Fruquintinib for previously treated metastatic colorectal cancer

For public –
Fully redacted

Technology appraisal committee B 11 July 2024

Chair: Charles Crawley

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Company: Takeda

Fruquintinib for previously treated metastatic colorectal cancer

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

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Background on metastatic colorectal cancer

mCRC is a common cancer with poor 5-year survival rate

Description and causes

- Most cases are adenocarcinoma of the colon and rectum that has spread (metastasised) to other organs (such as the liver)
- Risk factors include family history and lifestyle e.g. low fibre and processed diet

Epidemiology and prognosis

- Around 43,000 new cases of colorectal cancer in the UK – 4th most common

  → 4 in 10 of all new cases are in people aged 75 and over
- 5-year survival rate for stage 4 mCRC is 10.5%

Symptoms

- Can include weight loss, change in bowel habit, rectal bleeding, and fatigue

Patient and clinical perspectives

mCRC has a life-changing impact, treatment options for advanced stage needed

Submissions from Bowel Cancer UK

- Can be life-changing for people diagnosed, including their family
- Impact critical for people with late-stage disease - there is lower survival chance
- Limited treatment options, fruquintinib expands treatment options for advanced disease

Debilitating. [Chemotherapy] affects quality of life greatly and in my case did not work

[Fruquintinib] should be available for those who want it, providing they feel fit enough to carry on with treatment

Submissions from clinical expert

- Fruquintinib well tolerated including in heavily pre-treated population, and preserves quality of life
- No other robust evidence for 4th-line treatment with high efficacy

Key issues

Issue	ICER impact
What is the appropriate position for fruquintinib in the mCRC pathway? • UK MA not yet received but could position fruquintinib as a 3L or 4L treatment • What are the relevant comparators at 3L and 4L?	Large 
What is the preferred method for extrapolating survival? • Does the proportional hazard assumption hold? • Should jointly or individually fitted models be applied? • How should comparator survival be extrapolated: digitized KM plots or NMA HR applied to fruquintinib curves or NMA HR applied to T/T SACT data? • Should the SACT dataset with NMA HRs be used for extrapolating OS?	Large 
What is the preferred method for modelling comparator relative dose intensity and time to treatment discontinuation? • Should the NHSE data be used for modelling subsequent treatment?	Large 

MA, marketing authorisation; HR, hazard ratio; mCRC, metastatic colorectal cancer; NMA, network meta-analysis; KM, Kaplan-Meier; RDI, relative dose intensity

Fruquintinib (Fruzaqla, Takeda)

Anticipated marketing authorisation	• [redacted] • Positive EMA CHMP opinion in April 2024 • UK MA expected [redacted] Positions as 3L
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	• Taken orally • 5 mg 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: £[redacted] per pack of 21 capsules 1 mg capsules: £[redacted] per pack of 21 capsules A confidential discount is in place for fruquintinib

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CHMP, Committee for Medicinal Products for Human Use; EGFR, epidermal growth factor receptor; EMA, European Medicines Agency; mCRC, metastatic colorectal cancer; VEGF, vascular endothelial growth factor

mCRC treatment pathway

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

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

Where would fruquintinib be positioned in NHS practice?

See NHS England data on subsequent treatment in mCRC

mCRC

	RAS wild-type	Other CRC	BRAF 600 mutation	MSI/MMR
1st line	Cetuximab (EGFR+) + Chemotherapy (TA439) Panitumumab + Chemotherapy (TA439)	Chemotherapy	Chemotherapy	Pembrolizumab (TA709) Chemotherapy
2nd line	Chemotherapy	Chemotherapy	Encorafenib + cetuximab (TA668)	Nivolumab + ipilimumab (TA716) Pembrolizumab (TA914)
3rd line	?Fruquintinib	Regorafenib (TA866)	Trifluridine/tipiracil (TA405)	BSC
4th line and 5th line	?Fruquintinib	Treatment (including BSC) not previously used at 3L		

*ongoing appraisals

Tucatinib + trastuzumab (ID6227)*

Trifluridine/tipiracil + bevacizumab (ID6298)*

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

Key Issue: Position in treatment pathway

ICER Impact: Large

Background

- Company positioned fruquintinib as a treatment for 3L onwards
- EMA opinion suggests use at 4L onwards (that is, after trifluridine-tipiracil or regorafenib)
- UK MA not yet received

Company

- Provided separate clinical data for both 3L+ (FRESCO) and 4L+ (FRESCO-2) use
- Base case used pooled data

EAG comments

- FRESCO-2 study is the most robust approach for 4L+ setting
- Active relevant comparator at 4L would be either regorafenib or T/T but not both
  →No subsequent treatment (5L) in modelling

"…previously treated with available standard therapies, including fluoropyrimidine-, oxaliplatin-, and irinotecan-based chemotherapies, anti-VEGF agents, and anti-EGFR agents, and who have progressed on or are intolerant to treatment with either trifluridine-tipiracil or regorafenib"

Summary of clinical trials

- What are the relevant comparators at 3L+ and 4L+?

NHS England data on subsequent treatment in mCRC

EMA, European Medicines Agency; mCRC, metastatic colorectal cancer; MA, marketing authorisation; 3L, third line; 4L, fourth line; T/T, trifluridine-tipiracil

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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	

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Clinical trial baseline characteristics

Baseline characteristics in fruquintinib trials

EAG:

- Ethnicity not a treatment modifier but prior VEGF is
- Mean age lower than UK clinical practice
- FRESCO-2 more pretreated people – reduced benefit

Pooled data 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
Mean age (SD)	54.3 (10.70)	55.1 (10.53)	62.2 (10.41)	62.4 (9.67)	59.2 (11.17)	59.7 (10.60)
Female, n (%)	120 (43.2)	41 (29.7)	216 (46.9)	90 (39.1)	336 (45.5)	131 (35.6)
Race, Asian, n (%)	278 (100)	138 (100)	43 (9.3)	18 (7.8)	321 (43.4)	156 (42.4)
ECOG PS 0, n (%)	77 (27.7)	37 (26.8)	196 (42.5)	102 (44.3)	273 (36.9)	139 (37.8)
ECOG PS 1, n (%)	201 (72.3)	101 (73.2)	265 (57.5)	128 (55.7)	466 (63.1)	229 (62.2)
Time since first diagnosis, months	21.48*	24.48*	47.18	49.38	[redacted]	[redacted]
Had mCRC for ≥18 months	115 (41.4)	63 (45.7)	424 (92.0)	217 (94.3)	[redacted]	[redacted]
Previously treated, n (%)						
VEGF inhibitor	84 (30.2)	41 (29.7)	445 (96.5)	221 (96.1)	529 (71.6)	226 (71.2)
EGFR inhibitor	40 (14.4)	19 (13.8)	180 (39.0)	88 (38.3)	220 (29.8)	107 (29.1)
trifluridine-tipiracil	0	0	240 (52.1)	121 (52.6)	240 (32.5)	121 (32.9)
regorafenib	0	0	40 (8.7)	18 (7.8)	40 (5.4)	18 (4.9)
trifluridine-tipiracil and regorafenib	0	0	181 (39.3)	91 (39.6)	181 (24.5)	91 (24.7)
>3 previous treatment lines for metastatic disease, n (%)	57 (20.5)	31 (22.5)	336 (72.9)	166 (72.2)	393 (53.2)	197 (53.5)

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ECOG PS; Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; mCRC, metastatic colorectal cancer; VEGF, vascular endothelial growth factor

*amended from years

Is it appropriate to pool these trials?

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, 3.8)*	1.8* (1.8, 1.9)*	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

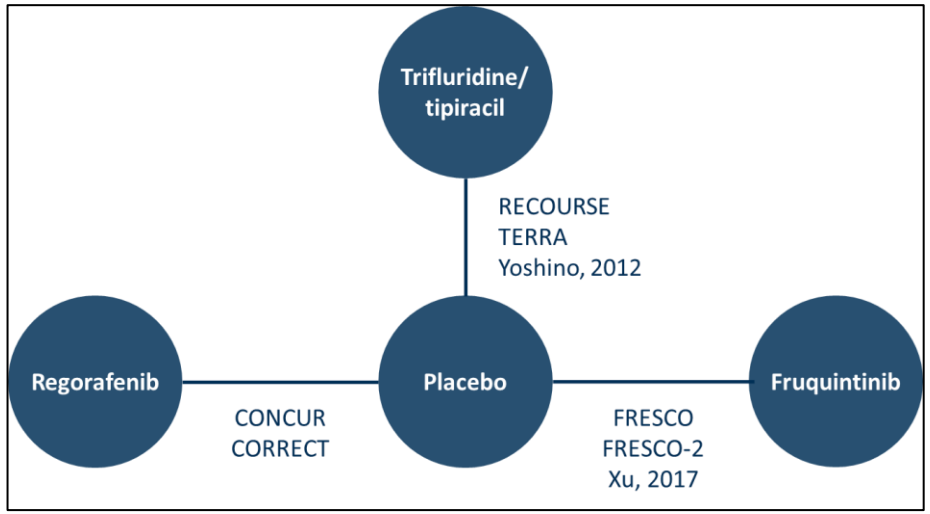
Indirect treatment comparison

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

Further details on NMA results

Fruquitinib 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

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- Are the NMA results plausible?
- Would better PFS be expected to lead to better OS?

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

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Key Issue: Survival models (1/2)

Company and EAG disagree on survival extrapolation

Company model: 3-state partitioned survival model

ICER Impact: Large

Background

- Company base case assumed proportional hazard (PH) and constant treatment effect
- Used jointly fitted parametric model for fruquintinib and BSC survival extrapolation
- For regorafenib and trifluridine-tipiracil, company applied HRs from the NMA to extrapolated fruquintinib curves

Company

- Although global test for PH not met, visual assessment of statistical plots and clinical advice suggests PH assumption holds
- Scenarios using independently fitted curves showed minimal impact on ICERs

EAG comments

Fruquintinib and BSC

- All jointly fitted curves with a good statistical fit underestimate BSC OS at year 1
  - → May bias results to favour fruquintinib
- Global PH test suggests PH assumption not met (p-value <0.05) for both OS and PFS
  - → **OS:** PH assumption may be reasonable based on visual assessment of plots
  - → **PFS**: PH assumption not reasonable based on similar visual assessment to OS
- Prefer individually fitted curves for fruquintinib and BSC survival extrapolations

Key Issue: Survival models (2/2)

Company and EAG disagree on survival extrapolation

ICER Impact: Large

EAG comments

Regorafenib and trifluridine-tipiracil

- Company base case not appropriate – proportional hazard assumption may not be met
- Prefer digitised KM curves from regorafenib (CORRECT) and trifluridine-tipiracil (RECOURSE and Yoshino) trials taken from literature and fitted with independent models
  - → Accept approach relies on naïve comparison across trials
  - → But not appropriate to fit HRs to parametric curves derived from non-proportional hazards models (such as log-normal used for company PFS)

Additional analysis using SACT OS data

- Further OS analysis using trifluridine-tipiracil SACT data and the following assumptions:
  - Applied parametric survival model to T/T OS SACT data (gen. gamma preferred)
  - Used the extrapolated T/T curve as reference curve
  - Applied company NMA HRs for fruquintinib, regorafenib and BSC to the reference curve.

BSC, best supportive care; HR, hazard ratio; KM, Kaplan-Meier; PFS, progression-free survival; PH, proportional hazard; OS, overall survival; SACT, systemic anti-cancer therapy; T/T, trifluridine/tipiracil

PFS extrapolation

Company: Jointly fit log-normal

EAG: Independently fit –
- Fruquintinib: log-normal
- BSC: log-logistic
- Regorafenib and T/T: log-normal

BSC, best supportive care; HR, hazard ratio; NMA, network meta-analysis; KM, Kaplan-Meier; PFS, progression-free survival; T/T, trifluridine-tipiracil

*undiscounted

Link to trial results

	Progression free at 2 years				Mean modelled PFS (months)*			
	Fruquintinib	T/T	Regorafenib	BSC	Fruquintinib	T/T	Regorafenib	BSC
Overall survival								
Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

OS extrapolation

Company: Jointly fit gen. gamma

EAG: Independently fit –
- Fruquintinib and BSC: log-normal
- Regorafenib and T/T: gen. gamma

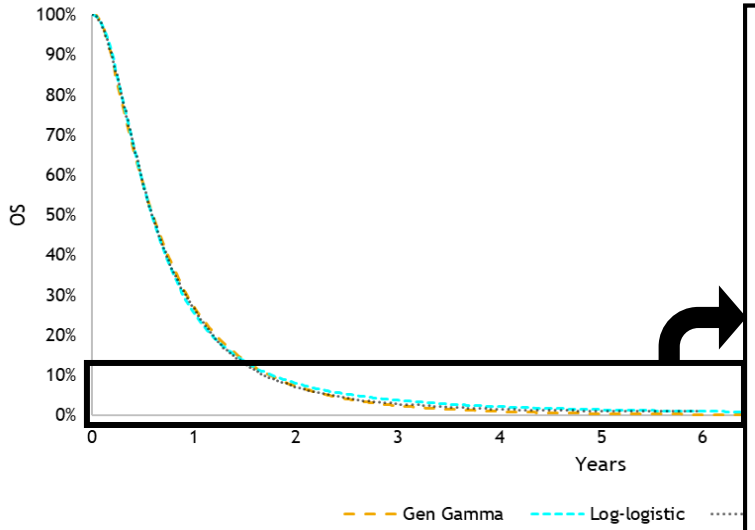
BSC, best supportive care; HR, hazard ratio; NMA, network meta-analysis; KM, Kaplan-Meier; OS, overall survival; T/T, trifluridine-tipiracil

*undiscounted

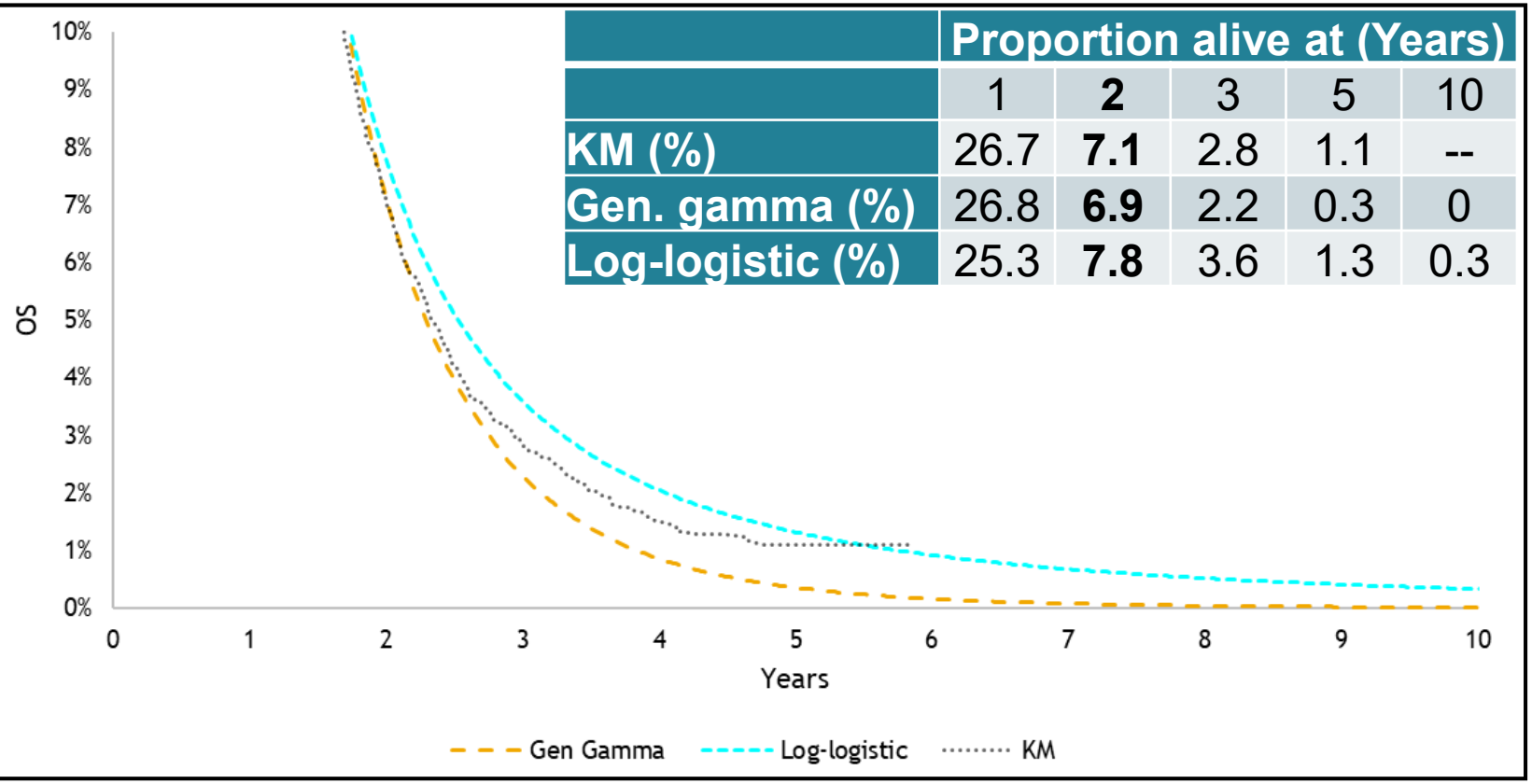
Link to trial results

	Proportion alive at 2 years				Mean modelled OS (months)*			
	Fruquintinib	T/T	Regorafenib	BSC	Fruquintinib	T/T	Regorafenib	BSC
Overall survival								
Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
EAG base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

OS extrapolation - additional analysis with T/T SACT data



	Proportion alive at (Years)				
	1	**2**	3	5	10
KM (%)	26.7	**7.1**	2.8	1.1	--
Gen. gamma (%)	26.8	**6.9**	2.2	0.3	0
Log-logistic (%)	25.3	**7.8**	3.6	1.3	0.3



EAG:

- Prefer gen. gamma fit to SACT OS data
- Gen. gamma better estimates at years 2 and 3
- Log-log. lacks face validity, n survival expected at year 10
- Log-log. extend OS benefit indefinitely, may require treatment waning applied

What is the preferred method for extrapolating survival?

- Does proportional hazard assumption hold?
- Should jointly or individually fitted models be applied?
- How should comparator survival be extrapolated: digitized KM plots or NMA HR applied to fruquintinib curves?
- Should the SACT dataset with NMA HRs be used for extrapolating OS?

HR, hazard ratio; KM, Kaplan-Meier; NMA, network meta-analysis; OS, overall survival; T/T, trifluridine-tipiracil

Key Issue: Relative dose intensity and treatment discontinuation

ICER Impact: Large

Background

- Company assumed equal RDI (89.6%) for fruquintinib, regorafenib, and trifluridine-tipiracil
- Applied PFS HRs from NMA to fruquintinib TTD curves to calculate acquisition cost for regorafenib and trifluridine-tipiracil

Company

- RDI estimates for pooled regorafenib and trifluridine-tipiracil trial data not public

Non-pooled trial RDIs available for regorafenib (CORRECT) and trifluridine-tipiracil (RECOURSE, Yoshino)

EAG comments

- Company approach overestimates comparator acquisition costs
- Assumes all discontinuation similar to PFS and constant over time
  - →Unlikely because treatments have different AEs
  - →Regorafenib may have higher initial discontinuation due to toxicity concerns
- EAG prefers exponential discontinuation based on median TTD reported in regorafenib trial and log-normal curve for digitized TTD KM from T/T trials
- For RDI, prefer treatment-specific RDI reported in the clinical trials

RDI, relative dose intensity; PFS, progression-free survival; HR, Hazard ratio, TTD, time to discontinuation; KM, Kaplan-Meier; AEs, adverse events, T/T, trifluridine-tipiracil

Treatment discontinuation

[redacted]

Company
Fruquintinib: log-normal
Regorafenib and T/T: PFS HRs from the NMA applied to extrapolated fruquintinib curves

EAG
Fruquintinib: Gen. Gamma
Regorafenib: exponential curve to median TTD reported in trial
TT: log-normal for digitised TTD KM from trial

NMA, network meta-analysis; PFS, progression-free survival; HR, hazard ratio; T/T, trifluridine-tipiracil; TTD, time to discontinuation; RDI, relative dose intensity

Relative dose intensity

RDIs used for company and EAG base case

	Fruquintinib	Regorafenib	T/T	Sources
Company base case	89.6%	89.6%	89.6%	Pooled FRESCO and FRESCO-2
EAG base case (RDIs from individual trial data)	89.6%	78.9%	89%	Pooled FRESCO and FRESCO-2, CORRECT and RECOURSE trials

Additional analysis - treatment discontinuation and subsequent treatment

EAG comment

Regorafenib TTD

- For consistency with recent NICE appraisal (ID6298), explored analysis assuming a fixed proportion of people who are progression free would have regorafenib, using:
  - Mean time on treatment from regorafenib trial (CORRECT) divided by mean modelled regorafenib progression-free survival in company base case

Subsequent treatment

- NHSE data suggests after 3L treatment, around 35% of people will have post-progression treatment
- Applied this value in scenario analysis

- What is the preferred method for modelling comparator RDI and TTD?
- Should the NHSE data be used for modelling subsequent treatment?

TTD, time to discontinuation; NHSE, NHS England

Utility values

#Company base case. Committee preferred CORRECT (post-progression: 0.59)

FRESCO-2 EQ-5D-3L utility values (base case) compared with previous NICE appraisals

	FRESCO-2	TA866	TA405#	ID6298* (EAG)
Progression-free	0.71	0.72	0.73	0.759
Post-progression	0.65	0.59	0.64	0.681
Progression decrement	-0.06	-0.13	-0.09	-0.08

*ongoing appraisal

- Severity weighting sensitive to source of utility values
- ID6298, TA866 and TA405 utilities from 3L population
- Fruquintinib utilities from FRESCO-2 trial → people who have had or cannot have regorafenib or T/T (4L population, more pretreated)

Which utility values are preferred?

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Severity – company and EAG agree on 1.7 weighting

Source	Characteristic		T/T	Regorafenib	BSC
Pooled FRESCO and FRESCO-2 (3L)	Mean age: 59.4	QALYs*	0.58	0.57	0.42
	% women: 42.2	Absolute shortfall	12.44	12.45	12.60
		Proportional shortfall	95.55%	95.62%	96.78%
		Weighting		**x1.7**	
FRESCO-2 only (4L)	Mean age: 62.2	QALYs#	0.55	0.52	0.44
	% women: 44.3	Absolute shortfall	11.44	11.47	11.55
		Proportional shortfall	95.41%	95.66%	96.33%
		Weighting		**x1.7**	
SACT data (with pooled FRESCO and FRESCO-2 % women; 3L)	Mean age: 65	QALYs#	0.53	0.52	0.39
	% women: 42.2	Absolute shortfall	10.38	10.41	10.54
		Proportional shortfall	95.15%	95.24%	96.43%
		Weighting		**x1.7**	

*Company base case
#Based on EAG model

Details of utility values | Details of shortfall calculation | Details of SACT data

QALY, quality-adjusted life year

Summary of company and EAG base case assumptions

Assumptions in company and EAG base case

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Assumption	Company base case	EAG base case
OS extrapolation (Fruquintinib and BSC)	Jointly fit curves (gen. Gamm)	Independently fit curves (log-normal)
PFS extrapolation (Fruquintinib and BSC)	Jointly fit curves (log-normal)	Independently fit curves, Fruquintinib: log-normal BSC: log-logistic
OS extrapolation (regorafenib and T/T)	Applied HR from NMA to fruquintinib curve (gen. Gamma)	Independently fit curves to digitised KM data (gen. Gamma)
PFS extrapolation (regorafenib and T/T)	Applied HR from NMA to fruquintinib curve (log-normal)	Independently fitted curves to digitised KM data (log-normal)
TTD: Fruquintinib	Log-normal	Gen. gamma
TTD: Regorafenib and T/T	Applied PFS HR from NMA to fruquintinib curve	Used median time on treatment reported in trials and digitised TTD KM
RDI	Same RDI for fruquintinib, regorafenib and T/T	Treatment specific RDIs based on key clinical trials
Background treatment cost	BNF	eMIT
Resource use	Medical oncology visit every 4 weeks	Additional 2 visits for regorafenib
Subsequent treatment	Pooled FRESCO and FRESCO-2	Company clinical expert opinion
Duration of subsequent treatment	1 week	8 weeks

Summary of cost-effectiveness estimates

ICERs reported in Part 2 because they include confidential comparator PAS

Company base case: above the range normally considered cost-effective use of NHS resources regardless of the severity weighting applied

EAG base case: above the range normally considered cost-effective use of NHS resources regardless of the severity weighting applied

PART 2:

- Committee to discuss company and EAG preferred assumptions including assumptions with the greatest impact on the ICER:
  - Regorafenib & trifluridine-tipiracil TTD curves based on median time on treatment in trials
  - OS and PFS extrapolations
  - Positioning of fruquintinib in the mCRC pathway

TTD, time to discontinuation

Company and EAG preferred assumptions

Base case: fully incremental

Fruquintinib for previously treated metastatic colorectal cancer

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

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Equality considerations

Company and patient organisation (Bowel Cancer UK):

No equality issues relating to the use of fruquintinib have been identified.

Managed access

Company has not made a managed access proposal

The committee can make a recommendation with managed access if:

- the technology cannot be recommended for use because the evidence is too uncertain
- the technology has the **plausible potential** to be cost effective at the **currently agreed price**
- new evidence that could **sufficiently support the case for recommendation** is expected from ongoing or planned clinical trials, or could be collected from people having the technology in clinical practice
- data could feasibly be collected within a reasonable timeframe (up to a **maximum of 5 years**) without **undue burden**.

Fruquintinib for previously treated metastatic colorectal cancer

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

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Key issues

Key issue	ICER impact	Slide
What is the appropriate position for fruquintinib in the mCRC pathway?	Large	8
What is the preferred method for extrapolating survival?	Large	15
What is the preferred method for modelling comparator relative dose intensity and time to treatment discontinuation?	Large	20

mCRC, metastatic colorectal cancer

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Thank you.

Supplementary appendix

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Decision problem

Population, intervention, comparators and outcomes from the scope

	Final scope	Company	EAG comments
Population	People with metastatic colorectal cancer (mCRC) who have had two or more previous treatments	[redacted]	No comment
Intervention	Fruquintinib	As per final scope	No comment
Comparators	• Trifluridine-tipiracil monotherapy • Regorafenib • Best supportive care	As per final scope	No comment
Outcomes	• OS, PFS, AEs, HRQoL, RR	As per final scope	No comment

AEs, adverse events; HRQoL, health-related quality of life; PFS, progression-free survival; OS, overall survival; RR, response rate

Overall survival results

Pooled FRESCO and FRESCO-2 overall survival Kaplan-Meier curves

BSC, best supportive care

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Progression-free survival results

Pooled FRESCO and FRESCO-2 progression-free survival Kaplan-Meier curves

BSC, best supportive care

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Adverse events

EAG clinical expert: AEs are as expected, no further concerns

	FRESCO		FRESCO-2	
	Fruquintinib + BSC N=278	Placebo + BSC N=137	Fruquintinib + BSC N=456	Placebo + BSC N=230
People with any TEAE, n (%)	274 (98.6)	121 (88.3)	451 (98.9)	213 (92.6)
CTCAE Grade ≥3	170 (61.2)	27 (19.7)	286 (62.7)	116 (50.4)
Treatment-related	266 (95.7)	97 (70.8)	395 (86.6)	130 (56.5)
Treatment-related CTCAE Grade ≥3	128 (46.0)	10 (7.3)	164 (36.0)	26 (11.3)
Leading to dose reduction	67 (24.1)	6 (4.4)	110 (24.1)	9 (3.9)
Leading to dose interruption	98 (35.3)	14 (10.2)	213 (46.7)	61 (26.5)
Leading to treatment discontinuation	42 (15.1)	8 (5.8)	93 (20.4)	49 (21.3)
Treatment-related leading to dose reduction	61 (21.9)	3 (2.2)	93 (20.4)	7 (3.0)
Treatment-related leading to dose interruption	87 (31.3)	10 (7.3)	134 (29.4)	14 (6.1)
Treatment-related leading to treatment discontinuation	22 (7.9)	1 (0.7)	45 (9.9)	7 (3.0)
TEAE leading to death	9 (3.2)	2 (1.5)	49 (10.7)	45 (19.6)
Treatment-related TEAE leading to death	4 (1.4)	0	1 (0.4)	1 (0.5)
People with any serious TEAE, n (%)	43 (15.5)	8 (5.8)	172 (37.7)	88 (38.3)

NICE

TEAE, Treatment-emergent adverse event; CTECAE; Common Terminology Criteria for Adverse Events

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Potential treatment modifiers on ITC results

Company:

- Did scenario analysis (fixed effect) on the impact of the listed effect modifiers on OS and PFS results for fruquintinib vs its comparators – trifluridine-tipiracil, and regorafenib
- Results consistent with the base case NMA
  → OS for 'no prior anti-VEGF' subgroup from a small population

Potential treatment modifiers
Prior anti-VEGF
No prior anti-VEGF
With liver metastasis
No liver metastasis
Asian
Non-Asian
ECOG PS 0
ECOG PS 1

OS:
Trifluridine-tipiracil - no significant difference
Regorafenib – significant difference in 'No prior anti-VEGF' subgroup"
→HR 1.89 (1.05, 3.40)

EAG: data should be interpreted with caution due to the small population numbers informing these analyses

ECOG PS; Eastern Cooperative Oncology Group performance status; EGFR, epidermal growth factor receptor; HR, hazard ratio; NMA, network meta-analysis; OS, overall survival; VEGF, vascular endothelial growth factor

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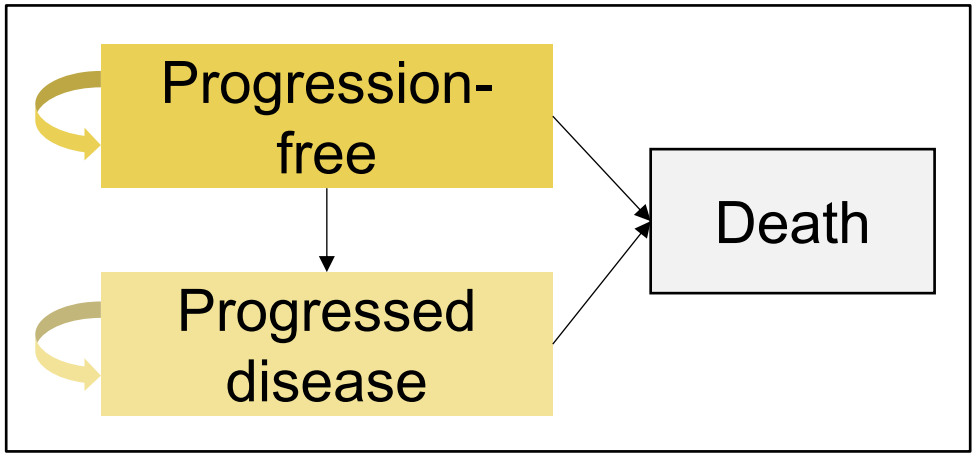
Company's model overview

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

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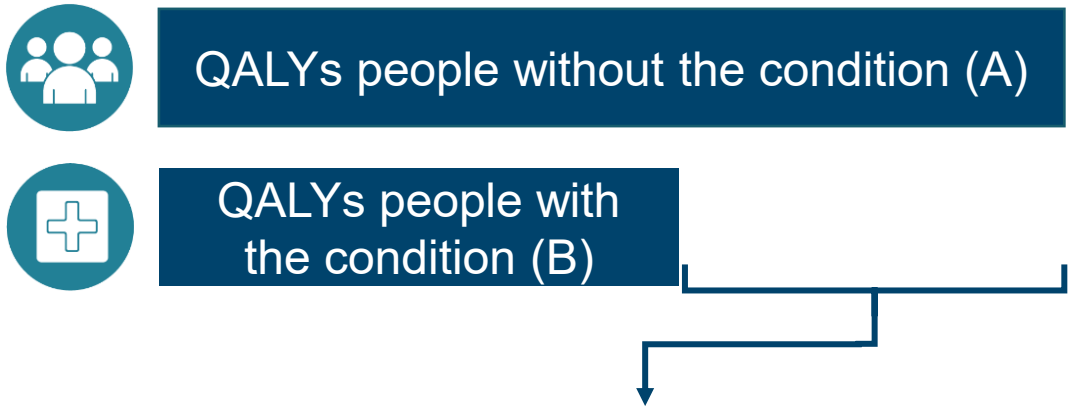
QALY weightings for severity

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

→ **whichever implies the greater severity**.

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, quality-adjusted life year

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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 FRESCO-2
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

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Subsequent treatment

NHS England data on subsequent treatment numbers at 3L and 4L

	T/T	Regorafenib
3L	1200	500
4L	500	100

Subsequent treatment estimates aligned with company clinical expert opinion (used for EAG base case)

Primary treatment	Proportion receiving subsequent anti-cancer treatment	Subsequent therapy: regorafenib (%)	Subsequent therapy: trifluridine-tipiracil (%)
Fruquintinib	20%	0%	100%
Regorafenib	5%	0%	100%
Trifluridine-tipiracil	20%	100%	0%
BSC	0%	0%	0%

BSC, best supportive care; T/T, trifluridine-tipiracil

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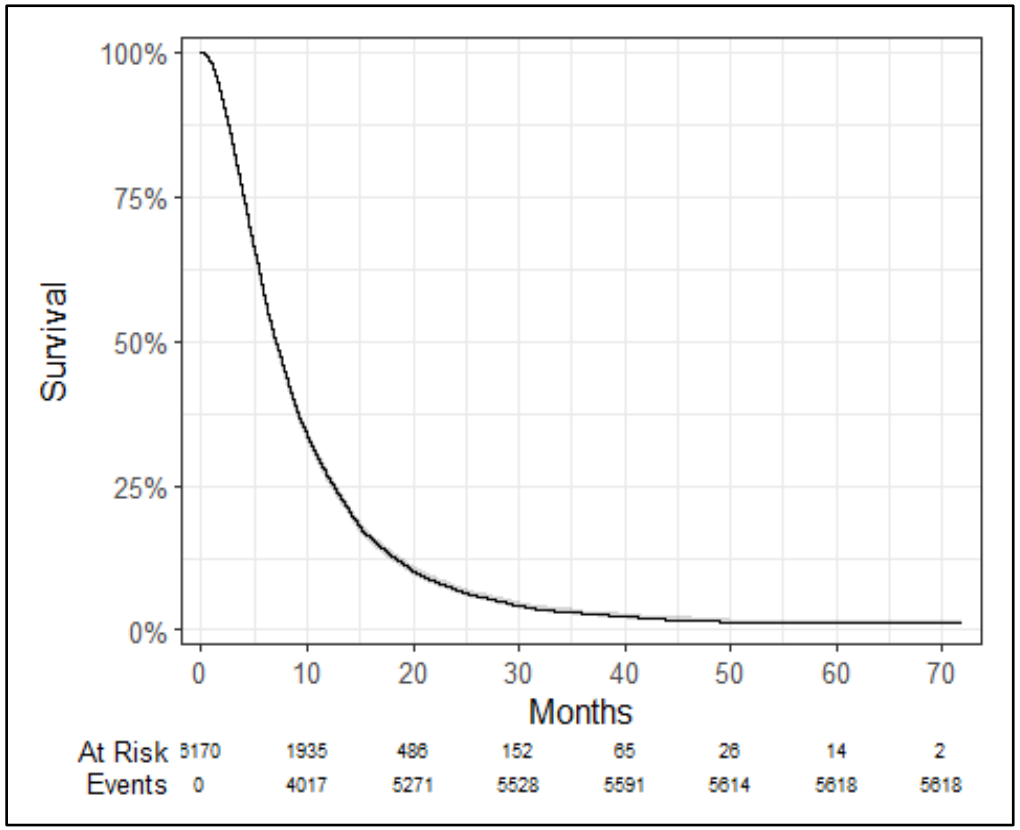
Additional RWE – SACT data analysis pilot

- 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

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