Regorafenib for treating metastatic colorectal cancer

Slides for PUBLIC – redacted

Technology appraisal committee B 10 November 2022

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Background on metastatic colorectal cancer (mCRC)

mCRC has high number of new cases with poor 5-year survival rates

Definition

- Malignant tumour arising from the lining of the large intestine (colon and rectum), which has spread beyond the large intestine and lymph node
- Most colorectal cancers are adenocarcinomas, these start in glands that line the insides of the colon and rectum and often first spread (metastasise) to the liver

Causes

- Uncertain but higher frequency seen in people who consume high-fat, low-fibre diet
- Higher risk in people with ulcerative colitis, Crohn's disease, and two inherited diseases: familial adenomatous polyposis and hereditary non-polyposis colon cancer

Epidemiology and prognosis (colorectal cancer)

- 33,815 cases of colon cancer and 16,628 cases of rectum cancer in the UK in 2020
- For people diagnosed at stage IV (mCRC), the 1 and 5-year survival rates are 44% and 10% respectively

Regorafenib (Stivarga, Bayer)

Technology details

Marketing authorisation	• Granted in August 2013 • For the treatment of adult patients with metastatic colorectal cancer (CRC) who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy
Mechanism of action	• A multi-kinase inhibitor. It blocks several enzymes that are important for the development of a blood supply to the tumours and development of cancer cells, stopping the growth and spread of the cancer
Administration	• Administered orally • 160 mg (4 tablets of 40 mg) taken once daily for 3 weeks followed by 1 week off therapy. This 4-week period is considered a treatment cycle
Price	• £3,744 per pack (84 x 40mg tablets) • One pack covers a 28-day treatment cycle • A confidential discount is in place for regorafenib and some of its comparators

EGFR, epidermal growth factor receptor; VEGF, vascular endothelial growth factor

Key issues

Issue	Resolved?	ICER impact
What is the appropriate treatment population for regorafenib and what are the relevant comparators?	No – for discussion	Large
Which data sources are most appropriate for estimating the relative treatment effect of regorafenib vs T/T?	No – for discussion	Large
What is the impact of different study population on pooled and comparative estimates and how relevant is the trial population to UK clinical practice?	Partially – for discussion	Unknown
Is it appropriate to apply a severity weighting for regorafenib in mCRC?	No – for discussion	Unknown
Is it appropriate to include subsequent treatments in the cost-effectiveness estimates for regorafenib?	No – for discussion	Unknown
What is the correct method of survival extrapolation for regorafenib?	No – for discussion	Small
Should grade 1 and 2 (mild and moderate) adverse events be included in the cost-effectiveness estimates for regorafenib?	Partially – for discussion	Small
What is the correct method of estimating the RDI for T/T?	No – for discussion	Small

mCRC, metastatic colorectal cancer; RDI, relative dose intensity; T/T, trifluridine/tipiracil

Decision problem

Regorafenib being considered for a more precise population than in the final scope

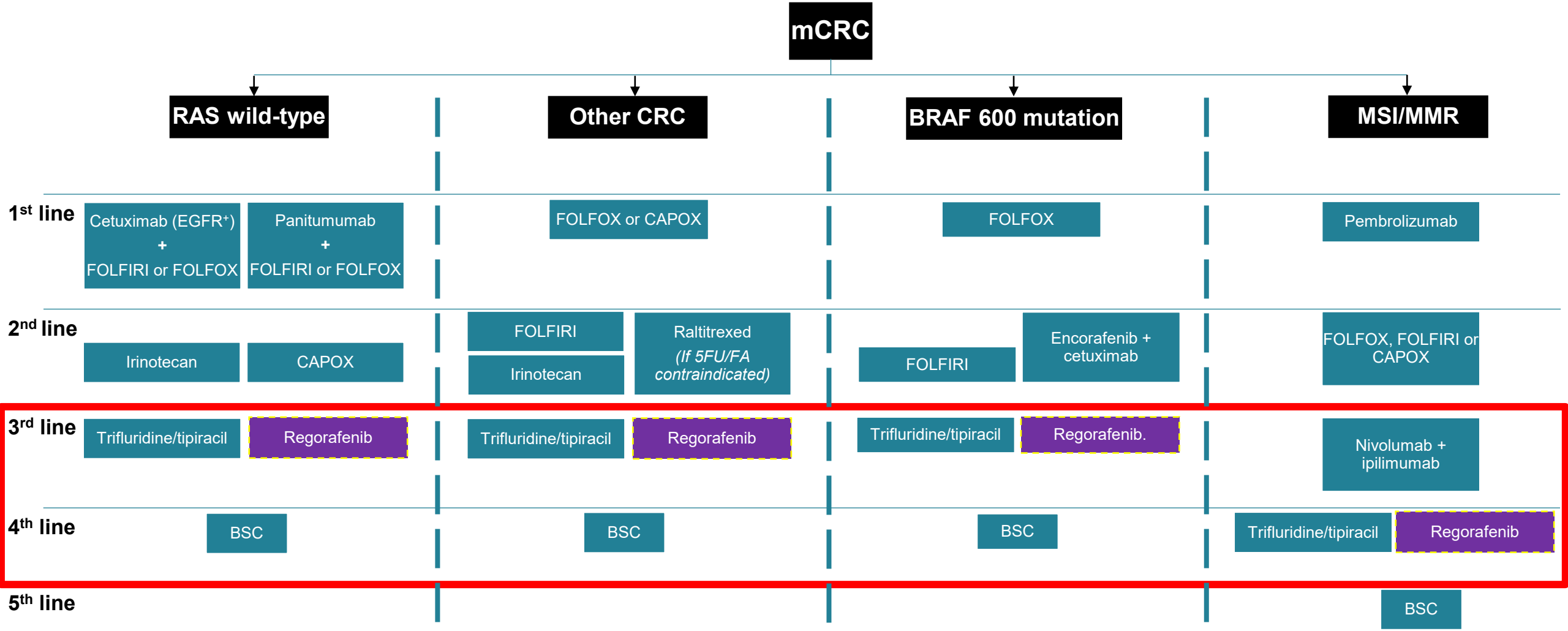
Optimised

	Final scope	Company	EAG comments
Population	Adults with mCRC previously treated with or not considered candidates for available therapies	Adults with mCRC who have failed on first-line chemotherapy/first-line biologic and are being considered for ≥third-line treatment. Specifically, patients for whom T/T is being considered	More precise population
Intervention	Regorafenib		
Comparators	Irinotecan, FOLFOX, FOLFIRI, CAPOX, raltitrexed, T/T, and BSC	• T/T (main comparator) • only active treatment at ≥3rd-line • BSC (minor comparator)	• T/T justification acceptable but unclear how BSC can also be a comparator • BSC as a "minor comparator" contradicts definition according to eligibility for T/T
Outcomes	Overall survival, progression free survival, response rates, adverse events and HRQoL	Overall survival, progression free survival, response rates, adverse events and HRQoL	Only overall survival and progression free survival for comparison with T/T

T/T, trifluridine/tipiracil, FOLFOX, folinic acid, fluorouracil and oxaliplatin; FOLFIRI, folinic acid, fluorouracil and irinotecan; CAPOX, capecitabine and oxaliplatin; BSC, best supportive care, HRQoL, health-related quality of life;

Treatment pathway

Regorafenib is being considered for third or subsequent-line in the mCRC pathway



NICE

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

Key issue: Appropriate population

Unclear definition of eligible population and suitable placement in treatment pathway

ICER impact: Large

Background

- In 2017 NICE TA405 recommended T/T, if fluoropyrimidine-, oxaliplatin-, or irinotecan-based chemotherapies, anti-VEGF agents and anti-EFGR agents have failed or when these agents are not suitable
- 2013 regorafenib licence: “treatment of adult patients with mCRC who have been previously treated with, or are not considered candidates for, available therapies. These include fluoropyrimidine-based chemotherapy, an anti-VEGF therapy and an anti-EGFR therapy”

Company

- Narrows population: “those who are being considered for ≥ 3rd-line treatment. Specifically, we are seeking a recommendation for patients for whom treatment with trifluridine/tipiracil (T/T) is being considered”
- T/T is the only treatment available at ≥3rd-line for people who are fit enough to receive active treatment
- Other active treatments in scope were available before regorafenib licenced so fall under “available therapies”
- After failure of ≥3rd line (currently T/T), majority of patients no longer fit enough for active treatment
- BSC not a comparator as regorafenib used earlier than BSC, limited BSC analyses provided for completeness

EAG comments

- “Available therapy” suggests all therapies including T/T. With this definition, regorafenib would be offered later than the company proposes and BSC would be the relevant comparator

What is the appropriate positioning of regorafenib in the treatment pathway?
Is BSC an appropriate comparator for all or a particular subgroup?

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

Patient perspectives

Patients report the impact of mCRC on daily life, and welcome more treatment options

Submission from Bowel Cancer UK

- Diagnosis of mCRC is life-changing for individual and their family especially for those diagnosed at later stages when it is harder to treat and chances of survival is low
- Impacts daily life and mental health
- Survival rates for advanced colorectal cancer patients are poor, <10% survive beyond 5 years
- Essential that patients gain timely access to treatment
- Limited options for people at third-line and beyond
- People have reported resorting to fundraising for private treatment
- Regorafenib is given as a tablet and has a different side effect profile giving people more options

"It's devastating for everyone involved with that person. It changes your life forever"

"Extremely stressful knowing the treatment currently available will sooner, or later stop working"

"Provided another line of defence. Instead of only 3 lines of treatment"

Patient expert comments

- Chemotherapy side effects affected my quality of life, new treatment with different side effect welcome

"[After] one cycle…it has been pretty positive - milder side effects … I have had more energy to take part in normal activities"

Clinical perspectives

Clinical experts welcome regorafenib as an alternative option at third or subsequent line

Submission from NCRI

- There is an unmet need in people with mCRC whose disease has progressed on earlier lines of treatment
- The current options for this group of people are limited: palliative care or supportive care, and referral to early phase clinical trial (where available)
- Regorafenib could provide longer period of disease control and overall survival in people with mCRC who are fit enough after third-line treatment - there is no approved alternative
- Current practice typically restricts use of T/T to those with good performance status and with clear evidence of response to earlier lines of therapy. Regorafenib provides an alternative treatment for this group of people
- Related side effects can be managed by dosing adjustments
- Similar administration to T/T (both oral) so no additional healthcare resource use expected

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key intervention clinical trials

Two phase III RCTs were pooled to provide efficacy results for regorafenib

Regorafenib clinical trial designs and outcomes

	CORRECT	CONCUR
Completed	2011 (primary completion)	2013 (primary completion)
Design	Randomised, double-blind, placebo-controlled multi-centre phase III study	Randomised, double-blind, placebo-controlled multi-centre phase III study
Population	Adults ≥18 years with mCRC (stage IV) who had progressed disease within 3 months on approved standard treatment	**Asian** adults ≥18 years with mCRC (stage IV) who had progressed disease within 3 months on **two-lines** of approved standard treatment
Intervention	Regorafenib plus BSC	Regorafenib plus BSC
Comparator(s)	Placebo plus BSC	Placebo plus BSC
Primary outcome	OS	OS
Key secondary outcomes	PFS, ORR, and DCR	PFS, ORR, and DCR
Locations	Global: 15 countries; no UK patients	Asia; no UK patients
Used in model?	Yes	Yes

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BSC, best supportive care, PFS, progression-free survival; DCR, disease control rate; AEs, adverse events; ORR, overall response rate; DOR, duration of response

Results: CORRECT and CONCUR (efficacy regorafenib vs placebo)

Results of individual trial – CORRECT and CONCUR

	CORRECT		CONCUR	
	Regorafenib + BSC (N=505)	Placebo + BSC (N=255)	Regorafenib + BSC (N=136)	Placebo + BSC (N=68)
Overall survival				
Events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median, months (95% CI)	6.4 [redacted]	5.0 [redacted]	8.8 [redacted]	6.3 [redacted]
Hazard ratio (95% CI)	0.77 (0.64, 0.94)		0.55 (0.40, 0.77)	
Progression-free survival				
Events, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median, months (95% CI)	1.9 [redacted]	1.7 [redacted]	3.2 [redacted]	1.7 [redacted]
Hazard ratio (95% CI)	0.49 (0.42, 0.58)		0.31 (0.22, 0.44)	

Results of direct meta-analysis (CORRECT+CONCUR pooled)

Used for ITC

	Overall survival	Progression-free survival
Fixed effect model hazard Ratio (95% CI)	0.68 (0.59, 0.79)	0.42 (0.39, 0.45)
Random effect model hazard Ratio (95% CI)	0.66 (0.47, 0.91)	0.39 (0.25, 0.61)

NICE

Adverse events reported in regorafenib clinical trials

Incidence rates of any grade (1-5) adverse events occurring in >10% of people in the regorafenib trials

	CORRECT		CONCUR	
	Cut-off date of 22 January 2014, n (%)		Cut-off date of 14 January 2016, n (%)	
	Regorafenib (N=500)	Placebo (N=253)	Regorafenib (N=136)	Placebo (N=68)
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]
Anorexia	[redacted]	[redacted]	[redacted]	[redacted]
Hand-foot skin reaction	[redacted]	[redacted]	[redacted]	[redacted]
Diarrhoea	[redacted]	[redacted]	[redacted]	[redacted]
Weight loss	[redacted]	[redacted]	[redacted]	[redacted]
Voice changes	[redacted]	[redacted]	[redacted]	[redacted]
Hypertension	[redacted]	[redacted]	[redacted]	[redacted]
Rash/desquamation	[redacted]	[redacted]	[redacted]	[redacted]
Fever	[redacted]	[redacted]	[redacted]	[redacted]
Mucositis (functional/ symptomatic), oral cavity	[redacted]	[redacted]	[redacted]	[redacted]
Bilirubin (hyperbilirubinemia)	[redacted]	[redacted]	[redacted]	[redacted]

Key comparator clinical trials

No direct evidence for comparison with T/T.
Three separate T/T RCTs vs placebo were considered for indirect comparison

	RECOURSE (N=800)	TERRA (N=406)	Yoshino 2012 (N=169)
Completion	2014 (primary completion)	2016 (primary completion)	2010 (primary completion)
Design	Multicentre, double-blind phase III placebo-controlled RCT	Multicentre, double-blind phase III placebo-controlled RCT	Multicentre, double-blind **phase II** placebo-controlled RCT
Population	Adults ≥ 18 years with mCRC who have received two previous courses of treatment	Adults ≥ 18 years with mCRC who have received two previous courses of standard treatment	Adults ≥20 years with mCRC who have received two previous courses of standard treatment
Primary outcome	OS	OS	OS
Secondary outcomes	PFS, RR, DCR, and AEs	PFS, ORR, DCR, DOR, and AEs	PFS, ORR, DCR, DOR, and AEs
Locations	Europe (including UK), USA, Japan, Australia	China, South Korea and Thailand	Japan
Used in NMA?	Yes	Yes	Yes
Results			
Overall survival HR	0.68 (0.58, 0.81)	0.79 (0.62, 0.99)	0.56 (0.39, 0.81)
Progression free survival HR	0.48 (0.41, 0.57)	0.43 (0.34, 0.54)	0.41 (0.28, 0.59)

T/T, trifluridine/tipiracil; PFS, progression-free survival; DCR, disease control rate; AEs, adverse events; ORR, overall response rate; DOR, duration of response

Comparison of key baseline characteristics

There are differences in the participants of the trials included in the ITC

	CORRECT		CONCUR		RECOURSE		TERRA		Yoshino 2012	
	Regorafenib	Placebo	Regorafenib	Placebo	T/T	Placebo	T/T	Placebo	T/T	Placebo
Sample size (N)	505	255	136	68	534	266	271	135	112	57
Age (years, median)	61	61	57.5	55.5	63	63	58	56	63	62
Women	38%	40%	38%	51%	39%	38%	37%	38%	43%	51%
Race (Asian)	15%	14%	100%	100%	34%	35%	100%	100%	100%	100%
Prior targeted biological treatment	100%	100%	59%	62%	100%	>99%	45%	51%	88%	82%
≥4 previous treatment lines on/after metastases	49%	47%	38%	40%	60%	63%	50%	55%	NR	NR
KRAS mutation	54%	62%	34%	26%	51%	51%	37%	37%	55%	52%
Time from diagnosis of first metastases (<18 m)	18%	19%	39%	47%	21%	21%	49%	39%	NR	NR
ECOG PS 0	52%	57%	26%	22%	56%	55%	24%	22%	64%	61%

NICE

Have baseline characteristics for mCRC changed since regorafenib licence (2013)?

Overview of key differences in baseline characteristics of the studies included in the ITC

- All participants of CORRECT and most in RECOURSE (>99%) had received biological treatment (including anti-VEGF, bevacizumab)
    - CONCUR, TERRA, and Yoshino 2012 included a large number of people who had not received prior biological treatment
- CONCUR, TERRA and Yoshino 2012 only included people in Asia, while CORRECT and RECOURSE included people from across the world
- CONCUR and TERRA participants had a shorter median time since diagnosis of first metastases compared with patients in CORRECT and RECOURSE.
- CONCUR and TERRA had a smaller proportion of people with ECOG performance status of 0
- CONCUR and TERRA had higher proportion of people aged <65 years
- CONCUR and Yoshino 2012 had higher proportion of men in the treatment arm

Bevacizumab is not recommended by NICE for the treatment of mCRC

Are these baseline characteristics generalisable to NHS clinical practice?

NICE

VEGF, vascular endothelial growth factor; ECOG, Eastern Cooperative Oncology Group

Indirect treatment comparison

Regorafenib vs T/T similarly effective, small but non-significant benefit for regorafenib

- In the absence of direct evidence company used NMA fixed effect model for regorafenib vs T/T efficacy
- Results show effectiveness of regorafenib and T/T similar, small but non-significant advantage for regorafenib
- Sensitivity analyses conducted:
  - Anchored matching-adjusted indirect comparison (MAIC) to weight baseline characteristics for possible effect modifiers (sex, age, prior biological treatment)
  - Removal of studies from NMA to allow for differences between studies: (1) phase II studies, (2) 100% prior anti-VEG treatment, (3) Asian patients only, (4) treatments with less prior anti-VEGF
- HRs and 95% CIs remained similar which demonstrated limited impact on results
- Random effects model gave similar point estimates but not appropriate given number of studies in network
- Ten observational studies of regorafenib in clinical practice are consistent with CORRECT, CONCUR results

NMA fixed effects model Regorafenib vs T/T	Sources					Overall Survival Hazard Ratio (95% CrI)	Progression free survival Hazard Ratio (95% CI)
	CORRECT	CONCUR	RECOURSE	TERRA	Yoshino 12		
Base case	**x**	**x**	**x**	**x**	**x**	**0.99 (0.84, 1.17)**	**0.93 (0.85, 1.03)**
MAIC weighted NMA	x	x	x	x	x	[redacted]	[redacted]
(1) No phase II study	x	x	x	x		0.95 (0.84, 1.14)	0.92 (0.83, 1.02)
(2) 100% prior anti-VEGF therapy	x		x			1.13 (0.58, 1.46)	1.02 (0.81, 1.29)
(3) Asian patients only		x		x	x	0.80 (0.61, 1.04)	0.73 (0.62, 0.86)
(4) Less prior anti-VEGF		x			x	0.70 (0.47, 1.04)	0.72 (0.48, 1.09)

Only significant difference

Key issue: Treatment effect and limitation of NMA

ICER impact: Large

Relative treatment effect of regorafenib versus T/T varies by evidence source

EAG:

- Subgroup and post hoc results from regorafenib versus placebo add uncertainty to RCT estimates:
  - Point estimate in CONCUR suggests better OS HR for people not previously treated with anti-VEGF
  - Point estimate in CORRECT suggests better PFS HR for people in Asia than Europe
  - Point estimate in CONCUR suggests better OS HR for people who have more lines of treatment (unexpected)
- High heterogeneity between populations in NMA, sensitivity analyses may not explore all inconsistencies
- 4 observational studies available of regorafenib or T/T in clinical practice, 3 support the company's ITC results
- However, the largest study (Nakashima 2020) strongly suggests better OS for T/T (OS HR = 0.66, P<0.001)

	Nakashima 2020 (N=2,529)		Tanaka 2018 (N=44)		Sueda 2016 (N=37)	
Data reported for	Patients with no crossover		Regardless of crossover		Patients with no crossover	
Study Location	Japan		Japan		Japan	
Prior treatment	NR		2-4 prior treatments		100% had prior anti-VEGF	
OS, median, months (95% CI)	Regorafenib	T/T	Regorafenib	T/T	Regorafenib	T/T
	6.4 (5.9, 7.0)	10.2 (9.5, 10.1)	9.1 (4.1, 13.4)	9.3 (5.5, 12.3)	4.5 (3.34, 10.3)	5.3 (0.92, 8.62)
	Adjusted T/T HR 0.66 (p<0.001)					
PFS, median, months (95% CI)	-	-	2.1 (1.3, 3.6)	3.1 (1.7, 4.1)	3.0 (1.64, 4.52)	2.1 (0.92, 6.39)

Showed best baseline balance

CI, confidence interval; HR, Hazard ratio; OS, overall survival; PFS, progression free survival;T/T, trifluridine/tipiracil; NR, not reported

Key issue: Treatment effect and limitation of NMA

ICER impact: Large

Relative treatment effect of regorafenib versus T/T varies by evidence source

Company

- Subgroups not powered to rely on differences reported
- Nakashima 2020 is a retrospective observational study and does not provide a credible estimate of relative efficacy
- Extent of benefit of T/T over regorafenib (OS HR = 0.66) not credible because it is similar to the benefit of T/T over placebo in RECOURSE (OS HR = 0.68), TERRA (OS HR = 0.79) and Yoshino 2012 (OS HR = 0.56)
- Patients in Nakashima 2020 were selected not randomised, so unknown confounders could affect results
- Study has high risk of bias and inclusion into the ITC would increase rather than decrease uncertainty
- A different observational study (Moriwaki 2018, N=550), showed no difference in efficacy – unadjusted T/T OS HR = 1.03 (0.85,1.26)

EAG comments

- Pooling RCTs of low risk does not mean the pooled estimate is of low risk, this depends on the comparability of the RCTs
- Differences in trials used for the ITC creates uncertainty in effectiveness of regorafenib vs T/T
- While the observational studies likely have selection bias, Nakashima 2020 has the best baseline balance
- Further NMA could be conducted combining evidence from RCTs and observational studies
- Company cite Moriwaki 2018 as supportive evidence for similar efficacy to T/T but study permitted crossover which introduces uncertainty

Should observational studies be considered for the efficacy of regorafenib vs T/T?

NICE

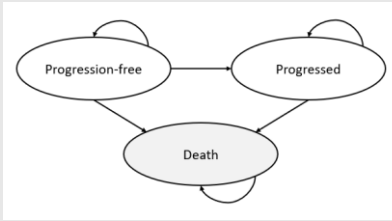
RCT, randomised controlled trials; ITC, indirect treatment comparison; CI, confidence interval; HR, Hazard ratio; OS, overall survival; PFS, progression-free survival; T/T, trifluridine/tipiracil

Cost effectiveness

NICE National Institute for Health and Care Excellence

Company's model overview

Model description

Model structure	3-state partitioned survival model: • progression-free • progressed • death 
Population	people with mCRC who have progressed on first line treatment and are being considered for ≥third-line treatment
Intervention	regorafenib
Comparators	trifluridine/tipiracil and best supportive care
Time horizon	10 years
Model cycle	1 week
Discount rates	3.5% for costs and QALYs
Utility values	pooled EQ-5D-3L from CORRECT and CONCUR
Perspective	NHS and Personal Social Services (PSS)

- Technology affects **costs** by:
  - [redacted]
  - [redacted]
- Technology affects **QALYs** by:
  - [redacted]
  - [redacted]

T/T, trifluridine/tipiracil; QALY, quality-adjusted life-year; HR, hazard ratio

How company incorporated evidence into the model

	Assumption and evidence source	
Input	**Company**	**EAG**
Baseline characteristics	Pooled participants from CORRECT and CONCUR	
Extrapolation of regorafenib	Pooled CONCUR and CORRECT data **ToT and PFS:** Pooled KM data **OS:** Parametric survival curves	Pooled CONCUR and CORRECT data **TOT and PFS**: Fully parametric survival curves **OS:** Fully parametric survival curve
T/T efficacy	NMA HR (RECOURSE, TERRA, Yoshino 12) applied to regorafenib extrapolations PFS HR used as a proxy for modelling ToT	Also considered RWE (Nakashima 2020) in scenario analysis
BSC efficacy	**ToT and PFS:** Pooled KM data **OS:** log-logistic extrapolation preferred	Fully parametric curves fit for ToT and PFS **OS**: log-normal extrapolation preferred
Utilities	Pooled EQ-5D-3L from CORRECT and CONCUR	
Adverse events	Grade 3 and 4 only	
Costs	NHS reference costs 2019-20, BNF, and Personal Social Services Research Unit (PSSRU). Confidential PAS also applied	
Resource use	Published literature and expert opinion as agreed for NICE TA405	
Subsequent treatment	None applied to base case	
Treatment waning	None applied	

NICE

BNF, British National Formulary; OS, overall survival; PAS, patient access scheme; PFS, progression free survival; RWE, real world evidence; TOT, time on treatment

Decision modifier: severity

Updated NICE methods applied

- In the updated 2022 NICE health technology evaluation manual, the evidence-based **severity modifier was introduced** while **end-of-life criteria was excluded**
- The updated manual states that in exceptional and relevant cases, factors not already included in the QALY (such as severity) can be taken into account
- Severity reflects future health lost by people living with a condition receiving current standard treatment
- Severity is assessed based on the absolute and proportional shortfall in QALY
- A QALY weighting for severity can be applied depending on the absolute or proportional shortfall, whichever implies the greatest severity

NICE QALY weightings for severity

QALY weight	Proportional shortfall (fraction of health lost)	Absolute shortfall (total amount of health lost)
1	Less than 0.85	Less than 12
x1.2	0.85 to 0.95	12 to 18
x1.7	At least 0.95	At least 18

Severity

Severity weighting applied to the company's cost-effectiveness estimates

- The company noted that people being considered for ≥3L mCRC treatment experience a substantial QALY shortfall compared with the general population
- It applied a severity weighting of 1.7x derived using pooled baseline characteristics and utility results from CORRECT and CONCUR
- Regorafenib licence was granted before the data sources used to estimate general population QALY were collected – could affect estimates used

Health state benefits and utility values for QALY shortfall analysis

State	Utility value	Undiscounted life years	
		T/T	BSC
Pre-progression	0.72	[redacted]	[redacted]
Progressed disease	0.59	[redacted]	[redacted]

Estimates used for shortfall calculation

	Estimate
Age of the population (mean)	60
Sex distribution (women)	56%
Total QALY	
General population[#]	12.36
People with mCRC having T/T	[redacted]
People with mCRC having BSC	[redacted]

QALY weighting applied by company

	T/T	BSC
Proportional shortfall	[redacted]	[redacted]
Absolute shortfall	[redacted]	[redacted]
Severity modifier weighting applied	**1.7x**	
EAG estimated the same modifier weighting		

[#]Life expectancy estimates based on 2017 – 2019 National Life Table
[#]Utility estimates from Health Survey for England 2017 and 2018 data
Regorafenib trials completed in 2013

*estimate by technical team

QALY, quality-adjusted life-year; T/T, trifluridine/tipiracil; BSC, best supportive care

Key issue: Survival models

Base case PFS and ToT uses KM data not parametric survival models

ICER impact: Small

Company

- OS, PFS and ToT modelling considered statistical fit (AIC/BIC) and visual inspection. Clinical opinion was considered for long-term OS estimates only
- OS was modelled using fully parametric models; best fit for regorafenib and BSC is log-logistic. Clinical opinion suggests both log-normal and log-logistic plausible but log-logistic chosen to align with previous committee preference (TA405)
- PFS and ToT modelled using KM data, parametric models used only when KM data was no longer available
- KM data mature and trials reflect clinical practice
- Fully parametric models were explored in scenario analyses with limited impact on ICER

EAG

- Fully parametric models are preferred for the base case, in line with NICE methods
- KM curves 'stepped' - could cause overfitting of trial data
- Prefer log-normal for BSC extrapolation as better statistical fit and aligns with TSD 14

Survival model assumptions in company and EAG base case

	Treatment	Company	EAG
OS	Regorafenib	Log-logistic	
	BSC	Log-logistic	**Log-normal**
	T/T	ITC OS HR	
PFS	Regorafenib	KM data until unavailable then exponential model	**Log-logistic**
	BSC	KM data until unavailable then exponential model	**Log-logistic**
	T/T	ITC PFS HR	
ToT	Regorafenib	KM data until unavailable then log-logistic model	**Log-logistic**
	BSC	KM data until unavailable then log-logistic model	
	T/T	Assumes ITC PFS HR	

Most appropriate extrapolation of data for regorafenib, T/T and BSC?

KM, Kaplan–Meier; PFS, progression-free survival; OS, overall survival; ToT, time on treatment; HR, hazard ratio; T/T, trifluridine/tipiracil; BSC, best supportive care

How the company modelled survival

For PFS – company used KM data then applied parametric model when KM data no longer available

For OS – company used parametric model throughout

KM, Kaplan–Meier; PFS, progression-free survival; OS, overall survival; BSC, best supportive care

Key issue: Adverse events (AEs)

Mild and moderate AEs (grade 1 and 2) excluded from economic model

ICER impact: Small

- Regorafenib is a treatment with an alternate safety profile to T/T
- Only grade 3 and 4 (severe and life-threatening) AEs occurring in ≥2% of people were included in the cost-effectiveness analyses
- NMA showed higher likelihood of experiencing any AEs with regorafenib than with T/T (OR = 1.94 (1.20, 3.17)
- NMA comparing grade 3 and 4 AEs for regorafenib and T/T not included in the company's model

	OR (95% CrI) - NMA		
Comparison	**Grade 3 or 4 AEs**	**Discontinuation due to AEs**	**All TEAEs**
Regorafenib vs T/T	0.90 (0.55, 1.47)	1.10 (0.53, 2.24)	1.94 (1.20, 3.17)

Company

- Grade 1 and 2 adverse events not expected to have an impact on costs or quality of life, generally not modelled
- No robust method for using OR to adjust for survival data (HR is required)
- Scenario analyses conducted - grade 1 and 2 AEs were modelled in two ways: by applying a fixed cost of £5 per AE (i) with a disutility of 0.01 per AE and (ii) without disutility
- Both methods had minor impact on the cost-effectiveness estimates

EAG comments

- Despite the limitations to applying OR for adjustment of survival data, NMA for all AEs suggested higher likelihood of AEs with regorafenib than T/T
- Observational evidence from Nakashima 2020 suggests greater A/E burden with regorafenib than T/T
- The scenario analyses are satisfactory but require certain assumptions

Should grade 1 and 2 AEs be included?

AEs, adverse events; TEAEs, treatment emergent adverse events; CrI, credible interval; NMA, network meta-analysis; OR, odds ratio; T/T, trifluridine/tipiracil

Key issue: Relative dose intensity (RDI)

ICER impact: Small

Regorafenib and T/T RDI modelled differently

Background

RDI estimates for regorafenib based on CORRECT and CONCUR data ([redacted]) –includes cycle delay

- T/T: dose reduction (97.4%) and cycle delays (2.72 days) modelled separately using data from TA405 because no RDI measure was reported
- Scenario analyses conducted: (1) applying RDI to the number of regorafenib tablets dispensed and (2) equal RDIs were assumed for regorafenib and T/T

Company

- For T/T, using a combination of dose reductions and cycle delays approximates how RDI was assessed for regorafenib in CORRECT and CONCUR
- Approach reflects clinical practice, T/T AEs managed by dose delay, regorafenib by dose reduction
- All T/T dose reduction applied at first dose and continue for the full treatment course – this is a conservative approach

EAG comments

- Real world evidence (Nakashima 2020) directly comparing regorafenib and T/T does not support company's view on management of AEs by dose delay/reduction
- Similar dose reduction was reported for regorafenib (54%) and T/T (48%)
- The EAG assumed equal RDI for regorafenib and T/T in its base case

What is the appropriate method for estimating T/T RDI?

RDI, relative dose intensity; AE, adverse event; T/T, trifluridine/tipiracil

Key issue: Subsequent treatment

Proportion of people receiving subsequent treatment is unclear

ICER impact: Unknown

Background

- No post-progression treatment costs were included in the company's base case
- Post-progression cost included in TA405

Subsequent treatment use in regorafenib trials

	CORRECT	CONCUR
Regorafenib	25.9%	30.9%
Placebo	29.8%	42.6%

Company

- Experts suggest <10% of people would be fit enough for active post-progression treatment
- Post hoc analysis of CONCUR only, censoring people who received post-progression treatment, estimates regorafenib OS HR of 0.41 (0.274, 0.623)
- Likely because more people in the placebo arm received post-progression treatment
- Scenario analysis with post-progression costs from TA405 inflated to 2021 prices (£1,633.18) and applied as a one-off cost to both regorafenib and T/T showed negligible impact on the ICER

EAG comments

- Post hoc analysis method prone to bias due to informative censoring (loss of patients to follow up due to study-related reasons)
- Adjusting for post-progression treatment likely favours regorafenib, but the extent is uncertain, cannot be fully resolved without data from T/T trials

Should the same subsequent treatment rates from the trial be included in the model?

RCT, randomised controlled trials; OS, overall survival; HR, hazard ratio; NMB, net monetary benefit; T/T, trifluridine/tipiracil

Cost-effectiveness results

All ICERs are reported in PART 2 slides

because they include confidential

comparator PAS discounts

EAG preferred assumptions and impact on company's base case ICER

How EAG preferred assumptions impact the company's base case

		Trifluridine/tipiracil			Best supportive care		
Assumption		Incremental cost (£)	Incremental QALY	ICER (£/QALY)	Incremental cost (£)	Incremental QALY	ICER (£/QALY)
Survival extrapolation	Fully parametric survival curves for BSC OS (log-normal)	=	=	=	↑	↑	↓
	Fully parametric survival curves for regorafenib and BSC PFS	↑	=	↑	↓	=	↓
	Fully parametric survival curves for regorafenib ToT	↑	=	↑	↑	=	↑
Costs and dosage of treatment	Equal RDI for regorafenib and trifluridine-tipiracil	↑↑	=	↑	=	=	=
EAG base case		↑↑	=	↑	↑	↑	↓
Additional scenario analysis							
Treatment effect	OS HR of regorafenib versus trifluridine-tipiracil from observational study ○ *Largest impact on ICER*	↓	↓↓	↑↑	↑	↑	↓

Arrows indicate the direction and magnitude of change to company's base case. Equal sign indicates no change.

ICER, incremental cost-effectiveness ratio, QALY, quality-adjusted life years, OS, overall survival; PFS, progression-free survival; HR, hazard ratio; ToT, time on treatment; RDI, relative dose intensity; BSC, best supportive care

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Thank you.

32

Backup slides

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Adverse events (AEs) reported in observational study

AEs are common for both regorafenib and T/T

RWE study (Nakashima 2020) compares AEs for regorafenib and T/T

Adverse events reported in Nakashima 2020		
	Regorafenib (n=1,501)	T/T (n=3,777)
Any AEs	777(52%)	1,622(43%)
Hand-foot syndrome	257(17%)	182(5%)
Peripheral neuropathy	114(8%)	290(8%)
Hypertension	287(19%)	446(12%)
Nausea	127(8%)	371(10%)
Diarrhoea	116(8%)	249(7%)
Oral mucositis	119(8%)	167(4%)
Rash/desquamation	73(5%)	56(1%)
Fever	44(3%)	117(3%)
Hepatotoxicity	20(1%)	9(0%)
Fatigue	14(1%)	31(1%)
Leukopenia	33(2%)	597(16%)
Interstitial pneumonitis	8(1%)	12(0%)