Slides for public

Lead team presentation Cabozantinib for previously treated advanced renal cell carcinoma – STA

1st Appraisal Committee meeting

Background and Clinical effectiveness

Committee B

Lead team: Ken Stein, Mark Chapman, Danielle Preedy

Chair: Amanda Adler

ERG: BMJ Technology Assessment Group

NICE technical team: Aminata Thiam, Ahmed Elsada

Company: Ipsen

25 January 2017

Cabozantinib

MARKETING AUTHORISATION
Advanced renal cell carcinoma in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy

KEY RESULTS

Clinical data
- 1 open-label RCT, cabozantinib vs. everolimus (METEOR)
- Cabozantinib reduced risk of death vs. everolimus; HR 0.66 (95% CI 0.53-0.83)
- Company's network meta-analysis: median OS longer with cabozantinib (22.9 mo) than with axitinib (15.7 mo), everolimus (16.3 mo) or nivolumab (20.8 mo)

Cost-effectiveness data
Results including **PAS for cabozantinib and comparators** are confidential and presented in PART 2

KEY ISSUES

2nd/3rd line positioning
Appropriate comparators depend on place of cabozantinib in therapy

Network Meta-analysis (NMA)
Unreliable results because populations are heterogeneous, cross-over present, OS data immature, and no adjustment for subsequent treatment

Survival estimates
- Limitation in extrapolation of OS and PFS
- Waning effect not considered by the company

End of life
- Company: life expectancy < 24 mo with axitinib, everolimus, nivolumab (median OS)
- Mean estimates of life extension are confidential and presented in PART 2

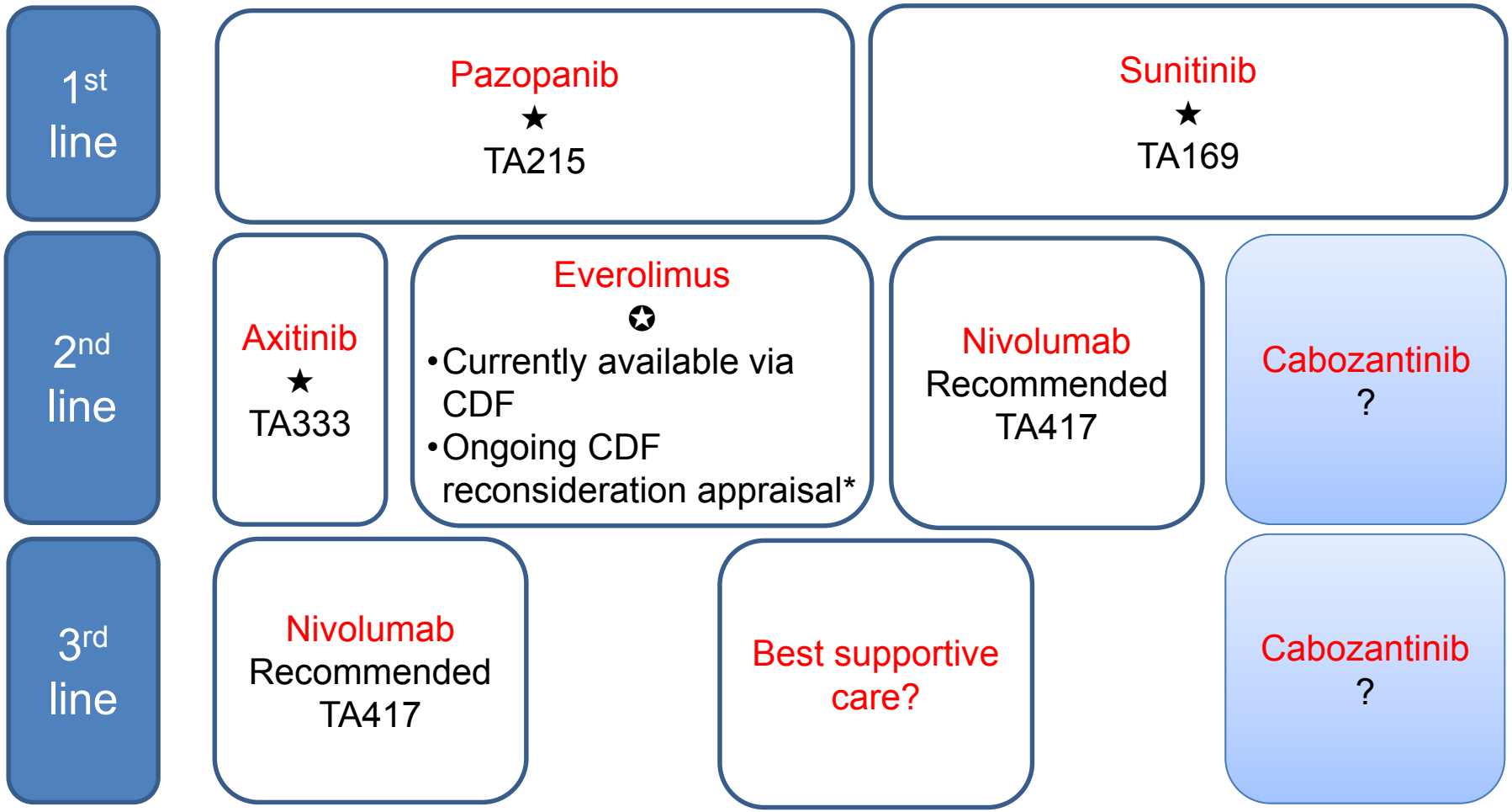
Cabozantinib (Cabometyx) Ipsen

- Protein kinase
- Inhibits multiple receptor tyrosine kinases implicated in tumour growth and angiogenesis, pathologic bone remodelling, and metastatic progression of cancer
- Indicated for:

'advanced renal cell carcinoma in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy'

- Administered orally, 60 mg once daily
- List price £5,143 for a 30-tablet pack of 60 mg cabozantinib (£171.43 per tablet)
  - Patient access scheme discount in place

Current management



★: oral tyrosine kinase inhibitors
✪: oral mammalian target of rapamycin (mTOR) inhibitor

*Final draft guidance issued recommending everolimus for advanced renal cell carcinoma that has progressed during or after treatment with vascular endothelial growth factor targeted therapy

- *Would cabozantinib be used as a 2nd- or 3rd-line treatment, or both?*
- *Is best supportive care a comparator?*

Impact on patients and carers

- Diagnosis of kidney cancer may be delayed, so life-prolonging treatment becomes even more necessary
- There are few 2nd line NICE approved treatments for patients with kidney cancer – cabozantinib would be an important alternative option especially as it is an oral therapy
- Toxicity seems to be similar to other VEGF-targeted therapies – clinicians already have experience with these
- There may be additional benefits from this therapy for some patients because of its multi-targeted approach
- Any improvements in quality of life with this therapy would have an important impact for both patients and carers

Decision problem

Company submission matched scope

	NICE scope
Population	People who have received previous VEGF-targeted therapy for advanced renal cell carcinoma
Comparators	• Axitinib • Everolimus • Nivolumab • Best supportive care
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects • Health-related quality of life

VEGF, vascular endothelial growth factor

Company's clinical evidence

1 main trial vs. everolimus (ongoing CDF reconsideration)

Trial	METEOR
Design	**Open-label** RCT (n=658, randomised 1:1 to cabozantinib or everolimus; **no cross-over** allowed)
Population	Adults with advanced RCC that progressed after at least 1 VEGFR-TKI therapy (no limit on the number of previous anti-cancer therapies)
Intervention	Cabozantinib 60 mg orally once daily
Comparator	Everolimus 10 mg orally once daily
Outcomes	• **1°**: progression-free survival – Time from randomisation to IRC-assessed disease progression per RECIST criteria or death from any cause • **2°**: overall survival, overall response rate • '**Additional**': health-related quality of life, safety and tolerability
Treatment period	For as long as treatment conferred a clinical benefit as per the investigator (including after progression); until toxicity; or until subsequent anti-cancer treatment needed
Subsequent treatments	55% (cabozantinib) vs. 50% (everolimus) of patients received subsequent treatment after stopping study drug

IRC, Independent radiology committee; VEGF-TKI, vascular endothelial growth factor tyrosine kinase inhibitor

Baseline characteristics in METEOR

Characteristic	ITT	
	Cabozantinib n=330	Everolimus n=328
Age — year		
Median (range)	63	62
Range	32-86	31–84
ECOG performance-status score — no. (%)		
0	226 (68)	217 (66)
1	104 (32)	111 (34)
Prior VEGFR tyrosine kinase inhibitors — no. (%)		
1	235 (71)	229 (70)
≥2	95 (29)	99 (30)
Previous systemic therapy — no. (%)		
Sunitinib	210 (64)	205 (62)
Pazopanib	144 (44)	136 (41)
Other	137 (42)	164 (50)

ECOG, Eastern Cooperative Oncology Group; ITT, intention-to-treat; VEGF-TKI, vascular endothelial growth factor tyrosine kinase inhibitor

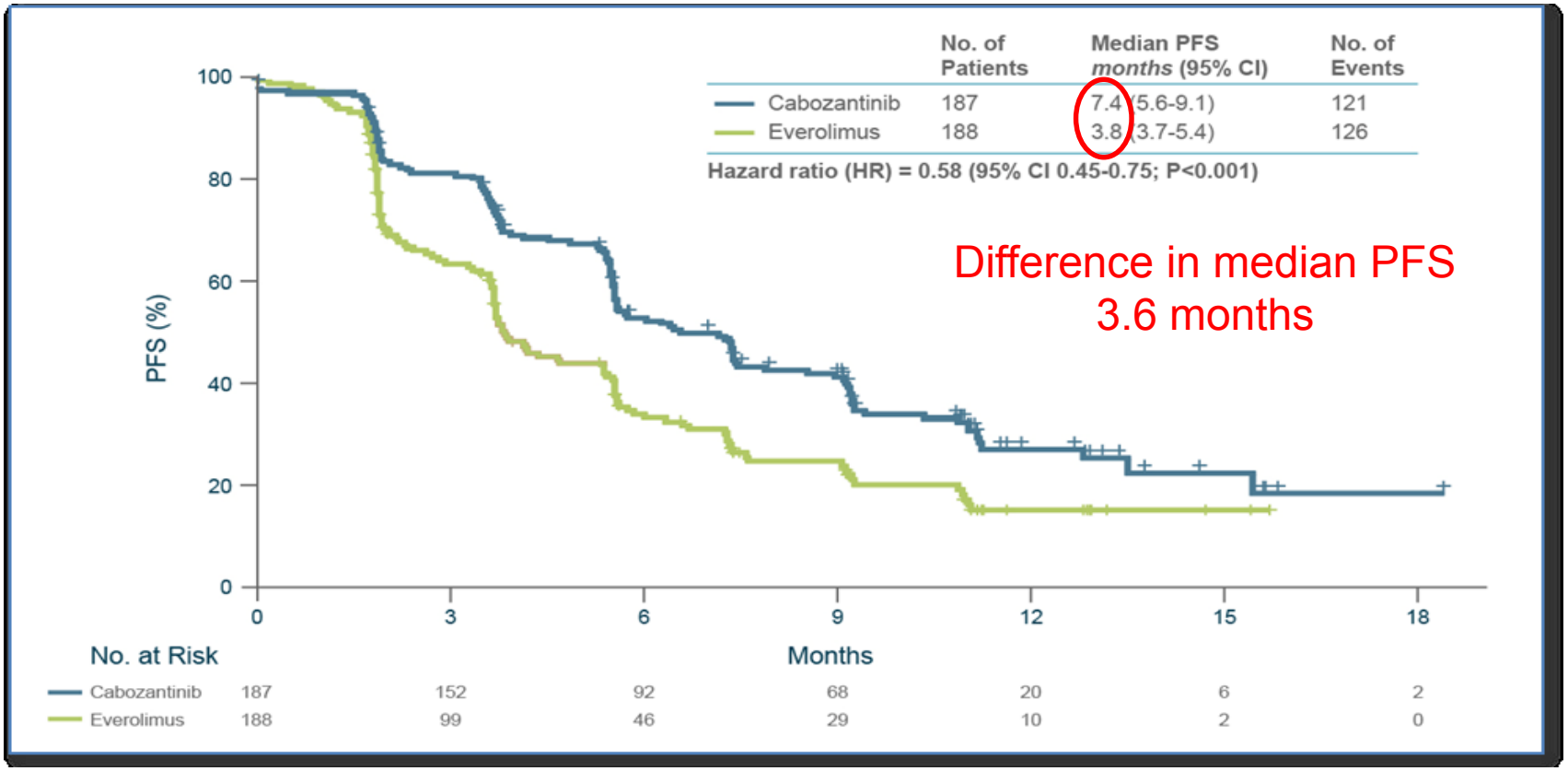
ERG: reflects fitter patients in clinical practice

Over 70% of patients received second-line treatment

⊙ *Is the METEOR population generalisable to NHS patients?*

METEOR Kaplan-Meier curve for PFS

Cabozantinib significantly increases PFS (PITT* population)



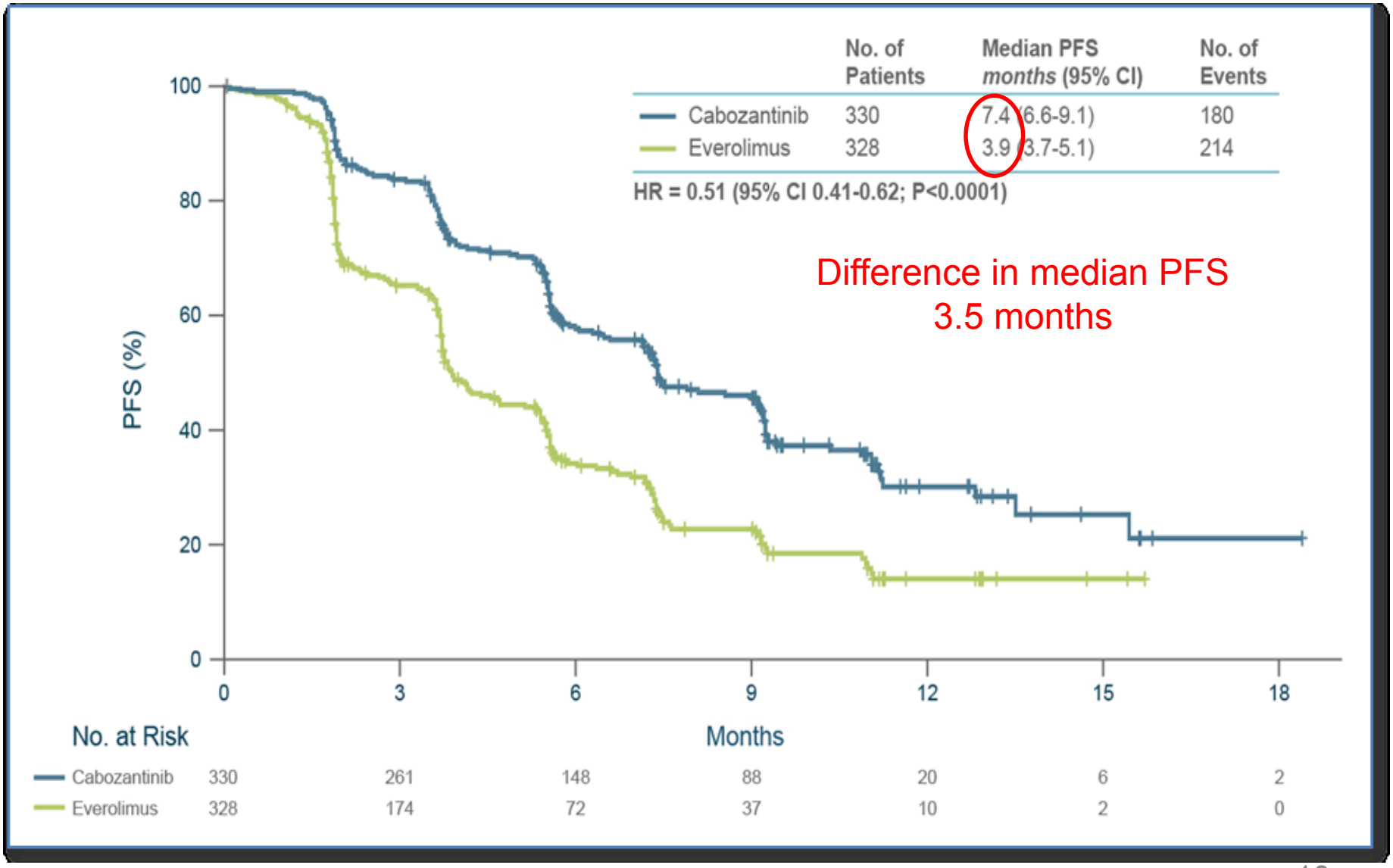
*PITT: primary end point intention to treat population which comprised of the first 375 patients randomised

ERG: primary end point intention to treat analysis (PITT) has limited use in decision-making compared with full ITT population

⊙ *Is the PITT analysis appropriate to assess PFS?*

METEOR Kaplan Meier estimates of PFS

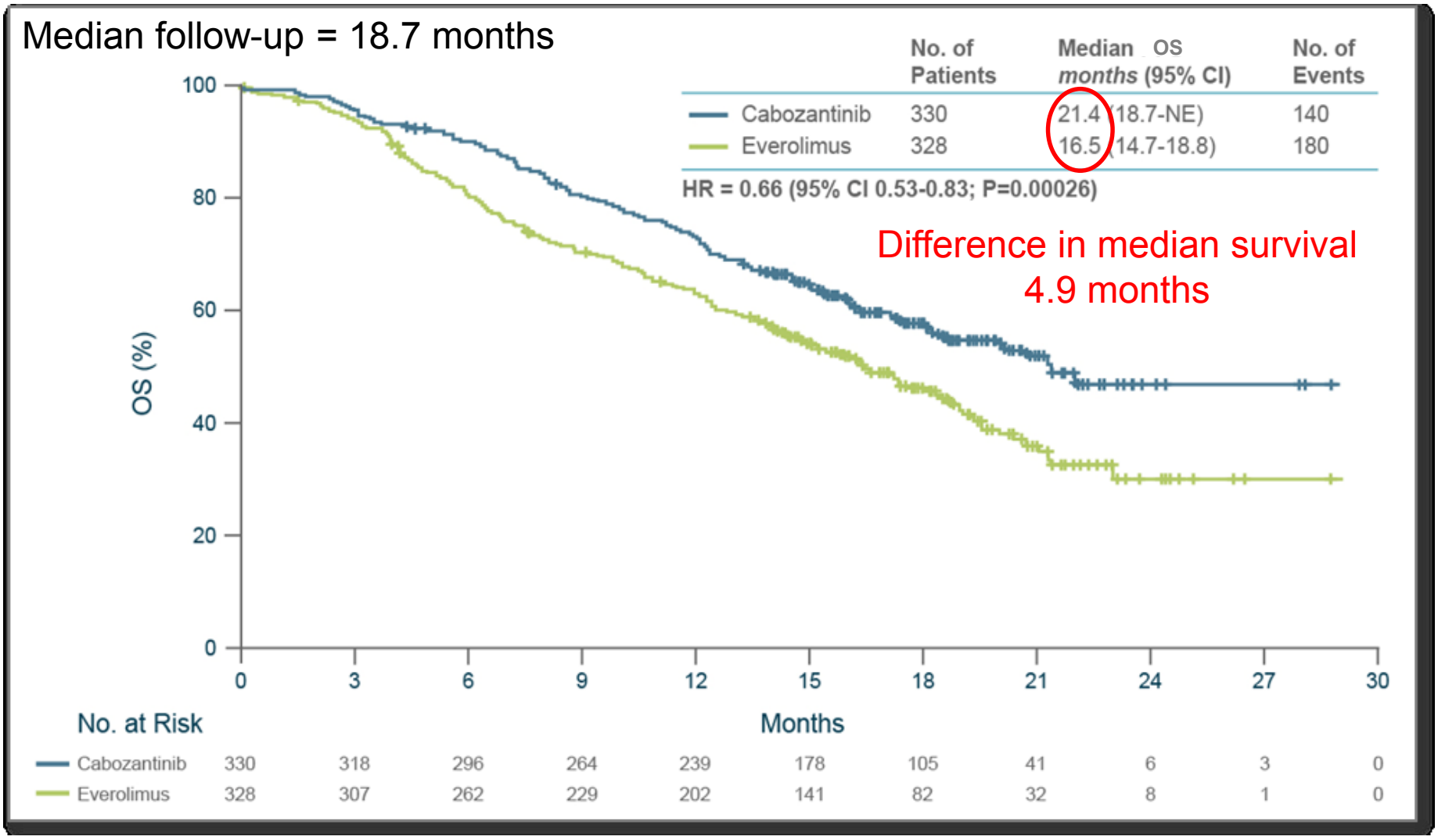
Cabozantinib significantly increases PFS (ITT*)



*ITT: intention to treat population

METEOR Kaplan Meier estimates of OS

Cabozantinib significantly lowers risk of death (ITT)



⊙ *Is the effectiveness of cabozantinib likely to wane beyond the end of the trial?*

Post-hoc subgroup analyses[1]

OS favours cabozantinib in ≥2 prior VEGFR-TKI, broadly similar to 1 prior VEGFR-TKI

[1]Patients either had sunitinib or pazopanib or both as previous therapy

Adverse events

Consistent with other VEGF-TKI treatments, and managed through dose reductions

	Cabozantinib (n=331)	Everolimus (n=322)
Grade ≥3 serious adverse events, n (%)	130 (39)	129 (40)
Median duration of exposure (months)	8.3 (IQR 4.2-14.6)	4.4 (IQR 1.9-86)
Most common Grade ≥3 serious adverse events, n (%)		
Abdominal pain	9 (3)	3 (1)
Pleural effusion	8 (2)	7 (2)
Pneumonia	7 (2)	13 (4)
Pulmonary embolism	7 (2)	1 (<1)
Anaemia	5 (2)	10 (3)
Dyspnoea	4 (1)	10 (3)
Deaths	26 (8)	25 (8)
Deaths assessed as treatment-related	1	2

Similar frequency of grade ≥ 3 serious adverse events (39% vs. 40%), despite an almost 2-fold longer exposure to cabozantinib

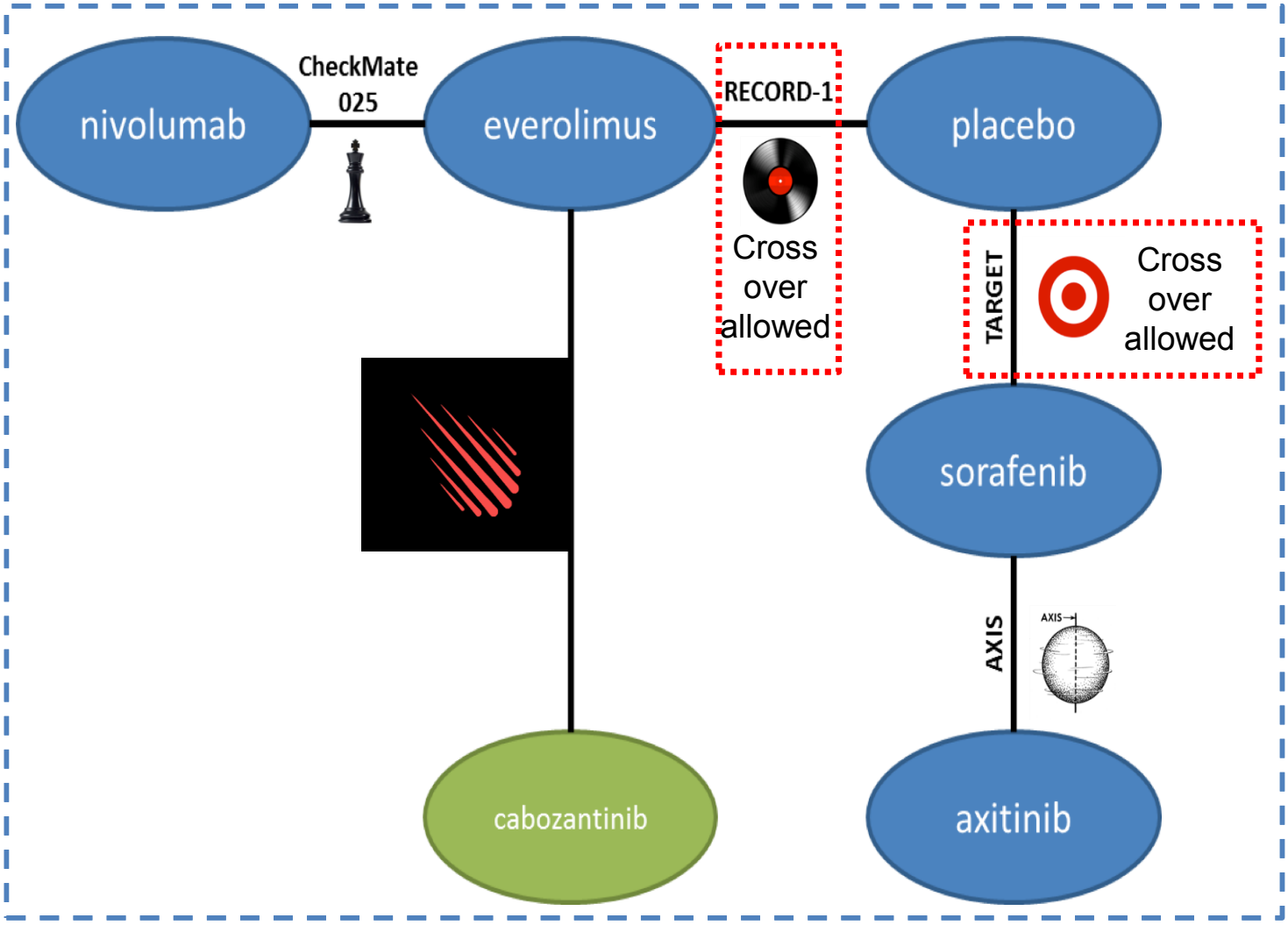
ERG comments on METEOR

- No sufficient data to assess cabozantinib as third-line treatment
  - Everolimus, the comparator in METEOR, mainly used in second-line setting
  - Key comparator in third-line setting is nivolumab and best supportive care

Network meta-analysis

No trials directly comparing cabozantinib to axitinib, nivolumab, or best supportive care

Network for OS and PFS (separate network for TTD)



- Proportional hazards (PH) assumption did not hold in TARGET and CheckMate 025 (first 6 weeks)
- NMA based on parametric curves (does not assume PH), rather than hazard ratios, to avoid violating PH assumption

Company's network meta-analysis

Considerable differences between included trial populations

Difference	Degree of heterogeneity and availability of subgroup results
Cross-over study design	• RECORD-1 (everolimus) and TARGET (sorafenib) allowed treatment switching (cross-over) • The company used: – From RECORD-1: HR for OS adjusted for cross-over using the RPSFT model – From TARGET: analysis censoring patients at time of cross-over
Type and number of prior therapies	• Variation in number of previous therapies allowed, distribution of these therapies in patient cohorts, and availability of results for subgroups by prior therapy • The company could not estimate results for subgroups by prior therapy
Baseline prognosis scores	• TARGET did not include any patients with 'poor' MSKCC prognosis • Some trials did not present subgroup analyses by MSKCC prognosis • The company could not estimate results for subgroups by MSKCC prognosis (poor/intermediate/favourable) based on available HRs or Kaplan-Meier curves

Key: HR, hazard ratio; MSKCC, Memorial Sloan-Kettering Cancer Centre; OS, overall survival; PFS, progression free survival

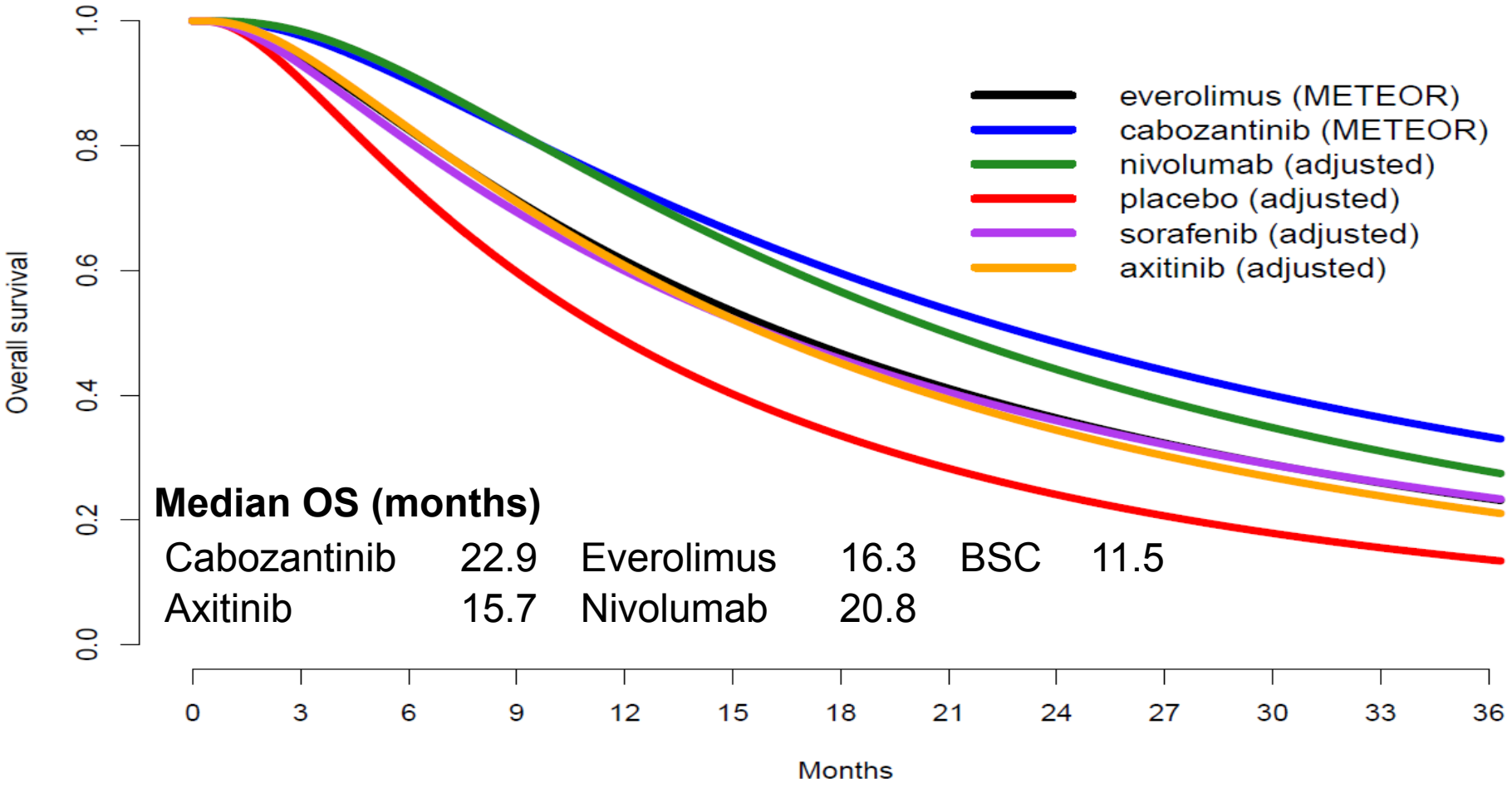
Company's network meta-analysis

Considerable differences between included trial populations

	Prior VEGF therapies (across both arms)		**Cross-over**	**Subsequent therapies**	
	1	*2+*		*Intervention*	*Comparator*
METEOR Cabozantinib vs. everolimus	71%	29%	No	55% of whom 29% had everolimus	50% of whom 2% had cabozantinib
RECORD-1 Everolimus vs. placebo	74%	26%	Yes	Not reported	
CheckMate 025 Nivolumab vs. everolimus	72%	28%	No	55% of whom 26% had everolimus	63% unclear how many had nivolumab
TARGET Sorafenib vs. placebo	0%	0%	Yes	Not reported	
AXIS (prior sunitib subgroup) Axitinib vs. sorafenib	100%	0%	No	Not reported	

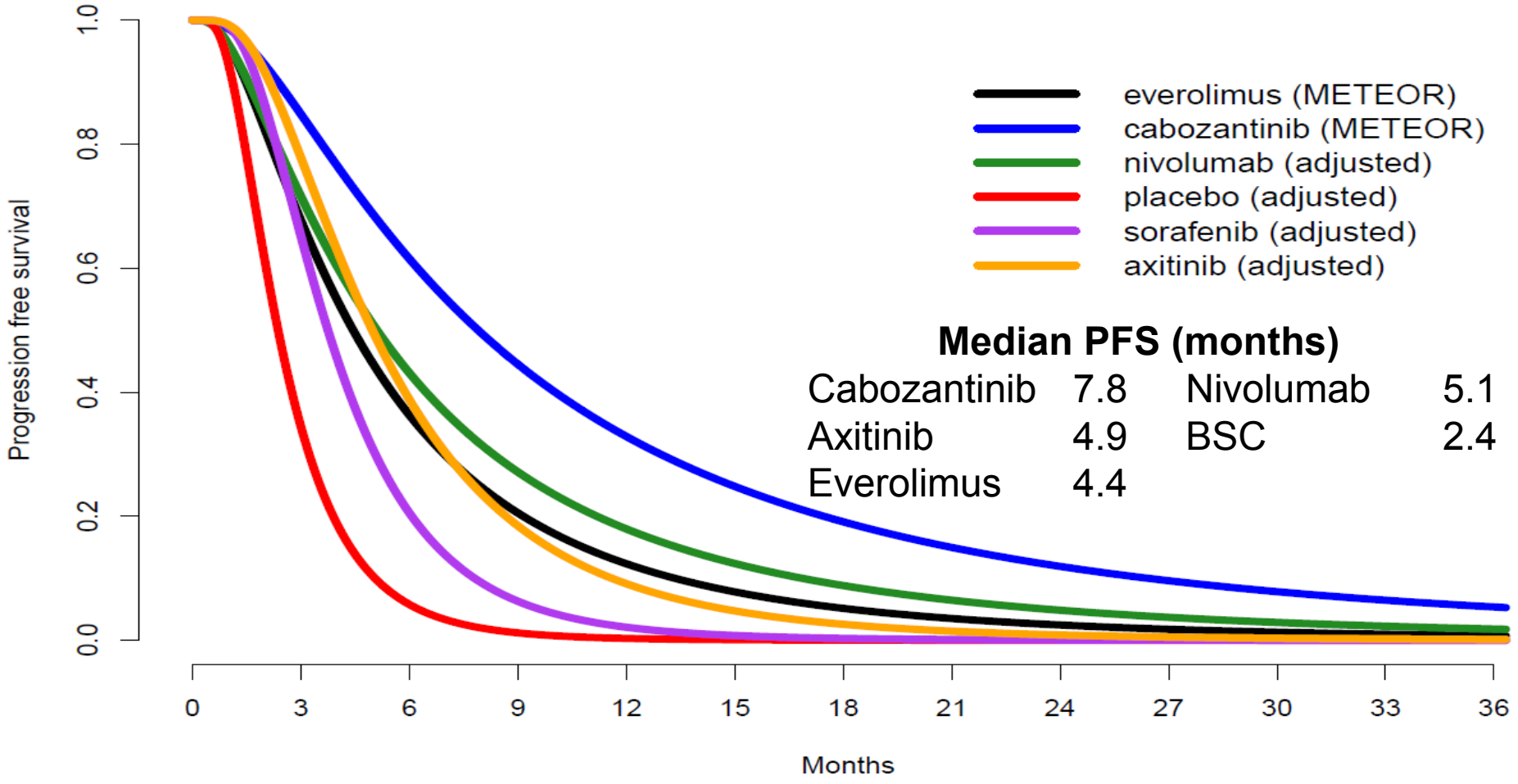
Company's network meta-analysis

Cabozantinib compared with each of the comparators improves OS



Company's network meta-analysis

Cabozantinib compared with each of the comparators improves PFS



Company's network meta-analysis (TTD)

No data to include axitinib and BSC in network

- TTD longer with cabozantinib compared with everolimus and nivolumab

	Median TTD (months)
Cabozantinib	9.0
Everolimus	5.0
Nivolumab	7.4

Key: TTD, time to treatment discontinuation

ERG comments on network meta-analysis

1. **Methodology**: ERG considered a key limitation is that company applied same parametric distribution to all treatments in the network
   - Goodness of fit refer to 'average fit' across network
   - So, chosen distribution may not fit individual treatment
2. **Everolimus 'underperforming'** in METEOR compared with CheckMate 025
3. **Heterogeneity** between trials in subsequent treatments
4. **Cross-over** in trials
5. No suitable **subgroup data** to inform separate networks for 2nd and 3rd-line treatments

ERG advises **caution** interpreting possibly unreliable results

ERG comments on network meta-analysis

Everolimus 'underperforms' in METEOR compared with CheckMate 025

- Impacts the comparison of carbozantinib with nivolumab

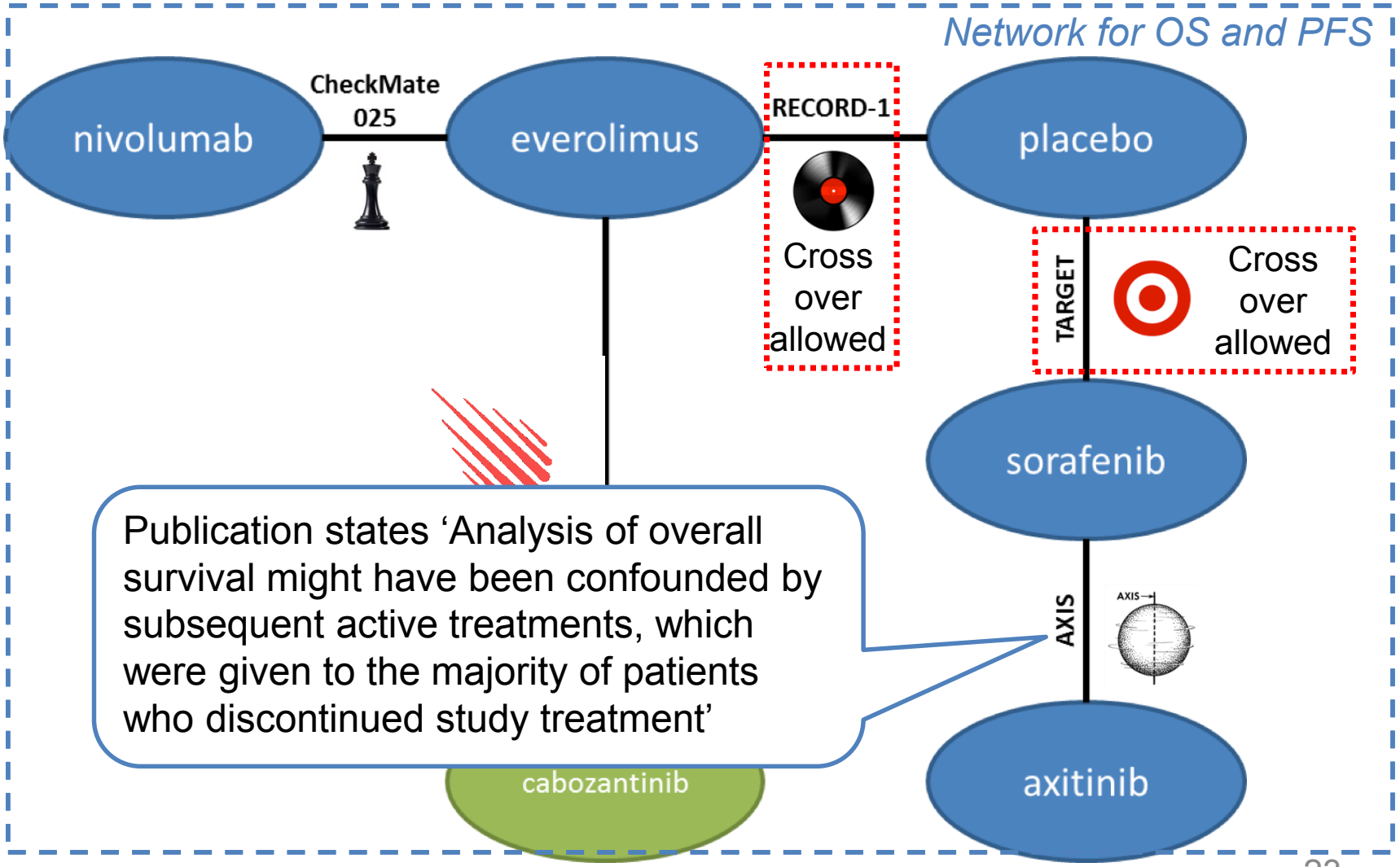
	METEOR	CheckMate 025
Death rate	54.9%	52.3%
Median OS (mo)	16.5	19.6
HR everolimus vs. intervention (95% CI)	1.52 (1.20–1.89) Risk of death increased by **52%** compared with **cabozantinib**	1.37 (1.08–1.75) Risk of death increased by **37%** compared with **nivolumab**

- Difference in effect could just reflect spectrum of efficacy, or unobserved prognostic factor
- ERG notes that METEOR appears to include patients with better prognosis than CheckMate 025, yet patients in everolimus arm have poorer outcomes

⊙ *Is the OS estimate for everolimus from METEOR robust?*

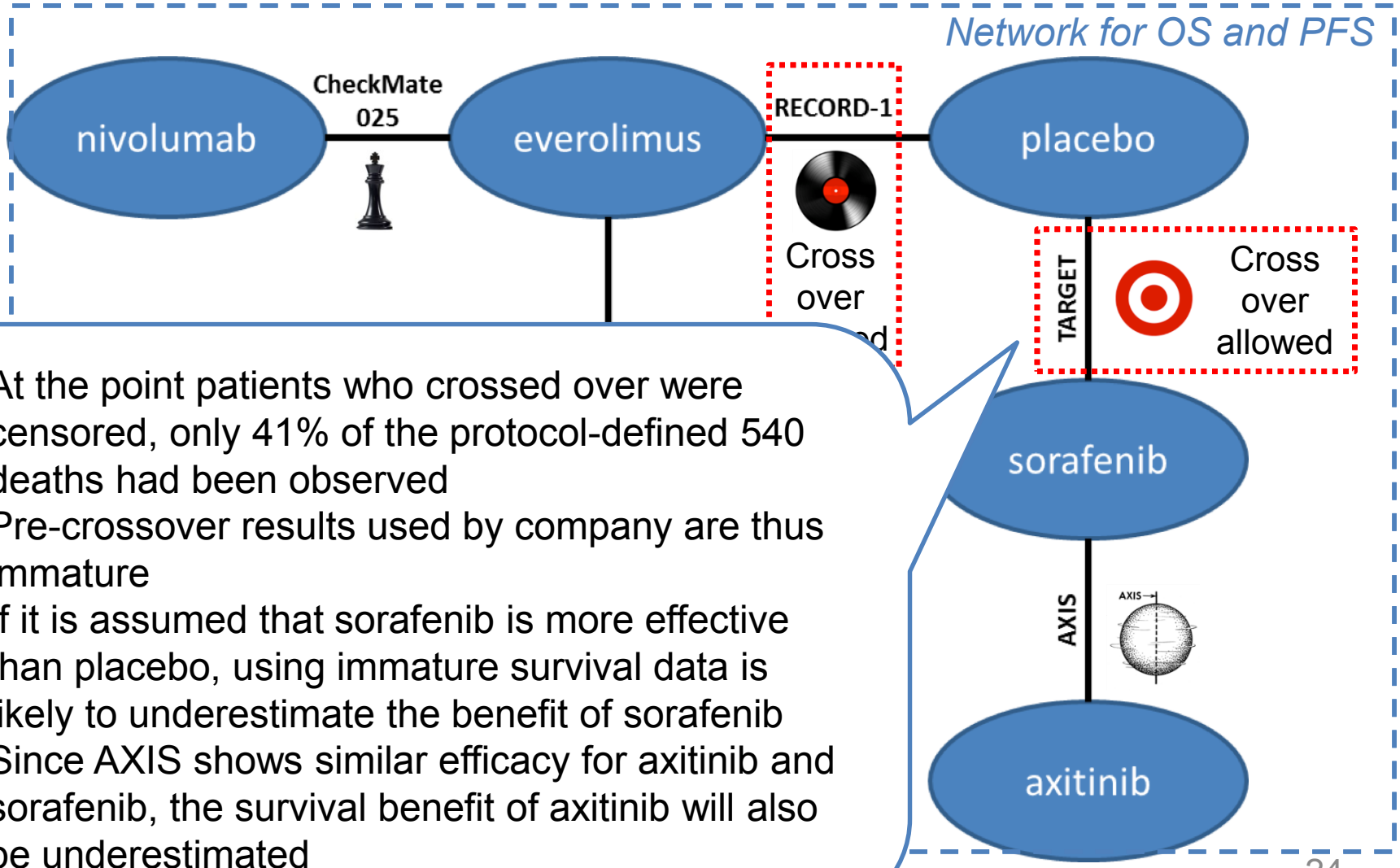
ERG comments on network meta-analysis

Subsequent treatments received in all trials ‘a potential source of bias’ for overall survival



ERG comments on network meta-analysis

Cross-over in trials



- At the point patients who crossed over were censored, only 41% of the protocol-defined 540 deaths had been observed
- Pre-crossover results used by company are thus immature
- If it is assumed that sorafenib is more effective than placebo, using immature survival data is likely to underestimate the benefit of sorafenib
- Since AXIS shows similar efficacy for axitinib and sorafenib, the survival benefit of axitinib will also be underestimated

ERG exploratory analysis

Similar treatment ranking to company's NMA

- ERG assumed axitinib and everolimus equally effective (assumption also used and accepted in nivolumab TA417)
- Because TARGET no longer used, ERG assumed PH for OS (but not PFS) as PH held in other trials (except first 6 weeks of CheckMate 025)

Treatment	Median OS (months)		Median PFS (months)	
	Company's NMA	ERG's amended NMA	Company's NMA	ERG's amended NMA
Cabozantinib	22.9	22.0	7.8	7.8
Axitinib	15.7	16.3	4.9	4.7
Everolimus	16.3	16.3	4.4	4.7
Placebo	11.5	10.1	2.4	1.9
Nivolumab	20.8	20.4	5.1	5.2

⊙ *Is the ERG's NMA assuming that axitinib and everolimus have equal efficacy more appropriate than the company's NMA?*

Key clinical issues for consideration

- Would cabozantinib be used as 2nd- or 3rd-line treatment or both? Do trial results permit us to look at these separately?
- Is best supportive care a comparator in the second- or third-line setting?
- Are there distinct patient subgroups for the different treatments?
- Given the high proportion of patients with an ECOG performance status of 0, is METEOR generalizable to NHS patients?
- Does line of treatment influence cabozantinib's effectiveness?
- Is treatment duration likely to differ in practice from METEOR?
- Which analysis is the more appropriate for PFS, the primary endpoint intent-to-treat, or the intent-to-treat?
- Is cabozantinib's effectiveness likely to wane beyond the trial's end?

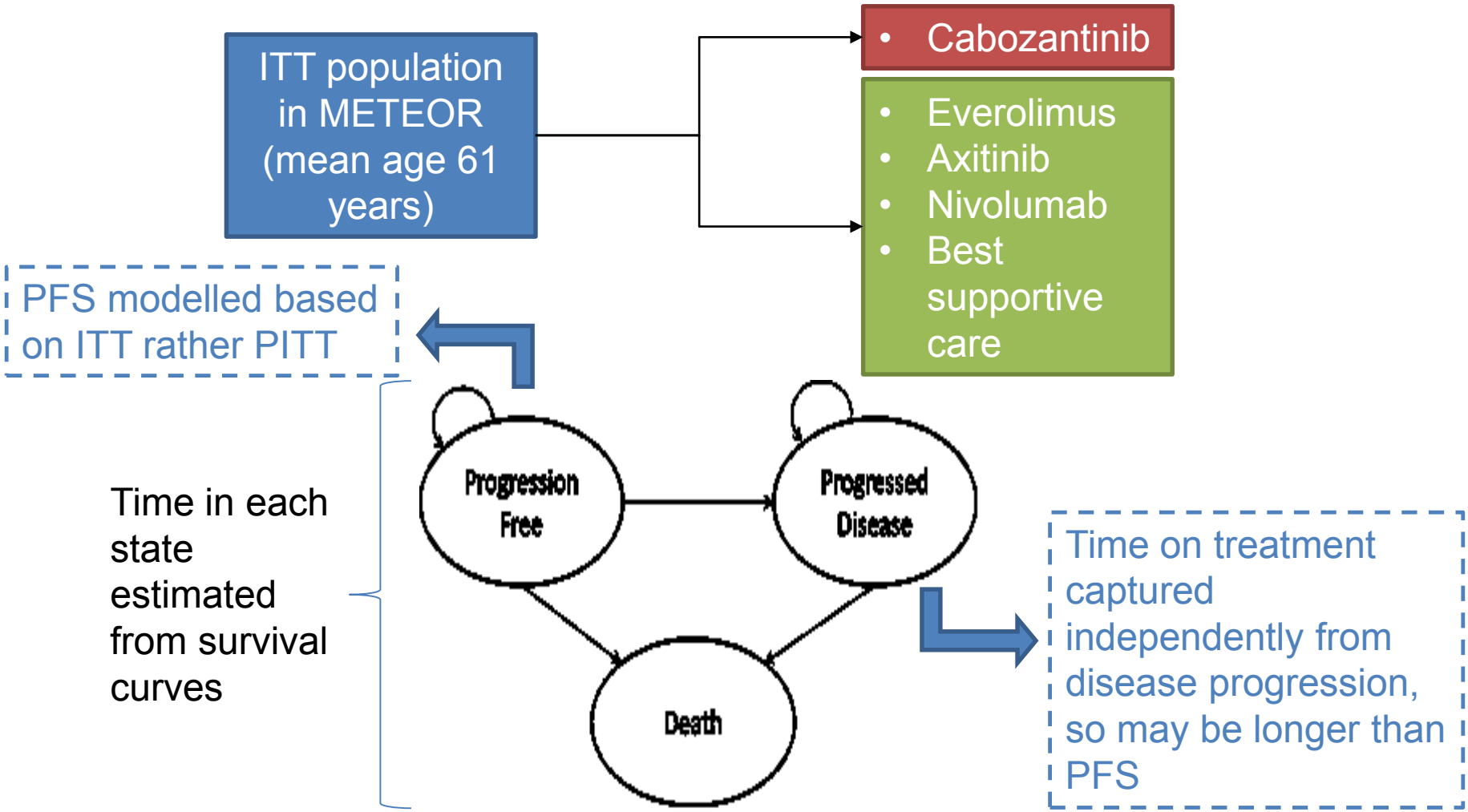
Key clinical issues for consideration (cont.)

- Network meta-analysis
  - Is the OS estimate for everolimus from METEOR robust?
  - Trial populations differed in ‘maturity’, and adjustments for cross-over and subsequent treatments. Is this analysis robust enough to inform decision-making?
  - Is the ERG’s NMA assuming that axitinib and everolimus have equal efficacy more appropriate than the company’s NMA?

Cost effectiveness

Model structure

Partitioned-survival (area-under-curve) model



4-week cycle length (reflecting frequency of follow-up visits in METEOR); 30-year time horizon

Company's analyses

2 analyses presented

	'NMA-based' analysis	'Trial-based' analysis
Comparators	• Everolimus • Axitinib • Nivolumab • Best supportive care	• Everolimus
Data source	Network meta-analysis (NMA)	METEOR only
Survival modelling	• Re-generated Kaplan-Meier data from CheckMate 025, AXIS, RECORD-1 and TARGET, as well as METEOR • Efficacy curves of axitinib, nivolumab and BSC estimated from the NMA adjusted to the everolimus group of METEOR	• Parametric survival curves fitted to Kaplan-Meier data from METEOR, and extrapolated beyond trial follow-up

⊙ *How does the committee wish to use the trial-based analysis?*

Clinical parameters and variables

NMA-based analysis

	PFS nivolumab, axitinib and BSC	OS nivolumab, axitinib and BSC	TTD nivolumab, BSC
Assume PH	No	No	No
Model type	Same distribution fitted to all treatments (based on 'average' fit to data)		
Distribution	Log-normal	Log-normal	Log-normal
ERG comments: curve choice	Log-normal reasonable, but poor fit to data	Log-normal shows poor fit to sorafenib (AXIS link) so effect of axitinib uncertain; ERG assumed axitinib = everolimus and PH holds)	Log-normal appropriate
	Key limitation is that same distribution had to be used for all comparators to estimate PFS and OS – Some of the curves had a poor fit – 'A serious limitation', potentially unreliable estimates of treatment effect, and uncertain ICERs		

⊙ *Is it appropriate to assume OS for axitinib = OS for everolimus (ERG base case)?*

Clinical parameters and variables

Trial-based analysis

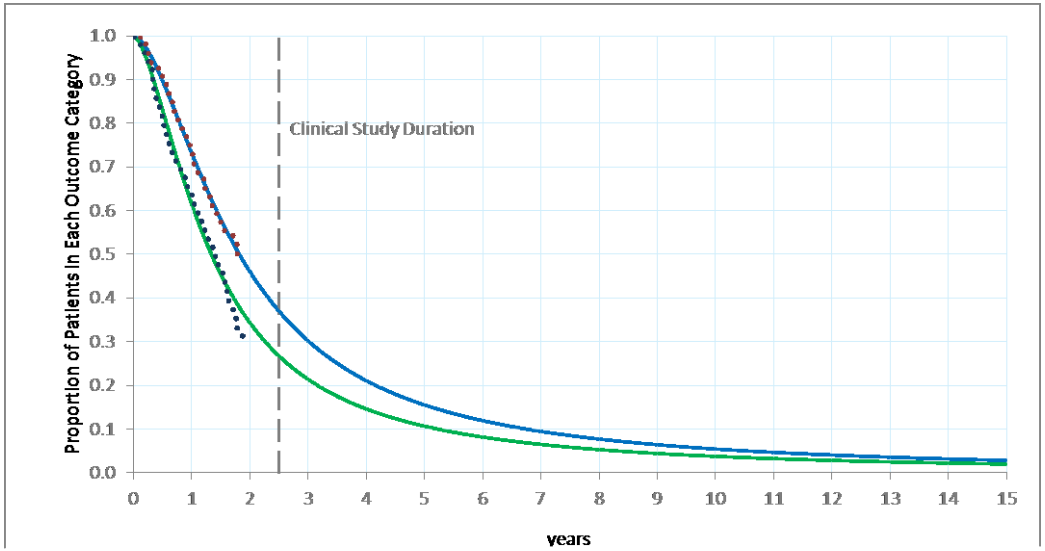
	PFS	OS	TTD
Assume PH	No	No	No
Model type	Independent models for each treatment group		
Distribution	Log-logistic	Log-logistic	Log-normal
ERG comments: curve choice	Log-normal best fit for cabozantinib but not everolimus	Weibull more appropriate: avoids long tail and log-cumulative hazard plots reflect hazard functions of a Weibull	Appropriate but choice of distribution not justified
	Other alternatives not fully considered/tested as scenario analyses		

⊙ *Which distribution is more appropriate for OS (see next slide)?*

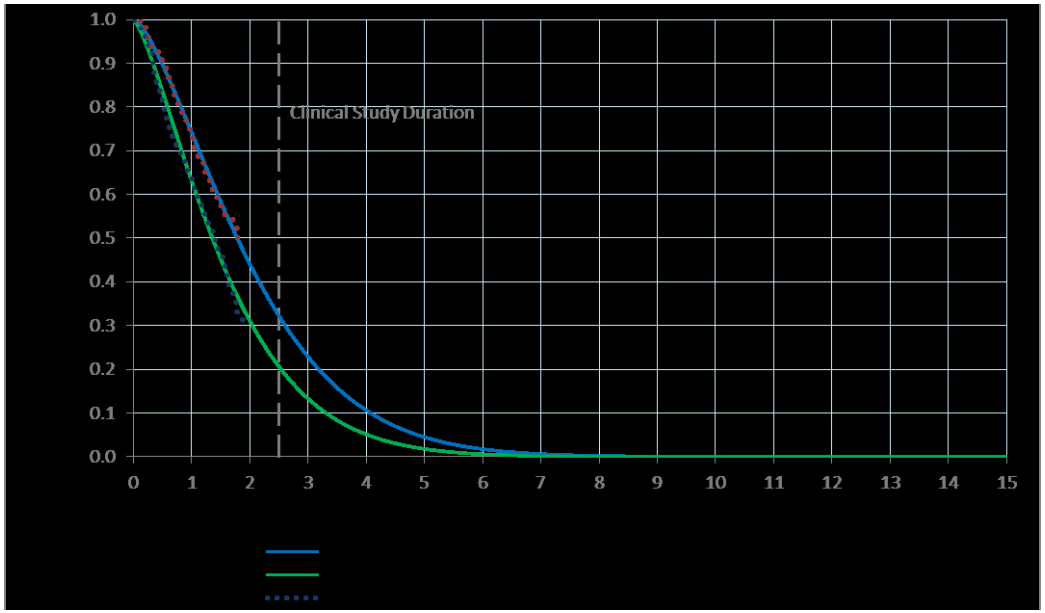
Curve fits for OS: company vs. ERG

Model highly sensitive to choice of distribution

Company's preferred distribution, **log-logistic**



ERG's preferred distribution, **Weibull**



Health-related quality of life

Utility values sourced from METEOR for all treatments

	PFS	PPS	Trial	Measure
All treatments	0.817	0.777	METEOR	EQ-5D-5L
Key: PFS, progression-free survival; PPS, post-progression survival				

- **ERG**: Utility values higher than expected in clinical practice
  - Utility values for PFS and PPS would be closer to those used for axitinib in TA333 (assessed in a ERG scenario analysis)

Source	PFS	PPS	Trial	Measure
Axitinib TA	0.692	0.610	AXIS	EQ-5D US tariff
Nivolumab TA	0.800	0.730	CheckMate025	EQ-5D
Swinburn et al. 2010	0.795	0.355	-	EQ-5D
Everolimus TA	0.710-0.760	0.680	TA178 (RCC MTA)	EQ-5D
Key: PFS, progression-free survival; PPS, post-progression survival				

⊙ *Is it appropriate to take the utility values directly from METEOR for all treatments?*
⊙ *Should the utility values be adjusted for age?*

Health-related quality of life

Utility decrements for adverse events

- Utility decrement of -0.055 estimated from METEOR, then weighted by the proportion of patients who had grade 3-4 adverse events for each treatment

Treatment	Weighted AE disutility
Cabozantinib	-0.03
Everolimus	-0.02
Axitinib	-0.03
Nivolumab	0.00

- **ERG**: initial utility decrement used by the company (-0.055) estimates smaller impact on quality of life than literature values
  - Impact of utility decrement for adverse events minimal on ICER, although clinical experts expected it to be significant

⊙ *Should a greater impact of adverse events on quality of life be assumed?*

Resource use and costs

- Company assumed
  - No wastage for nivolumab
  - Patients seen by GP every 4 weeks before and after disease progression
  - Sorafenib included as a subsequent treatment option in model

ERG:

- Patients more likely to be seen by consultants rather than GP every 4 weeks (explored assumption in scenario analysis)
- Sorafenib should not be included as subsequent therapy as it is not reimbursed in the UK

⊙ *Should the model include waste for nivolumab?*
⊙ *Are patients seen by GPs or consultants during treatment?*
⊙ *Should sorafenib be included as a subsequent treatment?*

ERG base case

	Assumptions from ERG	Original assumptions from company	Analysis where assumption applied
A	Using Weibull distribution to extrapolate OS	Using log-logistic	Trial
B	Effect of axitinib and everolimus equal, NMA based on hazard ratios (assumes PH)	Effect of axitinib and everolimus different (based on NMA), NMA based on parametric curves (does not assume PH)	NMA
C	Utility values for PFS and PPS of 0.692 and 0.610 (from AXIS trial)	Values for PFS and PPS of 0.817 and 0.777 (from METEOR)	Trial, NMA
D	Includes wastage costs for nivolumab	No wastage	NMA
E	Excludes cost of GP visit before disease progression	Includes GP costs	Trial, NMA

⊙ *Which assumptions does the committee prefer?*

ERG scenario analyses

NMA based analysis (vs. all comparators)	Trial-based analysis (vs. everolimus only)
1. Assuming **proportional hazards** for PFS curves 2. *Not originally included in the ERG but requested by NICE at later stage:* assuming **treatment effect on OS wanes** Hazard ratios relative to everolimus (reference treatment) gradually increase or decrease to 1 over a period of 12 months, starting from month 25, then remain 1 until the end of the time horizon	1. Extrapolating overall survival using log-logistic distribution for cabozantinib (same distribution used in company base case) 2. Assuming proportional hazards hold a) OS only b) OS and PFS

Summary of cost-effectiveness results

- Results are presented in PART 2 as they include PAS discount for cabozantinib and the comparators

Company	ERG
Base case[1] • Deterministic • Probabilistic	**Base case** • Deterministic • Probabilistic
	Scenario analysis • Original analyses included in ERG report • 'Waning effect' requested by NICE

[1]The company corrected its original base case in response to a request for clarification from the ERG. The results presented here are those of the corrected base case.

Innovation according to company

- Cabozantinib is the first therapy for advanced RCC that has evidence versus an active comparator (everolimus) of significant improvement in OS, PFS and ORR
- Cabozantinib met the “promising innovative medicine” criteria of
  - Treatment of a life-threatening or seriously debilitating condition with high unmet need
  - Likelihood of major advantage over current treatments
  - Reasonable expectation of a positive benefit-risk profile

Equality issues

- There are no equality issues related to the use of cabozantinib.

Key cost issues for consideration

- Should the model use estimates of relative effectiveness from the network meta-analysis (as in the company's base case) or assume that axitinib is as effective as everolimus (as in the ERG's analyses)?
- How does the committee wish to use the trial-based analysis?
- Is it appropriate to take the utility values directly from METEOR for all comparisons? Should the values be age-adjusted?
- Should the model include waste for nivolumab? For cabozantinib?
- Should the model include treatment waning for cabozantinib?
- The model is most sensitive to the modelling of PFS and OS. Which parametric distributions and assumptions are most appropriate?
- Does cabozantinib meet the criteria for a 'life-extending treatment at the end of life'?

CDF Recommendation Decision Pathway

Starting point: drug not recommended for routine use

Proceed down if answer to each question is yes

1. Why is drug not recommended? Is it due to clinical uncertainty?

2. Does drug have plausible potential to be cost-effective at the current price, taking into account end of life criteria?

3. Could data collection reduce uncertainty

4. Will ongoing studies provide useful data?

and

5. Is CDF data collection feasible?

Recommend enter CDF

Define the nature of clinical uncertainty and the level of it. Indicate research question, required analyses, and number of patients in NHS in England needed to collect data