Public observer slides

Lead team presentation Nivolumab for previously treated advanced or metastatic renal cell carcinoma (STA)

8 June 2016 Committee B

1st Appraisal Committee meeting

Background and Clinical Effectiveness

Lead team: Anne Joshua, Stephen Palmer, Nigel Westwood

ERG: BMJ

NICE technical team: Anna Brett, Rosie Lovett

Chair: Amanda Adler

Decision problem

Company submission matched scope

	NICE scope
Population	Previously treated advanced or metastatic renal cell carcinoma
Comparators	• Axitinib • Everolimus (not recommended by NICE; via Cancer Drugs Fund if contraindication/intolerance to axitinib) • Best supportive care
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects • Health-related quality of life

Summary of evidence and key issues

CheckMate 025:
Reduced risk of death
nivolumab vs everolimus
HR 0.73,
(95% CI 0.57-0.93)

Network meta-analysis:
nivolumab vs axitinib HR
****[AIC]
(95% CI ****[AIC]) but differences in trial populations

ICERs
nivolumab vs. axitinib, list price
Company: £42,417
ERG: £74,132
Part 2 shows analyses with axitinib PAS (higher ICERs)

Nivolumab

Innovation
1st checkpoint inhibitor immunotherapy to gain marketing authorisation in advanced renal cell carcinoma

End of life
- Company: life expectancy c. 20 months with axitinib or everolimus
- **Median** 5.4 months extension to life vs everolimus in CheckMate
- Extension vs axitinib?

Model uncertainty:
- Utility values from trials with different populations
- Effectiveness of axitinib vs everolimus?

Nivolumab (Opdivo)
Bristol-Myers Squibb

- Antibody that blocks PD-1 (programmed cell death protein 1) to promote anti-tumour response
- Indicated for treating “advanced renal cell carcinoma after prior therapy in adults”
  - (marketing authorisation May 2016[1])
- Administered intravenously, 3 mg/kg every 2 weeks
- Also marketed for melanoma and non-small cell lung cancer
- List price £439 for 40 mg vial or £1,097 for 100 mg vial
  - Average cost of a course of treatment is £71,260 including administration costs (median duration of treatment in pivotal trial of 5.5 months)

[1] This was identified as an error after the committee meeting; marketing authorisation was received in April 2016.

Treatment pathway

1st line	**Pazopanib** ★ TA215	**Sunitinib** ★ TA169			
2nd line	**Axitinib** ★ TA333	**Everolimus** ✪ Not NICE recommended (TA219). Available via CDF if contraindication or toxicity to **axitinib**	**Best supportive care?**	**Nivolumab ?**	
3rd line	**Axitinib?** Not NICE recommended as 3rd line (TA333)	**Best supportive care**	**Nivolumab ?**		

⊙ *Issues to discuss:*
2nd line: is BSC a comparator?
2nd line: is everolimus a comparator – which patients?
3rd line: is axitinib a comparator?

★: oral tyrosine kinase inhibitors
✪: oral mammalian target of rapamycin (mTOR) inhibitor
CDF: Cancer Drug Fund

Impact on patients and carers

- Renal cell carcinoma is most common type of kidney cancer
- ~30% have advanced disease at diagnosis
- Tyrosine kinase inhibitors and everolimus improve outcomes, but most people have side effects
- Benefit of 2nd-line and subsequent treatments usually modest
- No biomarkers predict which patients respond to which treatments, so important to have a range of treatments
- Patients report that nivolumab improves their quality of life
- NICE lead team: intravenous treatment when compared with oral treatment (axitinib and everolimus) may lower quality of life

Company's clinical evidence

1 main trial vs. everolimus (not recommended by NICE)

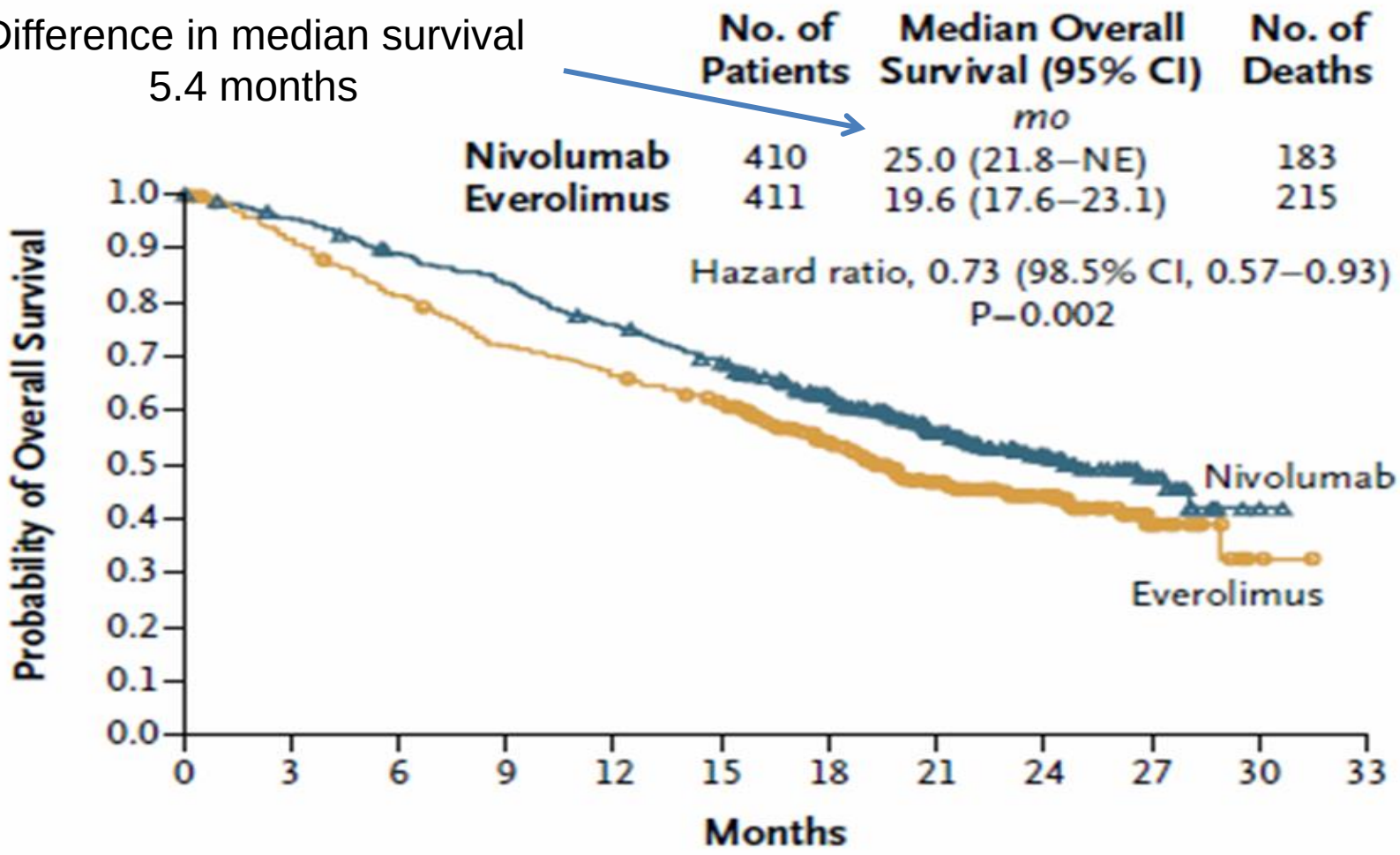
Trial	CheckMate 025
Design	Open-label n=821; randomised 1:1 nivolumab or everolimus
Population	• Adults with advanced renal cell carcinoma • '1 but not more than 2 antiangiogenic treatments' • 72% 1 prior treatment, 28% 2 prior treatments • Excluded prior treatment with mTOR inhibitor
Intervention	Nivolumab 3 mg/kg intravenously every 2 weeks
Comparator	Everolimus 10 mg orally every day
Outcomes	• Overall survival - 1° outcome • Progression-free survival • Adverse effects • Health-related quality of life - EQ-5D
Stopping	Patients in both groups could continue treatment beyond progression if benefiting and tolerating drug

- *Is CheckMate 025 population generalisable to NHS patients?*
- *Would NHS patients continue treatment after progression?*

CheckMate 025

Nivolumab lowers risk of death

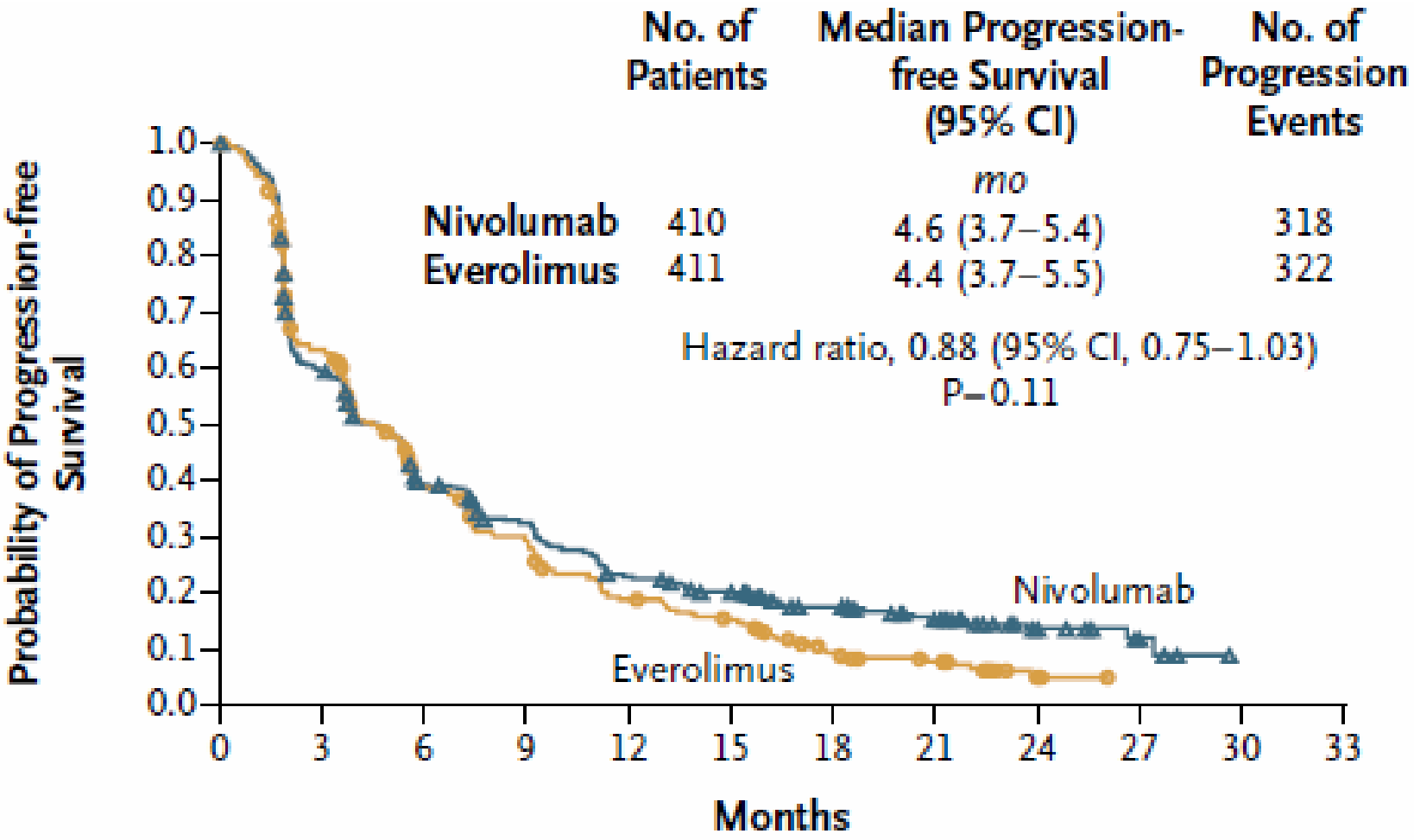
Difference in median survival
5.4 months



No. at Risk												
Nivolumab	410	389	359	337	305	275	213	139	73	29	3	0
Everolimus	411	366	324	287	265	241	187	115	61	20	2	0

CheckMate 025

No significant difference in progression-free survival

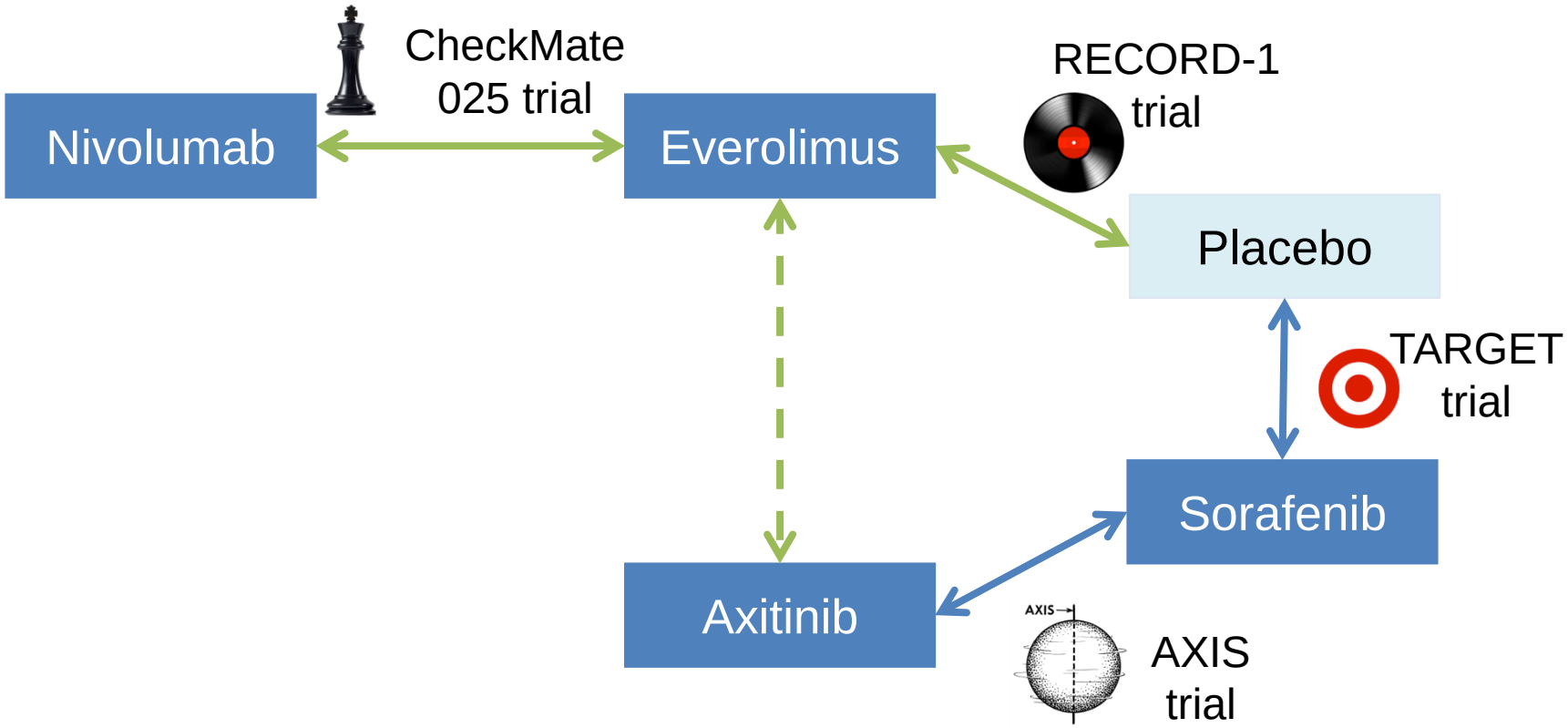


ERG comments on CheckMate 025

Issue	ERG's comments
Overall survival and progression-free survival	Using hazard ratios to summarise treatment effect may be misleading because the data for PFS and OS do not meet the proportional hazards assumption

- *In which direction might this bias the results? Is treatment effect likely to be over or under-estimated?*
- *Is nivolumab more effective than everolimus in terms of PFS and OS?*

Company's network meta-analysis



Key	Direct trial data	Indirect efficacy estimates
Informs economic model	⟷	⟵ - - ⟶
Not in economic model	⟷	Not shown

Company's network meta-analysis

Point estimates favour nivolumab vs axitinib, but not statistically significant

These hazard ratios not used in model

Outcome	Nivolumab vs axitinib	Nivolumab vs best supportive care
Overall survival		
Intention-to-treat hazard ratio (95% CrI)	****[AIC] ********[AIC]	****[AIC] ********[AIC]
Crossover-adjusted hazard ratio (95% CrI)	****[AIC] ********[AIC]	****[AIC] ********[AIC]
Progression-free survival		
Intention-to-treat Hazard ratio (95% CrI)	****[AIC] ********[AIC]	****[AIC] ********[AIC]

ERG's comments

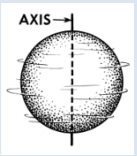
*Relative effectiveness of **axitinib** and **everolimus** – potentially biased*

- Company's network meta-analysis shows everolimus is more effective than axitinib (HR for death ****[AIC]) – this estimate is **used in company's model**
- ERG's clinical experts say this is not plausible and consider axitinib more effective than everolimus
- ERG: network meta-analysis may **underestimate effectiveness of axitinib** because of:
  - differences in trial populations (previous treatment, baseline characteristics)
  - methodology used to adjust for crossover
- NB: company also referred to Sherman et al. (2015), an adjusted indirect comparison using RECORD-1 and AXIS
  - Median progression-free survival similar with everolimus and axitinib (4.7 and 4.8 months respectively)

⊙ *Is network meta-analysis adequate to inform decision-making? Is axitinib less effective than everolimus?*

Company's network meta-analysis

Trial populations differed in previous treatments

	Trial treatments	Previous treatments	Line of treatment in trial
CheckMate 025 	Nivolumab vs everolimus	Sunitinib Pazopanib Axitinib	2nd and post-2nd line
AXIS 	Axitinib vs sorafenib	Sunitinib* Cytokines Bevacizumab Temsirolimus	2nd line
RECORD-1 	Everolimus vs placebo	Sunitinib Sorafenib Bevacizumab	2nd line
TARGET 	Sorafenib vs placebo	Cytokines	2nd line

*Company's network used subgroup of AXIS patients who had prior treatment with sunitinib

Cytokines include interferon and interleukin-2; TKIs include sunitinib

Company's network meta-analysis

Patients in AXIS had poorer prognosis than patients in CheckMate 025

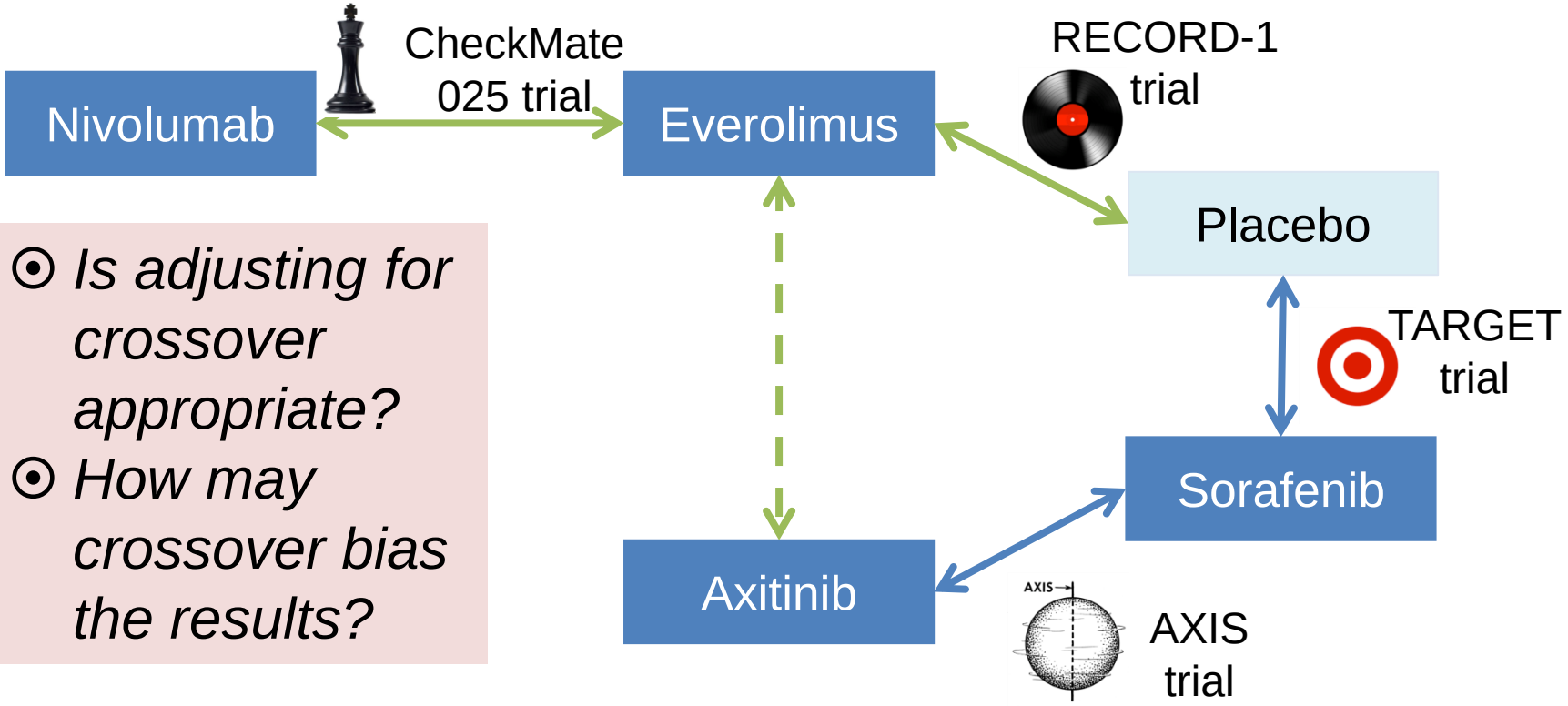
Memorial Sloan Kettering Cancer Center risk scores at baseline				
		Favourable	**Intermediate**	**Poor**
CheckMate 025	Nivolumab	35%	49%	16%
	Everolimus	36%	49%	15%
AXIS	Axitinib	28%	37%	33%
	Sorafenib	28%	36%	33%

- **ERG:** trials differ in type/number of previous treatments
- **ERG:** patients in CheckMate 025 had better prognosis than AXIS (likely to underestimate effectiveness of axitinib)
- **Company:** although absolute treatment effects vary with population, network uses relative treatment effects

⊙ *Which trial population is more generalisable to NHS patients (and should inform the model)?*

Company's network meta-analysis

Company's preferred analysis adjusted for crossover but adjustment varied between trials

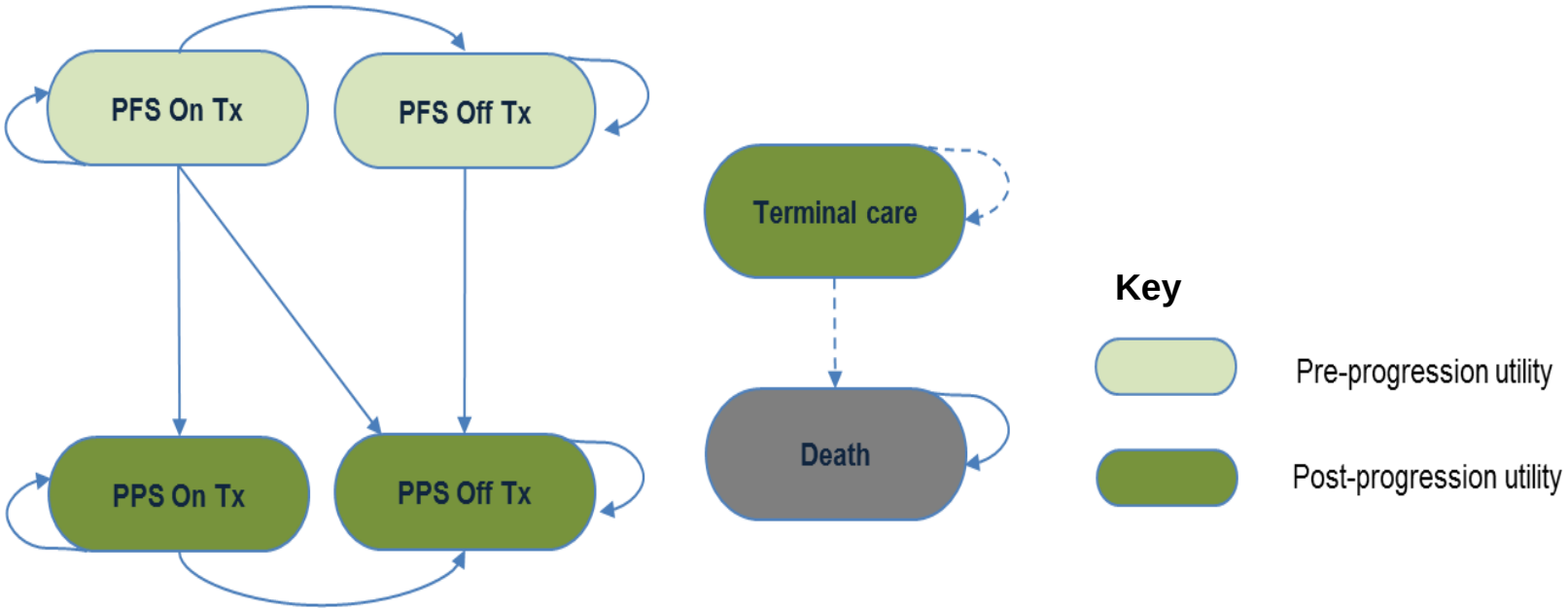


- *Is adjusting for crossover appropriate?*
- *How may crossover bias the results?*

- **ERG:** AXIS did not adjust for subsequent treatments; could underestimate effectiveness axitinib vs sorafenib. **Company:** subsequent treatments similar in each group and reflect NHS practice.
- **ERG:** Did RECORD-1 use appropriate methods to adjust for treatment switching? **Company:** Method used in NICE appraisal of everolimus.

Cost effectiveness

Company's model



- Partitioned-survival (area under curve) model
  - time in each state calculated from survival curves
- 1-week cycles, 30-year time horizon
- Nivolumab, axitinib, everolimus, best supportive care (BSC)
- Nivolumab and everolimus: permit treatment beyond progression

⊙ *Does model represent 2nd or 3rd line use of nivolumab, or both?*

⊙ *When should model assume PH or AfT?*

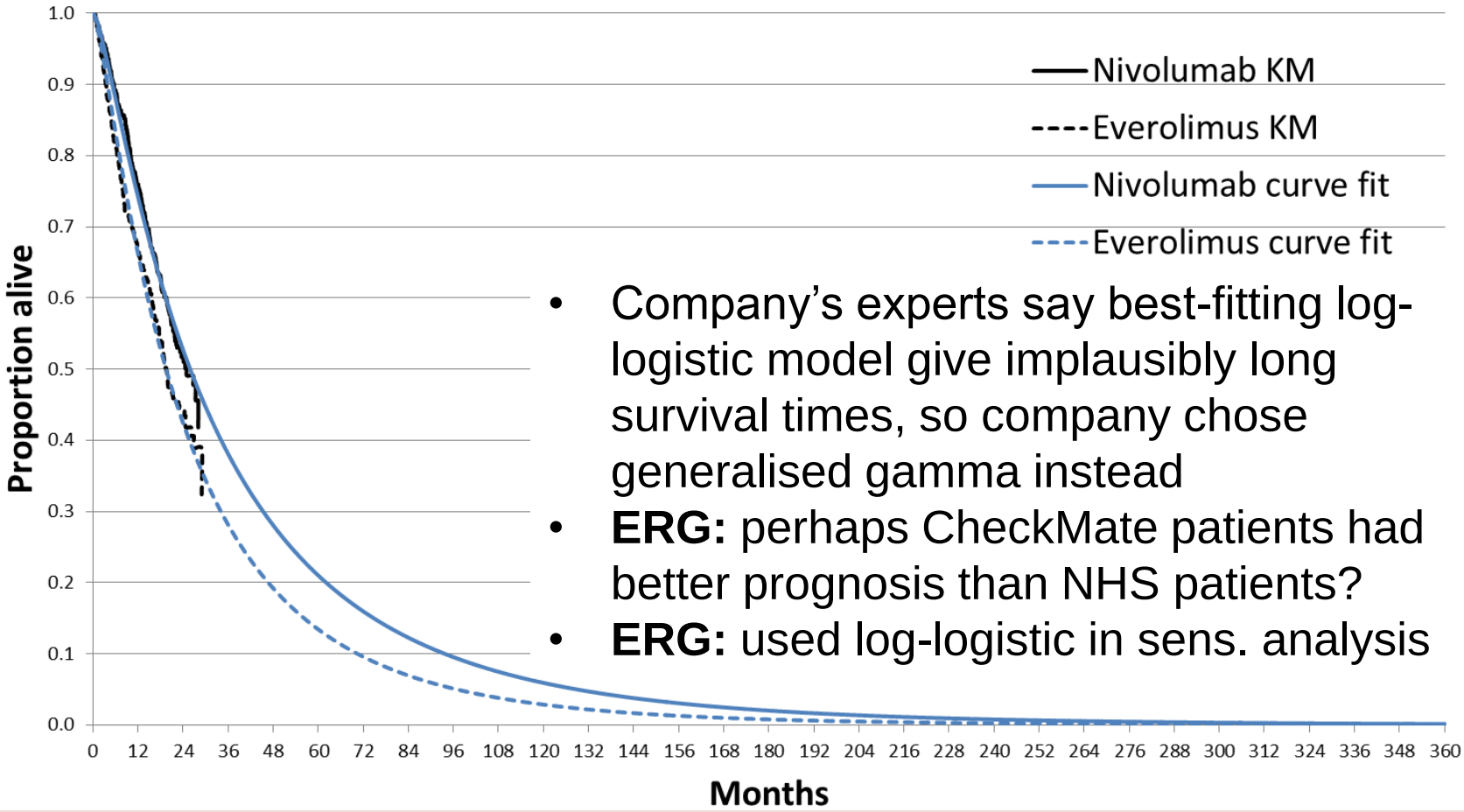
Inputs to model

Nivolumab and everolimus: CheckMate 025 data

	PFS	OS	Time to stop tx
Type of model	Independent models for each tx group	1 model with predictor for treatment group	1 model with predictor for tx group
Assume PH or AfT	No	Yes	Yes
ERG: was PH/AfT met?	N/A	**PH no; AfT?**	Yes
Distribution	Spline **odds** 2 knot	Generalised gamma	Spline **hazard** 2 knot
ERG comments: curve choice	Appropriate	Not sufficiently justified; used log-logistic in sensitivity analyses	Spline not justified; used log-normal and generalised gamma in sensitivity analyses

AfT, accelerated failure time; PH, proportional hazards; Tx, treatment

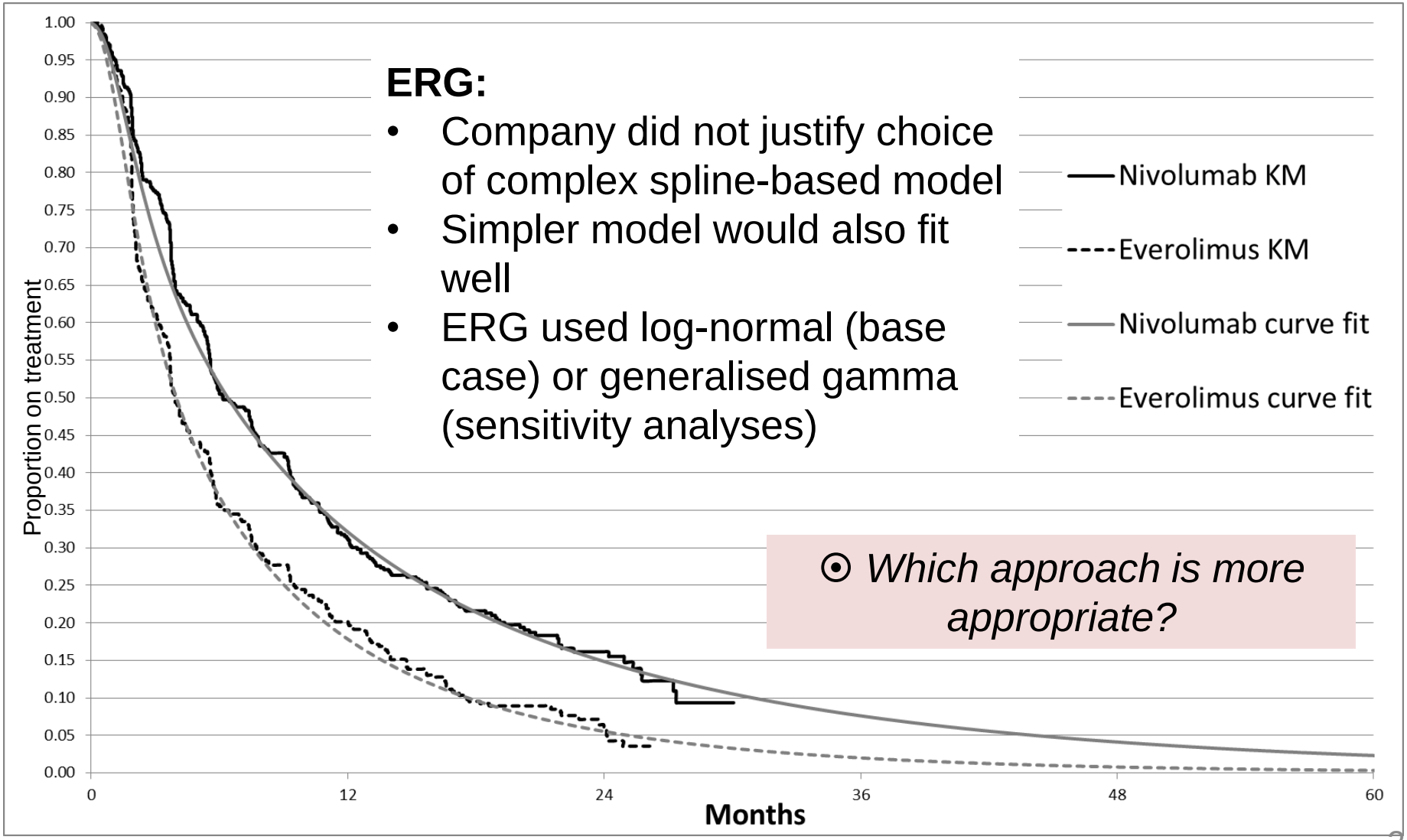
Overall survival
Base case used generalised gamma model - treatment as a predictor



- Company's experts say best-fitting log-logistic model give implausibly long survival times, so company chose generalised gamma instead
- **ERG:** perhaps CheckMate patients had better prognosis than NHS patients?
- **ERG:** used log-logistic in sens. analysis

⊙ *Which curve is most plausible? Are any adjustments needed to better reflect NHS patients?*

Time to stopping treatment
Base case used spline (2 knots) model - treatment as a predictor



Clinical inputs: axitinib and best supportive care

*Model assumes **axitinib** worse than **everolimus***

- Company took hazard ratios from network meta-analysis and applied to survival curves for **everolimus**

	Everolimus vs axitinib	Everolimus vs BSC
Overall survival (crossover-adjusted)	**********[AIC]	**********[AIC]
PFS (intention-to-treat)	**********[AIC]	**********[AIC]

⊙ *Is it appropriate to assume hazard ratios constant over a lifetime and to apply to non-proportional hazard models?*

- Assumed patients stop axitinib when disease progresses
- ERG comments on axitinib:
  - ERG raised concerns about network meta-analysis
  - ERG's clinicians expected axitinib to be more effective
  - **ERG base case assumed axitinib as effective as everolimus**: increased ICER nivolumab vs axitinib

⊙ *What is best estimate of relative effectiveness of axitinib and everolimus? Network meta-analysis or assume equal?*

Health state utility values

Company assumed lower utility for patients having axitinib

	Pre-progression	Post-progression	Source
Nivolumab	0.80	0.73	CheckMate 025 EQ-5D
Everolimus	0.76	0.70	
Axitinib	0.69	0.61	AXIS EQ-5D; TA333
BSC	0.69	0.61	Assumption

ERG

- Utility values not plausible - nivolumab and everolimus higher after progression than axitinib before progression
- Likely reflects differences in trial populations
- 2 exploratory analyses:
  - Use everolimus utility from CheckMate for axitinib and BSC
  - Use axitinib utility from AXIS for everolimus (AXIS utilities are lower, trial population may be more similar to NHS patients). NB: nivolumab increment vs. everolimus taken from CheckMate 025.

⊙ *Which utility values are most appropriate to inform the model? Is potential disutility from IV therapy with nivolumab reflected?*

Costs

- Analyses in this presentation use list price; analyses in part 2 use confidential discounted price for axitinib
- Company assumed no vial sharing for nivolumab (that is, included costs of wastage)
- Relative to licensed dose, company included cost of:
  - 92% dose of nivolumab
  - 94% dose of everolimus
  - 102% dose of axitinib
  - All assumptions based on trial data; for nivolumab company excluded cost of delayed (5%) and missed doses (3%)
- **ERG:** deducting cost of delayed doses may not be appropriate if these are eventually received

⊙ *Is it appropriate to deduct costs of delayed doses? Appropriate to assume no vial sharing?*

Cost of 3rd line treatments and beyond

In company's model – used in NHS? extend life?

- Treatment mix based on CheckMate 025 but bevacizumab removed
- Assumed people receive no further treatments after BSC
- One-off cost £9,026 for nivolumab, £10,771 for everolimus and axitinib

Subsequent treatments	Arm of model	
	Nivolumab	Everolimus or axitinib
Axitinib	25.2%	38.8%
Everolimus	26.7%	6.0%
Pazopanib	9.4%	16.7%
Sorafenib	6.6%	9.9%
Sunitinib	7.1%	8.9%

- **ERG:** subsequent treatments not recommended by NICE, not offered in clinical practice, not expected to provide clinical benefit

⊙ *Should model include cost of subsequent treatments?*

Company's deterministic base case with minor model errors corrected by ERG

Treatment	Total values		Increments		ICER
	Costs (list price)	QALYs	Cost	QALYs	
Pairwise ICERs nivolumab vs each comparator					
Nivolumab	£91,326	2.30			
Axitinib (no PAS)	£46,113	1.25	£45,213	1.05	**£43,109**
Everolimus	£38,933	1.69	£52,393	0.61	**£86,136**
BSC	£10,525	0.88	£80,801	1.42	**£57,096**
Fully incremental analysis					
BSC	£10,525	0.88			
Everolimus	£38,933	1.69	£28,408	0.81	**£35,205**
Axitinib (no PAS)	£46,113	1.25	£7,180	-0.44	**Dominated**
Nivolumab	£91,326	2.30	£52,393	0.61	**£86,136**

Source: ERG report table 62; ERG's amended model

Company's scenario analysis
Assume larger survival benefit for nivolumab

- **Company:** for melanoma, nivolumab shows a 'long tail' meaning some patients survive for a long time after immunotherapy
- **Company:** this benefit not observed for renal cell carcinoma because insufficient follow-up and lack of statistical power
- **Scenario analysis:** nivolumab patients who survive for 5 years then have a similar mortality risk to age-matched general population (whereas base case used extrapolated trial data and hazard ratios from NMA)
- ICER for nivolumab compared with axitinib (at list price) reduced from £42,417 to £22,923

⊙ *Which assumption is more appropriate?*

ERG's preferred base case

ICER Nivolumab vs axitinib (list price no PAS)	ICER Nivolumab vs everolimus	ICER Nivolumab vs BSC
A) Assume axitinib as effective as everolimus for PFS and overall survival		
£48,218	£86,136	£57,096
B) Log-normal distribution for time to stopping treatment		
£42,599	£82,419	£56,718
C) Assume patients receive all planned doses of nivolumab and everolimus		
£48,375	£93,384	£61,016
D) Utility values for axitinib and BSC equal to everolimus group in CheckMate 025		
£50,946	£86,136	£62,379
E) Remove subsequent therapy costs		
£44,798	£89,421	£52,760
ERG's preferred base case (A + B + C + D + E)		
£74,132	**£91,989**	**£61,317**

⊙ *Which assumptions are appropriate? See next slide*

Company comments on ERG's base case

A) Assuming that axitinib as effective as everolimus for PFS and overall survival

- Company prefers to rely on trial data synthesised via network meta-analysis, not clinical opinion with unclear elicitation method

C) Assuming patients receive all planned doses of nivolumab and everolimus

- Company: unlikely that 100% of doses in practice will be administered for intravenous drugs; CheckMate 025 is best source

D) Assuming utility values for axitinib and BSC equal to everolimus group in CheckMate 025

- Company: did ERG's clinical experts validate ERG's preferred utility values?
- Company's experts disagreed with ERG's preferred utility values – suggest patient experience on axitinib is 'unfavourable' because of 'clinical tendency to treat…with the highest possible dose…(i.e. until a toxicity reaction)'

ERG's scenario analyses

Scenarios increase ICERs for nivolumab

ICER nivolumab vs axitinib (list price no PAS)	ICER nivolumab vs everolimus	ICER nivolumab vs BSC
Reminder: Company base case corrected by ERG (spline model for time to stopping treatment; utility values from CheckMate 025)		
£43,109	£86,136	£57,096
ERG base case + generalised gamma for time to stopping treatment		
£81,696	£96,107	£64,869
Company base case + utility values for everolimus and BSC equal to axitinib group in AXIS trial*		
£56,315	£94,320	£69,106
ERG base case + utility values for everolimus and BSC equal to axitinib group in AXIS trial*		
£81,176	£100,730	£67,930
* Requested by committee lead team, provided shortly before meeting		

Source: ERG 'PMB queries' table 2

End of life

Criterion	Data
Short life expectancy, normally less than 24 months	Median survival with everolimus **19.6** months (CheckMate 025, mean not reported) Company – median life expectancy: • **<12** months with BSC (population studies, trial data) • **~20** months with axitinib (population studies, trial data)
Extension to life, normally of at least 3 months, compared with current NHS treatment	Median survival **5.4** months longer nivolumab than everolimus (CheckMate 025, mean not reported) Company's network meta-analysis: • survival benefit nivolumab vs axitinib **not statistically significant** • survival benefit nivolumab vs BSC significant in intention-to-treat analysis, but not when adjusting for crossover Company's base-case, mean gain in life years: • **1.4** years nivolumab versus axitinib • **0.9** years nivolumab versus everolimus • **2.0** years nivolumab versus best supportive care

⊙ *Does nivolumab meet end of life for each population defined by comparator? Does nivolumab extend life compared with current NHS treatments?*

Equality issues and innovation

- No equality issues raised during scoping or in submissions

Innovation

- Nivolumab is first checkpoint inhibitor immunotherapy to gain a marketing authorisation in this indication
- Innovative mechanism – uses body's own immune system to destroy cancer cells
- First immunotherapy available for patients with advanced RCC through Early Access to Medicines Scheme
- First therapy to demonstrate survival benefit compared with everolimus
- Any benefits not captured in model?

⊙ *Does nivolumab reflect a step change in treatment? Any benefits not captured within the model?*

Key issues for consideration

Model	• Which type of survival model is most appropriate for OS, PFS, TTD?
	  • OS: *Proportional hazards? AFT appropriate?*
	  • All: *Independent vs treatment as a covariate?*
	  • Time on treatment: *Spline vs more conventional parametric approach?*
	• Have differences in trial populations been accounted for within: (i) network meta analysis; (ii) utilities and (iii) survival data?
	• Should model take estimates of relative effectiveness from network meta-analysis or assume that axitinib is as effective as everolimus?

Utility	Is it appropriate to take utility values from trials with different populations?
Costs	• Does company's base case reflect number of doses of nivolumab that would be received in practice? • Should model include costs of subsequent treatments?
PPRS	Should PPRS Payment Mechanism be regarded as relevant?
Other	Are there any other issues identified?