Slides for public

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

2nd Appraisal Committee B meeting 23 March 2017
(1st Appraisal Committee B meeting 25 January 2017)

Lead team: Ken Stein, Mark Chapman, Danielle Preedy

Chair: Amanda Adler

ERG: BMJ Technology Assessment Group

NICE technical team: Aminata Thiam, Ahmed Elsada, Melinda Goodall

Company: Ipsen

Appraisal Consultation Document (ACD) preliminary recommendation

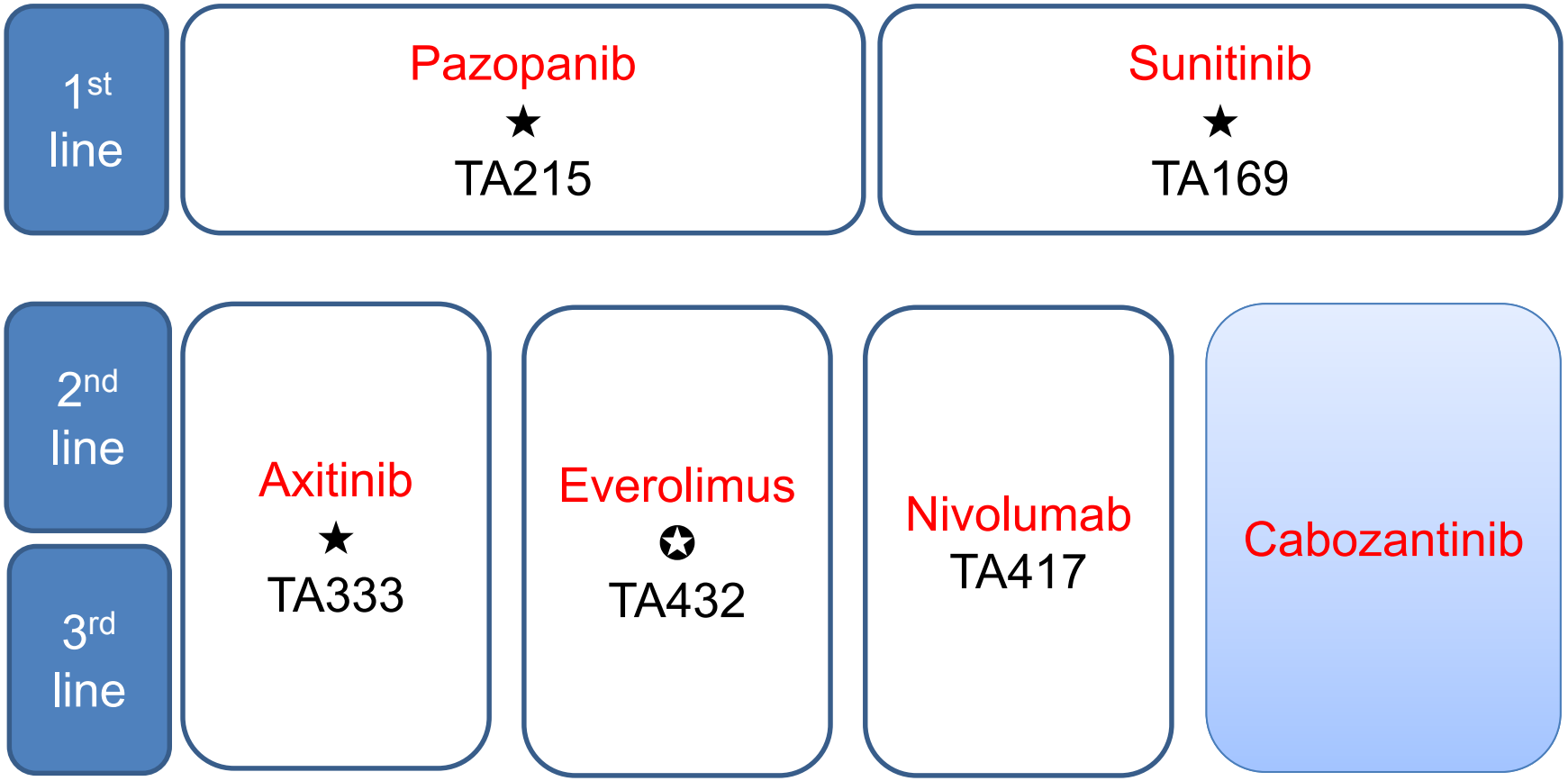
Cabozantinib is not recommended within its marketing authorisation for treating advanced renal cell carcinoma in adults after vascular endothelial growth factor (VEGF)-targeted therapy.

Decision problem

Marketing authorisation	Advanced renal cell carcinoma (RCC) in adults following prior vascular endothelial growth factor (VEGF)-targeted therapy
Route	Oral
Population	Same as marketing authorisation
Comparators	• Axitinib • Everolimus • Nivolumab • Best supportive care
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects • Health-related quality of life
Price	• Patient access scheme – simple discount

Current treatment pathway

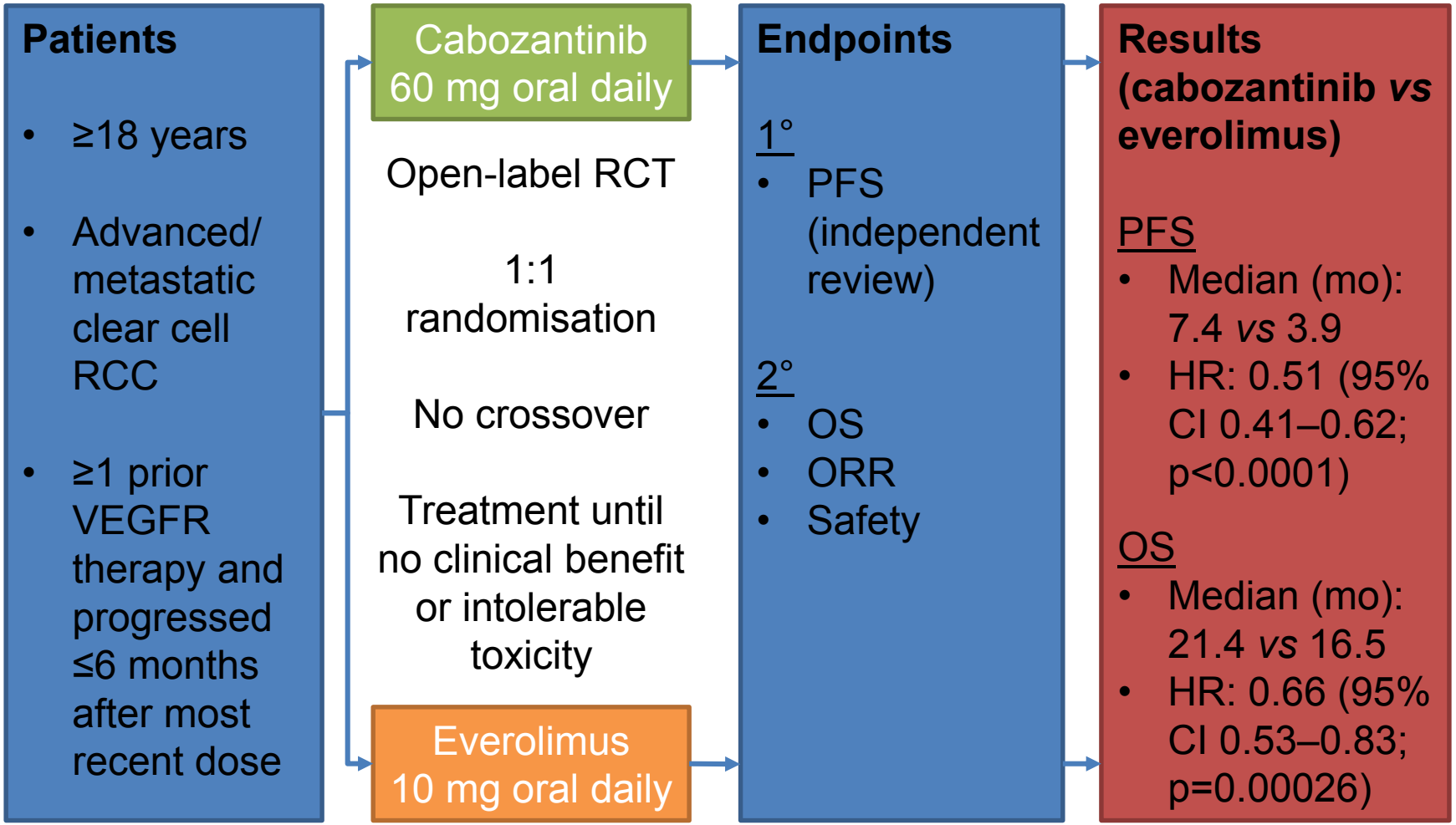
Agreed at previous committee meeting



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

Company's clinical evidence

Cabozantinib vs everolimus: METEOR trial (n=658)

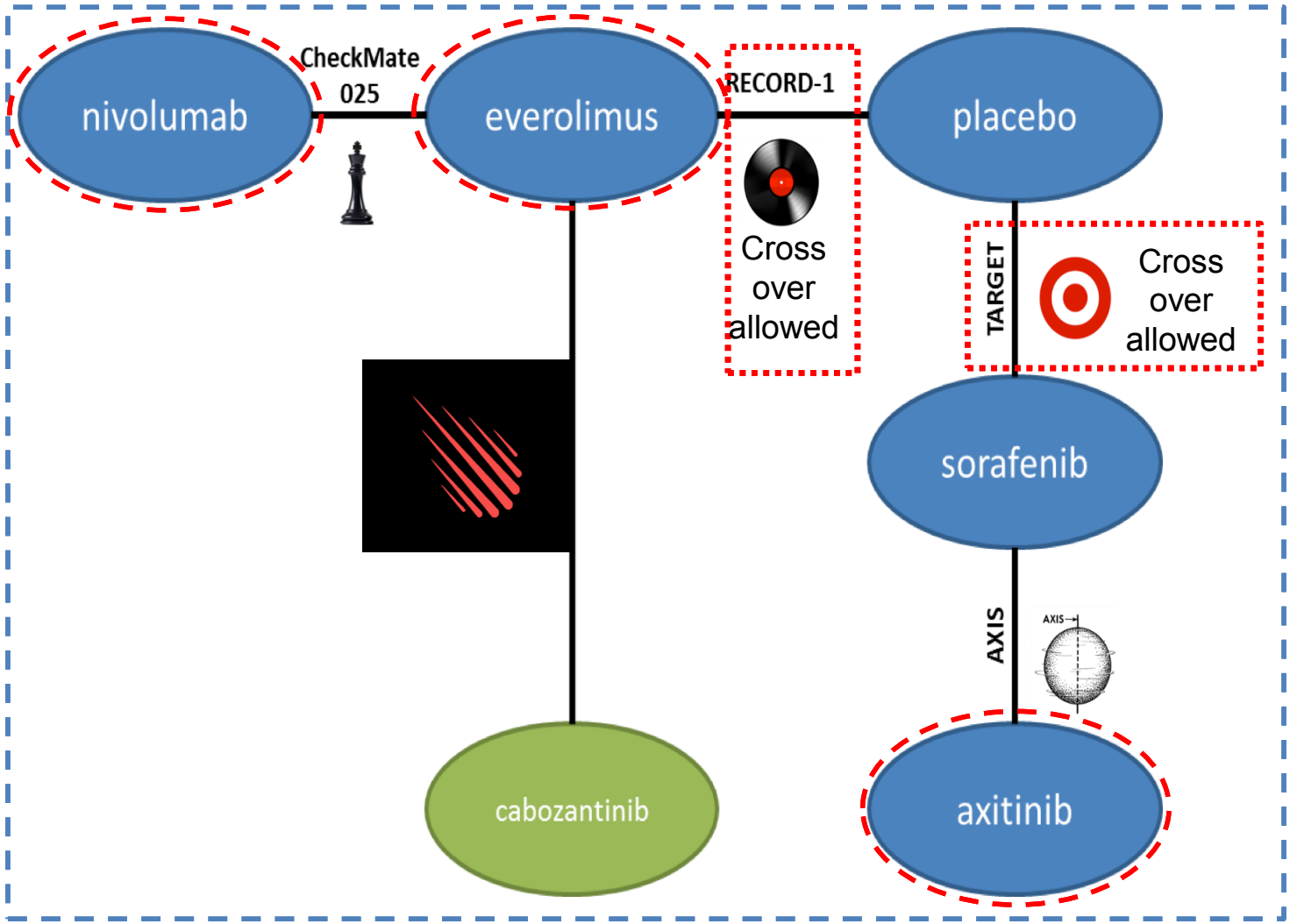


Key: ORR, overall response rate; OS, overall survival; PFS, progression-free survival, RCT, randomized controlled trial; VEGFR, vascular endothelial growth factor

Company's clinical evidence

Cabozantinib vs other comparators: network meta-analysis

Network for OS and PFS (separate network for TTD)



Company's cost-effectiveness analysis

Company presented 2 separate analyses

Trial-based analysis

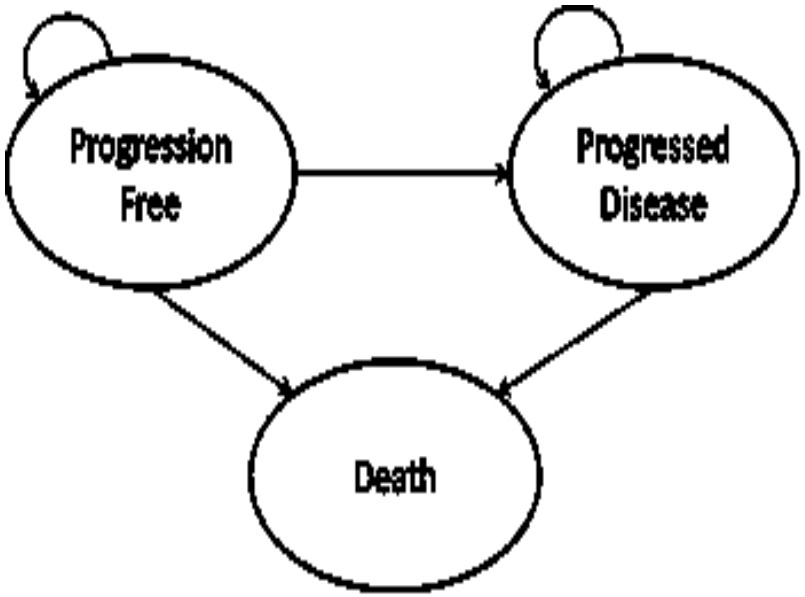
Uses METEOR data

- Cabozantinib
- Everolimus

NMA-based analysis

Uses network meta-analysis data

- Cabozantinib
- Everolimus
- Axitinib
- Nivolumab
- Best supportive care



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

ERG comment: Company used same 'family of distributions' for all treatments – a key limitation, as some curves had a poor fit to individual treatments

Committee's discussions: survival modelling

Issue	Committee conclusion	Committee request
Effect of axitinib *vs* everolimus on OS	Company used immature, pre-cross-over OS data from TARGET trial (sorafenib *vs* placebo), which underestimated axitinib effect	• Exclude TARGET by assuming axitinib as effective as everolimus
Method of network meta-analysis	Using 'family of distributions' to fit all curves not flexible enough, and did not fit well individual treatment curves	• Use methods allowing better-fitting distributions to model OS and PFS (e.g. Janssen et al. 2011)
Extrapolation of OS and PFS	ICERs very sensitive to distribution used	• Use evidence on the natural history of the disease to guide the extrapolation of OS • Present QALY gains before and after progression to assess plausibility of estimates
Modelled effect of nivolumab	Immunotherapy effect of nivolumab may result in 'long tail', as discussed in the appraisal of nivolumab	• Explore, in scenario analyses, predictions of better survival for nivolumab

Committee's discussions: other conclusions

Issue	Committee conclusion/request
Comparators	Exclude best supportive care as a comparator
Utility values	Adjust utility values for age
Cost of nivolumab	Account for wastage for nivolumab as per TA417 (nivolumab)
Cost and effect of subsequent treatments	Exclude costs and any survival benefit of subsequent treatments not available in the NHS such as sorafenib
Cost of monitoring patients	Assume that oncologists, rather than GPs, monitor patients for an average of 4 weeks before disease progression
End of life	Until revised analyses, committee could not make an informed decision
Presentation of results	Incremental, probabilistic

ACD consultation responses

- Consultees
  - Ipsen (company): only additional analyses submitted
    - ◊ New data cut
    - ◊ New modelling
    - ◊ New PAS
  - Patient/professional organisations
    - ◊ Kidney Cancer UK
    - ◊ Kidney Cancer Support Network
- Clinical expert
- No comments from members of the public

ACD consultation responses
Benefit of cabozantinib

- First TKI to act on multiple tyrosine kinase receptors
- Designated as ‘breakthrough therapy’ by US FDA
- Addresses unmet need
- Proven ‘more effective than everolimus’, ‘probably more effective than axitinib’, ‘comparable efficacy to nivolumab’
  - Preferred to nivolumab in patients with autoimmune disease
- Particularly effective against bone metastases
- Similar safety profile to other TKIs, but effectiveness outweighs adverse events

Key: FDA, Food and Drug Administration; TKI, tyrosine kinase inhibitor

ACD consultation responses
End of life

- 'Not reasonable to assume [survival] is >24 months in the second/third line setting'
- Trial populations do not reflect NHS because trials exclude patients with poor prognosis
  - Audit data suggest pre-nivolumab/cabozantinib, survival is 18.0 for good, 9.5 for intermediate and 3.5 months for poor prognosis (median 10.5 months)
- Current ICER decision rules used by NICE can be unfair to patients with rare cancers
  - "NICE and manufacturer need to […] work collaboratively to negotiate an acceptable patient access scheme to ensure […] access"

Key: ICER, incremental cost-effectiveness ratio

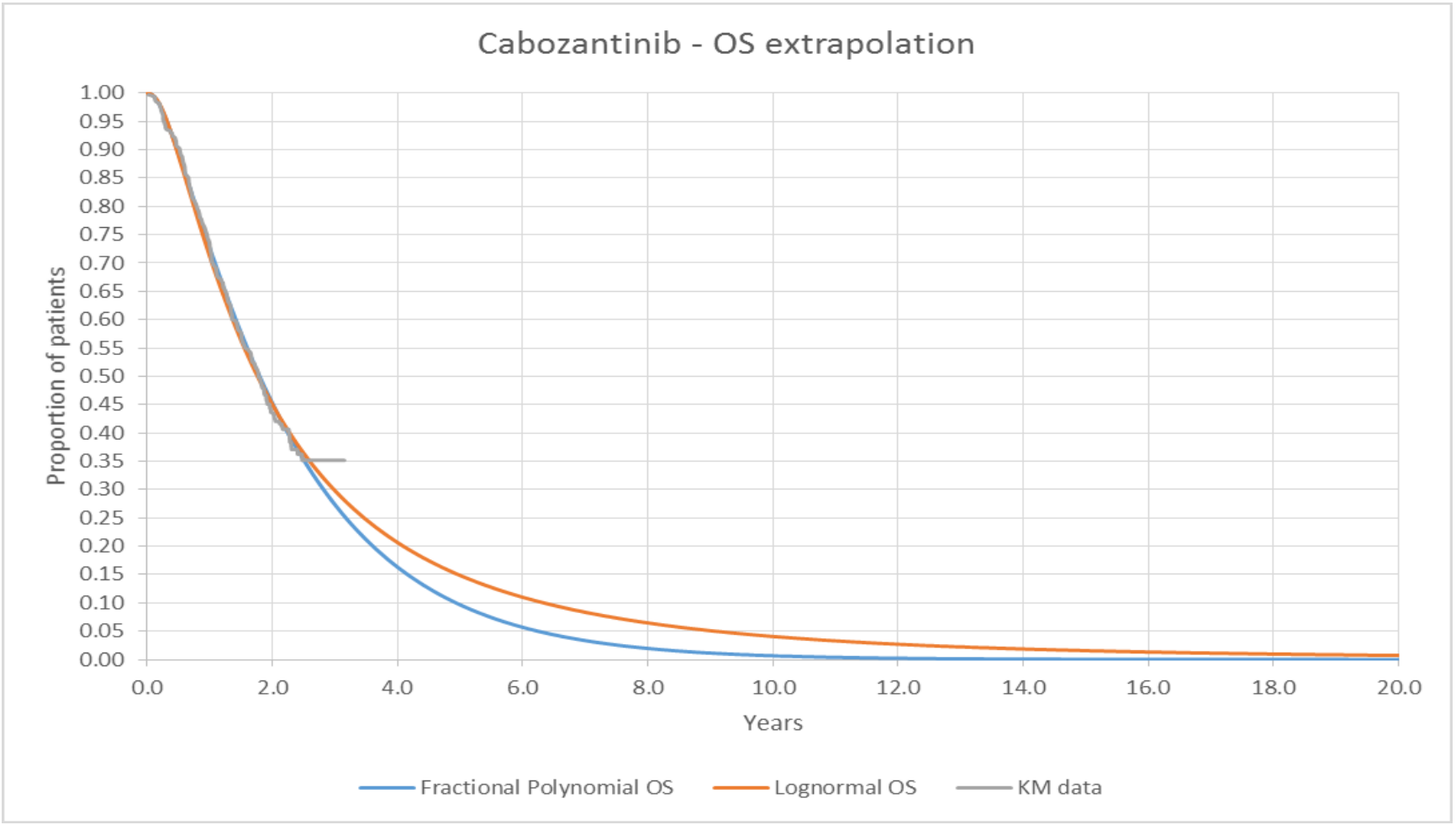
Overview of company's revised model

Company reflected all changes requested in ACD

	Original model	Company revised analysis
Effectiveness axitinib and everolimus	Different, based on network meta-analysis	Assumed equal for both PFS and OS – TARGET falls out of network
Curve fitting	Parametric survival modelling (Ouwens et al. 2010)	Fractional polynomial modelling as base case (Jansen et al. 2011)
Comparison with data on natural history of the disease	Not presented	Base case validated against 'real-world' data (Ruiz-Morales et al. 2016), and 'hybrid' analysis
Long-term effectiveness of nivolumab	Not adjusted for immunotherapy effect ('long tail')	Explore predictions of better survival than in original model

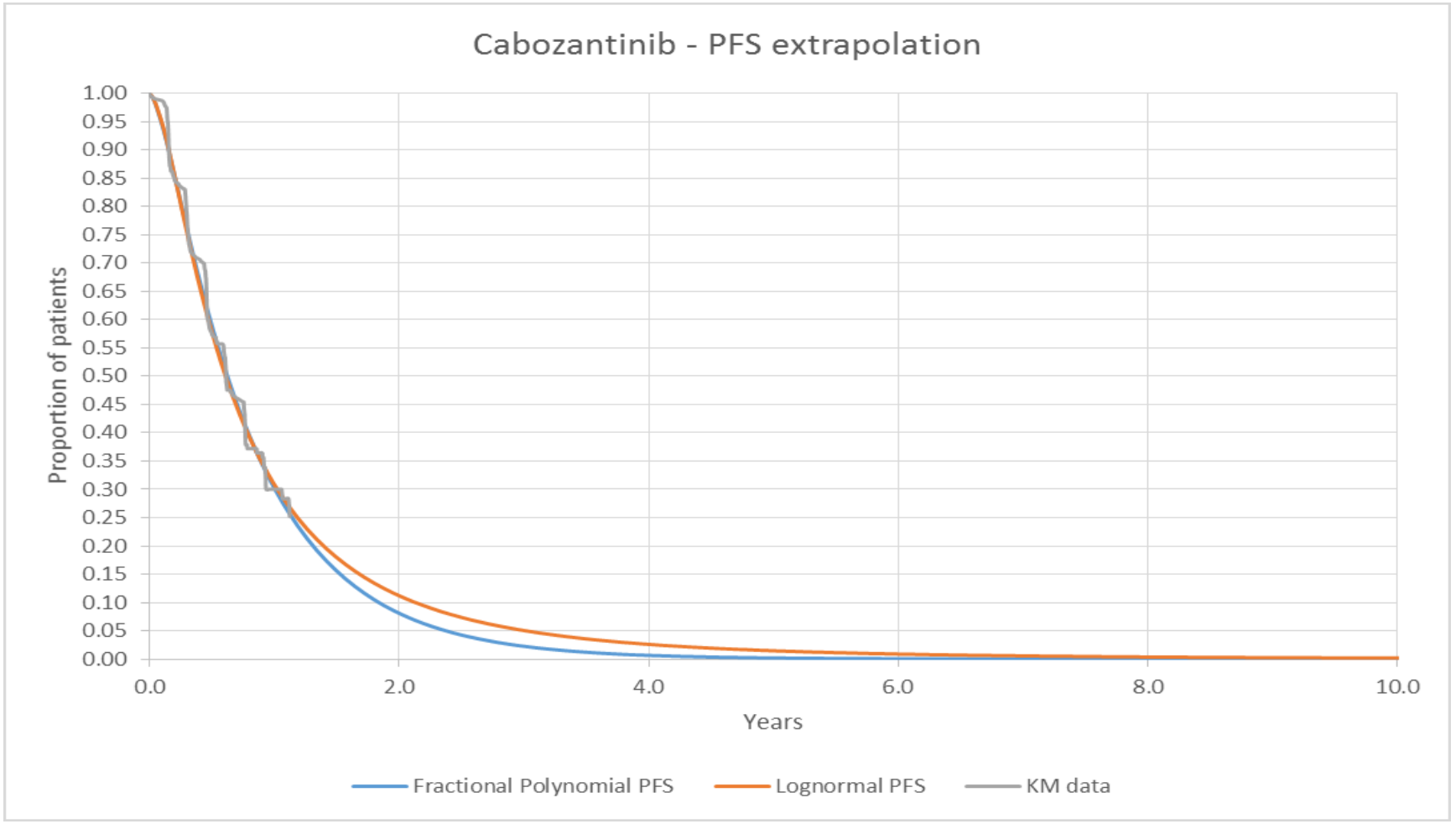
Original *vs* revised curve fits

Cabozantinib, overall survival



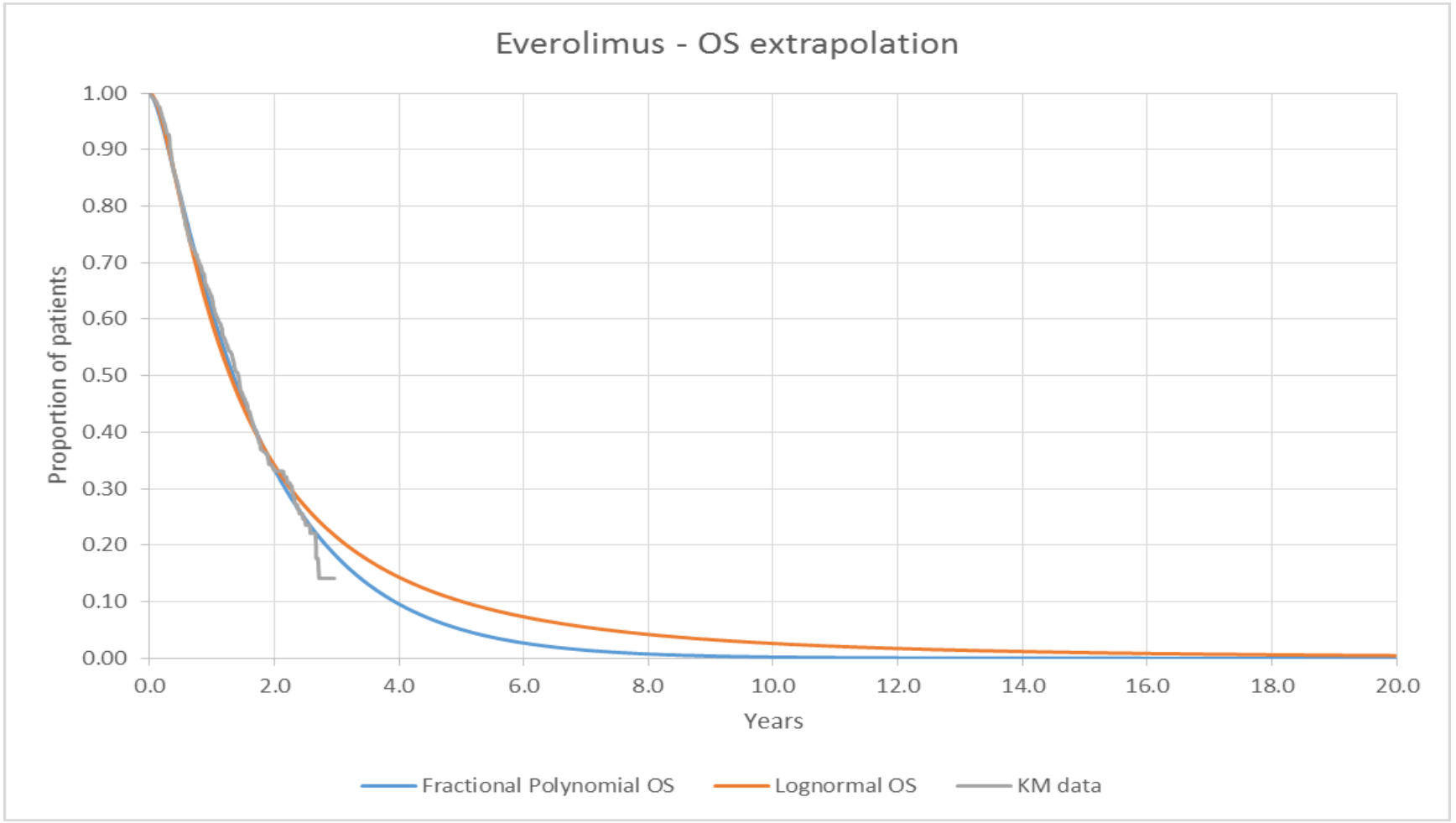
Original *vs* revised curve fits

Cabozantinib, progression-free survival



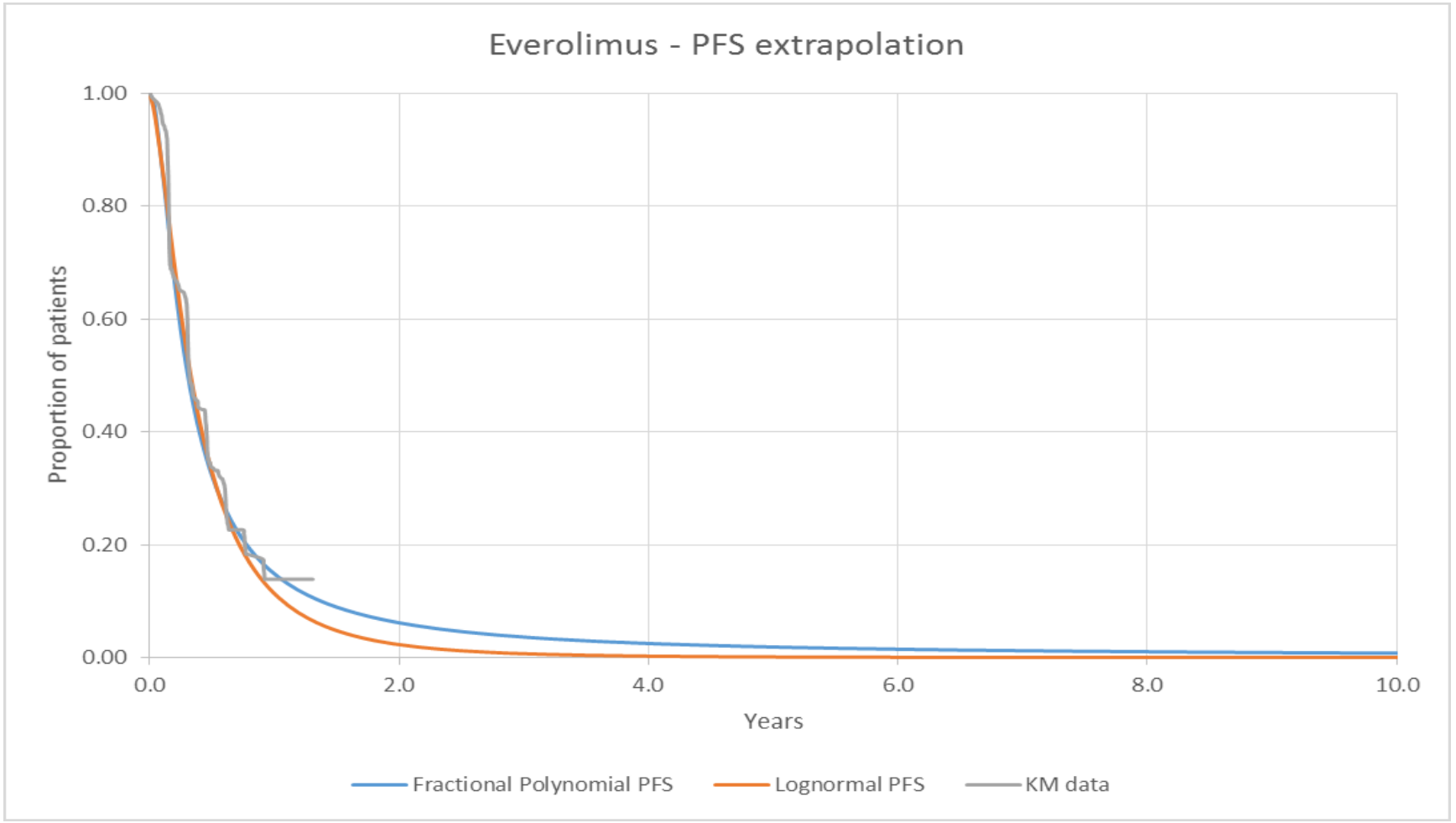
Original vs revised curve fits

Everolimus, overall survival



Original vs revised curve fits

Everolimus, progression-free survival



ERG comments on company's revised modelling

- Fractional polynomial appropriately implemented
- Provided good fit for all PFS and OS curves
- However, single 'family of related survival curves' still used for all treatments
  - Considered less of on issue than in original model (parametric survival model)

⊙ *Do the revised curve fits address the committee's previous concerns?*

Survival estimates

Comparison of original and revised estimates

	Original base case log-normal		**Revised base case fractional polynomial**	
Mean (median) in months	*Overall survival*	*Progression-free survival*	*Overall survival*	*Progression-free survival*
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]

Company identified 2 issues with the revised estimates:

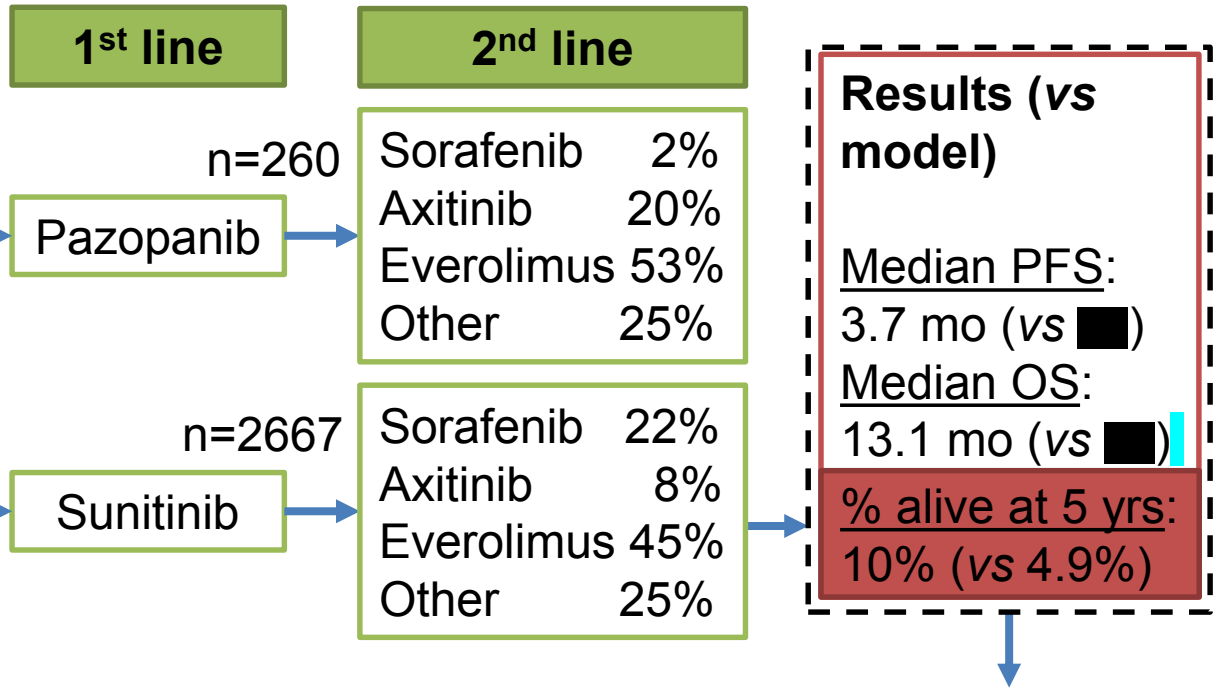
- Issue #1: Prediction inconsistent with real-world data (Ruiz-Morales et al. 2016)
- Issue #2: PFS greater than OS for nivolumab… 'implausible?'

Issue #1: Prediction inconsistent with real-world data

Evidence submitted by company: Ruiz-Morales et al. (2016)

Patients

- Patients with mRCC International mRCC Database Consortium (IMDC)
- No UK patients
- Company states patients from countries similar to UK in baseline characteristics, socio-economic profiles, and health systems



Company used data from prior-sunitinib subgroup because sample size larger

Key: mRCC, metastatic renal cell carcinoma; OS, overall survival; PFS, progression-free survival

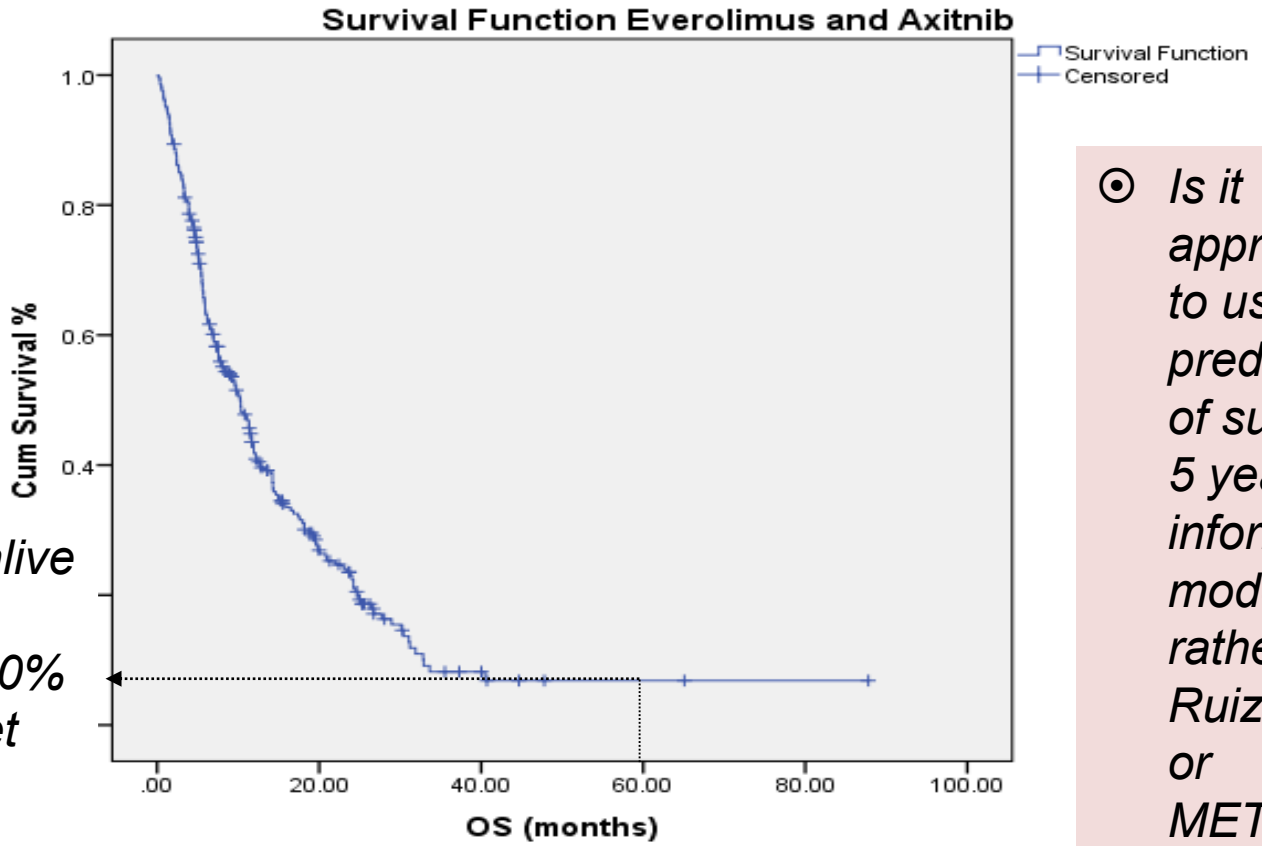
ERG critique of Ruiz-Morales et al. (2016)

- Patient baseline characteristics
  - Appear comparable to patients in METEOR
  - However, characteristics only reported for patients starting 1st line treatment
  - More appropriate than METEOR as evidence on natural history of the disease
- Significant uncertainty if extrapolation chosen based purely on meeting notional 5-year survival estimate
  - Shape of extrapolated curve at least as important
- ICER using fractional polynomial method (company base case) likely conservative given evidence from Ruiz-Morales et al.

⊙ *Is the Ruiz-Morales paper relevant?*

Issue #1: Prediction inconsistent with real-world data

Audit data submitted by clinical expert: OS post 2nd line axitinib/everolimus in Christie Hospital (n=282)



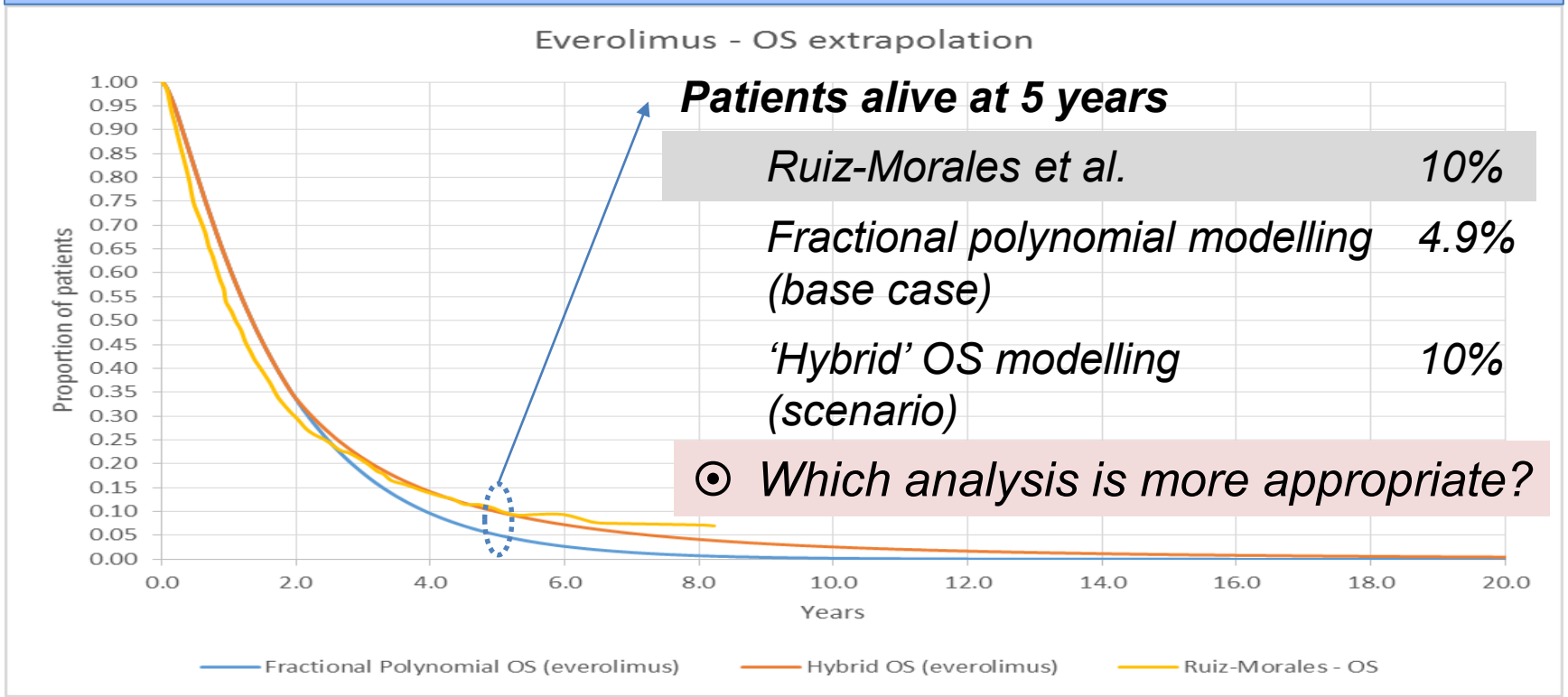
~6% of patients alive at 5 years (compares with 10% in Ruiz-Morales et al. 2016)

- *Is it appropriate to use these predictions of survival at 5 years to inform the modelling rather than Ruiz-Morales or METEOR?*

Issue #1: Prediction inconsistent with real-world data

Company's proposed scenario analysis

- Use 'hybrid' OS model (no change to PFS)
  - Fractional polynomial during trial follow-up – up to 2.5 years
  - Log-normal during extrapolation period



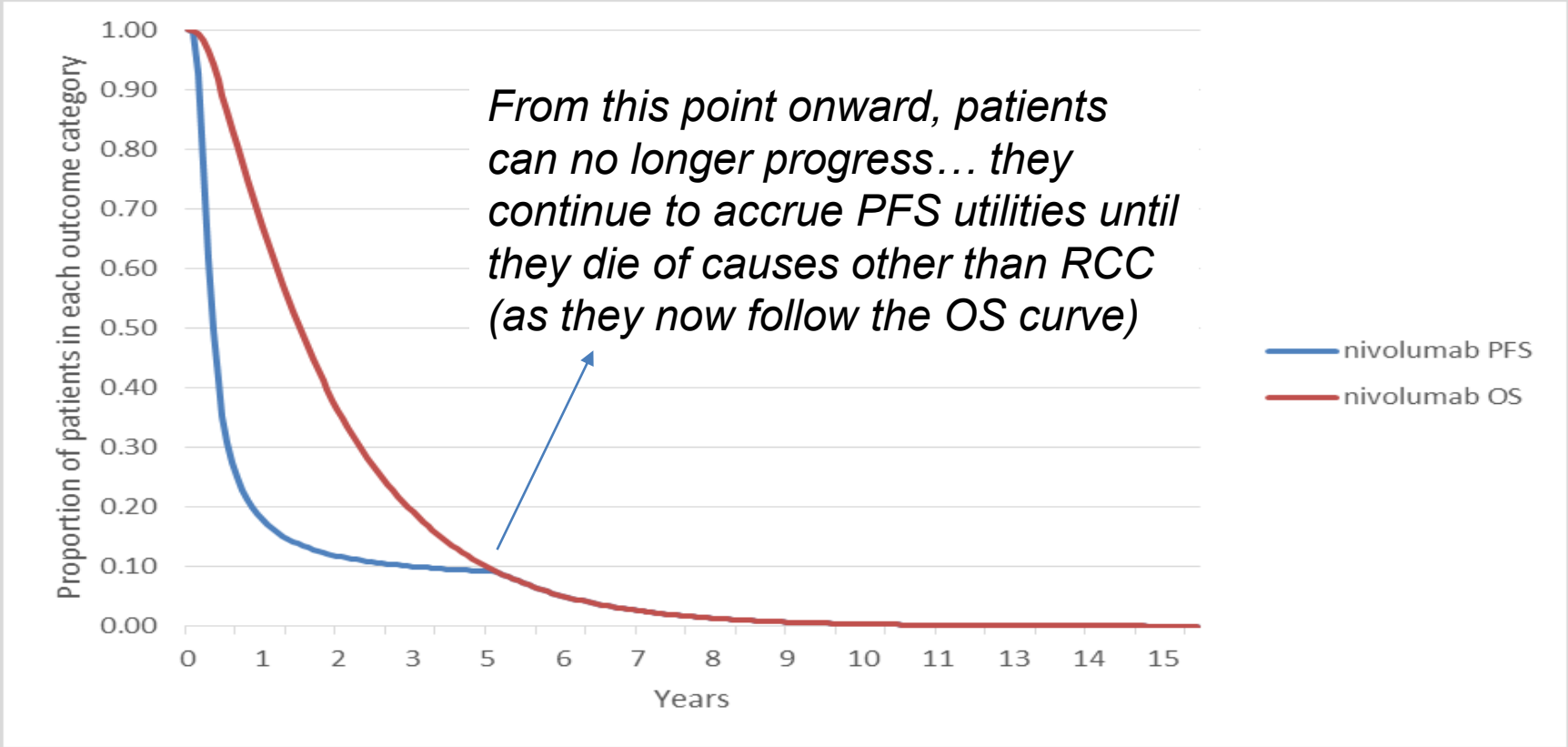
Patients alive at 5 years

Ruiz-Morales et al.	*10%*
Fractional polynomial modelling (base case)	*4.9%*
'Hybrid' OS modelling (scenario)	*10%*

⊙ *Which analysis is more appropriate?*

Issue #2: PFS greater than OS for nivolumab

Company considered implausible



- *Is it clinically plausible that from year 5/6 onward, patients treated with nivolumab are unlikely to progress after being progression-free for this long?*

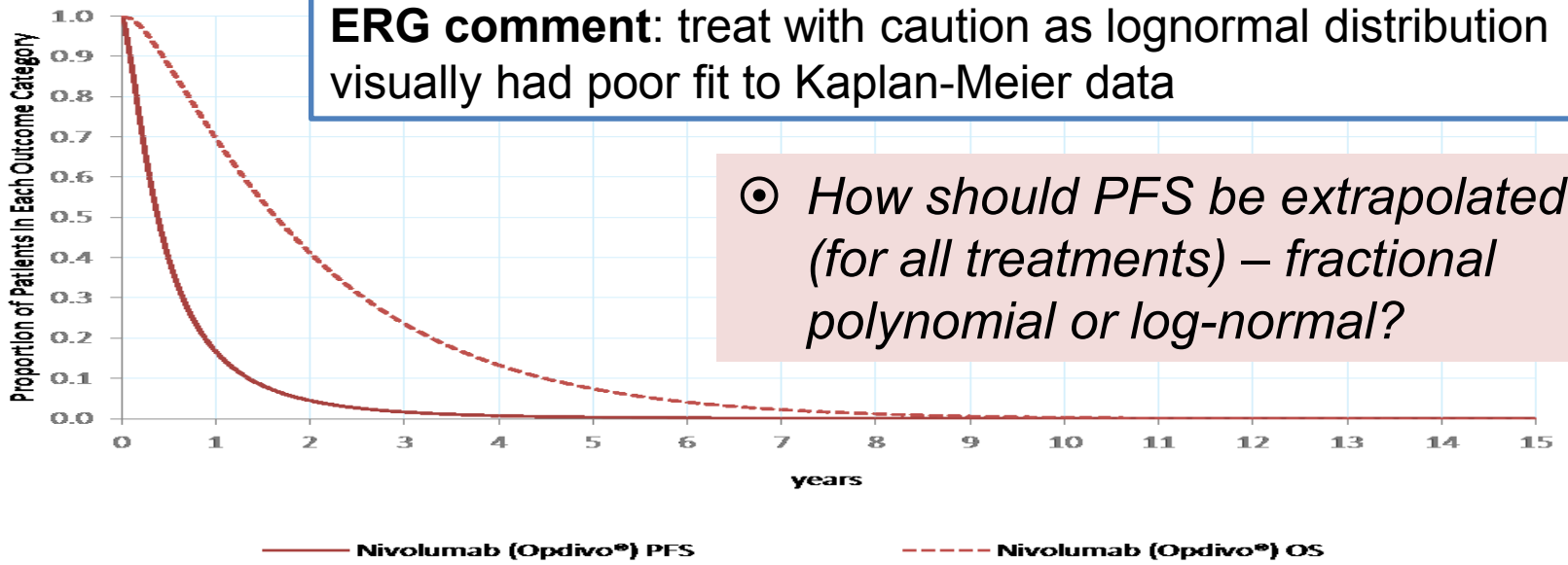
Issue #2: PFS greater than OS for nivolumab

Company's proposed scenario analysis

- Use log-normal distribution to model PFS over entire time horizon (no change to OS) – this applies to all treatments
- To reflect committee request, company also combined this scenario with assumption that 50% of patients alive after 5 years and still receiving nivolumab have general population mortality

ERG comment: treat with caution as lognormal distribution visually had poor fit to Kaplan-Meier data

⊙ *How should PFS be extrapolated (for all treatments) – fractional polynomial or log-normal?*



Summary of curves used in company's analyses

	Overall survival		Progression-free survival	
	Trial	*Extrapolation*	*Trial*	*Extrapolation*
Base case	**Fractional polynomial**	**Fractional polynomial**	**Fractional polynomial**	**Fractional polynomial**
'Hybrid' OS model	Fractional polynomial	Log-normal	Fractional polynomial	Fractional polynomial
Log-normal PFS	Fractional polynomial	Fractional polynomial	Log-normal	Log-normal
Log-normal PFS + nivolumab 50% gen pop mortality	Fractional polynomial	Fractional polynomial	Log-normal	Log-normal

Survival estimates (undiscounted)

Comparison of base case and scenario analysis

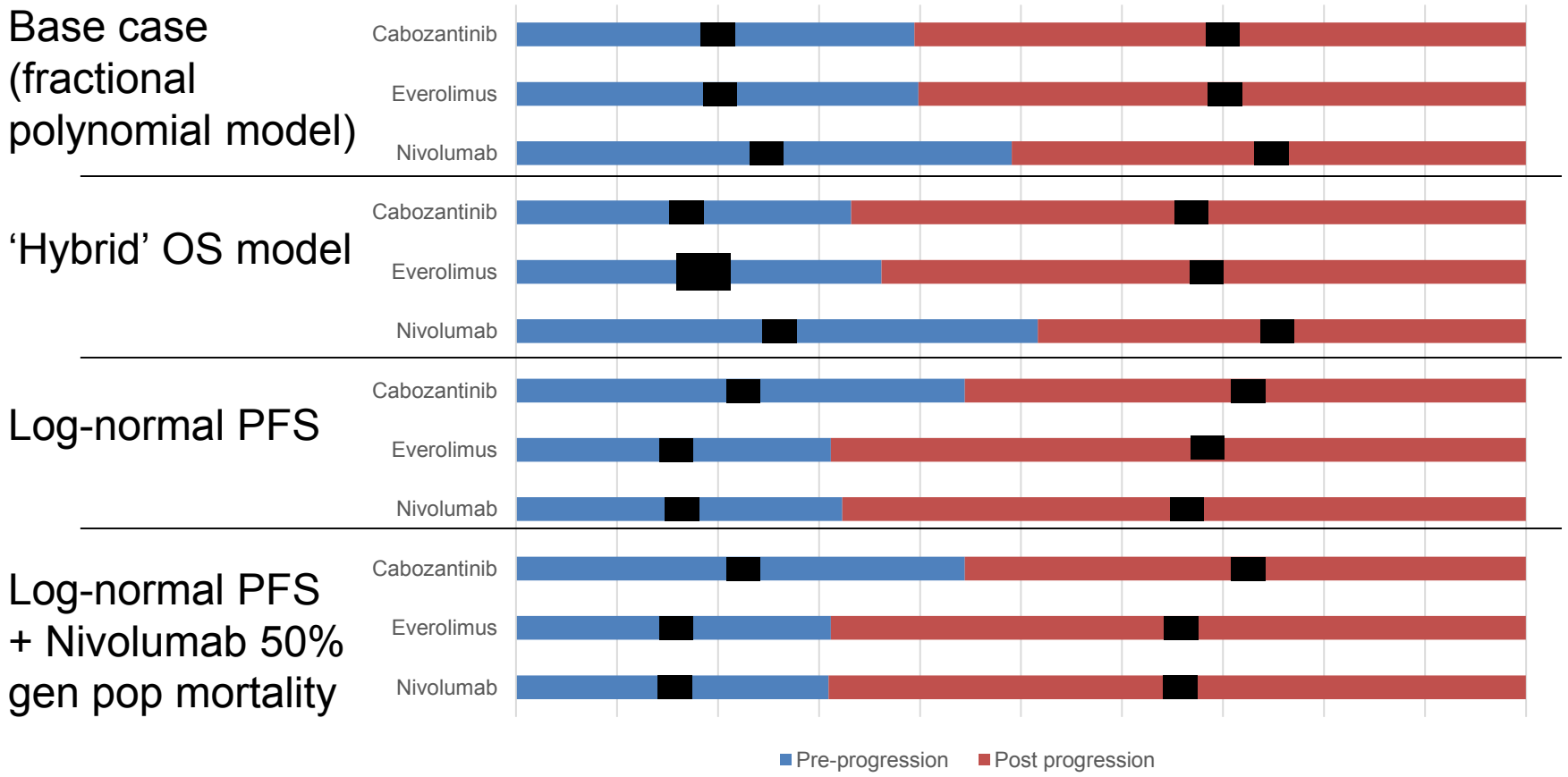
Months	**Base case**		‘Hybrid’ OS model		Log-normal PFS		Log-normal PFS + nivolumab 50%	
Mean (median)	*OS*	*PFS*	*OS*	*PFS*	*OS*	*PFS*	*OS*	*PFS*
Cabozantinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Axitinib	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Everolimus	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Increased mean OS for all treatment

Mean PFS decreased by 26 mos, median increased by 1 mo

Mean OS increased by 1 mo for nivolumab

Comparison of QALYs before and after disease progression*



*Extracted from the company's model

⊙ *Which of these scenarios has a QALY distribution most representative of RCC?*

METEOR updated survival data

No results presented by company

Cost-effectiveness results presented by company using both data cuts

	Original METEOR data	Updated METEOR data
Date of data cut	December 2015	October 2016
Maximum follow-up (months)	28.7	[redacted]
Number of events	259	[redacted]
% patients alive at 30-month follow-up	Not reached	Cabozantinib [redacted] Everolimus [redacted]

ERG additional analyses

All ERG analyses based on new data-cut from METEOR

ERG modified base case

- Fractional polynomial to model OS and PFS for all interventions (i.e. company's base case)
- Other minor changes to average adverse event utility decrement and assumptions about resource use

Scenario analyses (on ERG modified base case)

- Using age-adjusted AXIS utilities (rather than METEOR utilities)
- Assuming 100% of nivolumab 5 year survivors move on to general population mortality rates
- Assuming clinical equivalency for OS between nivolumab and cabozantinib

Cost-effectiveness results

- Presented in part 2 to show ICERs reflecting confidential PAS discounts for comparators
- All results will reflect new data cut

End of life

New data cut

Criterion	Comparator	Overall survival estimates (months)			
Short life expectancy (normally < 24 months)		**Median (based on modelling)**			
		Company's revised base case			
	Everolimus Axitinib Nivolumab	[redacted]			
Prospect of offering an extension to life (normally of a mean value of ≥ 3 months)		**Mean (based on modelling)**			
		Company revised base case	*Hybrid OS model*	*Log-normal PFS*	*Log-normal PFS + nivolumab 50% gen pop mortality*
	Everolimus Axitinib Nivolumab	[redacted]	[redacted]	[redacted]	[redacted]

Issues for discussion

- Source of evidence on natural history of the disease (Ruiz-Morales et al., audit data, or METEOR)
- Most valid survival extrapolation (fractional polynomial, or ‘hybrid OS model)
- OS and PFS for nivolumab (fractional polynomial, or log-normal PFS)
- Survival prediction for nivolumab (no better survival, general population mortality for 50% after 5 years, or general population mortality for 100% after 5 years)
- Use age-adjusted AXIS utilities rather than METEOR utilities?
- End of life