ID6274 Fruquintinib for previously treated metastatic colorectal cancer

For public
CON information redacted

Technology appraisal committee B 12 December 2024

Chair: Baljit Singh

External assessment group: Aberdeen HTA Group

Technical team: Emma Bajela, Michelle Green, Richard Diaz

Company: Takeda

Fruquintinib for previously treated metastatic colorectal cancer

- ✓ **Recap**
- ❑ Response to consultation

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DG recommendation – July 2024

"Fruquintinib is not recommended, within its marketing authorisation, for treating metastatic colorectal cancer in adults who have had previous treatment, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, with or without an anti-vascular endothelial growth factor [VEGF] treatment, and if the cancer is RAS wildtype, an anti-epidermal growth factor receptor [EGFR] treatment if that is appropriate."

Reasons the committee made this decision:

- Uncertainty in appropriate comparator
- Uncertainty in company's NMA and proportional hazards; best approach for overall survival and progression free extrapolations
- Modelled acquisition cost of fruquintinib for people having a dose reduction
- Uncertainty in utility values used in the model
- Impact of updated analysis on QALY shortfall calculation needed

Consultation responses received from:

- Takeda (company) – **new analyses and base case provided, revised price**

Stakeholders:

- Clinical expert
- Comparator company

- **Web comments** (n=3)

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Abbreviations: DG, draft guidance; EGFR, Epidermal Growth Factor Receptor; NMA, network meta-analysis; QALY, quality-adjusted life year; RAS, reticular activating system; VEGF, anti-vascular endothelial growth factor

Fruquintinib (Fruzaqla, Takeda)

Marketing authorisation	• Fruquintinib (Fruzaqla, Takeda) is indicated for 'the treatment of adult patients with metastatic colorectal cancer (mCRC) who have been previously treated with available therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapy, with or without an anti-VEGF therapy, and if RAS wildtype and medically appropriate, an anti-EGFR therapy'. • UK MA granted September 2024
Mechanism of action	• Inhibits VEGF pathway signalling by inhibiting VEGF receptor -1, -2 and -3 tyrosine kinases • This interferes with blood supply to the tumours and development of cancer cells, stopping the growth and spread of the cancer
Administration	• 5 mg oral capsule taken once daily for 21 consecutive days, followed by a 7-day rest period • Treatment continued until disease progression or unacceptable toxicity. Dose adjustments recommended for adverse events
Price	5 mg capsules: £3,950.00 per pack of 21 capsules 1 mg capsules: £790.00 per pack of 21 capsules A confidential discount is in place for fruquintinib – updated since ACM1

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Abbreviations: EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; mCRC, metastatic colorectal cancer; VEGF, vascular endothelial growth factor

Recap: ACM1 conclusions

Issue	Committee conclusion at ACM1	Resolved?
Treatment pathway & relevant comparators	• Relevant comparators are what is used in NHS practice	No – for discussion
NMA results	• Unclear if proportional hazards hold • Uncertainty in results – discrepancy between OS and PFS	Partially – for discussion
OS and PFS – proportional hazards	• Assumes proportional hazards and relies on NMA	Partially – for discussion
Dosing and RDI	• Apply trial specific RDI • Accurately model acquisition costs	RDI: No – for discussion Costs: Yes
Time to treatment discontinuation	• Log normal curve for trifluridine tipiracil TTD data • Exponential curve to median time on treatment for regorafenib • Gen gamma curve for fruquintinib TTD data (option:Log normal)	Yes
Subsequent treatments	• Includes 35% of the post progression population receiving subsequent treatments, for 8 weeks	Yes
Health state utilities	• Scenarios using CORRECT and pooled data	Partially – for discussion
Mean age for severity weighting	• Mean age of 65 years (SACT data)	No – for discussion

Abbreviations: NMA, network meta-analysis; OS, overall survival; PFS, progression free survival; PH, proportional hazards; RDI, relative dosing intensity; TTD, time to treatment discontinuation

Remaining key issues - to be discussed

Issue	ICER impact
Treatment pathway & relevant comparators	Unknown
NMA results	Unknown
OS and PFS – proportional hazards	Unknown
RDI	Moderate
Health state utilities	Large
Mean age for severity weighting	Large

Abbreviations: ICER; incremental cost effectiveness ratio, NMA; network meta analysis, OS; overall survival, PFS; progression free survival, PH; proportional hazards, RDI; relative dosing intensity

Fruquintinib for previously treated metastatic colorectal cancer

- ❑ Recap
- ✓ **Response to consultation**

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Consultation responses

Company (Takeda):

- Provided a response to areas of uncertainty and additional analyses requested by committee (further detail in key issue slides) and updated base case

Comparator company (Servier):

- There should be consistency with TA1008, e.g. for RDI, severity, use of SACT data
- Concerns about generalisability of FRESCO population and FRESCO-2, in which people had more previous treatment, and pooling of the results
- Treatment discontinuation should consider adverse event profiles of treatments

Clinical expert:

- Since TA1008, TT/BVZ has quickly become 3L line treatment option
- Fruquintinib should be positioned at 4L compared with both regorafenib and BSC
- At 4L, OS extrapolations not that important as survival gain is small

Web comments:

- Fruquintinib should be positioned at 4L now that TT/BVZ is available
- Fruquintinib is better than regorafenib in all key clinical and patient-based outcomes
- Concerns over complexity of analyses, extrapolations and reliance on assumptions

Abbreviations: 3L, third line; 4L, fourth line; BSC, best supportive care; RDI, relative dosing intensity; OS, overall survival; SACT, systemic anti-cancer therapies; TTD, time to treatment discontinuation; TT/BVZ, trifluridine tipiracil with bevacizumab

Changes to the company base case for ACM2

Assumptions in updated company base case aligned with committee preferred assumptions:

Assumption	Company base case
OS extrapolation	• T/T data as the reference curve informed by SACT data • NMA hazard ratios applied for fruquintinib, regorafenib and BSC • Use an average of the log-logistic and generalised gamma curves
PFS extrapolation	• T/T data as the reference curve informed by digitised trial data • NMA hazard ratios applied for fruquintinib, regorafenib and BSC
TTD	• T/T: log normal curve fitted to pooled digitised data • Regorafenib: exponential curve to median time on treatment
Subsequent treatment	• Proportion having subsequent treatment (for 8 weeks) based on NHSE data, subsequent treatment proportions based on expert elicitation
Utility Values	• Utility values from CORRECT trial (TA405) • Scenario analysis with pooled utility values
Fruquintinib costing	• Updated pricing structure to linear pricing model (for 1mg pack size) and revised PAS

Committee preferences from ACM1 on RDI, starting age for severity modifier or comparators are not included company's revised base case

Abbreviations: BSC, best supportive care; NMA, network meta-analysis; PAS, patient access scheme; RDI, relative dosing intensity; SACT, systemic anti-cancer therapies; T/T, trifluridine-tipiracil

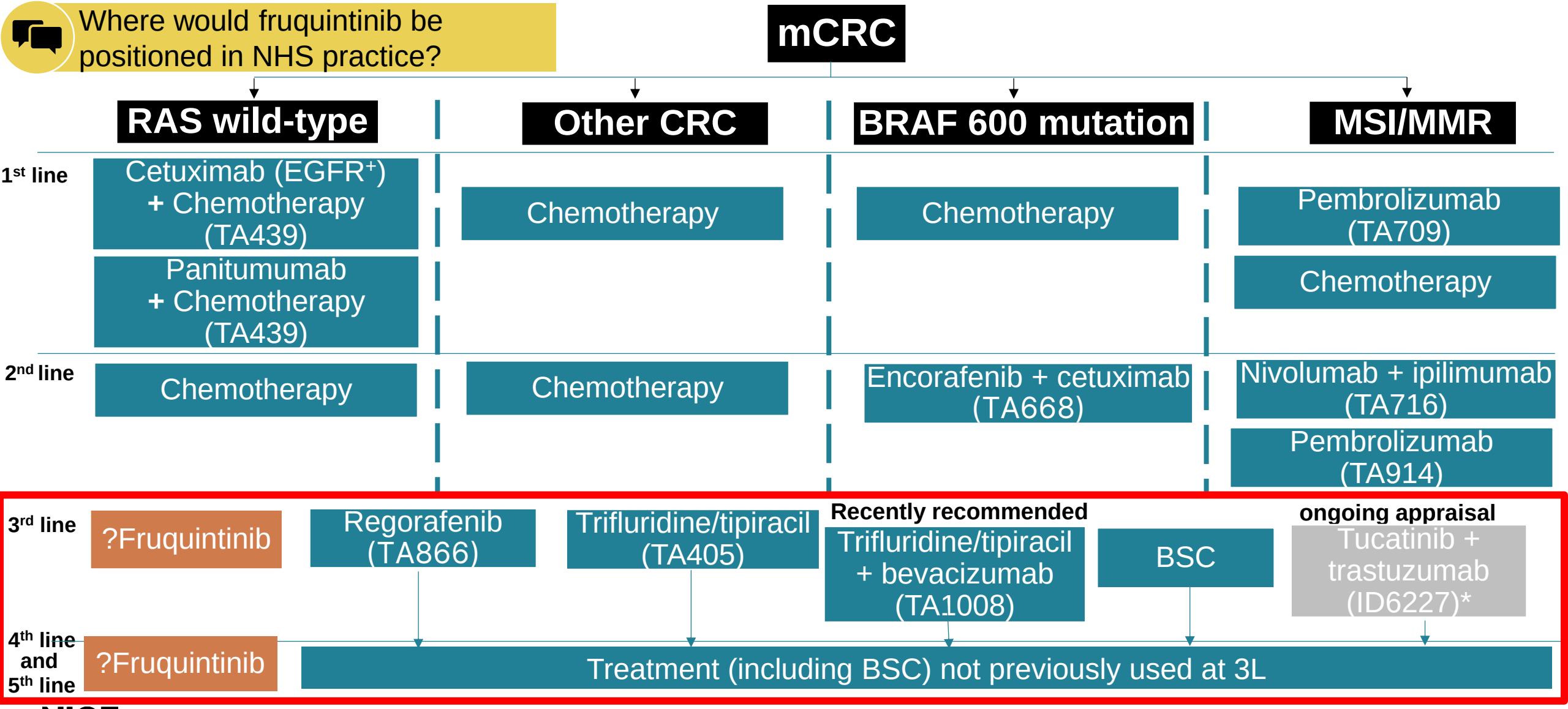
mCRC treatment pathway

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

RECAP

Company positioned fruquintinib for third or subsequent-line use in the mCRC pathway

Where would fruquintinib be positioned in NHS practice?



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

Key issue: Treatment pathway and relevant comparators

Committee at ACM1

- Requested further analyses considering treatments currently used in NHS clinical practice as comparators, if these change from trifluridine-tipiracil and regorafenib

Company

- People eligible for TT/BVZ (majority) – fruquintinib at 4L instead of regorafenib
- People not eligible for TT/BVZ (minority) – fruquintinib at 3L (or 4L) instead of regorafenib, T/T monotherapy or BSC
- Do not consider it reasonable for NICE to issue a revised scope

Clinical expert and web comments (detail)

- Following the introduction of TT/BVZ, fruquintinib should be positioned at 4L compared with regorafenib and BSC

EAG comments

People eligible for TT/BVZ

- Agree TA1008 likely moves fruquintinib to 4L and T/T monotherapy is not a relevant comparator in this setting
- BSC still a relevant comparator at 4L for some people - prior regorafenib treatment or tolerability concerns
- Use in 4L setting has implications for economic modelling. FRESCO-2 trial data may be more relevant, but current model does not allow this scenario to be run

People not eligible for TT/BVZ

- Both T/T monotherapy and regorafenib appropriate 3L comparators

- Which position in the treatment pathway is most appropriate for fruquintinib?
- What are the relevant comparators for fruquintinib?

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Abbreviations: EGFR, Epidermal Growth Factor Receptor; mCRC, metastatic colorectal cancer; RAS, reticular activating system; T/T, trifluridine-tipiracil; VEGF, anti-vascular endothelial growth factor

Key issue: NMA results

Committee at ACM1

- For overall survival, there was no difference between fruquintinib and trifluridine-tipiracil or regorafenib
- The Committee noted the discrepancy between the OS and the PFS results. It was concerned that the improvement shown by fruquintinib did not translate into better overall survival

Company

- NMA indicated a numerical improvement in overall survival for fruquintinib versus both trifluridine-tipiracil and regorafenib
- Clinical expert input - most clinically meaningful outcome is delayed progression with maintained QoL
- PFS should be the focus rather than OS:
  - NMA shows significant improvement in PFS versus regorafenib, trifluridine-tipiracil, and BSC
  - FRESCO-2 trial demonstrated that HRQoL was not negatively impacted by treatment with fruquintinib

EAG comments

- Improvement in OS from fruquintinib compared with regorafenib or T/T monotherapy is small in magnitude
- Both PFS and OS are relevant for decision making

Is PFS a more relevant outcome than OS for this population?

Abbreviations: HRQoL, health related quality of life; NMA; network meta analysis; OS, overall survival; PFS, progression free survival; QoL, quality of life; T/T, trifluridine-tipiracil

Key issue: OS and PFS – proportional hazards

Committee at ACM1

- Requested further analyses to explore if proportional hazards for OS and PFS hold before HRs from NMA are applied in model

Company

- Have implemented committee's preferences in model, but note that SACT data are limited by lack of baseline characteristics and lack of PFS, AE, subsequent treatment, or TTD data
- Proportional hazards assessed compared with T/T :
  - log-cumulative hazard plots
  - global test of the PH assumption
  - tests of the interaction between treatment group and time. But note not recommended in NICE DSU TSD 14 so previous tests more reliable

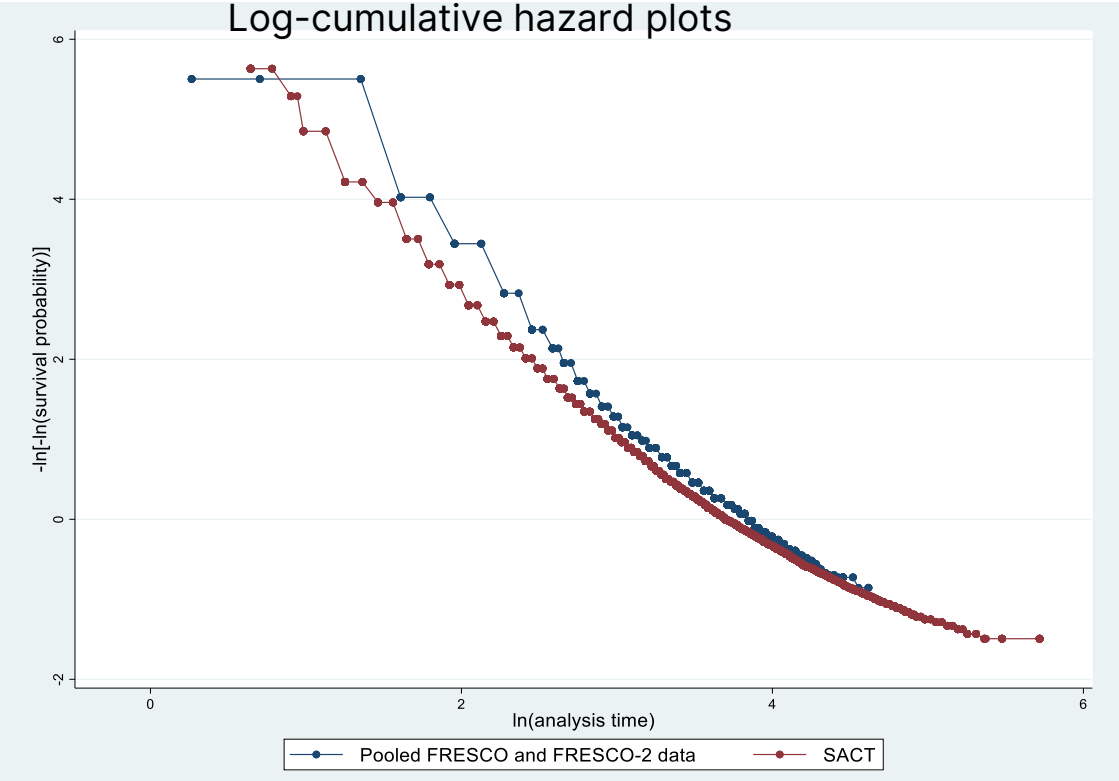
EAG comments

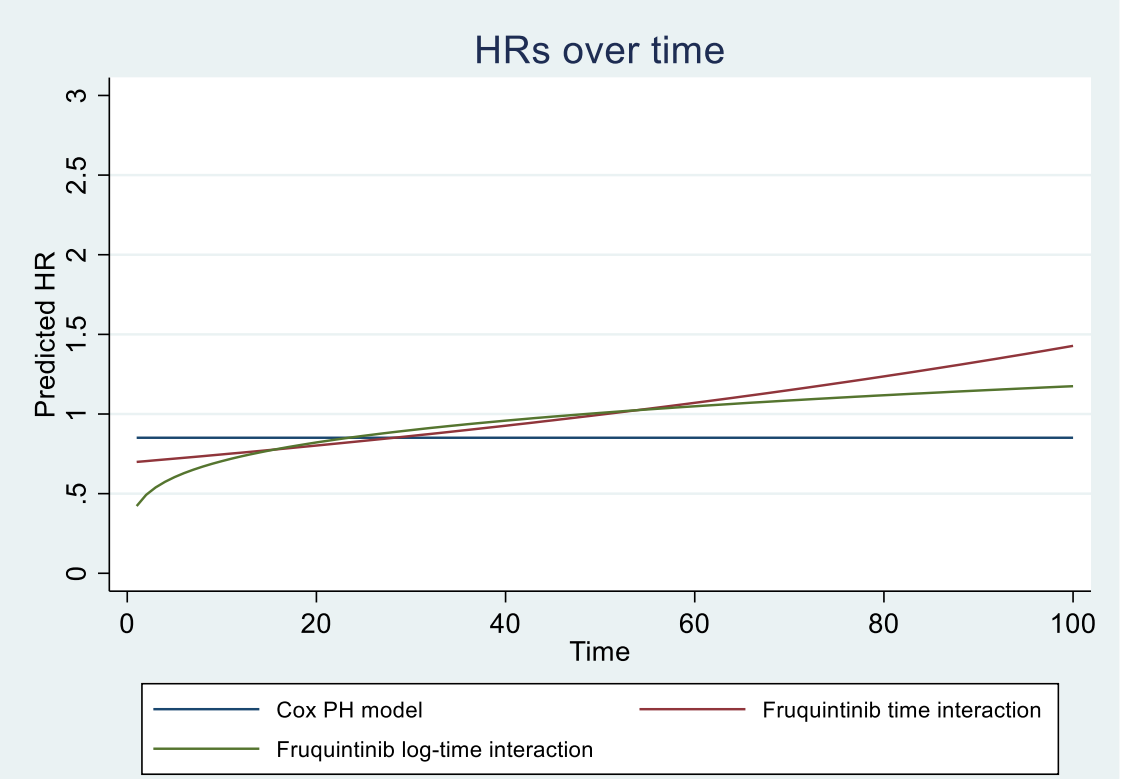
- Uncertainty remains around whether PH assumptions hold
- Sensitivity analysis using time-partitioned model would have allowed for more exploration of impact PH assumptions on ICER
- Scenario analysis using independently fitted curves relaxed PH assumption but only applies to T/T and fruquintinib (not regorafenib)

Abbreviations: AE, adverse event; ICER, incremental cost effectiveness ratio; NMA; network meta-analysis; OS, overall survival; PFS, progression free survival; PH, proportional hazards;; TTD, time to treatment discontinuation

OS: Log cumulative plots and time and treatment group interaction

SACT vs pooled FRESCO and FRESCO-2 OS data





Company (v. T/T):

- Log-cumulative hazard plot suggests no PH violation
- Global test does not reject PH (p=0.1476)
- Interaction between treatment and time suggests PH may not hold, but other tests are more suitable

	HR (CI)	p-value
Interaction with time	1.007 (1.002, 1.013)	0.009
Interaction with log-time	1.249 (1.082, 1.441)	0.002

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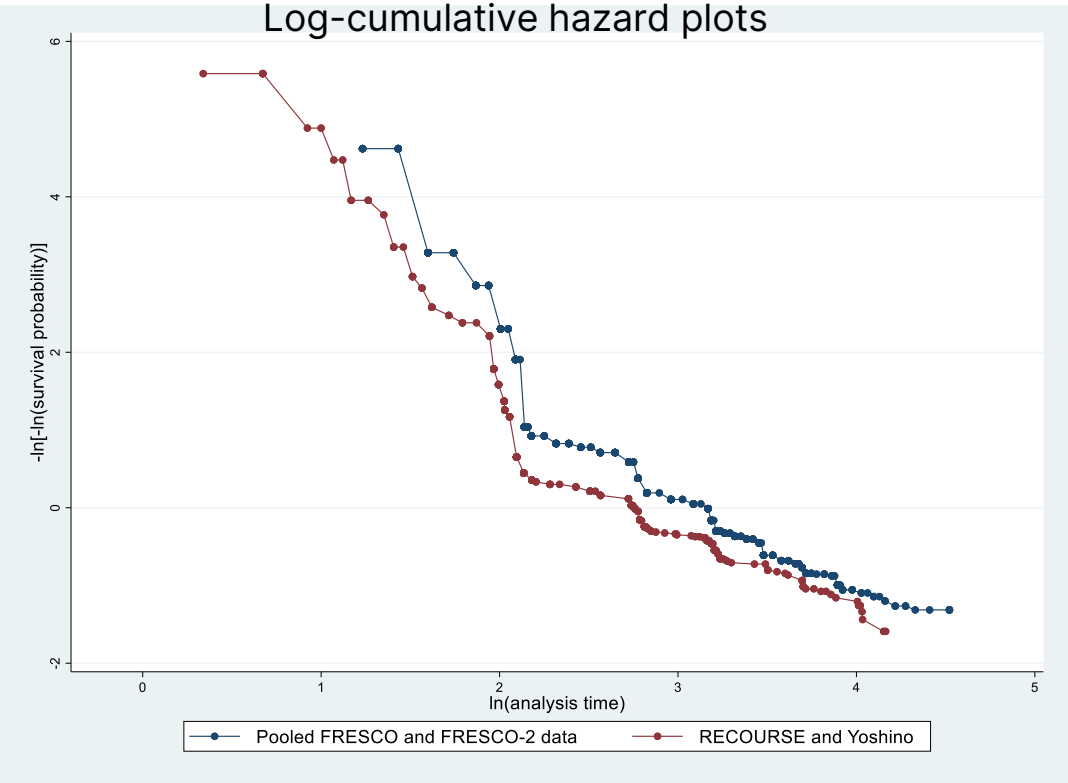
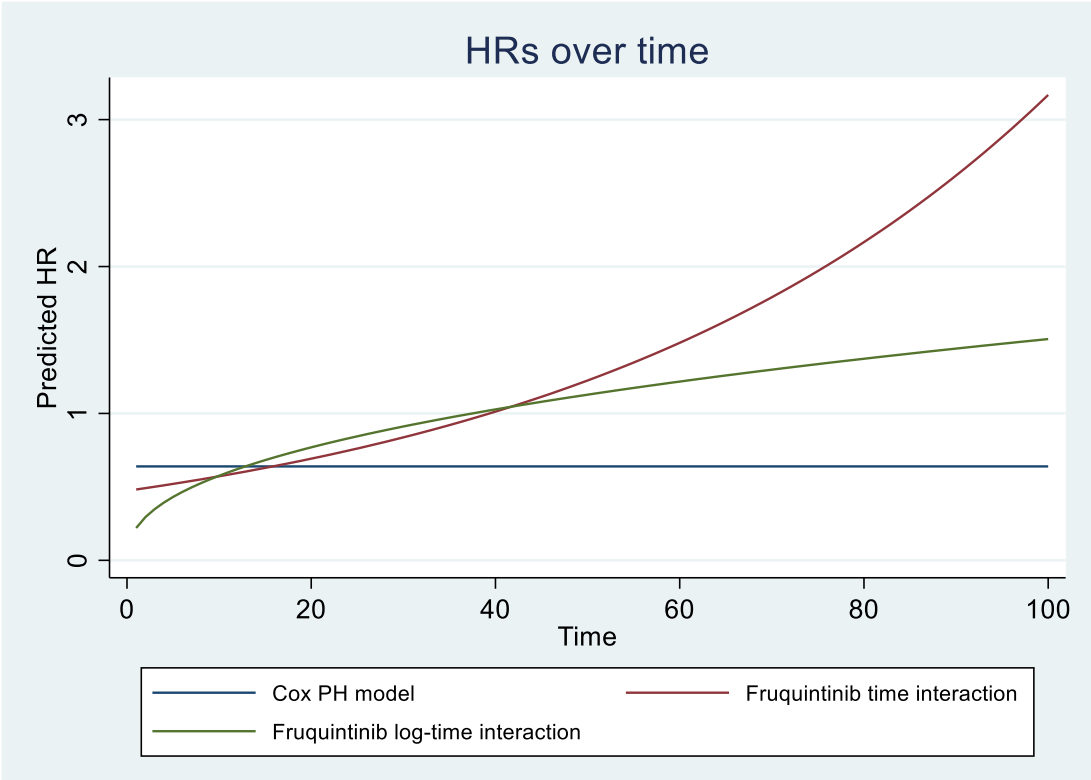
Abbreviations: CI, confidence intervals; HR, hazard ratios; OS, overall survival; PH, proportion hazards; T/T, trifluridine tipiracil

PFS: Log cumulative plots and time and treatment group interaction

RECOURSE/Yoshino vs pooled FRESCO and FRESCO-2 PFS data





Company (v. T/T):

- Log-cumulative hazard plot suggests no PH violation
- Global test rejects PH (p=0.0151)
- Interaction between treatment and time suggests PH may not hold, but other tests are more suitable
- Clinical experts expect PH to hold as fruquintinib, regorafenib and T/T do not change course of disease

	HR (CI)	p-value
Interaction with time	1.019 (1.004, 1.019)	0.011
Interaction with log-time	1.518 (1.188, 1.941)	0.001

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Abbreviations: CI, confidence intervals; HR, hazard ratios; OS, overall survival; PH, proportion hazards; T/T, trifluridine tipiracil

Summary of PH tests

Table summary of proportional hazard assumptions for OS and PFS

		Log-cumulative hazard plot inspection		Global test of Schoenfeld residuals		Interaction tests with time and log-time	
		OS	PFS	OS	PFS	OS	PFS
Original submission	Comparison of fruquintinib and BSC	"Relatively parallel" and curves do not cross	Cross at the start. "Relatively parallel"	Reject PH assumption	Reject PH assumption	N/A	N/A
Response to draft guidance	Comparison of fruquintinib and trifluridine-tipiracil	"Relatively parallel over time"	"Clearly parallel over time"	PH assumption is not rejected	Reject PH assumption	Treatment effect and outcomes not independent of time	Treatment effect and outcomes not independent of time
	Comparison of trifluridine-tipiracil and regorafenib	"Relatively parallel over time"	"No violation of the PH assumption…low numbers of patients at risk towards the end of the analysis"	PH assumption is not rejected	PH assumption is not rejected	Treatment effect and outcomes not independent of time	PH may be reasonable

Do proportional hazards apply for OS and PFS?

Abbreviations: BSC; best supportive care, OS; overall survival, PFS; progression free survival, PH; proportional hazards

Key issue: Relative dose intensity

Committee at ACM1

- Trial-specific relative dose intensity for fruquintinib (89.6%), regorafenib (78.9%) and T/T (89.0%) should be used in the model

Company

- Maintains that using the RDI of 89.6% from the pooled FRESCO and FRESCO-2 data for fruquintinib, regorafenib, and T/T is the most reasonable source
- RDI definitions varied among the key trials so are not comparable:
  - For regorafenib, cycle delay and dose reduction were factored into the RDI definitions trials
  - Values for T/T and fruquintinib are similar
- Clinical expert input suggested RDI of regorafenib would be expected to be lower than fruquintinib due to its toxicity profile but not as low as CORRECT trial RDI
- In TA866, pooled CORRECT and CONCUR data were used to model RDI for regorafenib and T/T
- The impact of unacceptable toxicity is already captured in TTD data used in the model
- A scenario analysis using a lower RDI value for regorafenib has minimal impact on ICER

EAG comments

- Acknowledge uncertainty but maintain treatment specific RDI assumption

Is pooled or treatment specific RDI data most appropriate for decision making?

Abbreviations: ICER, incremental cost effectiveness ratio; RDI, relative dosing intensity; T/T, trifluridine tipiracil; TTD, time to treatment discontinuation

Key issue: Utilities

Committee at ACM1

- Requested further analyses using the CORRECT trial utility values and applying pooled estimate of relevant utility values

Company

- Accept committee preference to use CORRECT utility values and did meta-analysis to inform scenario

Health state	CORRECT (base case)	Pooled FE (scenario)	Pooled RE	FRESCO-2	TA1008
PFS	0.73	0.72	0.73	0.71	0.73
PPS	0.59	0.64	0.64	0.65	0.64
Detail	Regorafenib trial, used in TA405	Pooled FE FRESCO-2, CONCUR/CORRECT and SUNLIGHT	Pooled RE FRESCO-2, CONCUR/CORRECT and SUNLIGHT	Fruquintinib, 4L	Average from CORRECT and 1L cetuximab (used in TA405 scenario)

Abbreviations: FE; fixed effects, PFS; progression free state, PPS; post progressed state, RE; random effects

Key issue: Utilities

EAG comments

- Company approach is to pooling values is appropriate
- Use of FE model is justified, FE and RE models generate similar point estimates
- Concerned that the utilities derived from the SUNLIGHT (T/T+BVZ) trial are substantially higher than compared to other appraisals, particularly in the progressed population (0.68)
- It may be more appropriate to use the lower overall values from TA405 for decision making, as opposed to using the higher FRESCO-2 or TA1008 utility values to reflect the further progressed population

Which utility values are preferred?

Abbreviations: FE, fixed effects; RE, random effects; TT/BVZ, trifluridine tipiracil with bevacizumab

Key issue: Severity modifier calculations

Committee at ACM1

- Preferred to use the SACT data for T/T OS and mean starting age (65 years)

Company

- Mean age of 65 years may overestimate age of people eligible for fruquintinib in NHS practice
- Majority of fruquintinib use in 4L may differ to positioning seen in majority in SACT data
- Validated mean age of 59.4 from FRESCO AND FRESCO-2 trials with clinical advisory board
- Average age is expected to reduce as people progress through lines of therapy - younger and fitter patients tolerate additional lines of therapy and choose to continue with active treatment
- Mean age of 60 years accepted in TA866 (regorafenib) which is expected to be displaced
- Evidence from 9 RCTs showed a median age of 61.1 years (range 50-64)
- Severity modifier calculations sensitive to mean age

EAG comments

- Prefers to maintain consistency between the mean starting age and the OS curves from SACT data for calculating QALY severity weightings for use in the economic model
- Severity weighting is sensitive to both the utility values used in the base case analysis and the preferred OS extrapolation curve, and this sensitivity is greater at a starting age of 65 than at 59

What is the relevant starting age?

Abbreviations: RCT, randomised controlled trial; OS, overall survival; QALY, quality adjusted life year; SACT, systemic anti cancer therapies; T/T, trifluridine tipiracil

Severity weighting for standard care

Severity modifier is sensitive to both the utility values and age used

	Company base case	EAG base case	EAG + pooled utility values	EAG + RGF as SoC	EAG + RGF as SoC + pooled utility values	EAG + BSC as SoC	EAG + BSC as SoC + pooled utility values
Age	59	65	65	65	65	65	65
Female (%)	42%	42%	42%	42%	42%	42%	42%
Remaining disc QALYs	T/T: [redacted]	T/T: [redacted]	T/T: [redacted]	RGF: [redacted]	RGF: [redacted]	BSC: [redacted]	BSC: [redacted]
Absolute shortfall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Proportional shortfall	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severity weighting	X1.7	X1.7	X1.2	X1.7	X1.2	X1.7	X1.7

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

Abbreviations: BSC, best supportive care; EAG, external assessment group; QALY, quality adjusted life year; RGF, regorafenib; SOC, standard of care; T/T, trifluridine tipiracil

Other considerations

Equality

- No equalities issues raised at draft guidance consultation

Managed access

- Company has not made a managed access proposal

Uncaptured benefits

- Population with high unmet need
- Oral treatment with favourable safety profile
- Fruquintinib could expand choice for people who cannot have treatment with trifluridine tipiracil or regorafenib and post-progression on both therapies

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential

comparator PAS discounts

- There are confidential discounts in place for fruquintinib, regorafenib and trifluridine–tipiracil
- Both company's and EAG's ICERs were above the range NICE normally considers acceptable

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Outstanding issues

Issue and committee position in DG	ICER impact	Company analyses
Position in pathway: • Committee concluded that fruquintinib would be used as 3L or later treatment • comparators may change if other treatments introduced	Unknown	• Company agrees 3L or later with majority of use expected in 4L • Maintain regorafenib is most appropriate comparator
NMA results • Discrepancy between OS and PFS results. Improvement shown by fruquintinib may not translate into better OS	Unknown	• Clinical survey opinion: PFS should be the focus rather than OS
Survival extrapolation - Proportional hazards • Uncertainty in PH assumption; NMA assumed PH assumption holds	Unknown	• Implemented curve preferences • Submitted further analyses testing PH assumption compared with T/T
Relative dose intensity: • Trial-specific relative dose intensity for fruquintinib (89.6%), regorafenib (78.9%) and T/T (89.0%) should be used	Moderate	• Maintains that using the RDI from the pooled FRESCO and FRESCO-2 data for all treatments is most reasonable
Health state utilities: • Scenarios with CORRECT trial utility values and pooled utility values	Moderate	• Provides both scenarios
Mean age for severity modifier: • Prefer to use SACT data mean age of 65 years	Large	• Validated mean age from FRESCO and FRESCO-2 (59.4 years) with clinical advisory board

Abbreviations: DG, draft guidance; EAG, external assessment centre; EGFR, epidermal growth factor receptor; SACT, systemic anti-cancer therapy

Committee decision making

What are the committee's preferred assumptions

Assumption	Question for committee
Position in pathway	• Which position in the treatment pathway is most appropriate for fruquintinib? • What are the relevant comparators for fruquintinib?
NMA results	• Is PFS or OS most relevant outcome for this population?
Survival extrapolation	• Do proportional hazards apply for OS and PFS?
RDI	• Is pooled or treatment specific RDI data most appropriate for decision making?
Utilities	• Which utility values should be used?
Severity weighting	• What is the relevant starting age? • Is a QALY weighting appropriate? • What QALY weighting should be applied for each comparator?
Other issues	• Are there any uncaptured benefits that committee wants to consider?
Cost effectiveness threshold	• What is the committee's preferred ICER threshold?

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Abbreviations: ICER, incremental cost-effectiveness ratio; OS, overall survival; PFS, progression free survival; QALY, quality adjusted life year

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Thank you.

Fruquintinib for previously treated metastatic colorectal cancer

Supplementary appendix

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Key clinical trials

Clinical trial designs and outcomes

BSC, best supportive care; EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer; VEGF, vascular endothelial growth factor; PFS, progression-free survival; RR, response rate; DOR, duration of response; AE, adverse event

	FRESCO	FRESCO-2
Design	Randomised, double-blind, placebo-controlled, multicentre, phase 3 study	Randomised, double-blind, placebo-controlled, multicentre, phase 3 study
Population	Adults whose mCRC has progressed after two prior lines of treatment: chemotherapy, ± VEGF or EGFR inhibitors	Adults with refractory mCRC who have progressed on or been intolerant to treatment: chemotherapy, biological therapy and trifluridine-tipiracil and/or regorafenib
Intervention	Fruquintinib + BSC	
Comparator	Placebo + BSC	
Median follow-up	Fruquintinib: 13.3 months Placebo: 13.2 months	Fruquintinib: 11.3 months Placebo: 11.2 months
Primary outcome	OS	
Key secondary outcomes	PFS, RR, DOR, AEs	HRQoL, PFS, RR, DOR, AEs
Locations	China	UK, Australia, Japan, USA, Europe
Used in model?	Yes, pooled results	

Clinical trial results

Compared with placebo, fruquintinib offered better survival

Used in model

	FRESCO		FRESCO-2		Pooled results	
	Fruquintinib (N=278)	Placebo (N=138)	Fruquintinib (N=461)	Placebo (N=230)	Fruquintinib (N=739)	Placebo (N=368)
Overall survival						
Median, months (95%CI)	9.30 (8.18, 10.45)	6.57 (5.88, 8.11)	7.4* (6.7, 8.2)*	4.8* (4.0, 5.8)*	8.02 (7.43, 8.74)	5.55 (4.80, 6.24)
HR (95%CI)	0.65 (0.51, 0.83)		0.66 (0.55, 0.80)		0.660 (0.570, 0.764)	
p-value	<0.001		<0.001		<0.0001	
Progression-free survival						
Median, months (95%CI)	3.71 (3.65, 4.63)	1.84 (1.81, 1.84)	3.7* (3.5, 3.80)*	1.8* (1.8, 1.90)*	3.71 (3.65, 3.75)	1.84 (1.81, 1.87)
HR (95%CI)	0.26 (0.21, 0.34)		0.32 (0.27, 0.39)		0.308 (0.267, 0.355)	
p-value	<0.001		<0.001		<0.0001	

HR, hazard ratio; SE, standard error; CI, confidence interval, dp, decimal place

*reported by company as 1dp

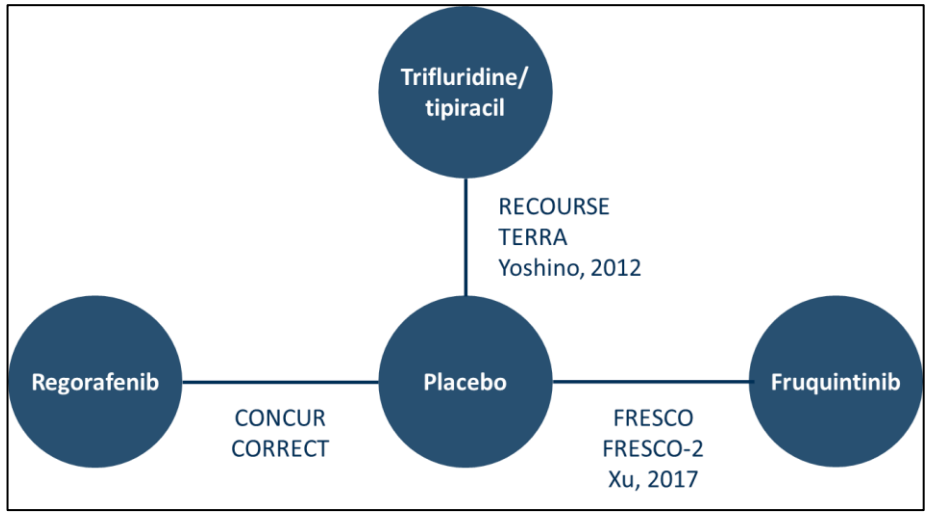
Indirect treatment comparison

No difference in OS between fruquintinib, regorafenib and trifluridine-tipiracil

Fruquintinib showed better PFS than regorafenib and trifluridine-tipiracil

- No clinical trial evidence directly comparing fruquintinib with the relevant active treatments
- Company submitted NMA

NMA methodology



Fixed effects NMA results

Fruquintinib vs	OS HR [95% CI]	PFS HR [95% CI]
BSC	0.66 [0.57, 0.76]	0.30 [0.26, 0.34]
Trifluridine-tipiracil	0.95 [0.78, 1.15]	0.67 [0.55, 0.80]
Regorafenib	0.93 [0.75, 1.16]	0.66 [0.54, 0.81]

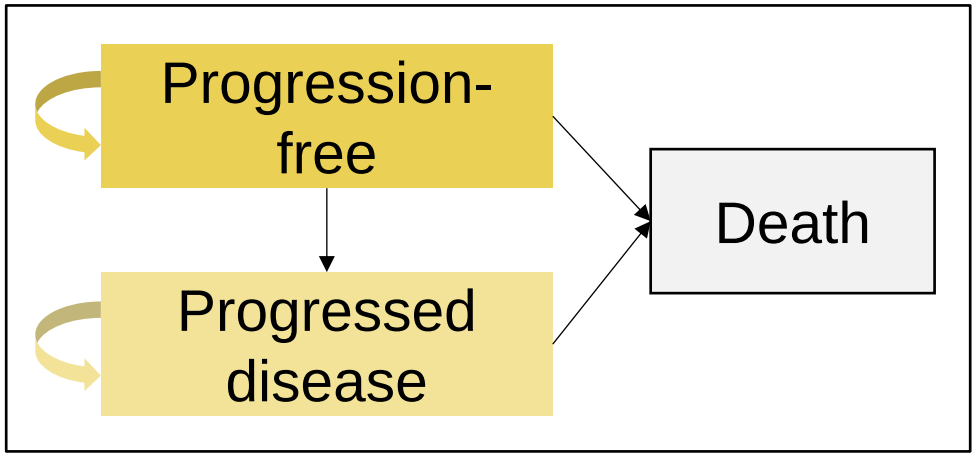
EAG:

- Satisfied with NMA methods and results
- Similar results obtained using fixed and random effects models

BSC, best supportive care; OS, overall survival; PFS, progression-free survival; NMA, network meta-analysis

Company's model overview

Model structure



- Technology affects **costs** by:
  - Increasing treatment costs compared with trifluridine-tipiracil and BSC
  - Increasing disease management costs, due to longer PFS
  - Reducing cost due to improved AE profile.
- Technology affects **QALYs** by:
  - Increasing overall survival
  - Increasing time in PFS state – improving quality of life
  - Improved AE profile – improving quality of life.
- Assumptions with greatest ICER effect:
  - Applying OS HRs directly from the NMA
  - Choice of RDI for comparators

BSC, best supportive care; PFS, progression-free survival; OS, overall survival; AE, adverse events; HR, hazard ratio; QALY, quality-adjusted life year; NMA, network meta-analysis; RDI, relative dose intensity

How company incorporated evidence into model

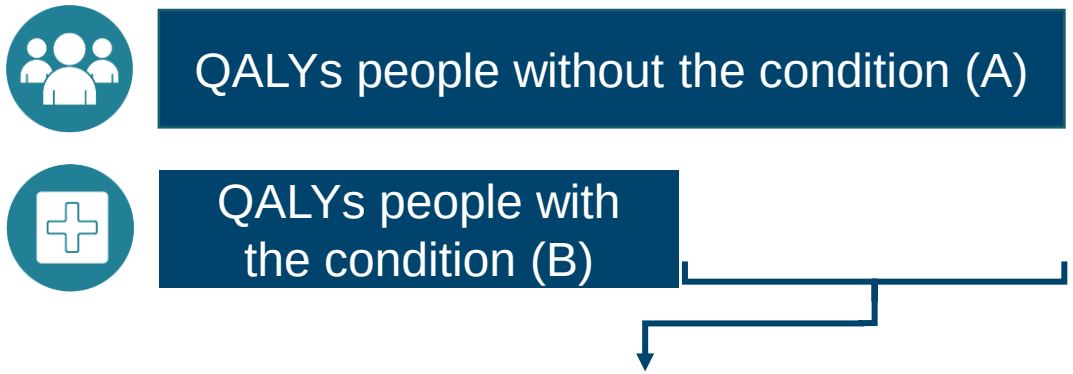
Input and evidence sources

Input	Assumption and evidence source
Baseline characteristics	Pooled FRESCO and FRESCO-2 data
Intervention efficacy	Pooled FRESCO and FRESCO-2 data
Comparator efficacy	Regorafenib and trifluridine-tipiracil: NMA HRs BSC: pooled FRESCO and FRESCO-2 data
Utilities	EQ-5D-3L data from CORRECT plus scenario using pooled values
Discount rate	3.5% for costs and QALYs
Time horizon	10 years
Cycle length	1 week
Costs	BNF, NHS reference costs 2021/22, PSSRU 2022
Resource use	TA866, SLR
Severity modifier	Baseline characteristics for pooled FRESCO and FRESCO-2 data

NMA, network meta-analysis; HR, hazard ratio; EQ-5D-3L; EuroQoL five-dimension three-level; PSSRU, Personal Social Services Research Unit; QALY, quality-adjusted life year

QALY weightings for severity

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