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

1st Appraisal Committee meeting

Background and Clinical Effectiveness

Committee D

Lead team: Malcolm Oswald

ERG: PenTAG

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For public observer

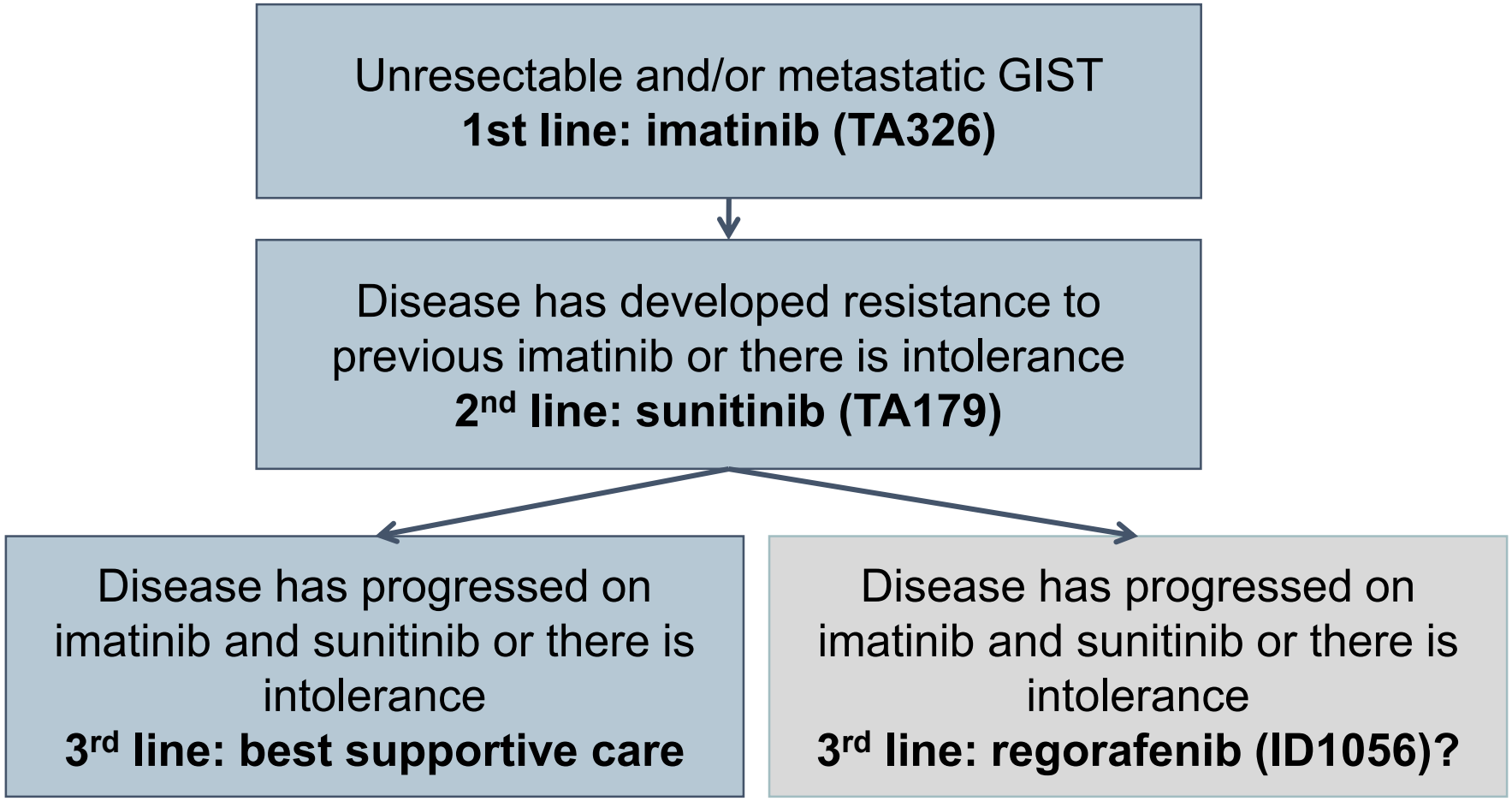
Key issues: clinical effectiveness

- GRID trial compared regorafenib with best supportive care (BSC)
  - Is BSC as defined in GRID similar to BSC in clinical practice?
- MA for regorafenib: “treatment should continue as long as benefit is observed” and GRID allowed regorafenib after disease progression
  - In clinical practice, will treatment continue after disease progression?
- GRID trial included people with performance status (PS) 0-1
  - In clinical practice, will people with PS 0-2 receive treatment?
  - Is GRID generalisable to clinical practice?
- In GRID there is quick disease progression in placebo arm (median PFS 0.9 months) and high cross over from placebo to regorafenib (88%). Company and ERG agree adjustment needed for overall survival
  - Is cross over adjusted OS appropriate?
- GRID results show improvements in PFS and OS after correction
  - Is regorafenib clinically effective compared with BSC?

Gastrointestinal stromal tumours (GIST)

- GISTs are rare connective tissue tumours – most GISTs are caused by mutations in either KIT or PDGFRA
- Incidence of GIST reported to vary from 11 to 20 cases per million per year, with slightly higher rates observed in men
- Prognosis depends mainly on whether the tumour is resectable but size, location, and stage of tumour at diagnosis also important factors
- When GIST is localised, standard treatment is surgery (complete removal is potentially curative when small and low risk classification)
- Risk of relapse after surgery can be substantial, and treatment with imatinib as an adjuvant treatment option in adults is recommended for up to 3 years

Treatment pathway for GIST



Recreated using Figure 1 in company submission

Decision problem

	NICE scope and company's decision problem
Population	People with unresectable or metastatic gastrointestinal stromal tumours (GIST) whose disease has progressed on, or who are intolerant to, previous treatment with imatinib and sunitinib
Intervention	Regorafenib
Comparator	Best supportive care
Outcomes	• Overall survival • Progression-free survival • Adverse events of treatment • Health-related quality of life
Subgroups	None

Regorafenib

UK Marketing authorisation	Treatment of adult patients with unresectable or metastatic gastrointestinal stromal tumours (GIST) who progressed on or are intolerant to prior treatment with imatinib and sunitinib
Administration	Administered as an oral therapy. There is limited data in patients with Performance Status 2 or higher.
Mechanism of action	Inhibits angiogenic kinase receptors, such as the vascular endothelial growth factor and the TIE2 receptor, which play a role in angiogenesis
Dosage	Recommended dose is 160 mg (4 tablets of 40 mg) taken once daily for 3 weeks followed by 1 week off therapy. 4-week period = a treatment cycle. Treatment should continue as long as benefit is observed or until unacceptable toxicity occurs.
Cost	• £3,744 per 28 day cycle (pack of 84 tablets at 40mg), list price (BNF, edition 72) • Approved patient access scheme (simple discount)
Eligible population	Company estimates 60 people in England may be eligible for regorafenib

Cancer Drugs Fund (CDF)

- Regorafenib is currently available on the CDF for treatment of adults with advanced GIST after failure of at least previous imatinib and sunitinib where the following criteria are met:
  - Application made by and first cycle of systemic anti-cancer therapy to be prescribed by a consultant specialist specifically trained and accredited in the use of systemic anti-cancer therapy
  - Histologically confirmed, metastatic or unresectable GIST
  - PS 0-1
  - Disease progression on or intolerance to previous imatinib
  - Disease progression on previous sunitinib

Patient perspectives

- Submissions from GIST Support UK, Sarcoma UK
- 800 new cases of GIST a year in the UK, most 50-70 years old
- Symptoms (e.g. bleeding, pain, anaemia, swallowing difficulty, fatigue) vary with tumour site e.g. stomach, liver, oesophagus, intestine
- “GIST is a rare cancer with few treatment options available”
- Patients want normal life to continue
- Regorafenib “well tolerated…improves progression free survival...outpatient oral drug…reduces psychological distress…enables a normal life-style”
- “Regorafenib has given me at least a further 2 years with my daughters – it is a lifeline not only for patients but for their families too”
- “Regorafenib is for some the first ever and only effective treatment” and “offers hope of a future”

Clinician perspectives

- Submission from GIST Support UK and Sarcoma UK clinical experts
- “The introduction of tyrosine kinase inhibitors in 2000” allowed patients “to live well, return to work and be active”
- “Life expectancy is less than a year, without the option of regorafenib”
- “No alternative active treatment options in third line setting”
- Little variation in practice and no extra training or resource required: regorafenib offered as 3rd line treatment to patients meeting CDF criteria
- GRID trial patients 0-1 performance status whereas 0-2 in real world
- More likely to benefit patients with Exon 11 mutation on the KIT gene
- Some patients require a dose reduction from 160mg to 120mg or 80mg
- Manageable side-effects: hypertension, hand foot syndrome, diarrhoea, mucositis, fatigue

GRID trial

Parameter	Description
Trial details	Double-blind, placebo-controlled trial with 2 arms: Regorafenib 160mg + BSC (N=133) vs. placebo + BSC (N=66)
Inclusion criteria	Histologically confirmed metastatic and/or unresectable GIST, with failure of at least: (1) prior imatinib (due to either disease progression or intolerance) and (2) prior sunitinib (due solely to progression to reduce heterogeneity). ECOG performance status 0-1
Exclusion	Prior treatment with any VEGFR inhibitor except sunitinib, use of any approved tyrosine kinase inhibitors in past 1 week
Location	57 study centres in 17 countries including UK
Outcomes	**Primary**: Progression free survival (PFS) **Secondary**: Overall survival (OS), time to progression (TTP), disease control rate (DCR), tumour response rate (RR), duration of response (DOR), and safety. Exploratory: HrQoL, pharmacokinetics, secondary PFS during open label treatment, and biomarker analysis
Pre-specified subgroups	Based on geographic region, prior line of treatment, age, sex, baseline BMI, duration of imatinib treatment, ECOG performance status, and mutational status

Table 16 company submission and table 7 ERG report

Best supportive care (BSC) in GRID

- BSC defined as any method to preserve the comfort and dignity of the patient, and included any concomitant medications or treatments:
  - antibiotics, analgesics
  - radiation therapy for pain control (limited to bone metastases)
  - corticosteroids, transfusions, psychotherapy, growth factors
  - palliative surgery, or any other symptomatic therapy necessary to provide BSC, except other investigational anti-tumour agents or anti-neoplastic chemo/hormonal/immune/radio-therapy

Disease progression in GRID

- People continued double blind treatment until disease progression
  - Placebo arm given option to cross over to regorafenib after progression
  - Regorafenib arm allowed open label regorafenib after progression if considered clinically beneficial
- People could continue regorafenib even after 1st progression (for regorafenib patients) or 2nd progression (for cross over patients)

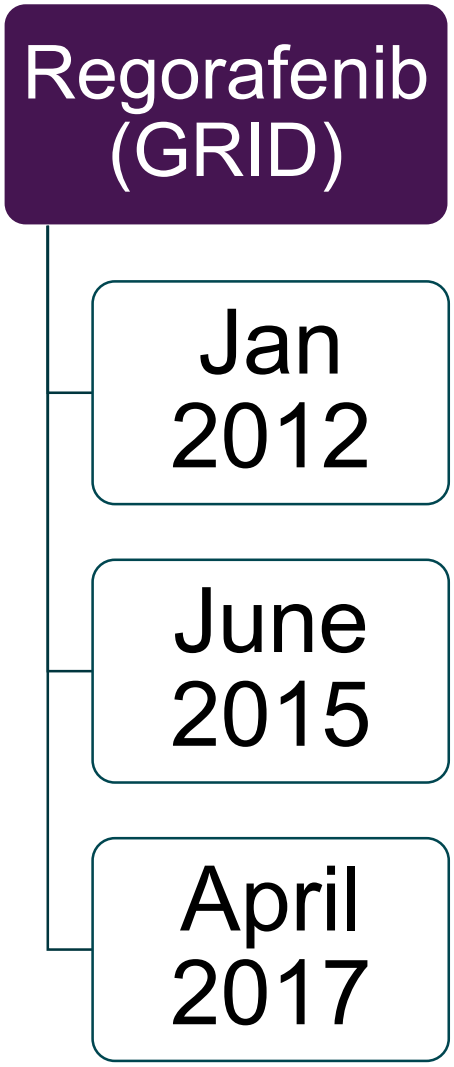
Baseline characteristics in GRID

Baseline characteristic	Regorafenib + BSC (n=133)	Placebo + BSC (n=66)
Median age	60 (51-67)	61 (48-66)
Male	85 (64%)	42 (64%)
Time since initial diagnosis to randomisation in weeks (mean, range)	296.4 (32.3 to 774)	310.6 (47.0 to 657)
Time since recent progression / relapse to randomisation in weeks (mean, range)	13.29 (0.7 to 145)	16.7 (0.4 to 421)
Metastatic disease (alone) at baseline	90 (67.7%)	38 (57.6%)
Unresectable disease (alone) at baseline	5 (3.8%)	10 (15.2%)
Metastatic & unresectable disease at baseline	35 (26.3%)	14 (21.2%)
2 lines of previous systemic anti-cancer therapy	74 (56%)	39 (59%)
≤ 6 months duration of previous imatinib therapy	18 (14%)	4 (6%)
6–18 months duration of previous imatinib therapy	26 (20%)	7 (11%)
> 18 months duration of previous imatinib therapy	89 (67%)	55 (83%)

- Over 40% received more than 2 lines systemic anti-cancer therapy and slight imbalance in duration of previous imatinib therapy

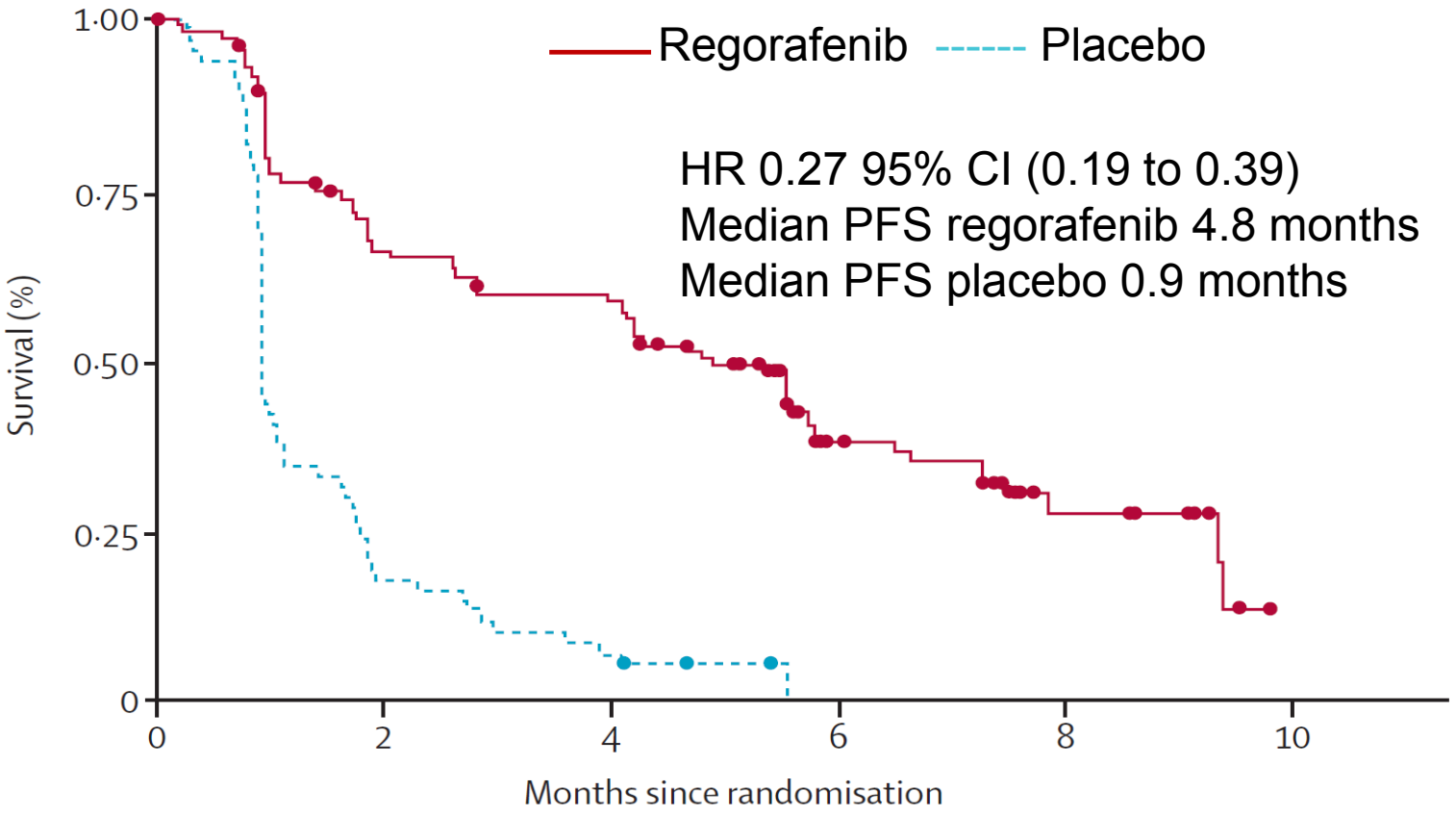
Source: Table 20 in company submission

GRID trial: data cuts



- 3 data cuts presented in company's submission and clarification
- **Jan 2012** final analysis for PFS (no further data collection needed) and 46 events for OS
- **June 2015** (total 162 events for OS). This data used in company submission
- **April 2017** updated data available for OS (total [redacted] events). Used in company's response to clarification and cost effectiveness model

GRID results: progression-free survival
(Jan 2012 intention to treat [ITT])



Number at risk				
Regorafenib	82	72	27	9
Placebo	12	5	0	0

Source: Figure 5 company submission

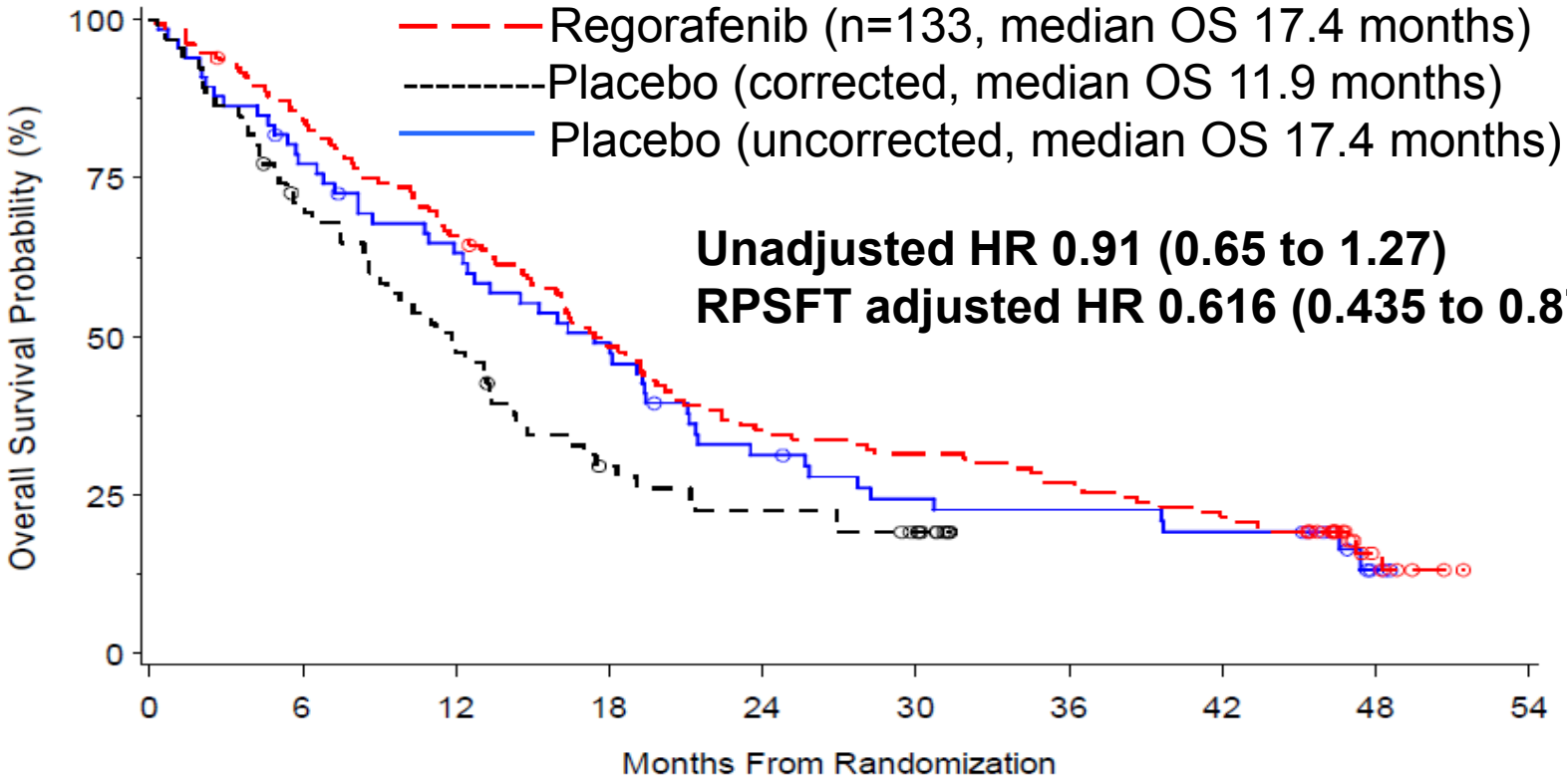
For PFS, patients without tumour progression or death at the time of analysis were censored at last date of tumour assessment

GRID results: overall survival
Cross over correction

- At June 2015 (final analysis point) 162 events occurred
  - Regorafenib: 109 events (82%) and placebo: 53 events (80%)
- 88% crossed over from placebo to open label regorafenib after disease progression
  - PFS curve suggests around 82% in placebo arm progress by 2 months
- Confounds assessment of overall survival (correction needed)
- Company use Rank Preserving Structural Failure Time (RPSFT) and Iterative Parameter Estimate (IPE) methods to adjust for cross over
  - Both methods aim to reconstruct individual patient data for OS in placebo arm as if there had been no cross over
  - Company prefers IPE method to reduce bias

GRID results: overall survival

June 2015 ITT and RPSFT cross over correction



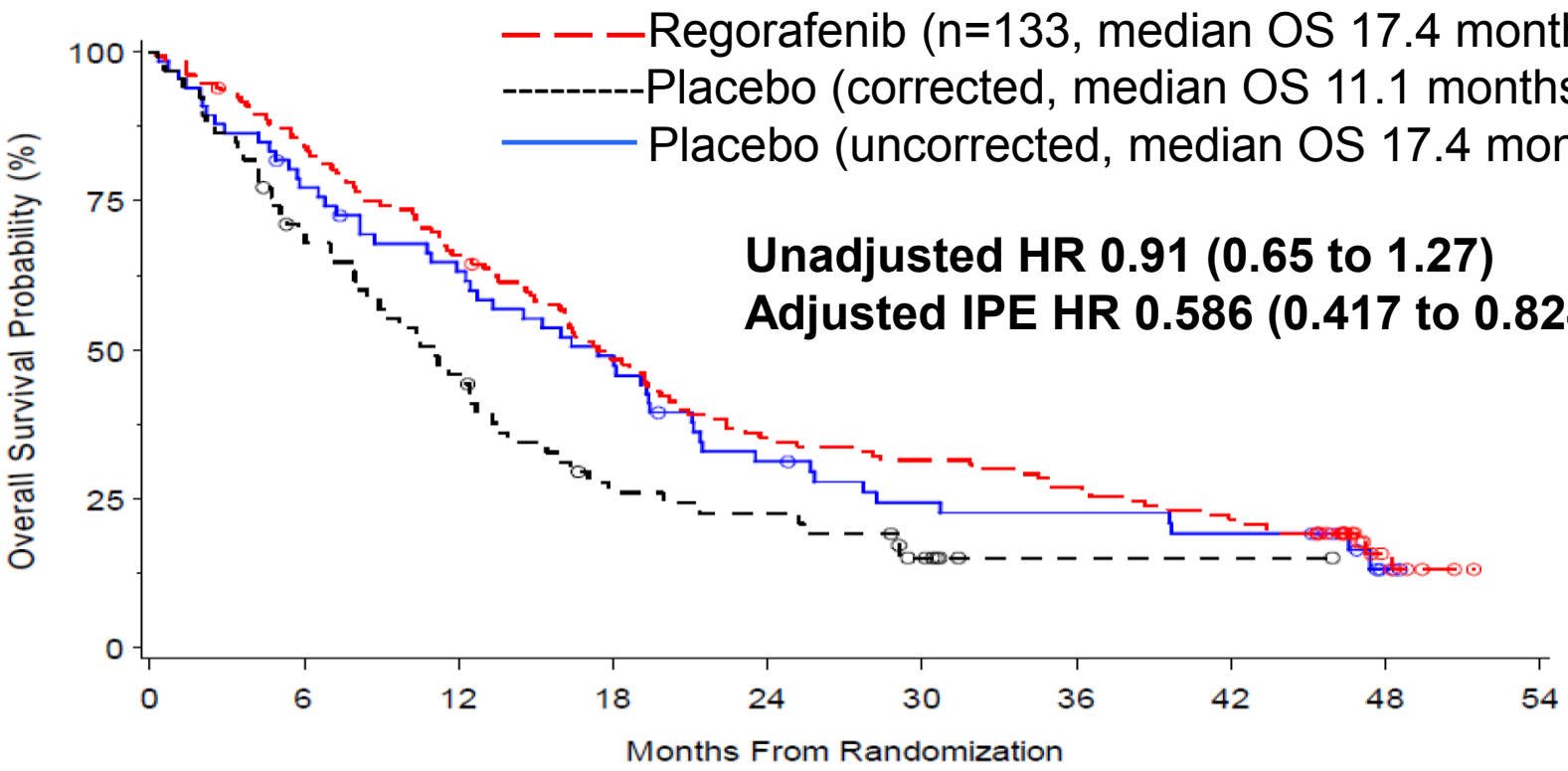
Patients at Risk

Placebo – Uncorrected	50	40	31	19	14	13	11	2
Regorafenib 160 mg	111	87	63	46	41	35	28	6
Placebo – Corrected	45	31	17	13	9	0	0	0

Source: Figure 7 company submission (circles represent censoring)
For overall survival, patients alive at the cut off date were censored

GRID results: overall survival

June 2015 ITT and IPE cross over correction



Patients at Risk

Placebo – Uncorrected	50	40	31	19	14	13	11	2
Regorafenib 160 mg	111	87	63	46	41	35	28	6
Placebo – Corrected	44	29	15	13	6	1	1	0

Source: Figure 8 company submission (circles represent censoring)
For overall survival, patients alive at the cut off date were censored

GRID results: New 2017 data

- Company present updated 2017 data in response to clarification
- Company: adjusted OS outcomes slightly reduce for placebo (greater follow up time allows for longer potential censoring date)

Outcome	2015	2017*
PFS	HR 0.27 (0.19 to 0.39)	HR 0.27 (0.19 to 0.39)
Median OS; months†	Regorafenib: 17.4 months Placebo unadjusted: 17.4 IPE adjusted: 11.1 RPSFT adjusted: 11.9	Regorafenib: [redacted] Placebo unadjusted: [redacted] IPE adjusted: [redacted] RPSFT adjusted: [redacted]
OS unadjusted	HR 0.91 (0.65 to 1.27)	[redacted]
OS IPE adjusted	HR 0.59 (0.42 to 0.82)	[redacted]
OS RPSFT adjusted	HR 0.62 (0.44 to 0.87)	[redacted]

All analyses include stratification by prior anti cancer drug group (3rd vs. 4th line or beyond) and geographical region (Asia vs. rest of world)
*Hazard ratios from 2017 data include recensoring
†Reported as days in Table 22 of company submission (2017 data from CSR)

Cross over correction of overall survival in GRID

Figure 1 clarification response

GRID results: adverse events

- Treatment emergent adverse events (TEAE) assessed during double blind period (n=132 regorafenib and n=66 placebo), regorafenib at any time (n=190) and in subgroup >1 year regorafenib treatment (n=75)
  - 98% in regorafenib and 68% in placebo arms reported drug related adverse events during double blind period
  - Most common TEAEs in regorafenib arm (any analyses) Palmar-Plantar Erythrodysaesthesia Syndrome (hand-foot skin reaction), hypertension, fatigue, and diarrhoea
- Of these, serious adverse events (SAE) reported in 29% (38/132) in regorafenib arm and 21% (14/66) in placebo
  - [redacted]

Evidence Review Group (ERG) report

- No additional RCTs identified
- 67% in regorafenib group and 83% in placebo had >18 months previous imatinib
- Stratified analyses by prior anti cancer drug group (3rd vs. 4th line or beyond) and geographical region (Asia vs. rest of world) of GRID appropriate and 58% of people in GRID from Europe
- Concerns with 2017 data (to discuss later)
- Both IPE and RPSFT methods appropriate to adjust for cross over

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