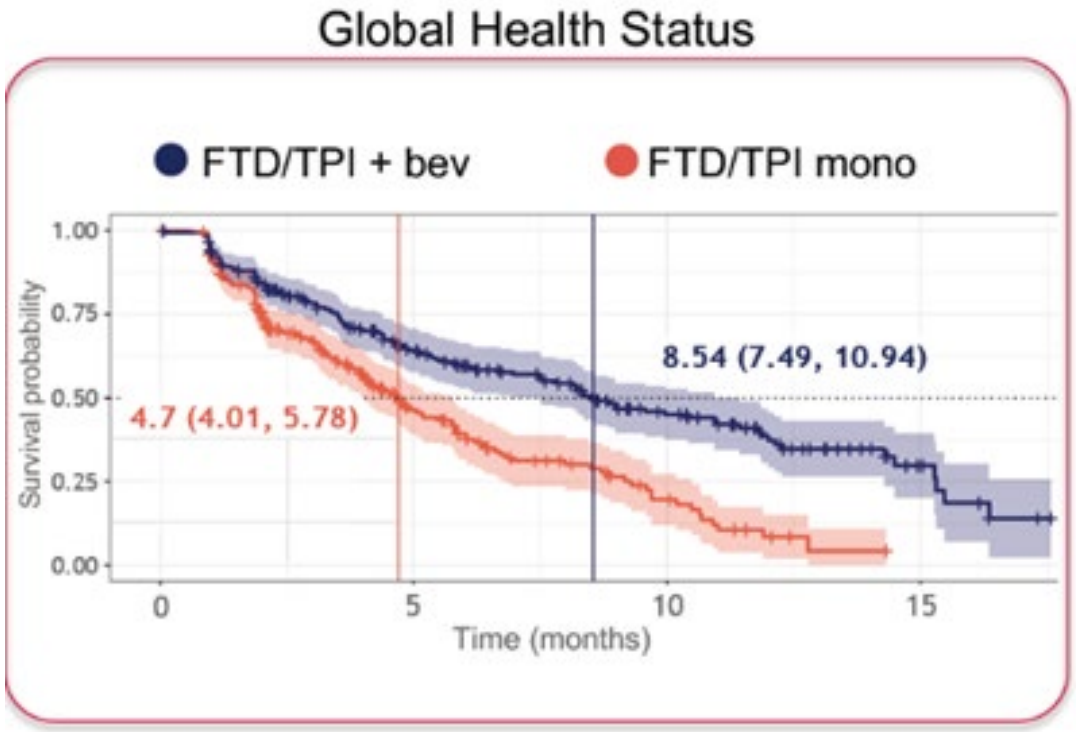
Key issue: Utility values – new company approach

ACM1 discussion

- Committee preferred pooled utility values – evidence for treatment specific utilities not convincing

Company response to consultation

- New approach – company has applied a utility increment (to the PD utility value) in the trifluridine-tipiracil plus bevacizumab arm for patients leaving the PFS health state for 3 months (i.e. utility waning)
  - Based on utility increment from the regression model in SUNLIGHT (0.043)
- 3 months corresponds to the difference between median PFS and median time to deterioration in QoL (EORTC-QLQ-C30 Global Health status)



Abbreviations: QoL, quality of life; PD, progressed disease; PFS, progression-free survival; QoL, quality of life; FTD/TPI, trifluridine-tipiracil

Key issue: Utility values – new company approach

EAG critique

- EAG considers the quality of life benefit is already captured in the model through the additional utility gains from extended PFS
- The longer time period until deterioration in QoL than for PFS in the trifluridine-tipiracil plus bevacizumab arm is also seen in trifluridine-tipiracil monotherapy arm of SUNLIGHT
  - Difference between arms is similar for QLQ-C30 and for PFS.
- The regression analyses (in response to clarification) provide no strong evidence in support of treatment specific HSUVs in progression-free or progressed disease health states
- EAG therefore retains its original position that treatment pooled HSUVs are the most appropriate approach for modelling quality of life benefit.

Is the company's treatment specific utility approach appropriate?

Abbreviations: QoL, quality of life; PFS, progression-free survival; HSUVs, health state utility values

Key issue: Source of utility values

Committee conclusion at ACM1 – pooled utility values preferred

Health state	SUNLIGHT treatment pooled	SUNLIGHT treatment independent (tri-tip + bev)	SUNLIGHT treatment independent (tri-tip)	TA866 (regorafenib appraisal)	TA405 (tri-tip appraisal)*
PFS	0.76	0.779	0.737	0.72	0.73
PPS	0.68	0.702	0.659	0.59	0.64

* Pooled CORRECT and 1L cetuximab for mCRC utility values

EAG

- Company and EAG preferred HSUVs both use data from SUNLIGHT
- Uncertainty around utilities should be considered – source of utility values important for severity modifier calculations

What is the appropriate source of utility values?

Abbreviations: HSUVs; health state utility values; PFS, progression-free state; PPS, post progression state

Key issue: Severity modifier

ACM1 discussion

- Uncertainty in QALY shortfall calculations due to uncertainty in overall survival modelling and model starting age
- Committee requested updated QALY shortfall calculations for trifluridine-tipiracil monotherapy - based on observational data on the mean age of people having trifluridine–tipiracil monotherapy, and revised OS extrapolations

Company response to consultation

- Updated QALY shortfall calculations for trifluridine–tipiracil alone and regorafenib based on updated OS projections and mean age + sex distributions from SUNLIGHT, NHS audit data, literature and SACT

EAG critique

- Updated QALY shortfall calculations using different OS extrapolation assumptions, SACT vs. SUNLIGHT data and differing utility assumptions
  - Additional analysis with lower utilities from previous TAs for regorafenib (TA866) and trifluridine-tipiracil (TA405)

Abbreviations: QALY, quality adjusted life year; OS, overall survival; SACT, Systemic Anti-Cancer Therapy;

Key issue: severity modifier – company analysis

1.2x weighting for trifluridine-tipiracil monotherapy and regorafenib (all sources)

Source	Characteristics		Trifluridine-tipiracil monotherapy	Regorafenib
SUNLIGHT (company base case)	Mean age = 62 % female: 48%	QALYs:	0.63	0.64
		Absolute:	11.38	11.37
		Proportional:	94.75%	94.67%
		Weighting:	**x1.2**	**x1.2**
Audit data [redacted]	Mean age = [redacted] % female: [redacted]	QALYs:	[redacted]	[redacted]
		Absolute:	[redacted]	[redacted]
		Proportional:	[redacted]	[redacted]
		Weighting:	**x1.2**	**x1.2**
SACT data	Mean age = 65 % female: 48%* (assumed same as SUNLIGHT)	QALYs:	0.61	0.61
		Absolute:	10.34	10.34
		Proportional:	94.43%	94.43%
		Weighting:	**X1.2**	**X1.2**

Is it appropriate to apply a QALY weighting for severity? What QALY weightings are preferred vs each comparator?

See appendix for literature based

Key issue: severity modifier – EAG analysis (1)

1.2x or 1.7x weighting depending on utility source

Source	HSUVs	Characteristics		Trifluridine-tipiracil monotherapy	Regorafenib
SUNLIGHT (GG OS)	Treatment specific (SUNLIGHT)	Mean age = 62 % female: 48%	QALYs:	0.60	0.61
			Absolute:	11.41	11.40
			Proportional:	95.00%	94.92%
			Weighting:	**x1.7**	**x1.2**
SACT data (LL OS)	Treatment pooled (SUNLIGHT)	Mean age = 65 % female: 48%* (assumed same as SUNLIGHT)	QALYs:	0.61	0.62
			Absolute:	10.34	10.33
			Proportional:	94.43%	94.34%
			Weighting:	**X1.2**	**X1.2**
SACT (GG OS) (EAG base case)	Treatment pooled (SUNLIGHT)	Mean age = 65 % female: 48%* (assumed same as SUNLIGHT)	QALYs:	0.57	0.58
			Absolute:	10.38	10.37
			Proportional:	94.79%	94.70%
			Weighting:	**x1.2**	**x1.2**

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Is it appropriate to apply a QALY weighting for severity? What QALY weightings are preferred vs each comparator?

*Info on severity weighting

Key issue: severity modifier – EAG analysis (2)

1.2x or 1.7x weighting depending on utility source

Scenario	HSUVs	Characteristics		Trifluridine-tipiracil monotherapy	Regorafenib
EAG base case (GG OS, SACT)	TA866	Mean age = 65 % female: 48%* (assumed same as SUNLIGHT)	QALYs: Absolute: Proportional: Weighting:	0.51 10.44 95.34% **x1.7**	0.52 10.43 95.25% **x1.7**
EAG base case (GG OS, SACT)	TA405	Mean age = 65 % female: 48%* (assumed same as SUNLIGHT)	QALYs: Absolute: Proportional: Weighting:	0.54 10.41 95.07% **X1.7**	0.55 10.40 94.98% **X1.2**

NICE

Is it appropriate to apply a QALY weighting for severity? What QALY weightings are preferred vs each comparator?

*Info on severity weighting

Key issue: Regorafenib time on treatment

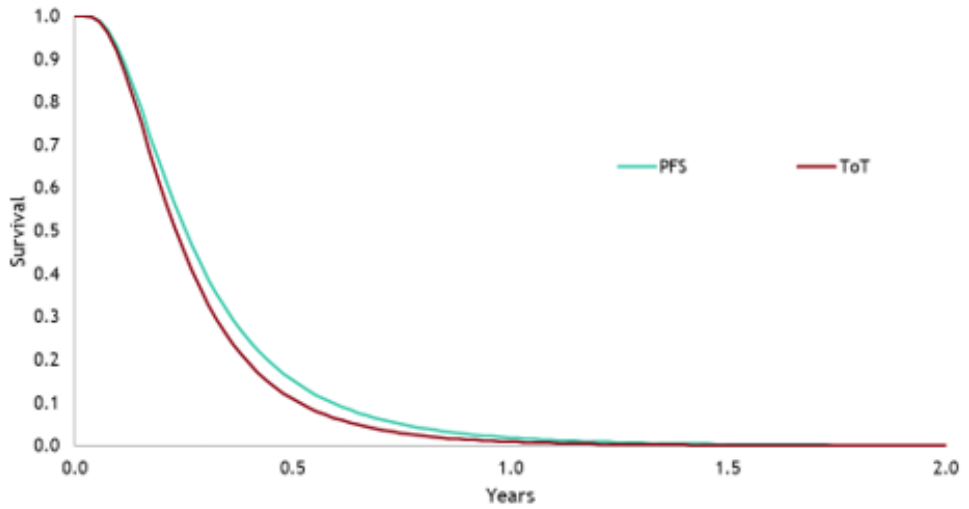
ACM1 discussion

- Committee agreed that time on treatment with regorafenib would be overestimated if treatment was assumed until progression and that it would like to see further sensitivity analysis that increased the proportion of the progression-free cohort on regorafenib.

Company response to consultation

- EAG's flat proportion approach implausible – assumes some patients do not receive treatment right away
- Revised base case uses HR for ToT vs. PFS to the regorafenib PFS curve. The proportion on treatment is calculated using the ratio of **median** ToT (1.7 months) to median PFS (1.9 months) from the CORRECT study resulting in equivalent to 89.4% of the mean modelled PFS time

Figure 11: Regorafenib PFS versus ToT using HR approach (HR=0.85; 89.4% ToT vs PFS)



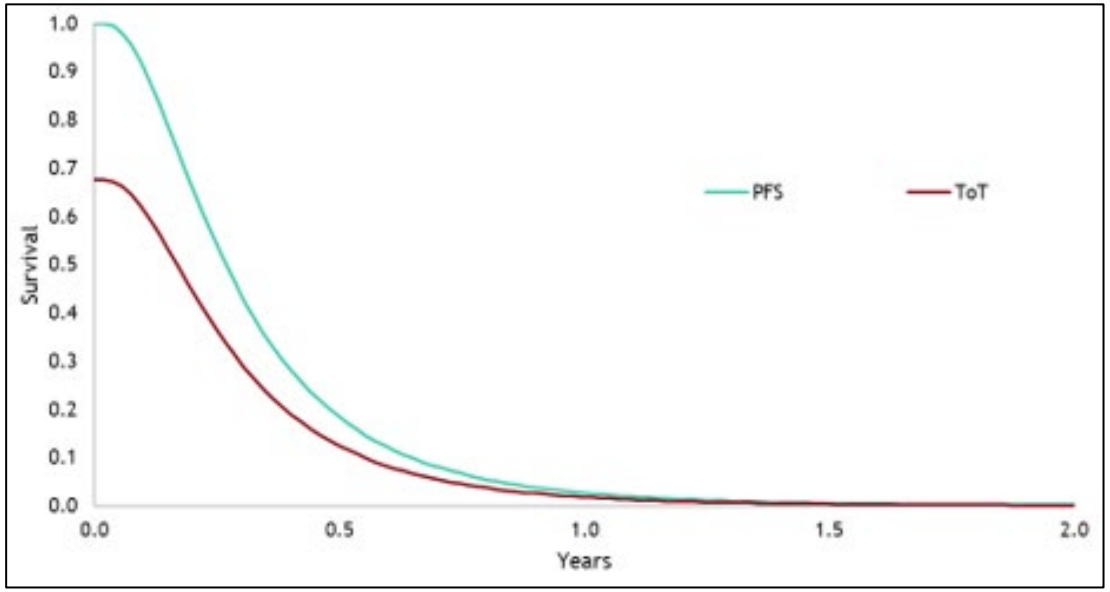
Key: HR, hazard ratio; PFS, progression-free survival; ToT, time-on-treatment

Key Issue: Regorafenib time on treatment

EAG response

- Acknowledges concerns about the shape of the ToT curve but do not consider it an important driver because the number of years is less than 1 so there is no introduction of discounting errors
- However, it fits PFS curve in a way that ensures close alignment with both the reported mean (and also the median) from the CORRECT study
- EAG consider it aligns regorafenib treatment acquisition costs with the modelled benefits
- Also uses means instead of medians which is more methodologically appropriate

Regorafenib ToT vs PFS (68% of progression-free patients using EAG's approach at ACM1)



EAG scenarios

- EAG base case uses original approach to align mean and median from CORRECT
- Additional scenario fitting an exponential curve to the median ToT

Key issue: Regorafenib RDI

ACM1 discussion

- Committee preferred using the relative dose intensity (RDI) for regorafenib from the CORRECT study as it was likely to match regorafenib use in clinical practice

Company response to consultation

- Company still assumes equal RDI for trifluridine-tipiracil monotherapy and regorafenib in revised base case – no additional analyses submitted
  - In line with TA866 committee conclusion, supported by RWE study suggesting similar proportions of dose reduction for both treatments
- Outcomes in revised base case similar between trifluridine-tipiracil monotherapy and regorafenib – reasonable that RDI would be similar between the two arms

EAG critique

- Clinical expert consultation comment – regorafenib associated with toxicity
- EAG clinical expert – dose adjustments needed in UK clinical practice
- RDI for regorafenib likely lower than trifluridine-tipiracil in UK clinical practice

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Is using RDI for regorafenib from the CORRECT study still appropriate?

Key issue - Ongoing administration costs of bevacizumab

Background: ACD consultation – Clinical expert raised issue of ongoing bevacizumab being given outside clinics, without blood tests – important to consider for costs

Company approach to bevacizumab administration

- Company uses HRG code SB12Z (deliver simple parenteral chemotherapy at first attendance) for administration costs (**£286.71**, NHS reference costs 2021/22)
- Applied every 2 weeks

EAG critique

- Agrees with company for first delivery of bevacizumab, but ongoing administration cost may not be equivalent to initial administration. Potential alternative cost codes:
  - SB15Z for delivering subsequent elements of a chemotherapy cycle, **£368.44 -** EAG believes this is **not** appropriate as code includes simple and complex chemo delivery
  - WF01A, non-admitted nurse led face-to-face medical oncology service, **£158.50**
- Current EAG base case uses SB12Z for all administration - scenario with WF01A used for ongoing administration included in analysis

Are nurse-led clinics used in NHS clinical practice for ongoing bevacizumab administration? What costs should be used for ongoing bevacizumab administration?

Summary of base case assumptions post consultation

Assumption	Company base case	EAG base case
Tri-tip + bevacizumab and tri-tip monotherapy OS	Ref. curve tri-tip (SUNLIGHT) HRs from NMA for all comparisons Log logistic curve	Ref. curve tri-tip (SACT) HR from SUNLIGHT for trifluridine-tipiracil plus bevacizumab, HR from NMA for regorafenib Generalised gamma curve
Treatment waning	Applied at 3-5 years	None (1-2 years as scenario)
ToT for regorafenib	Apply HR to PFS curve (based on CORRECT median ToT/PFS (89.4%)	Apply proportion of PFS curve on treatment, using CORRECT mean ToT (72%)
Utilities	Treatment-specific (SUNLIGHT)	Pooled (SUNLIGHT)
Regorafenib RDI	Equal to trifluridine-tipiracil	RDI from CORRECT
Severity modifier	1.2x trifluridine-tipiracil and regorafenib	1.2x trifluridine-tipiracil and regorafenib

Additional changes to base case assumptions post ACM1

	Revised company base case	EAG opinion
Regorafenib OS and PFS	HR from random-effects NMA – trifluridine-tipiracil as reference curve	Agree – used in EAG base case
Subsequent treatments	35% receive subsequent treatment: Trifluridine-tipiracil (with or without bevacizumab) receives regorafenib, regorafenib receives subsequent trifluridine-tipiracil	Agree – used in EAG base case

NMA, network meta-analysis;

Other considerations:

Potential equalities issues raised during consultation:

- Question in consultation comment about representation of different ethnic groups in the trial
- Uncertainties around age distribution of patients could underestimate increased benefit to younger patients

Managed access

- The company has not submitted a managed access proposal for trifluridine-tipiracil with bevacizumab

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts

Summary of cost-effectiveness results

When **all** confidential discounts are applied, CMU price of bevacizumab updated

Company ICERs

Base case – ICERs for trifluridine-tipiracil plus bevacizumab <£30,000 per QALY against both trifluridine-tipiracil monotherapy and regorafenib (regardless of severity modifier)

EAG ICERs

- Base case - ICERs <£30,000 per QALY against trifluridine-tipiracil monotherapy at 1.2x and 1.7x modifier, <£30,000 per QALY against regorafenib at 1.7x modifier only
- EAG scenarios increased or did not change company ICERs in all scenarios, except when assuming no treatment waning and an exponential to median approach for regorafenib ToT
- Assumption of treatment waning at years 1-2 has biggest impact on company ICERs, followed by EAG's preferred OS modelling for trifluridine-tipiracil + bevacizumab
- In scenario analyses of EAG base case, assumption of treatment waning (years 1-2) has biggest impact on ICERs (increase) followed by lower bevacizumab administration costs (decrease)

Abbreviations: ICER, incremental cost-effectiveness ratio; CMU, Commercial Medicines Unit; QALY, quality-adjusted life year

Summary of key issues for discussion

Key questions raised:

- How should overall survival be modelled? What source of data should be used for overall survival?
- Should a treatment waning effect be applied? If so, at what point should it be applied?
- Is the company's approach to treatment-specific utilities appropriate? What source of utility values should be used?
- Is it appropriate to apply a QALY weighting for severity? What QALY weightings are preferred vs each comparator?
- How should regorafenib ToT be modelled?
- Is using RDI for regorafenib from the CORRECT study still appropriate?
- Are nurse-led clinics used in NHS clinical practice for ongoing bevacizumab administration? What costs should be used for ongoing bevacizumab administration?

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Thank you.

Trifluridine-tipiracil with bevacizumab for treating metastatic colorectal cancer [ID6298]

Supplementary appendix

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Additional info and analysis requested following ACM1 (1)

- Observational data to validate overall survival for trifluridine–tipiracil alone in UK practice, and modelling of trifluridine–tipiracil plus bevacizumab OS by applying the SUNLIGHT overall survival hazard ratio to this data
- Data on the mean age of people having trifluridine–tipiracil alone for mCRC in current UK practice
- Updated QALY shortfall calculations for trifluridine–tipiracil alone that reflect the further analyses, particularly overall survival and mean age

Additional info and analysis requested following ACM1 (2)

- Analyses in which regorafenib survival estimates are modelled by applying hazard ratios from the network meta-analysis to the curve for trifluridine–tipiracil alone
- Analyses in which regorafenib time on treatment is modelled as a higher proportion of people in the progression-free state than in the EAG's base case (68%)
- Sensitivity analyses in which the treatment effect on survival with the intervention and comparators wanes over time

Key Issue: Appropriate overall survival extrapolation

EAG and company disagree on most appropriate OS extrapolation

Company

- Fitted a range of parametric survival curves: most provide good statistical and visual fit
- Log-logistic most appropriate to model overall survival, informed by clinical opinion

EAG comments

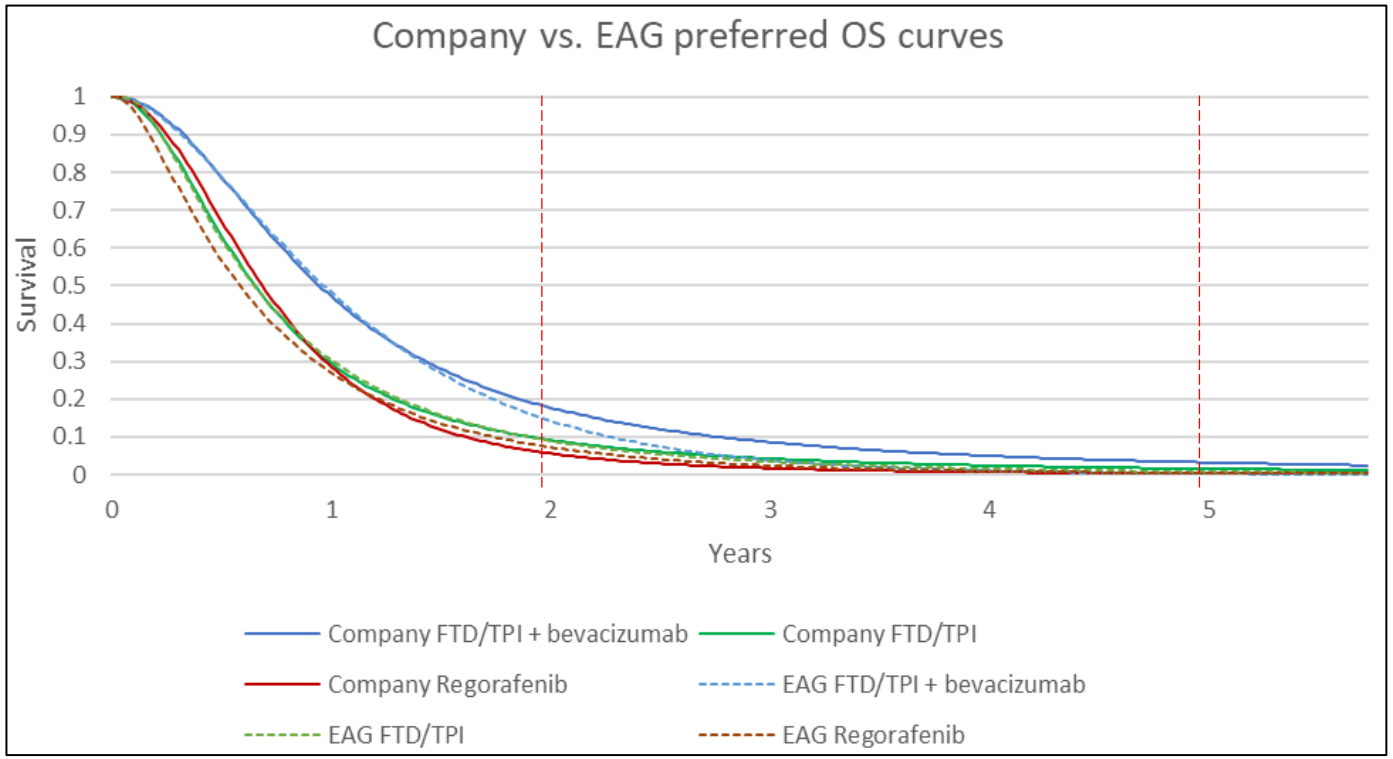
- Most parametric curve fits are plausible, choice should reflect plausibility of long-term projections
- EAG clinical expert – few patients will remain alive at 5 years, regardless of treatment arm; projections over 1% at 5 years lack face validity
- Company clinical expert saw data before giving views
- Magnitude of treatment effect estimated at year 2 by log-logistic fitted to both arms exceeds treatment effect from 1 year KM data (1.95 vs 1.5 respectively)
- Generalised gamma more appropriate – steeper decline in early survival in line with company and EAG clinical expert opinion

How should overall survival be modelled? Company = log-logistic. EAG = generalised gamma.

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

Key Issue: Appropriate overall survival extrapolation

EAG and company disagree on most appropriate OS extrapolation



Extrapolations only

How should overall survival be modelled? Company = log-logistic. EAG = generalised gamma.

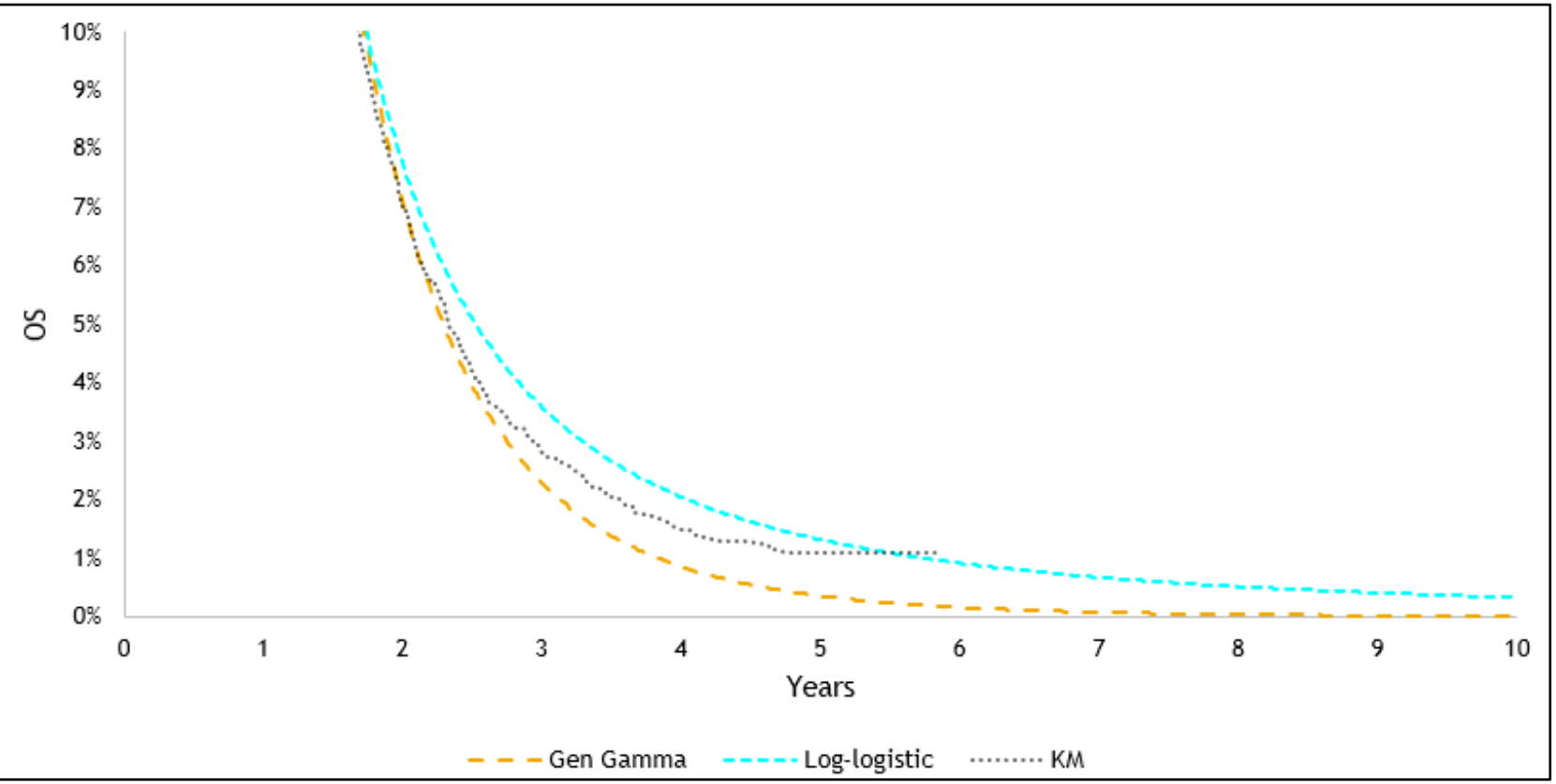
Year	Log-logistic (Company)	Generalised gamma (EAG)	Clinical expert opinion	Log-logistic (Company)	Generalised gamma (EAG)	Clinical expert opinion
	Trifluridine-tipiracil monotherapy OS			Trifluridine-tipiracil with bevacizumab OS		
2	8.5%	8.2%	2 to 10%	16.6%	12.8%	15 to 20%
5	1.4%	0.7%	“Few if any”	2.9%	0.2%	2.9%*

Abbreviations: FTD/TPI, trifluridine-tipiracil; OS, overall survival

*when provided with model output, stated 2.9% reasonable

Key issue: Appropriate overall survival extrapolation

EAG fitting of curves to SACT data – differences in extrapolations at 0-10% survival



EAG

- Small differences in curve at tail end have large effects on ICER
- GG has good statistical fit + acceptable AIC/BIC
- Log-logistic fitted to SACT extends OS benefit indefinitely for trifluridine-tipiracil + bevacizumab – not enough follow up to support this
- Log-logistic has proportion of people alive at 10 years – implausible, curve trending towards 0 preferred

How should overall survival be modelled?
What source of data should be used for overall survival?

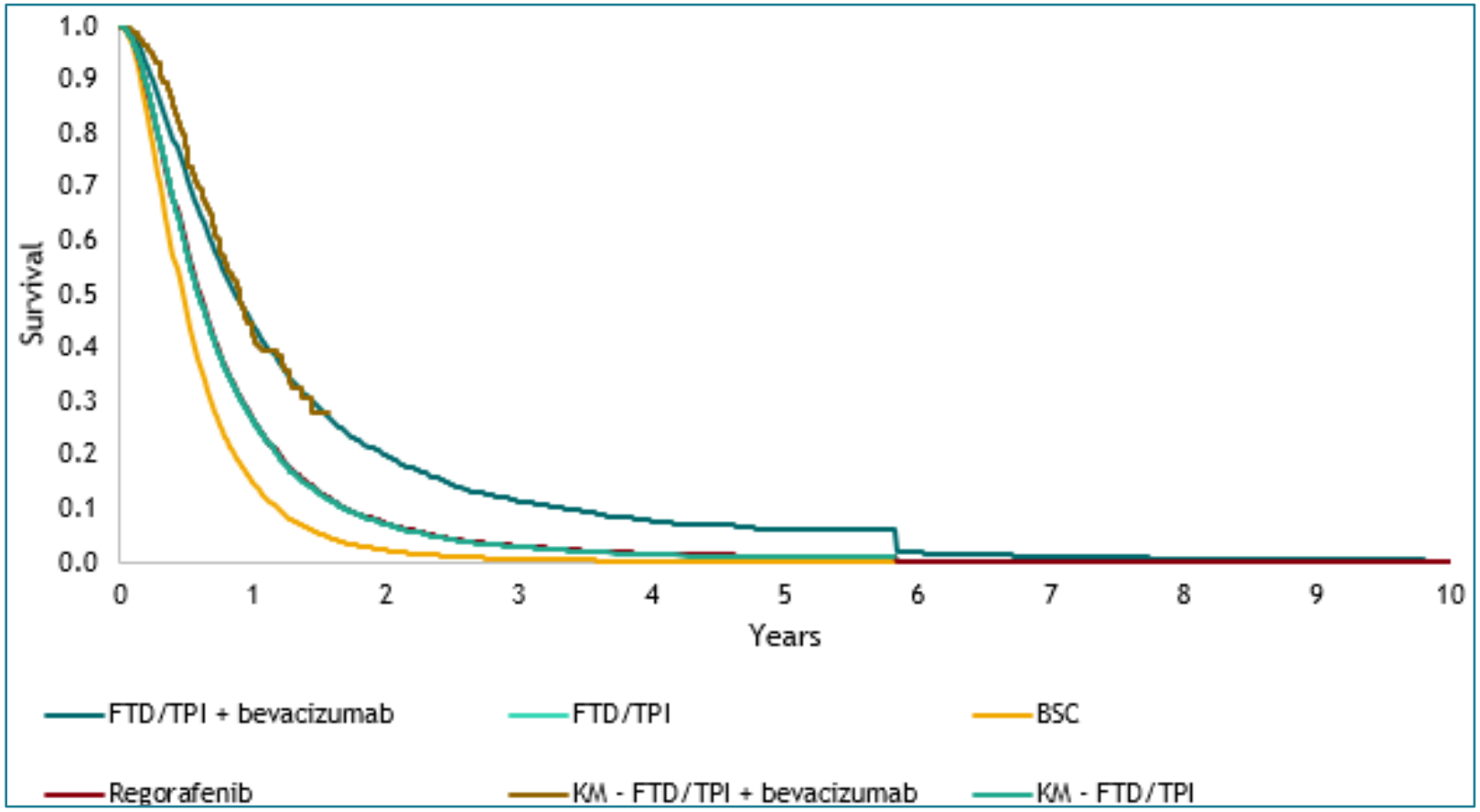
Abbreviations: GG, generalised gamma, OS, overall survival; Systemic Anti-Cancer Therapy

Return to main slides

Key issue: Appropriate overall survival extrapolation

Updated OS extrapolations - trifluridine-tipiracil monotherapy as reference curve

EAG scenario – KM curve from SACT up to 4 years, generalised gamma onwards



Abbreviations: FTD/TPI, trifluridine-tipiracil; OS, overall survival; KM, Kaplan-Meier

Return to main slides

Key issue: severity modifier – company analysis (2)

1.2x weighting for trifluridine-tipiracil monotherapy and regorafenib, all sources

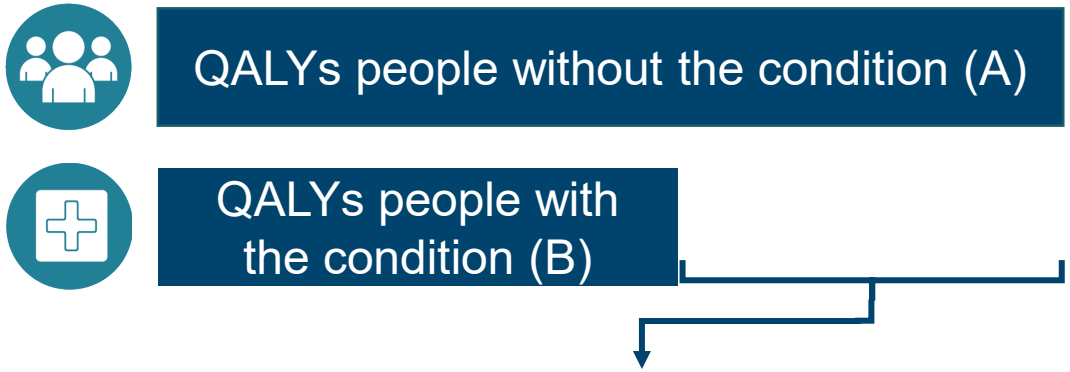
Source	Characteristics		Trifluridine-tipiracil monotherapy	Regorafenib
Wadd et al, 2022	Mean age= 68 % female: 26%	QALYs:	0.59	0.60
		Absolute:	9.21	9.20
		Proportional:	93.98%	93.88%
		Weighting:	**x1.2**	**x1.2**
Tong et al, 2021	Mean age = 66 % female: 41%	QALYs:	0.55	0.56
		Absolute:	10.02	10.01
		Proportional:	94.80%	94.70%
		Weighting:	**x1.2**	**x1.2**

Is it appropriate to apply a QALY weighting for severity? What QALY weightings are preferred vs each comparator?

*Return to main slides

QALY weightings for severity

Severity reflects future health lost by people living with a condition who have current standard care



Health lost by people with the condition:

- Absolute shortfall: total = A – B
- Proportional shortfall: fraction = (A – B) / A

Criteria used to decide QALY weighting

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

- QALY weighting can be applied based on whichever of absolute or proportional shortfall implies the greatest severity
- If either the proportional or absolute QALY shortfall calculated falls on the cut-off between severity levels, the higher severity level will apply
- Additional weight applied to QALYs within cost effectiveness calculation

Abbreviations: QALY, quality-adjusted life year

Return to main slides