Slides for projector part 1

Nivolumab for previously treated advanced renal cell carcinoma (STA)

7 September 2016
Committee B
2nd Appraisal Committee meeting
Lead team: Anne Joshua, Stephen Palmer, Nigel Westwood
Evidence review group: BMJ
NICE technical team: Anna Brett, Rosie Lovett
Clinical and patient experts: James Larkin, Paul Nathan, Jon Birchall, Alison Fielding
Chair: Amanda Adler

Appraisal Consultation Document (ACD): preliminary recommendation

Nivolumab is not recommended within its marketing authorisation for previously treated advanced renal cell carcinoma in adults

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

Because nivolumab and axitinib have patient access schemes, cost effectiveness results part 2A

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”
- Administered intravenously every 2 weeks
- Previously available in UK via Early Access to Medicines Scheme

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	**Best supportive care**	**Nivolumab?**		

★: oral tyrosine kinase inhibitors

✪: oral mammalian target of rapamycin (mTOR) inhibitor

CDF: Cancer Drug Fund

Committee conclusions: comparators for nivolumab

2nd line	**Axitinib** for most people	**Everolimus** if cannot have axitinib	**Best supportive care** if cannot have axitinib or everolimus
3rd line	**Best supportive care**		

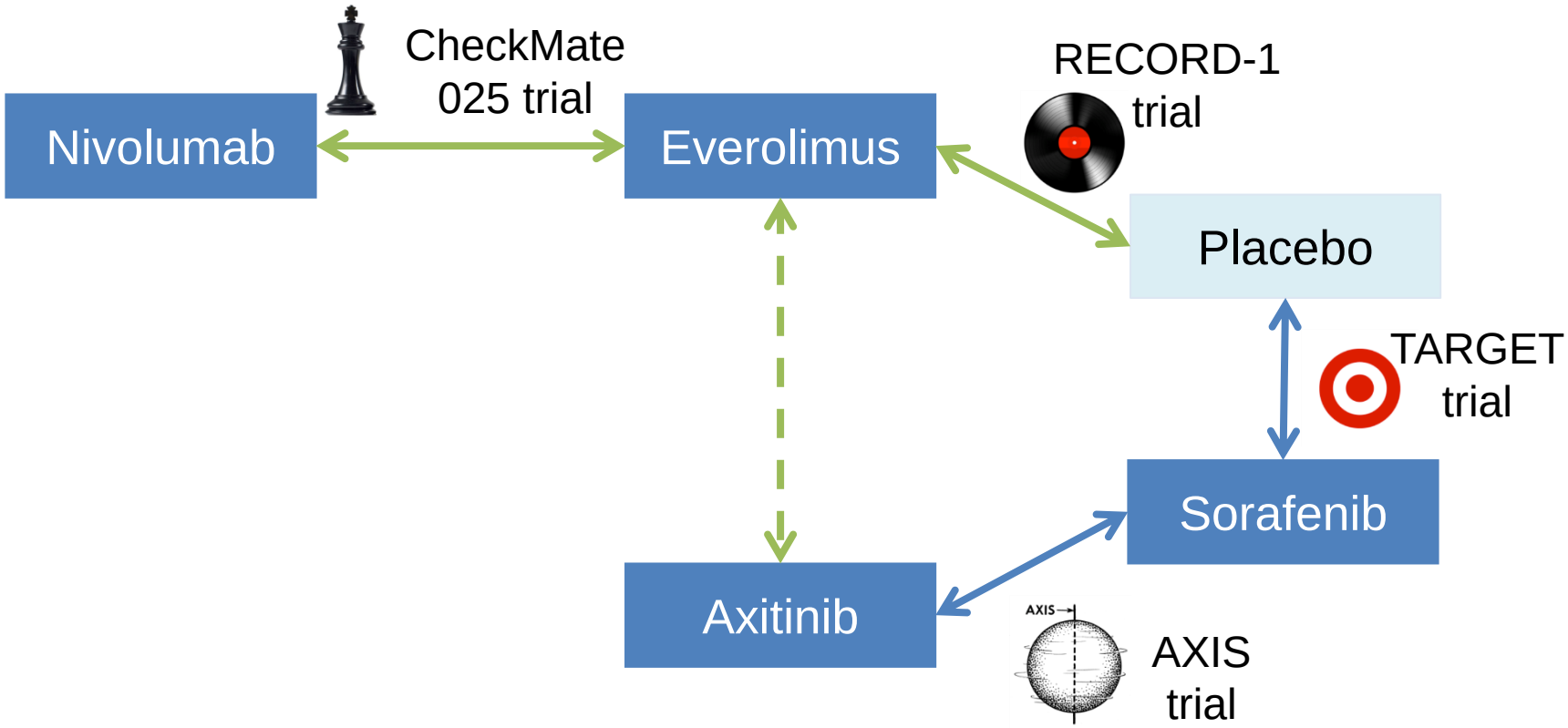
Company's clinical evidence

Nivolumab extended survival vs. everolimus

Trial	CheckMate 025
Design	Open-label n=821
Population	• Adults with advanced renal cell carcinoma • 72% 1 prior treatment (2nd line), 28% 2 prior treatments (3rd line)
Intervention	Nivolumab 3 mg/kg intravenously every 2 weeks
Comparator	Everolimus 10 mg orally every day
Stopping	Patients in both groups could continue treatment beyond progression if benefiting and tolerating drug
Follow-up	Minimum 14 months (median 17–18 across treatment groups)
Results	• Nivolumab reduced risk of death (primary outcome) **HR 0.73**, (98.5% CI 0.57–0.93, p=0.002) • Patients randomised to nivolumab lived longer (median 25.0 months) than patients randomised to everolimus (median 19.6 months) – difference median **5.4 months**

⊙ *Key issue for this meeting: will some patients live for long time with nivolumab ('survival curve with a long tail') – if so, how many? Discussed later.*

Company's network meta-analysis

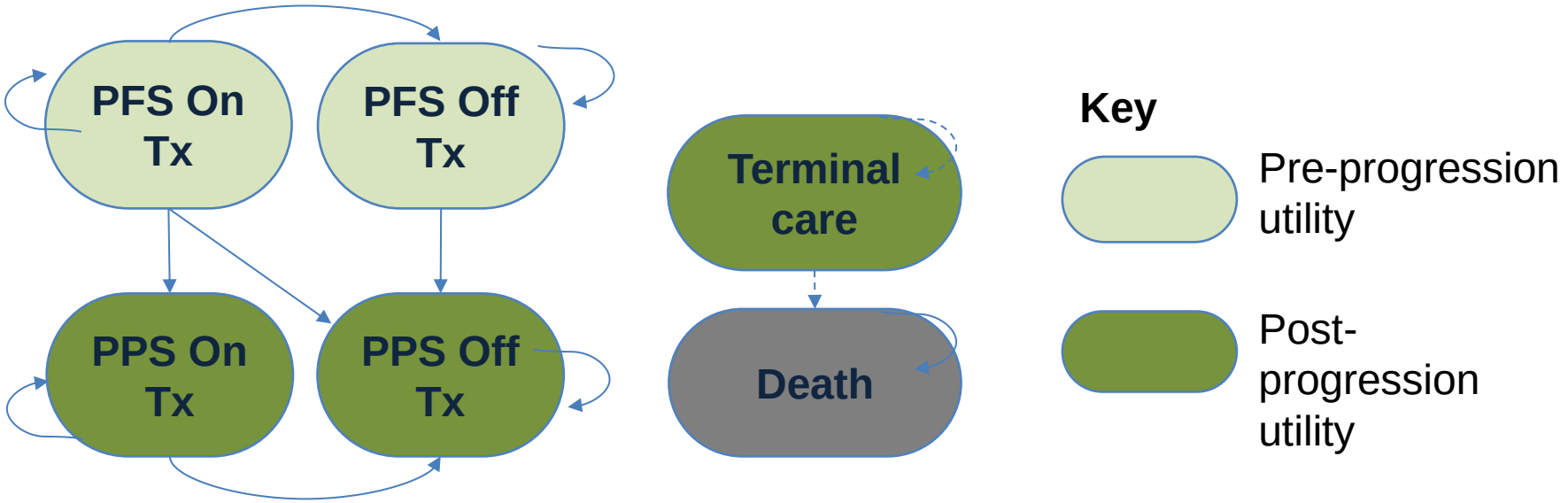


Key	Direct trial data	Indirect efficacy estimates
Informs economic model	⟷	⟵ - - ⟶
Not in economic model	⟷	Not shown

Committee's conclusions: clinical effectiveness

Issue	Committee's considerations in ACD
Overall survival (4.4)	Nivolumab extended overall survival compared with everolimus. Results generalisable to NHS.
Extent of survival benefit uncertain (4.5)	• **Immature survival data from CheckMate 025** • **Experts expect 'survival curve with long tail'** • **But only ~15% still having nivolumab after 2 years; implausible to assume more than a few people live to 5 years**
Subgroups (4.7)	**Unsure whether nivolumab equally effective in those with 1 or at least 2 previous treatments**
Effectiveness axitinib vs. everolimus (4.11)	Key driver of model. Network meta-analysis very uncertain, committee preferred to assume equal effectiveness (hazard ratios = 1)
End of life (4.25-6)	Agreed nivolumab met end of life criteria

Company's model



- Partitioned survival (area under curve) model
- Time in each state:
  - Calculated from extrapolated CheckMate 025 survival curves for nivoloumab and everolimus
  - Applied hazard ratios to everolimus arm to predict outcomes for axitinib and best supportive care

Committee's ACD conclusions: model inputs

Company's original base case	ERG's original base case	Committee's preferred assumptions
Treatment effect for axitinib vs everolimus from network meta-analysis	Equal effectiveness for axitinib and everolimus	ERG base case (4.12)
Time to stopping treatment - spline hazard 2 knot	Time to stopping treatment - log-normal distribution	ERG base case (4.16)
Include costs of subsequent therapy	Exclude costs of subsequent therapy	Company base case (4.18)
Utility values lower for axitinib than everolimus	**Utility values equal for axitinib and everolimus**	**ERG base case (4.19-20)**
Exclude cost of missing and delayed doses	**Include cost of missing and delayed doses**	**In between company and ERG (4.17)**

Committee's ACD conclusions: cost effectiveness

	ICER nivolumab (list price) vs		
	Axitinib (with PAS)	Everolimus (list price)	BSC
Company's original base case (ERG-corrected model)	**>£50,000**	**>£50,000**	**>£50,000**
ERG's original base case	**Higher than company**		

BSC, best supportive care; ICER: incremental cost-effectiveness ratio; PAS, patient access scheme

- Committee considered most plausible ICER to lie between company and ERG estimates
- Exact results not shown because axitinib patient access scheme (PAS) is confidential

Committee's conclusions: subgroups and survival

Issue	Committee's considerations
Subgroup analysis (4.13)	Would have preferred to see subgroup analyses for people with 1 or at least 2 prior therapies
Survival benefit (4.14)	• Large proportion of survival benefit extrapolated because of immature results from CheckMate 025 • Issue #1: scenario analysis assuming long term survival benefit reduced ICER – but based on assumption not trial data • Issue #2: would have liked to see independent models fitted to each arm for extrapolation

ACD consultation responses

- Web comments from:
  - Patients, relatives and carers
  - NHS professionals
  - Public
- Consultee comments from:
  - Bristol-Myers Squibb (BMS) – manufacturer of nivolumab
    - revised modelling and new patient access scheme for nivolumab
  - Kidney Cancer Support Network
  - Kidney Cancer UK
  - Royal College of Physicians, Association of Cancer Physicians, Clinical Studies Group (RCP-ACP-CSG)
  - Novartis (no comments)
- No equality issues were raised

Comments from patients, carers, professional groups (1)

Nivolumab is innovative, fulfils unmet need and improves quality of life

- Innovative breakthrough treatment (designated breakthrough therapy by US Food and Drug Administration, approved for Early Access to Medicines Scheme) – new immunotherapy treatments need to be promoted
- Fulfils unmet need and offers hope for those who already had tyrosine kinase inhibitors (TKI) – nivolumab different mode of action so more likely to work after TKI-failure than another TKI
- Improves quality of life, can enable people to continue working
- Better side effect profile than TKIs (side effects from TKIs can be debilitating)
- Is available in other countries; UK care will lag behind rest of world if nivolumab not approved – and UK cancer survival rates need to improve compared with other countries

Comments from patients, carers, professional groups (2)

Nivolumab is clinically effective

- Evidence of effectiveness (CheckMate 025) and longer term benefit (CheckMate 003 shows 1/3 patients treated with nivolumab alive after 5 years)
  - Patients in CheckMate 003 similar to those in NHS
  - CheckMate 025 trial stopping early does not overestimate treatment effect for immunotherapy because durable benefit not captured
  - Median survival may not reflect proportion of patients who had durable benefit
- Why nivolumab recommended for melanoma and not renal cell carcinoma, when:
  - 2 year survival data similar for melanoma and renal cell (~50%)
  - Overall survival data available for renal cell but only progression-free survival data was available for melanoma
- Nivolumab should enter Cancer Drugs Fund if not routinely commissioned (renal cell cancer is rare so disadvantaged)

Overview of comments from BMS (company)

- Clinical effectiveness in subgroups: clarification
- Simple discount Patient Access Scheme
- Re-calculated ICERs using “committee’s preferred assumptions” (slide 19)
- Provided evidence of long-term survival benefit of nivolumab; scenario analysis using ‘weighted’ model to include this

Company's updated evidence of efficacy in subgroups

- ACD 4.7: uncertain whether survival benefit in overall trial population would apply equally, regardless of number of previous treatments
- Company response:
  - Preferred hazard ratios come from clinical study report and submission to regulators; 'more robust' than data in trial publication
  - Hazard ratios for overall survival vs. everolimus:
    - Intention-to-treat: 0.73 (98.5% CI 0.57 – 0.93)
    - 1 prior anti-angiogenic: 0.79 (95% CI 0.63 – 0.99)
    - 2 prior anti-angiogenics: 0.65 (95% CI 0.43 – 0.99)

    (Heard from company at first meeting that in trial 'antiangiogenic'=TKI)

⊙ *Is nivolumab more effective than everolimus irrespective of number of previous treatments? NB: no modelling for subgroups*

Post consultation modelling

Revised base case from	Company	ERG
Committee assumptions/conclusions		
Time to stopping treatment - log normal	✔	✔
Costs of subsequent therapy - include	✔	✔
Axitinib + everolimus equally effective	✔	✔
Delayed doses (slide 20)	Difference of opinion	
Axitinib + everolimus equal utility values	✔	✔

Other issues for discussion:

- Different source of utility values (ERG scenario; slide 21)
- Ongoing utility benefit of nivolumab (committee concerned but all analyses include this; slide 22)
- Long tail for overall survival (new company and ERG scenarios; slides 23–6)
- Independent models for overall survival (new ERG scenario; slides 27–29)

Cost of delayed and missed nivolumab doses

	Cost reduction for		
	Delayed doses	**Missed doses**	**Total**
Company's original base case	5%	2.5%	**7.5%**
ERG's original base case	0%	0%	**0%**
Committee's considerations	Cost probably lay between company and ERG assumptions (ACD 4.17)		
Company's revised base case	4% (those with delay ≥7 days)	2.5%	**6.5%**
ERG's revised base case	Midpoint company's original total (7.5%) and ERG's original total (0%)		**3.8%**

At list prices, ERG's revised base case ICER vs axitinib about £3000 higher than company revised base case (only difference between base cases is nivolumab costs)

⊙ *Which reduction does committee prefer – 6.5% or 3.8%?*

Health state utility values

CheckMate 025 or AXIS?

Committee preferred same utility for axitinib and everolimus. 2 options:

	Axitinib and everolimus utility values	Nivolumab utility values
Company and ERG revised base case	Both from everolimus group **CheckMate 025**	Nivolumab group **CheckMate 025**
ERG scenario	Both from axitinib group **AXIS**	Axitinib group **AXIS**, plus nivolumab increment from CheckMate 025

- Company rationale for using CheckMate: 'gold-standard' utility data from pivotal trial, in line with NICE methods guide
  - During pre-meet, ERG agreed
- Using list prices, ERG scenario increases ICER by £6000–£8000 compared with ERG base case

⊙ *Which approach does committee prefer?*

Ongoing utility benefit of nivolumab

- ACD 4.19: concerned that model assumes constant benefit of having had nivolumab, even after disease progression and stopping treatment
- **Clinical experts at first meeting:** post-progression benefit may exist, because adverse effects with axitinib or everolimus take time to resolve, but differences expected for short time
- **Company response to ACD:** immune-response mechanism of nivolumab implies benefit beyond progression and stopping treatment; improves quality of life by reducing disease symptoms and providing hope

⊙ *Content to accept modelling including ongoing nivolumab benefit (included in all analyses)?*
⊙ *Does committee wish to change conclusions in ACD?*

Overall survival issue 1: long-term benefit

Company response to consultation

Opinion from company's 2 clinical experts

- Expect survival curve with long tail for nivolumab for renal cell carcinoma (echoes expert advice during first meeting)
- From ~3 years after starting nivolumab, expect mortality similar to overall population
- Model base case (using CheckMate 025) under-predicts survival with nivolumab because no survival curve with a long tail

Patients alive after…		2 years	3 years	4 years	5 years
CheckMate	003	48% (n=14)	41% (n=12)	38% (n=11)	34% (n=6)
CheckMate	010 *[range depends on dose]*	49% *[42-53%]* (n=80)	35% *[33-40%]* (n=58)	29% (n=47)	-
CheckMate	025	52% (n=204)	-	-	-
Company base case		53%	38%	28%	21%

Overall survival issue 1: long-term benefit

ERG: base case consistent with trial evidence

- Highlighted sample size – 34, 167 and 410 in CheckMate 003, 010 and 025 (nivolumab arm)
- Trials used different doses (only 025 used licensed dose)
- No measure of uncertainty in survival estimates
  - ERG estimated 95% confidence intervals for 5 year survival CheckMate 003 = 18–50%; "not inconsistent" with model prediction of 21%
- Company did not comment on why CheckMate 010 had fewer survivors at 3–4 years; model a good fit to this trial

Patients alive after…		2 years	3 years	4 years	5 years
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	025	52% (n=204)	-	-	-
Company base case		53%	38%	28%	21%

Overall survival issue 1: long-term benefit
Model scenarios

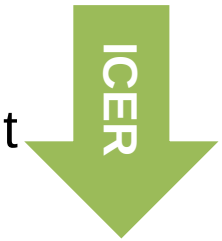
Company scenario

- 2 models, each given 50% weight:
  - Base case: OS from CheckMate 025, no 'long tail'
  - Immunotherapy tail after 5 years: same as base case up to 5 years, assume general population mortality thereafter

ERG scenario

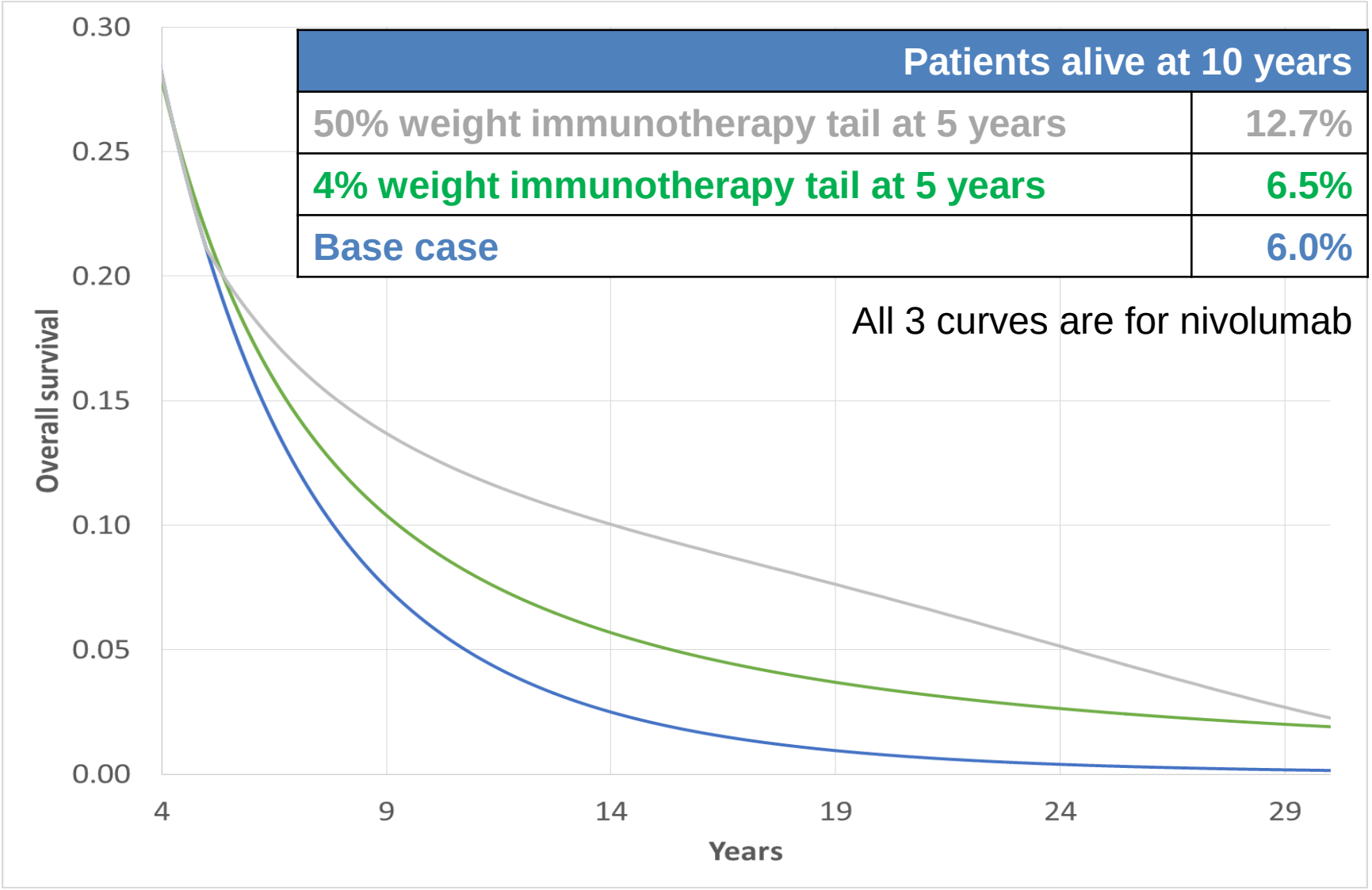
- Same 2 models, weighted 96% and 4% respectively
- Rationale: 'immunotherapy tail' model based on CheckMate 003, which has much smaller sample size than Checkmate 025
- ERG assigned weights based on sample size of 2 trials

Impact: both scenarios lower ICER compared with base case, but to lesser degree with ERG scenario (exact results confidential)



⊙ *Does committee prefer: 1) base case; 2) company 50% weight; 3) ERG 4% weight?*

Overall survival issue 1: long-term benefit
Model scenarios

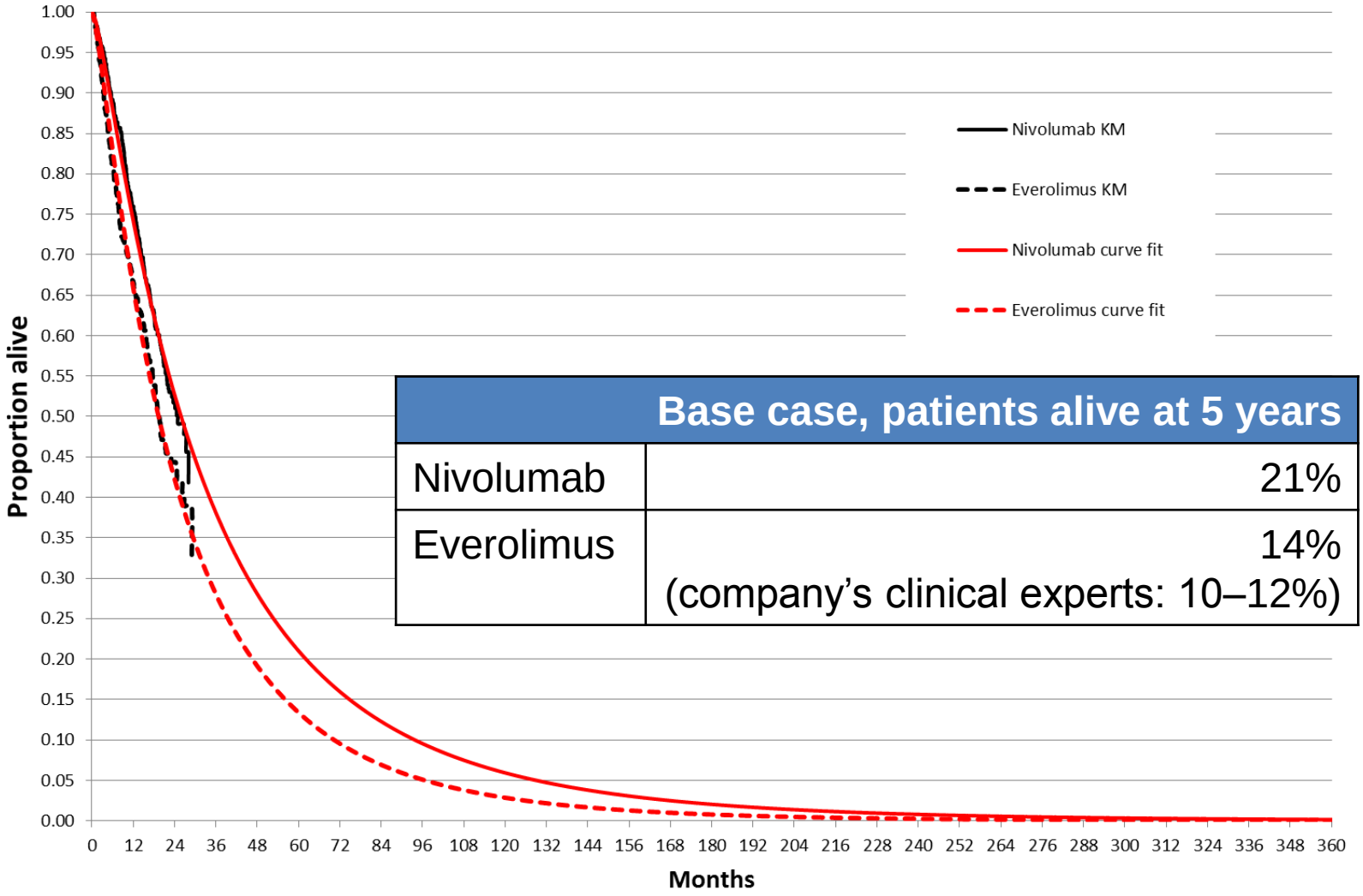


Overall survival issue 2: independent models

- Base case uses generalised gamma curve to extrapolate survival – single model with covariate for treatment group
- ACD 4.14:
  - committee concerned whether data met assumptions for accelerated failure time
  - alternative approach: fit independent models to each treatment group (ie separate models for nivolumab and everolimus)
- ERG scenario independent log-logistic models: at list prices, increases ICER by >£30,000 compared with base case (exact results confidential)
- But ERG had no time to validate predications with clinical experts
- Company submission: clinical experts considered that log-logistic model overestimated survival with everolimus

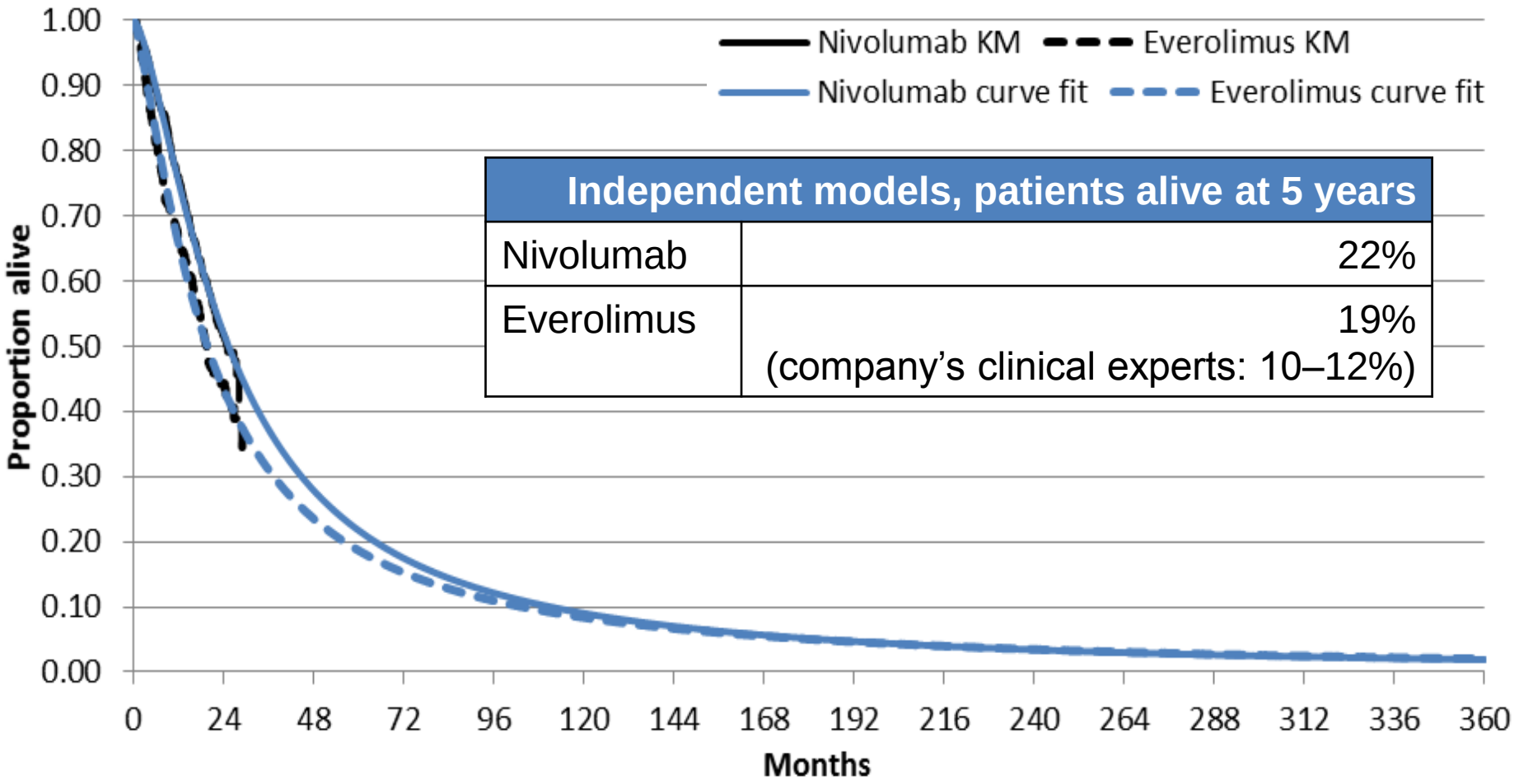
Recap: base case with single model and treatment as covariate

Long-term extrapolation



Base case, patients alive at 5 years	
Nivolumab	21%
Everolimus	14% (company's clinical experts: 10–12%)

Independent models
Long-term extrapolation



Independent models, patients alive at 5 years	
Nivolumab	22%
Everolimus	19% (company's clinical experts: 10–12%)

⊙ *Does committee prefer: 1) base case;*
2) scenario with independent survival models?

Comments – BMS (company)
Use of clinical opinion; network meta-analysis

- Assumptions of equal utility and equal effectiveness for axitinib and everolimus ‘based solely on clinical opinion’…for consistency, committee should also accept clinical opinion that survival curve with long tail is likely

- Disagree with ACD conclusion that network meta-analysis biased in favour of nivolumab *(now limited relevance because revised model assumes equal efficacy for axitinib vs everolimus)*

Key issues

- Is nivolumab more effective than everolimus irrespective of number of previous treatments?
  - Is one model for 2nd and 3rd line therapy appropriate for decision-making?
- In practice, will NHS incur costs of missed and delayed doses of nivolumab? If savings expected, will they be 6.5% (company base case) or 3.8% (ERG base case)?
- Prefer utility values from CheckMate (company and ERG base case) or AXIS (ERG scenario)?
- Does committee expect some patients to live for long time with nivolumab ('survival curve with long tail')? If so, how many?
  - Weight given to model with long tail: 50% (company scenario) or 4% (ERG scenario)
- For modelling survival, prefer single generalised gamma model (company and ERG base case) or independent log-logistic (ERG scenario)?