Lead team presentation Regorafenib for previously treated unresectable or metastatic gastrointestinal stromal tumours [ID1056] – STA

1st Appraisal Committee meeting

Cost Effectiveness

Committee D

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ERG: PenTAG

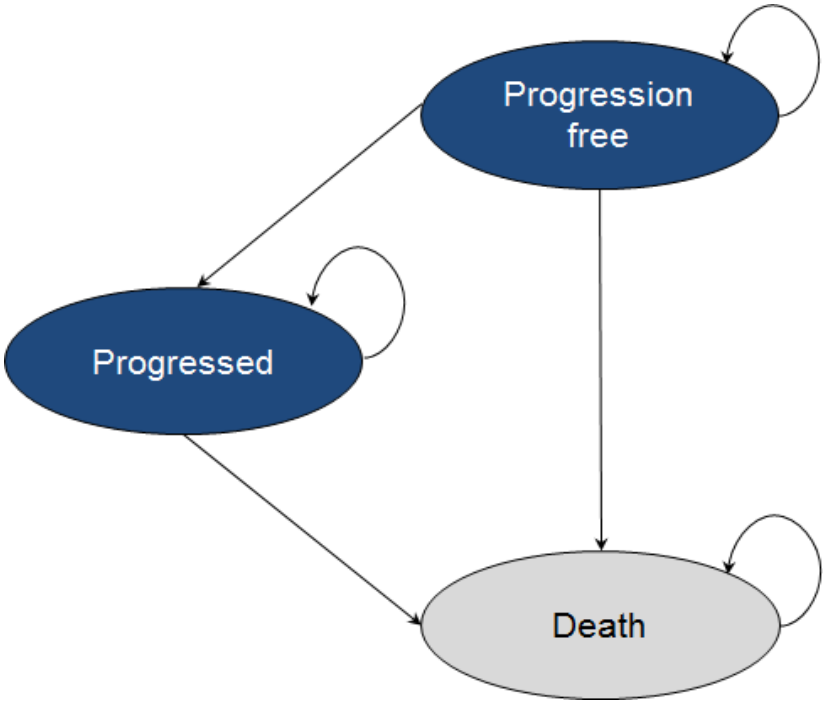
28 June 2017

For public

Key issues: cost-effectiveness

- Company and ERG agree treatment duration should be modelled in line with GRID and include cost of regorafenib post progression (regorafenib arm only)
  - Is this appropriate?
- Company prefer to use 2017 data for OS while ERG use 2015 data (not able to validate 2017 data and some inconsistencies)
  - What is the appropriate data to use for overall survival?
- Choice of distribution for OS extrapolation has large impact on results. ERG also suggest including additional general background mortality
  - Is the average of log logistic and Weibull models appropriate?
  - Is adding general background mortality appropriate?
- ERG add age-related utility decrements as utility often declines with age
  - Is this appropriate?
- Does regorafenib meet the end of life criteria?

Company's model structure



- Partitioned survival model (use Kaplan-Meier from GRID trial)
- Base case uses treatment duration from GRID trial
- Base case includes IPE method to adjust cross over for OS (recensoring applied to avoid bias)
- 28 day cycles (3 weeks on regorafenib 1 week off regorafenib)
- 40 year time horizon, discounted at 3.5% and half cycle correction

Source: Figure 15 in Company submission

Cross over correction and extrapolation
Company's model

Cross over correction

- In GRID people on placebo cross over to regorafenib after progression
- OS data in placebo arm confounded by benefits of regorafenib so adjusted to simulate people not crossing over to active treatment

Base case

- IPE method for cross over correction for OS in GRID placebo arm (reduce bias in true treatment effect)

Extrapolation

- Tested 5 parametric models (Weibull, exponential, log logistic, Gompertz and lognormal) to PFS and OS data from GRID
- Uncertainty after visual inspection so statistical fit used to determine appropriate model

Base case

- Lognormal for PFS & log logistic for OS extrapolation (with IPE correction to placebo arm)
- Parametric models fitted separately to individual PFS and OS curves

Extrapolation of overall survival in GRID 2017

Figure 25 ERG report

Extrapolation of overall survival in GRID 2017

Figure 26 ERG report

Clinical data used in base case

Outcome (base case)	Regorafenib vs. placebo
PFS (2015 data)	HR 0.27 (0.19 to 0.39)
PFS extrapolation	Lognormal
OS (IPE and 2017 data)*	[redacted]
OS extrapolation	Loglogistic
Time to treatment discontinuation (TTD)	Cost of regorafenib based on discontinuation curve and mean observed dose from GRID (no extrapolation as only 2% on treatment at end of follow up)
Abbreviations: HR, Hazard ratio; OS, overall survival; PFS, progression free survival *Hazard ratios from 2017 data include recensoring	

Health related quality of life
Company's model

- GRID measured EQ-5D and European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC: scenario)
- Company carry out paired samples comparison (overall and by treatment)
- Sensitivity analysis with repeated measures (company: biased as more measurements for people in progression free state, no homogenous progressed population for estimating utility)

- **Base case uses EQ-5D data from paired samples (not split by treatment arm as no statistically significant difference between treatment arms)**

Health state	Mean utility (95% confidence interval)	
	paired samples	**repeated measures**
Progression-free (n=77)	**0.767 (0.718 to 0.816)***	0.743 (0.712 to 0.775)
Placebo progression-free (n=12)	0.583 (not reported)	0.750 (0.698 to 0.802)†
Regorafenib progression-free (n=27)	0.702 (not reported)	0.741 (0.706 to 0.777)†
Progressed (n=49)	**0.647 (0.571 to 0.723)***	0.703 (0.657 to 0.748)

*Values in bold used in base case. †assumed to include treatment effect and adverse events. Source: tables 36 to 39 in company submission

Adverse events in company's model

- Most common adverse events (hand-foot skin reaction, diarrhoea and fatigue) easily manageable and negligible effect on HRQoL
- EQ-5D analyses using repeated measures (progression free split by treatment arm) assumed to represent treatment effects and adverse events. Utility in regorafenib (0.741) lower than placebo (0.750)

- **Base case:** adverse events not included (EQ-5D from paired samples)
- **Scenario with repeated measures:** lower utility values in regorafenib arm (progression free state) assumed to include adverse events

	Estimated incidence rate per cycle %		Cost per cycle (95% CI)
Adverse event	**Placebo**	**Regorafenib**	**Each treatment arm**
Hypertension	1.35	5.16	£11.86 (£9.48 to £14.23)
Hand-foot skin reaction	0	4.25	£0
Diarrhoea	0	1.07	£7.02 (£5.62 to £8.43)

Source: Table 35 and 53 in Company submission

Treatment duration and dose intensity

- Company's new base case uses treatment duration from GRID
  - No extrapolation of discontinuation curve (only 2% on treatment at end of follow up)
  - Treatment costs independent of progression (based on discontinuation curve and mean observed dose from GRID)
  - Mean observed dose (excluding dose 0 mg) by cycle applied to calculate treatment costs per cycle

	GRID
First 3 weeks in cycle	Oral regorafenib 160 mg (4 x 40mg once daily)
4th week	No regorafenib
Dose modifications	Can be delayed or reduced according to pre-specified schedule* Allowed 2 dose reductions (160 mg to 120 mg to 80 mg) due to toxicity. Dose re-escalation allowed if resolved to <grade 3
* For unacceptable side effects, hand-foot skin reaction, hypertension	

Source: Table 35 and 53 in Company submission

Company's resource use and cost

	Resource use	Progression free on TKI (£)	Progression free on BSC (£)	Progressed (£)
One time costs	Tests	55.72 (5.53)	13.82 (2.93)	N/A
	Palliative resection	Not included	Not included	[redacted] (129.38)
	Palliative radiotherapy	Not included	Not included	[redacted] (10.11)
	Total one-time costs	**55.72 (5.53)**	**13.82 (2.93)**	**[redacted] (129.77)**
Regular per cycle costs	Regular tests*	45.45 (5.46)	14.81 (4.08)	8.35 (36.00)
	Regular outpatient monitoring visits	60.49 (9.16)	46.91 (4.73)	53.68 (8.15)
	Pain management†	18.27 (2.97)	18.35 (2.97)	26.95 (3.77)
	Total per cycle costs	**124.21 (11.07)**	**80.07 (6.92)**	**88.98 (37.11)**

All values mean (standard error). Abbreviations: TKI, tyrosine kinase inhibitor; BSC, best supportive care. * Regular tests include: CT scan, MRI scan, full blood count and liver function test. †Pain management includes: co-codamol, tramadol, paracetamol, morphine sulphate, dexamethasone

Source: Table 54 in Company submission

Summary of company's model

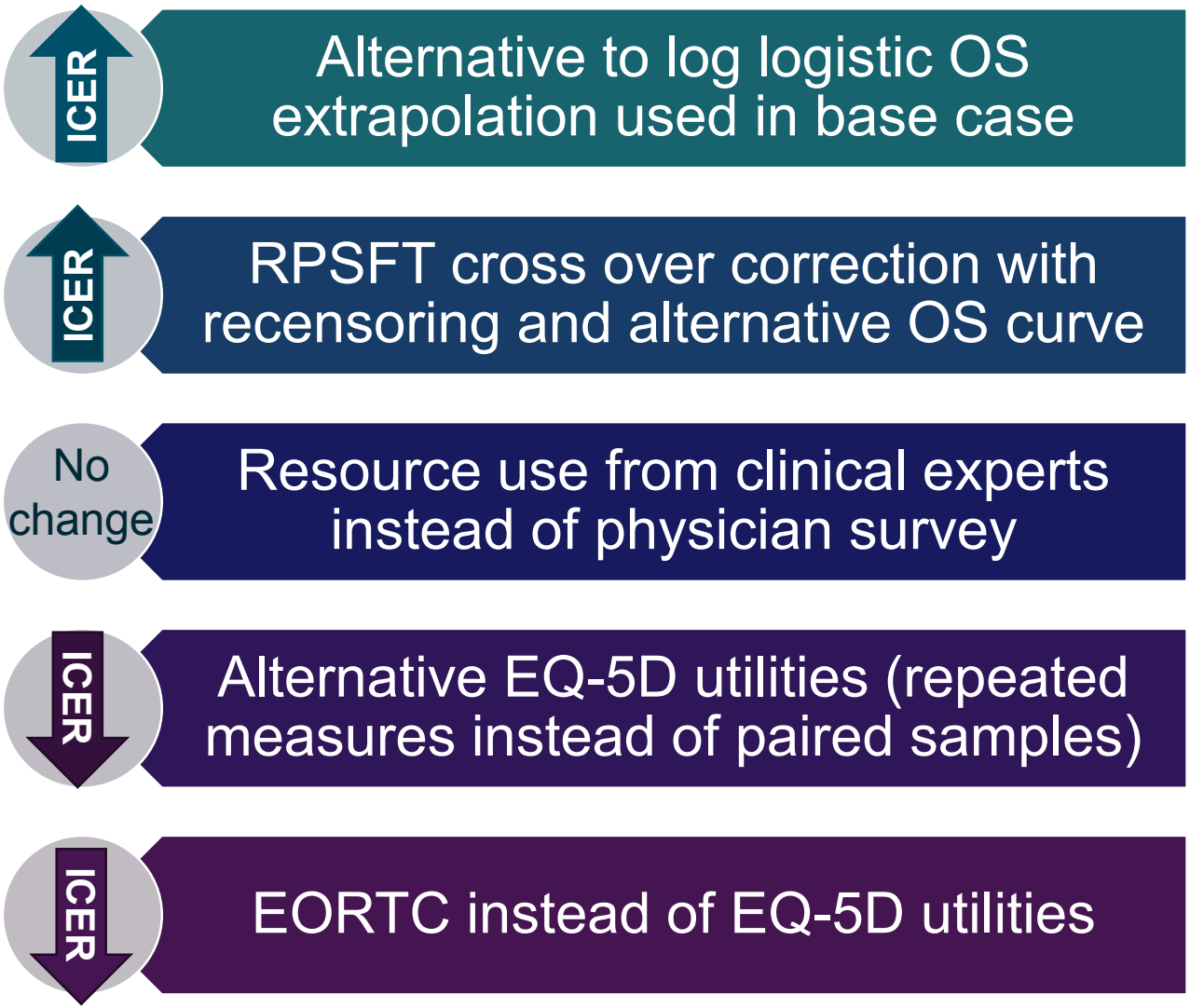
	Regorafenib	Best supportive care (BSC)
Health state	• All people start progression free (in line with trial) • OS curve determines transition to death (from progressed)	
Clinical data	2017 data used for OS	
Cross over adjustment	N/A	IPE method used to adjust BSC arm (high cross over to open label regorafenib) with recensoring
Extrapolation	PFS: lognormal OS: Log-logistic curve	PFS: lognormal OS: Log-logistic curve plus IPE correction
Discontinuation	Apply time to discontinuation of regorafenib data directly (treatment costs independent of progression)	
Utilities	Same utilities used for both arms	
Resource use	Based on 2013 physician survey (re-evaluated by clinical experts in 2016). Scenario analyses to explore assumptions	

Company's base-case results
Regorafenib with PAS

Base case	Total QALYs	Total costs	Inc. QALYs	Inc. costs	ICER
Placebo + BSC (2015)	0.969	£10,671	-	-	-
Regorafenib (2015 OS data)	1.717	£36,457	0.748	£25,786	£34,476
Placebo + BSC (2017)	0.761	£10,395	-	-	-
Regorafenib (2017 OS data)	1.733	£36,478	0.971	£26,082	£26,852
New base case: Regorafenib (2017 and GRID treatment duration)	**1.733**	**£47,249**	**0.971**	**£36,854**	**£37,941**

- Probabilistic ICERs for new base case £38,494 per QALY gained. 82% chance regorafenib cost effective at willingness to pay of £50,000 per QALY
- Model drivers: regorafenib cost, discount rate utilities and costs, utilities for progressed state, utilities for progression free state

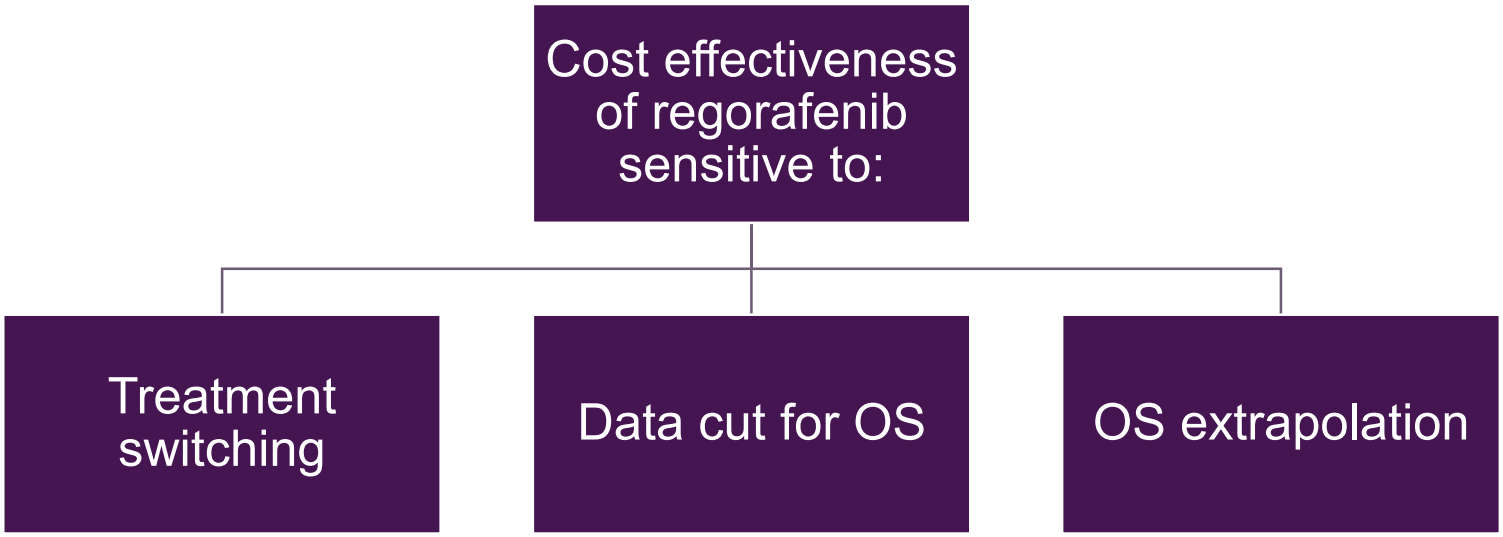
Company's scenario analyses



Company's results from scenarios
Regorafenib with PAS

Scenario	ICER vs. BSC
Company's new base case (with PAS, 2017 OS data & treatment duration from GRID)	**£37,941**
1a. Weibull parametric curve to extrapolate OS data	£45,498
1b. Gompertz parametric model to extrapolate OS data	£47,068
2a. RPSFT cross over correction and Log-logistic OS curve	£39,493
2b. RPSFT cross over correction and Weibull OS curve	£46,996
2c. RPSFT cross over correction and Gompertz OS curve	£48,360
3. Change all resource use in line with clinical opinion	£37,806
4a. Add regorafenib cost post progression	Not relevant*
5a. EQ-5D utilities from repeated measures	£36,765
5b. EQ-5D utilities from repeated measures (PFS split treatment)	£37,514
6a. Use EORTC from GRID for utilities (repeated measures)	£34,281
6b. Use EORTC from GRID for utilities (paired samples)	£33,964
* Treatment duration derived directly from GRID discontinuation curve	

Evidence Review Group (ERG)



- High uncertainty in the cost effectiveness of regorafenib vs. BSC
  - Substantial uncertainty in cross over adjustment
  - Uncertainty in extrapolation of overall survival

Treatment duration
ERG report

- Company originally modelled regorafenib up to disease progression. Updated company base case modelled regorafenib for entire duration as experienced in GRID
  - Total mean duration of double-blind and open label regorafenib (excluding time off treatment and interruptions): regorafenib arm [redacted] weeks, BSC arm [redacted] weeks
  - Mean post progression treatment duration [redacted] weeks in regorafenib arm
  - Treatment costs also based on time to discontinuation curve from GRID
- **Company's additional clarification:** estimates of dose intensity exclude values of 0mg. ERG agree with company approach as conservative and revise their base case

ERG base case

- Assume same regorafenib time on treatment curve as company and include additional cost post progression to regorafenib arm only
- Revised base case assuming company have correctly implemented revised dose intensity calculations

OS and treatment switching
ERG report

- Company use IPE adjustment and recensor data at earlier time-point to avoid informative censoring:
  - can lead to biased estimates of “average” treatment effect where proportional treatment effect assumption does not hold because longer term data on treatment effect may be lost (NICE TSD)
- ERG agree both IPE and RPSFT adjustments acceptable but should perform **adjustment with and without recensoring** (treatment effect generally greater when recensoring used)
- ERG unclear how relatively small increase in maturity of survival data can result in substantial reduction in estimated mean OS in placebo arm (24% lower)

Data cut	Mean OS in placebo arm	ERG base case
2015	Cross over corrected 1.64 years	Use similar recensoring and IPE adjustment (scenario for RPSFT)
2017	Cross over corrected 1.25 years	

Use of 2017 data - ERG report

1. At time of ERG report company CSR only contained 2015 data (no way to judge accuracy of 2017 data)

2. No change in maximum follow up time from 2015 to more mature data **(company: error [redacted] days 2017 and [redacted] in 2015. ERG: follow up in company's figures are equal for adjusted 2015 and 2017 data for placebo arm so this issue is still unresolved)**

3. Unclear how small increase in maturity, results in substantial reduction in estimated OS for placebo **(company: due to difference in events that gives greater certainty in tail and increase in follow up leads to less information lost through recensoring. ERG: 2017 tail longer but flat so would expect extrapolated OS to be longer with 2017 data)**

4. No access to IPD to check cross over adjustment

5. Company report different p-values for unadjusted and adjusted (IPE and RPSFT) OS hazard ratios **(company: agree but doesn't impact cost effectiveness results. ERG: still question whether switching adjustment has been implemented correctly)**

6. **Therefore ERG base case uses 2015 OS data**

OS extrapolation

Company Base case: log logistic

- Fitting of the 5 parametric models validated by 2 consultant oncologists in England who specialised in management of metastatic or unresectable GIST
- Log logistic, Weibull and Gompertz models considered clinically plausible

ERG base case: average of Weibull and log logistic distributions and adjusted for general background mortality

- Company's only justification for log-logistic model is that it provides the best fit to the trial OS data
- Evidence for longer and shorter-tailed distributions evenly balanced
- Fit to trial data important, but clinical plausibility is critical
- Scenarios with other clinically plausible distributions
- Company's base case does not account for additional post trial mortality unrelated to GIST

Summary of ERG changes

Model parameter	Change from company base case	Rationale
Treatment duration	No change	Agree with company to model treatment duration from GRID (allows regorafenib treatment costs after progression in regorafenib arm)
Survival data	PFS: no change **OS: 2015 data**	Can't validate company's 2017 data and inconsistencies in data reported
Cross over correction	No change (scenario analyses)	Agree both IPE and RPSFT appropriate methods (give similar estimates OS in placebo arm) and apply recensoring
Extrapolation of OS	**Distribution: average of log logistic and Weibull. ERG also add background mortality**	Company note Weibull and Gompertz models also clinically plausible. ERG: clinical plausibility is critical. Also additional general mortality likely to occur after trial
Utilities	Include **age related utility decrements**	Add aged related utility decrements - utility declines with age and not included in the company's base case

ERG explorations: base case results
Regorafenib with PAS

ERG base case	ICER vs. BSC
Company's base case	**£38,000**
1. OS data from 2015	£49,000
2. Add general mortality from UK population	£41,000
3. OS: average of log-logistic/Weibull	£41,000
4. Utilties decrease with age	£39,000
ERG base case (1 to 4)	**£56,000**
1 and 2*	£52,000
1 and 3*	£52,000
2 and 3*	£43,000
1 and 2 and 3*	£55,000
2 and 3 and 4*	£44,000
ERG's revised base case (revised dose intensity calculation)	**£53,000**
*carried out using ERG's original base case (excluding changes in dose intensity)	

ERG: High uncertainty, mostly due to switching adjustment, but also extrapolation

ERG results from scenarios
Regorafenib with PAS

Scenario	ICER vs. BSC	
	Company base case*	ERG base case
Base case	**£37,941**	**£56,000**
1. ITT analysis	£149,000	£235,000
2. Model costs and QALY to progression only	£52,000	£51,000
3. OS 2017 data	No change	£44,000
4. RPSFTM cross over adjustment	£39,000	£64,000
5. OS: Weibull	£45,000	£59,000
6. OS: Gompertz	£47,000	£64,000
ERG revised base case (revised dose intensity calculation)	**-**	**£53,000**
*Company's new base case (with PAS, 2017 data & treatment duration from GRID) Note: Scenarios carried out using ERG's original base case (excluding changes in dose intensity calculation)		

End of life criteria

- No 3rd line treatment option available in England currently
- Best supportive care only alternative to regorafenib
- **Short life expectancy:** median OS in placebo + BSC arm (11.9 months RPSFT correction and 11.1 months IPE correction)
- **Extension to life:** median OS difference regorafenib vs. BSC range 5.5 and 6.3 months
- ERG agree regorafenib meets end of life criteria

Innovation

- Company suggest regorafenib offers a step-change for the management of people with unresectable or metastatic GIST whose disease has progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib:
  - In England, no licensed option for 3rd line treatment
  - Cross-over adjusted OS analyses showed a median OS increase varying between 5.5 and 6.3 months in favour of regorafenib when compared against BSC
- Company do not make case for substantial benefits that are not captured by QALY

Potential equality issues

- Company not aware of any potential equality issues.
- Patient organisation submissions: regorafenib approved as third line therapy for GIST in Scotland and Wales

Key issues: cost-effectiveness

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  - Is this appropriate?
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