NICE National Institute for Health and Care Excellence

Part 1	No ACIC
Projector slides	

Pembrolizumab with axitinib for untreated metastatic renal cell carcinoma [ID1426]

Chair's presentation

2nd appraisal committee meeting, Committee C

Lead team: Nigel Langford, Derek Ward, Ugochi Nwulu

ERG/AG: Southampton HTA Centre

NICE technical team: Emma Douch, Christian Griffiths, Linda Landells

Company: Merck Sharp and Dohme

7th July 2020

Key issues for consideration

= Model driver

Survival extrapolation: What is the most clinically plausible distribution for pembrolizumab + axitinib?

Treatment effect duration: What method should be used to model treatment effect waning in the pembrolizumab + axitinib group?

Retreatment with pembrolizumab: What proportion of people in clinical practice would be retreated after discontinuation?

Health-related quality of life: What is the most appropriate source for post-progression utility values?

Poor/intermediate IMDC risk subgroup: Should the subgroup ICERs be considered separately?

Cancer Drug Fund: Could uncertainty be resolved within the proposed timeframe? Is there plausible potential to be cost-effective for routine commissioning?

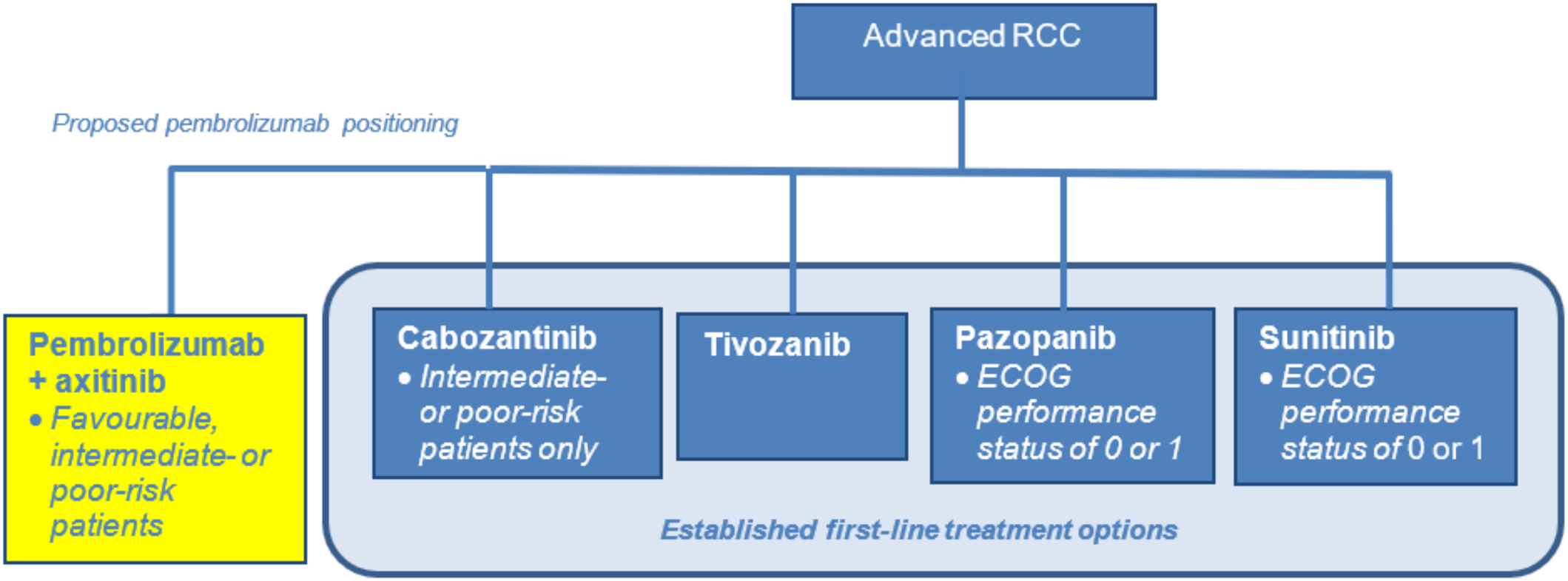
Pembrolizumab with axitinib

Description of technology	**Pembrolizumab** is a humanised monoclonal anti-programmed cell death-1 (PD-1) antibody involved in the blockade of immune suppression and the subsequent reactivation of anergic T-cells. **Axitinib** is a multi-targeted kinase receptor inhibitor with anti-tumour activity. Axitinib inhibits VEGFR -1, -2 and -3; PDGFR; and c-kit, which may result in inhibition of angiogenesis in tumours
Marketing authorisation	Pembrolizumab, in combination with axitinib, is indicated for the first-line treatment of advanced RCC in adults (granted 25 July 2019)
Dosage and administration	Pembrolizumab 200 mg intravenously every 3 weeks with axitinib 5 mg orally twice daily
Stopping rule	35 cycles (2 years) for pembrolizumab or until disease progression
Price (list price)	Pembrolizumab is £2,630 per 100 mg vial (single administration = £5,260). A commercial access agreement has been arranged with a simple discount in place. Axitinib is £3,517 per 56, 5mg tablets (average course of treatment = £120,572). A patient access scheme arrangement in place with a simple discount. First line treatment costs of pembrolizumab with axitinib are anticipated to be [redacted] over a patient's life time ([redacted] and [redacted] for drug acquisition and administration cost respectively)*

VEGFR = vascular endothelial growth factor receptor; PDGFR = platelet-derived growth factor receptor
*Company base case analysis ACM1 (list price), a 2-year stopping rule for pembrolizumab applied

Treatment pathway

Proposed treatment pathway which is based on the NICE pathway for renal cell carcinoma (RCC) and the updated European Association of Urologists guideline*



**Nivolumab with ipilimumab* is not a comparator as it is recommended for use through the CDF (please see TA581 and the NICE position statement on CDF products as comparators).*

***Avelumab in combination with axitinib* for advanced renal cell carcinoma [ID1547] is currently being appraised by NICE*

ACM1: Committee's considerations (1)

Issue	Committee's conclusion
Relevant comparators	• Pazopanib* (most common), tivozanib*, sunitinib • Cabozantinib for intermediate or poor risk disease • Nivolumab + ipilimumab not a comparator available through the CDF • Avelumab + axitinib currently being appraised by NICE
Placing in pathway	• Unmet need for advanced renal cell cancer • Impact on eligibility for subsequent treatments: no second-line access to nivolumab or axitinib if recommended
KEYNOTE-426 trial	Randomised, open-label study comparing pembrolizumab plus axitinib with sunitinib monotherapy
	Population: 861 people with untreated locally advanced or metastatic RCC with clear cell component with or without sarcomatoid features.

*Assumed equal efficacy with sunitinib in line with TA215, TA512, TA542, TA581

ACM1: Committee's considerations (2)

<table>
<tr><th>Issue</th><th>Committee's conclusion</th></tr>
<tr><td>Key results

August 2018 data cut</td><td>Median OS (primary outcome) not reached in either group
Statistically significant improvement in OS and PFS but data immature
<table>
<tr><th></th><th>Result</th><th>95% CI</th><th>P value</th></tr>
<tr><td>OS</td><td>HR 0.53</td><td>0.38, 0.74</td><td>0.00005</td></tr>
<tr><td>PFS</td><td>HR 0.69</td><td>0.57, 0.84</td><td>0.00014</td></tr>
<tr><td>ORR</td><td>Difference of 23.6%</td><td>17.2, 29.9</td><td><0.0001</td></tr>
<tr><td>EQ-5D-VAS cfb baseline to week 30</td><td colspan="3">No clinically meaningful difference</td></tr>
</table></td></tr>
<tr><td>Network meta-analysis</td><td>Model informed by NMA for intermediate/poor IMDC risk group: no direct RCT data
• Evidence base weak: small CARBOSAN trial (cabozantinib v sunitinib), no significant difference in PFS or OS</td></tr>
</table>

ACM1: Committee's considerations (3)

Issue	Committee's conclusion
Model structure	Three state partitioned survival model *Optimistic: switched to all cause mortality at 20 years, suggested 17% 'cured'. No consideration of 'cure' fractions.*
Extrapolation of OS	Company: log-logistic for pembrolizumab + axitinib, exponential for sunitinib ERG: Weibull for both *Considerable uncertainty due to immature data* • *Insufficient evidence to justify multiple distributions for OS* • *Most plausible survival between log-logistic (optimistic) and Weibull (pessimistic) estimates*
Treatment discontinuation	2 year stopping rule appropriate *In line with KEYNOTE-426 protocol* Preferred treatment effect waning after 5 years *No evidence of lifetime effect*

ACM1: Committee's considerations (4)

<table>
<tr><th>Issue</th><th>Committee's conclusion</th></tr>
<tr><td>Utility</td><td>Prefer values from published literature to time-to-death or pooled health state approach
KEYNOTE-426 did not collect EQ-5D data post-progression: HRQoL at end-stages of disease unclear

Unclear whether age-related disutility appropriate</td></tr>
<tr><td>ICERs</td><td>Most plausible ICER between company and technical team’s estimates.
Committee preferred ICER: lower end of acceptable range (~£20,000/QALY gained) due to uncertainty in survival data
<table>
<tr><th></th><th>Sunitinib</th><th>Pazopanib</th><th>Tivozanib</th><th>Cabozantinib**</th></tr>
<tr><td>Company base case*</td><td>£59,292</td><td>£57,540</td><td>£56,648</td><td>£21,452</td></tr>
<tr><td>Technical team*</td><td>£150,257</td><td>£144,425</td><td>£146,638</td><td>£75,589</td></tr>
</table>
</td></tr>
</table>

*Deterministic ICERs using list price for all treatment
**Poor/intermediate IMDC risk subgroup only

ACM1: Committee's considerations (5)

Issue	Committee's conclusion
End of life	First criterion not met: • *Life expectancy over 24 months in both full population and poor/ intermediate risk subgroup*
CDF	OS data immature. Further information could reduce uncertainty on: - number who stop pembrolizumab (after complete remission or 2 years) - frequency and time of relapse - response to retreatment *Does not meet CDF criteria:* • *Further expected data cuts for KEYNOTE-426 could not resolve uncertainty in the proposed timeframe* • *No plausible potential to be cost effective at the threshold for routine commissioning*

ACD: Preliminary recommendation

1. Long-term survival benefit uncertain
2. Not cost effective: most plausible ICER >£30,000/ QALY gained
3. Does not meet end of life criteria: Life expectancy over 24 months
4. Does not meet CDF criteria

*ACD: Pembrolizumab with axitinib is **not** recommended, within its marketing authorisation, for untreated advanced renal cell carcinoma in adults.*

Consultation

ACD consultation responses

Company

- Merck Sharp & Dohme

Web comments

- 1 clinical expert (on behalf of consultant group)

Patient & Professional

- Kidney Cancer UK (KCUK)
- Kidney Cancer Support Network (KCSN)
- NCRI Bladder and Renal Clinical Research Group (NCRI)

No new evidence requested by the committee

ACD consultation responses: Theme 1

Impact on RCC pathway

Company

Acknowledge positive recommendation would impact subsequent treatment options

Treatment pathway for RCC evolving:

- CDF approved combination regimens will have same impact on first- and second-line options

Focus on early access to efficacious therapy, not reduction of second-line options:

- Only 50-60% of people with RCC receive a 2L treatment

Patient & Professional

Highly positive effect on pathway, allowing access to the best treatments upfront with better long-term outcomes (KCUK)

Outcome disappointing: likely to become gold-standard if reimbursed (NCRI)

Current 1L drugs not effective / tolerated by all: access to innovation paramount (KCSN)

- Additional choice would allow individualised treatment pathways and increase quality of life

ACD consultation responses: Theme 2

Disregard of clinical expert advice

Company

Expert advice not used appropriately to inform areas of uncertainty:

- Long-term efficiency and duration of response
- Effectiveness of pembrolizumab + axitinib versus comparators

Limitations in data increase importance of clinical advice:

- Valuable experience of drug use in NHS, many as trial investigators

Expert opinions should allow judgement in the absence of long-term data (with support from CDF if necessary)

Patient & Professional

Disregard of clinical expert and patient first-hand experiences of tumour response (KCUK)

Increased quality of life not considered: good side effect profile, no pre-medications required, time saving of three weekly treatment (KCUK)

ACD consultation responses: Theme 3

Overall survival and duration of response

Company

Base case OS distributions justified:

1. All clinical expert input supports lifetime effect:
    - ~15% achieve durable remission with pembrolizumab + axitinib
    - Kaplan Meier 'curve of tail' likely – as per melanoma/ nivolumab + ipilimumab (TA581)
2. PD-L1 blocking mechanism of action:
    - Plausible maintenance of T-cell mediated cancer-immune equilibrium for decades
3. Long-term effect from other KEYNOTE trials:
    - KEYNOTE-006: 78% progression free at 24m post discontinuation (2 year stopping rule)

Level of uncertainty does not warrant ICER threshold of ≤ £20,000/QALY gained

- RCC TAs with similar uncertainty: ≤£30,000/QALY gained

Web comments

Alternative models appropriate:

- Likely life-long benefit (especially when used in 1L)
- Different pattern of decay in sunitinib arm: access to nivolumab and lower response rates in 2L

5-year effect waning unsuitable:

- KEYNOTE-426 suggests subgroup with lifelong disease control even with 2-year stopping rule: in line with longer-term follow up of other checkpoint inhibitors
- 'Cure' rate of 17% plausible

ACD consultation responses: Theme 4

Cancer Drugs Fund

Company

Strongly believe pembrolizumab / axitinib should be considered for the CDF:

- Combination offers clinically meaningful and statistically significant OS and PFS benefits
- Further data cuts of KEYNOTE-426 expected
- TA581 recommended via CDF with similar uncertainties
- Step change in treatment of advanced RCC

Further PFS data would not preclude extension of survival from long-term immunotherapeutic effect:

- Overall survival more clinically relevant

Web comments

KEYNOTE-426 data immature but access to potentially transformational treatment should be prioritised

Planned analysis in next 2 years should:

1. reduce clinical uncertainty
2. demonstrate impact of 2 year stopping rule on cost effectiveness estimates

CDF candidate

Patient & Professional

- Uncertainty would be resolved by further data collection in the CDF (KCUK)
- CDF would enable collection of further survival data (including in non-clear cell RCC) and resolve uncertainty regarding duration of response (KCSN)

ACD consultation responses: Theme 5
Unmet need

Company

First immuno-oncology combination to demonstrate statistically significant and clinically meaningful improvements in OS, PFS and objective response, irrespective of risk group classification.

Patient & Professional

CheckMate-214 overall survival of 26 months for sunitinib overestimated (KCSN)

- Data from clinical trial with pre-selected patients
- Real world evidence suggests survival of 9.8 months in poor- and 21.9 months in intermediate-risk population with two risk factors

FDA priority review status granted on Phase 3 trial data (KCSN)

UK cancer survival rates 10 years behind comparable European countries (KCSN)

- Innovative drugs with different modes of action should be made available

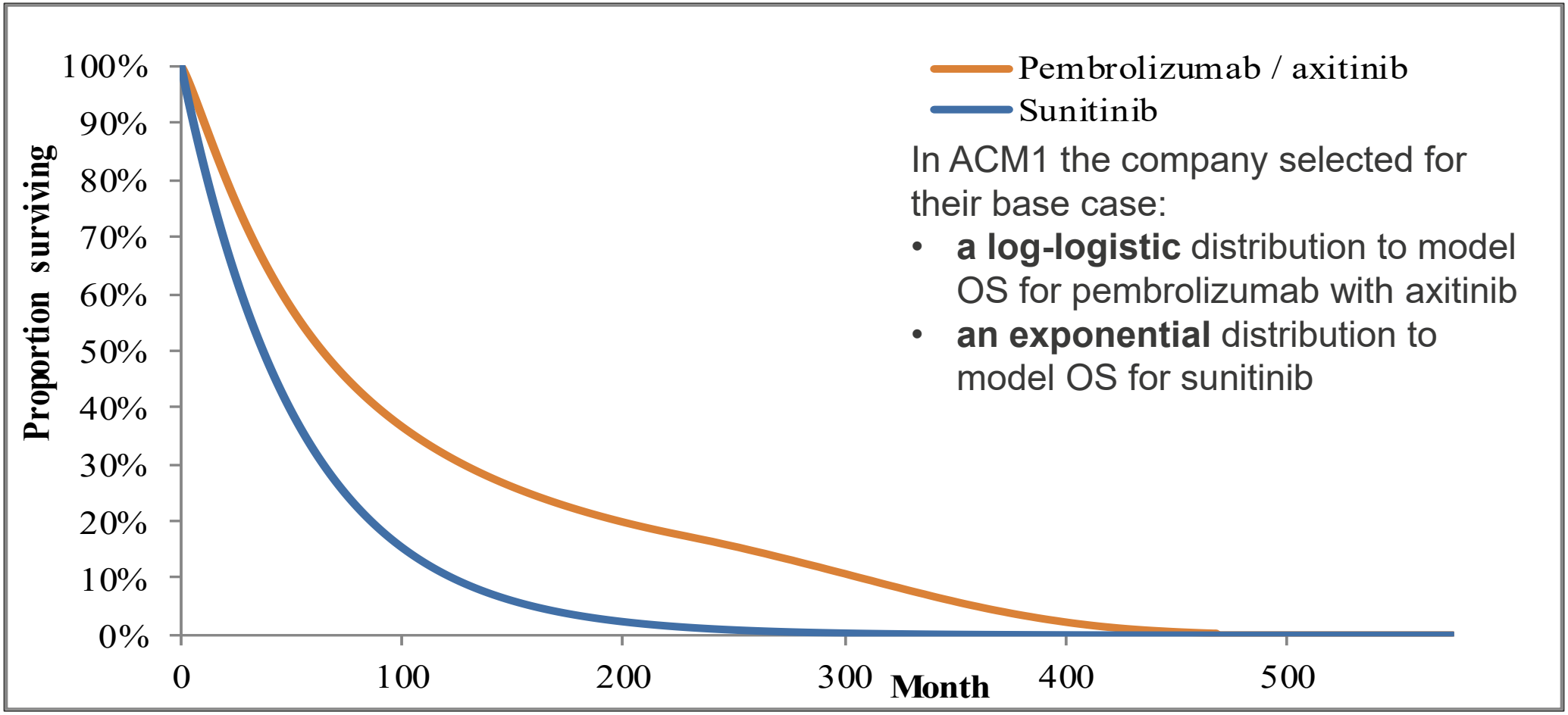
Company's new evidence

Company's new evidence

	Evidence	Description
1	Amended base case	1. Original base case adjusted for ERG preferences
		2. New base case using exponential distribution for both trial arms
		Supporting data: Phase 1b KEYNOTE-035 long-term survival results
2	Scenario analysis 1	Treatment effect waning after 5 years
3	Scenario analysis 2	Retreatment after discontinuation
		Supporting data: KEYNOTE-426 outcomes post treatment discontinuation

Refresher: ACM1 survival curves

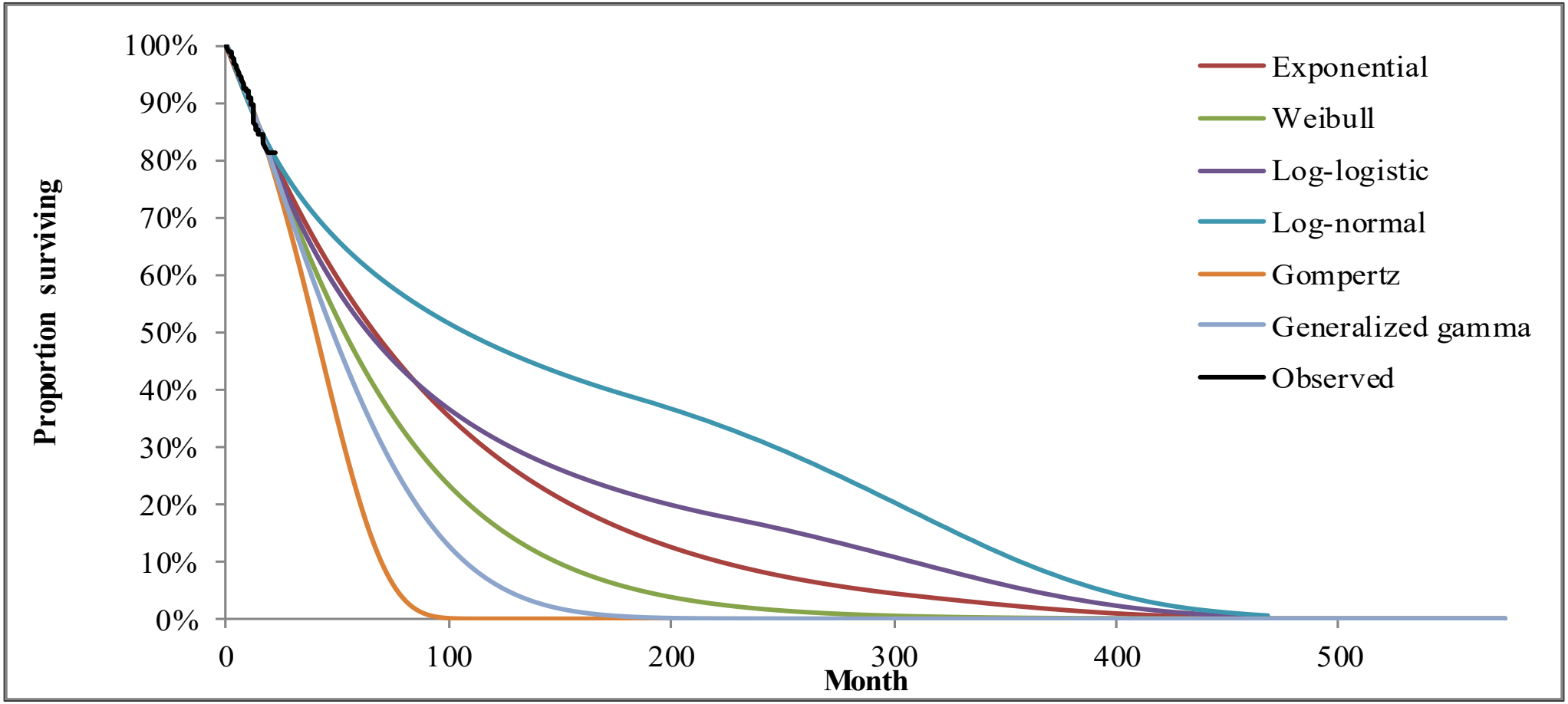
Overall survival



Company submission: Figure 25. ACM1 OS KM curves vs fully fitted parametric distributions for the OS of pembrolizumab + axitinib and sunitinib based on KEYNOTE-426 over a lifetime horizon

Refresher: ACM1 survival curves

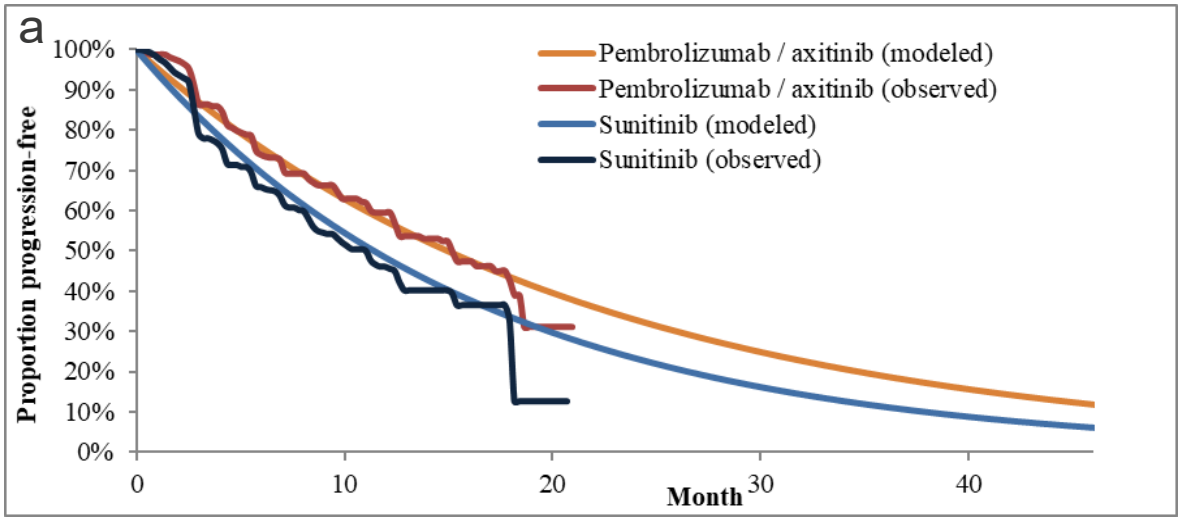
Overall survival

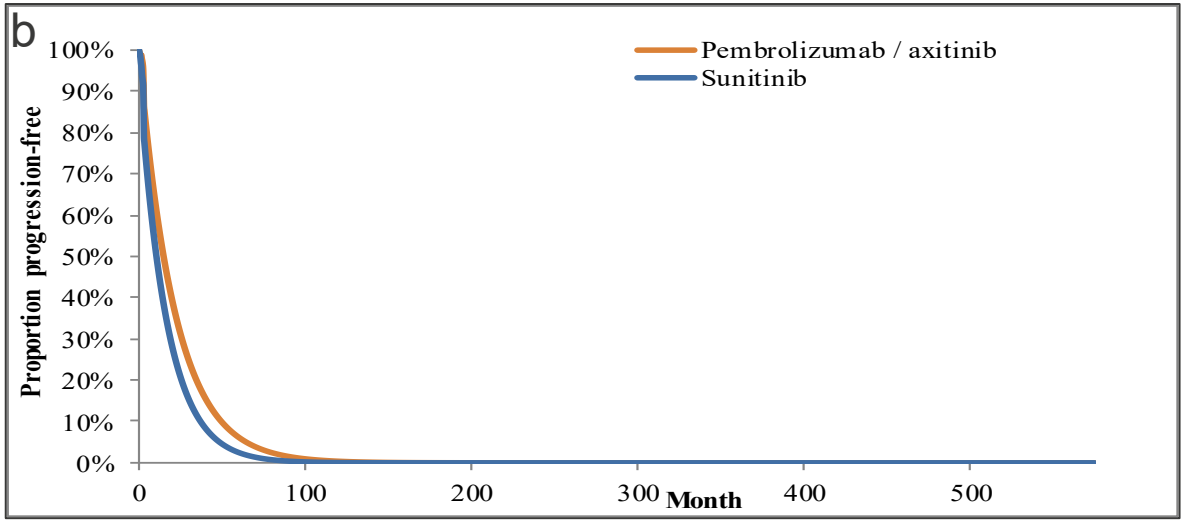


Company submission: Figure 21. ACM1 OS KM curve vs fitted one-piece model for pembrolizumab + axitinib based on KEYNOTE-426 (August 2018 data cut)

Refresher: ACM1 survival curves

Progression free survival





Company submission: Figure 30 and 31. ACM1 PFS KM curves vs fitted 2-phase **piecewise model**, with cut-off at 13 weeks and **exponential distribution** after, for pembrolizumab + axitinib and sunitinib based on KEYNOTE-426 (August 2018 data cut). a) over a 5-year horizon, b) over a lifetime horizon

Amended base case 1

Original base case adjusted for ERG preferences

	Assumption	Preference	Committee ACM1
Overall survival	Pembrolizumab + axitinib: log-logistic Sunitinib: exponential	Company	Log-logistic optimistic
Treatment effect	Lifetime	Company	5-year treatment effect waning should be used
Utilities	Time-to-death	Company, ERG	Bias in trial HRQoL data. Use utilities from literature.
Time on treatment	Weibull distribution used for all therapies	ERG	Not discussed
Oral therapy administration cost	Removed	ERG	Not discussed
Terminal care cost	Amended to £8,073 as per TA542	ERG	Not discussed
Distribution of subsequent therapies	As per ERG base case	ERG	Resolved at technical engagement

Amended base case 1

Supporting data: KEYNOTE-035 follow up

Company	ERG
KEYNOTE- 035: Open-label phase 1b study of pembrolizumab + axitinib in adult patients with untreated advanced RCC: ▪ Dose finding phase (n=11) ▪ Dose expansion phase (n=41) Follow up ~5 years indicative of long-term treatment effect. Justifies use of: • Log-logistic curve for pembrolizumab + axitinib • Separate distributions for each group	Clinical data encouraging but not necessarily generalisable to target population: • Phase 1b trial with aim to assess safety and tolerability • Overall survival secondary outcome in trial Data not used to inform cost-effectiveness in model

⊙ *Should KEYNOTE-035 data be used to model long-term pembrolizumab + axitinib survival?*

Amended base case 1

Supporting data: KEYNOTE-035 follow up

Results 03Jul2019

[redacted]

	Result	95% CI
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]		
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Amended base case 2

Exponential distribution for overall survival

*ACD: The committee concluded that the most plausible survival estimates were likely to fall **within the range** created by the log-logistic and Weibull distribution…*

Company

Weibull curve poor fit to data and produces clinically implausible survival estimates

Exponential curve conservative:

- Intersects log-logistic and Weibull curves
- In line with clinical expert opinion
- No 'tail of curve' effect: negligible fraction 'cured'

ERG

Weibull distribution preferred:

- KEYNOTE-426 data suggests increasing hazard for pembrolizumab + axitinib

Exponential distribution also reasonable

TA581 (nivolumab + ipilimumab):

- Log-logistic and exponential curves clinically plausible
- Insufficient long-term evidence to determine preferred distribution

Amended base case 2

Exponential distribution for overall survival

Source	Estimated survival pembro' + axitinib	Estimated survival sunitinib	Comments on immunotherapy duration of response
TA581 (nivolumab + ipilimumab)	N/A	19-24% at 5 years 4-11% at 10 years 1-7% at 15 years (intermediate/poor risk)	- Durable response plausible but no robust evidence on size of effect - No immunological effect preferred - CDF lead: durable effect expected in 20% of people taking nivolumab
Clinical experts to company	50% at 5 years	20-25% at 5 years 10-15% at 10 years	Percentage derive a long-term survival benefit from immunotherapy + TKI
Clinical experts to technical team	35% at 5 years 25% at 10 and 20 years	10% at 5 years 5% at 10 years 1% at 20 years	Longer OS expected beyond 3 years i.e. "tail of curve" effect. Not indicated in long-term sunitinib data
	90% at 1 year 82% at 18 months	10% at 5 years <1% at 10 & 20 years	Immunotherapy + TKI likely to have durable response in ~15%, not seen with sunitinib.

Amended base case 2

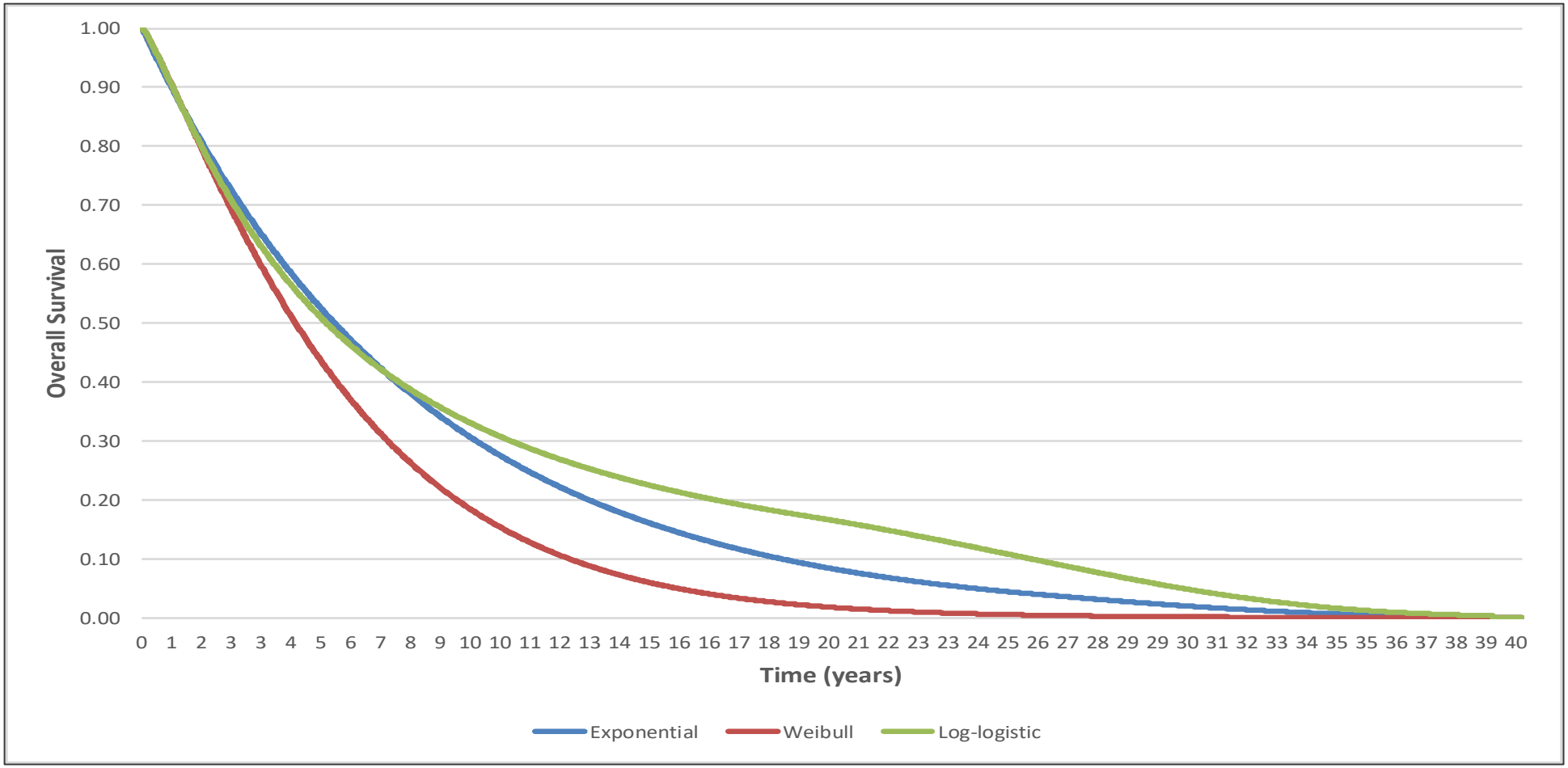
Exponential distribution for overall survival

	Log-logistic	Exponential	
Year	Survival pembrolizumab + axitinib	Survival pembrolizumab + axitinib	Survival sunitinib
1	88.5%	88.3%	79.9%
2	76.8%	78.0%	63.9%
3	66.7%	68.7%	50.9%
5	51.9%	53.5%	32.5%
10	31.6%	28.7%	10.6%
15	22.0%	15.4%	3.4%
20	16.5%	8.2%	1.1%

- *Which distribution produces the most plausible survival estimates for pembrolizumab + axitinib?*
- *Should cure fractions be considered in the model?*

Amended base case 2

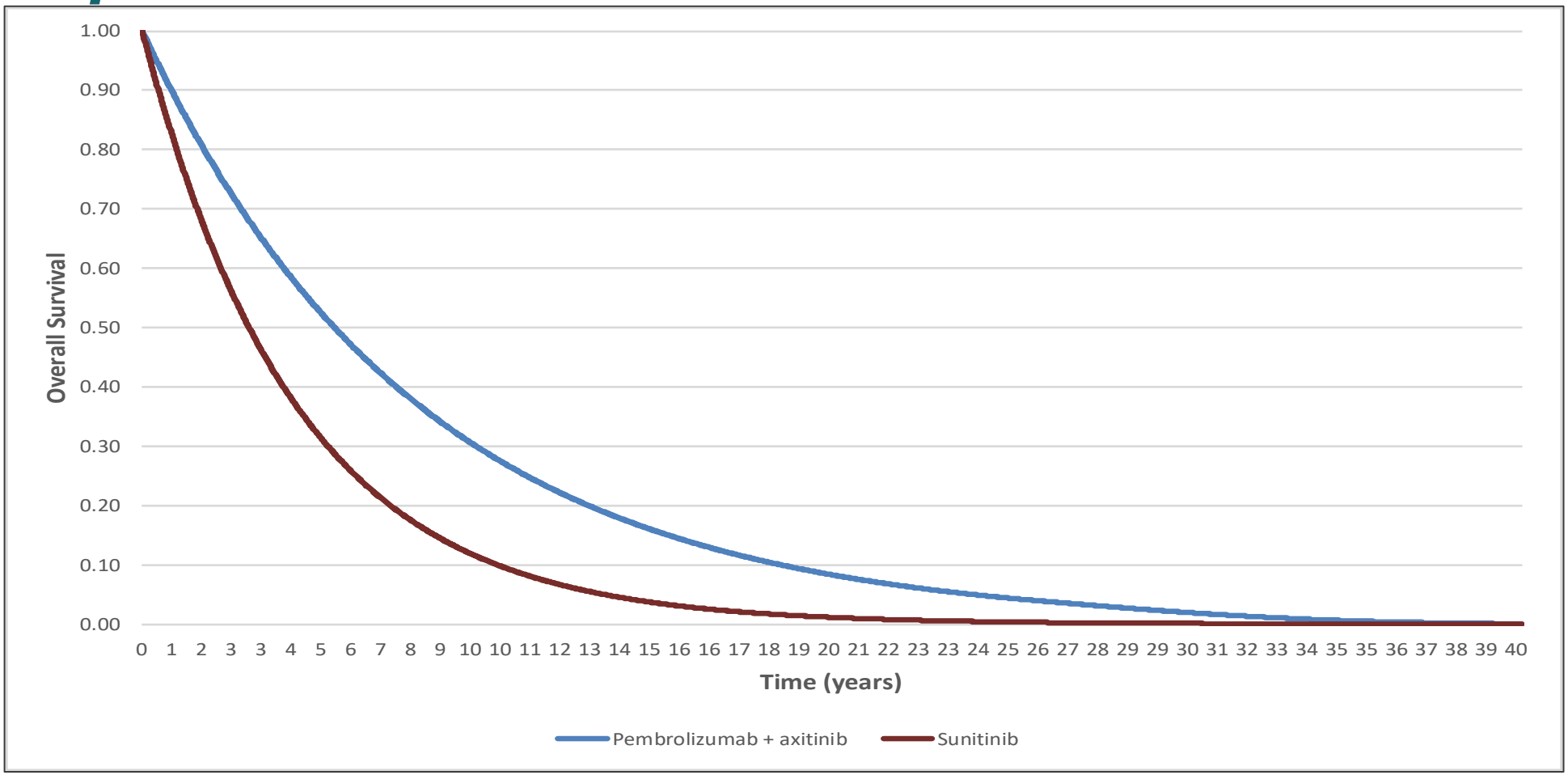
Exponential distribution for overall survival



Company response to ACD, Figure 2: Fully parametric distributions for **pembrolizumab + axitinib** based on KEYNOTE-426 data (August 2018 data cut)

Amended base case 2

Exponential distribution for overall survival



Company response to ACD, Figure 3: Fully parametric distributions for **pembrolizumab + axitinib versus sunitinib** using the exponential distribution based on KEYNOTE-426 data (August 2018 data cut)

Scenario 1: Treatment effect duration

ACD: The committee therefore concluded that there was not enough evidence to assume a lifetime treatment effect…...a treatment waning effect after 5 years was appropriate given the immaturity of the data.

Company

Scenario modelled on individual response to pembrolizumab + axitinib in KEYNOTE-426:

- ***Base case hazard ratio*:** complete response (5.8%), partial response (53.5%) and stable disease (24.5%)
- ***Effect waning***: no response (16.2%):
  - 5 to 10-years: gradual decrease in PFS and OS failure hazard rates
  - ≥10-years: equal hazard rates to sunitinib

Approach justified:

- Conservative - base case PFS and OS curves not stratified by patient response.
- Initial response prognostic of survival outcome

ERG

Unclear rationale for applying treatment effect waning to non-responders only:

- Previous model assumed PFS and OS eventually became equal in the two trial arms
- Most people had progressed at 5 years regardless of initial response

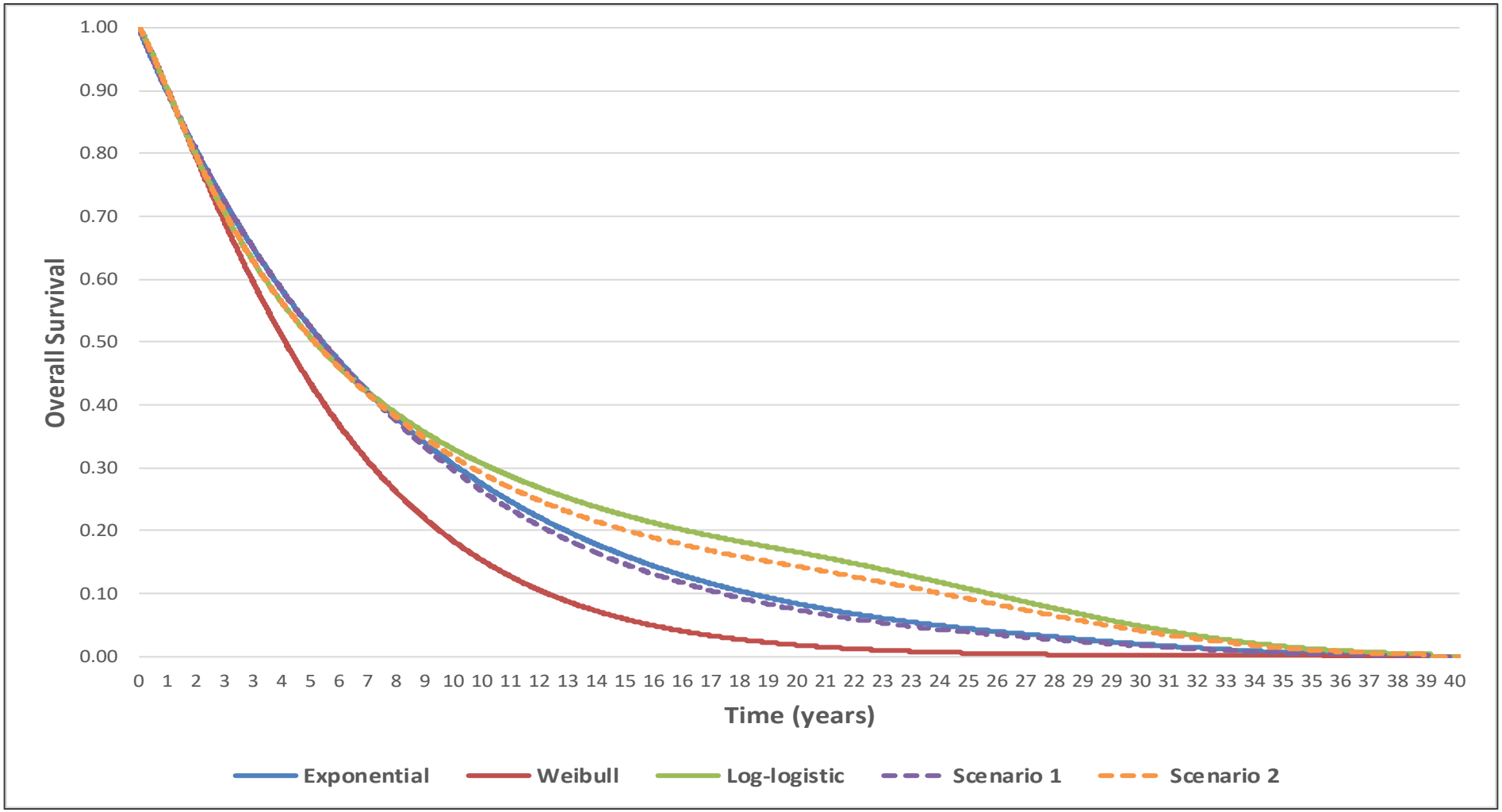
Unable to replicate company's results.

Effect waning after 5-years may be conservative.

Prefer treatment effect waning in entire pembrolizumab + axitinib group (ERG scenario provided)

⊙ *Is effect waning expected in people who respond to treatment?*

Scenario 1: Treatment effect duration



Company response to ACD: Figure 7. Overall survival extrapolations for pembrolizumab + axitinib using **alternative treatment effect duration** assumptions (August 2018 data cut).
Scenario 1: new base case assumptions (exponential distribution for both groups).
Scenario 2: original base case adapted with ERG assumptions.

NICE

Scenario 1: Treatment effect duration
Consistency with previous technology appraisals

Technical Team

Uncertainty as to size and duration of treatment effect in all pembrolizumab technology appraisals:

- Committee agreed lifetime treatment effect implausible / unlikely in TA366, TA428, TA519, TA522, TA531, TA533, TA557 and TA600

TA581: Nivolumab + ipilimumab (RCC)

- Company: 5-year stopping rule + immunological effect for a further 4 years
- Committee: stopping rule inappropriate as effect on clinical outcomes untested
- Long-term treatment effect plausible, but size of association between response and survival uncertain
- Observed duration of response in melanoma not generalisable to RCC
- Lifetime immunotherapeutic effect not substantiated by evidence

Scenario 2: Retreatment

Supporting data: Jan 2019 KEYNOTE-426

ACD: KEYNOTE 426 did not give any information about the likely effect of the 2 year stopping rule, the proportion of patients who would restart treatment with pembrolizumab after having had 35 cycles, or the effectiveness of retreatment.

Company

Pembrolizumab retreatment (after complete response or 35 cycles) not modelled in ACM1: No events as follow up >2 years when company submission made

KEYNOTE-426 January 2019 data cut:

- [redacted] had received pembrolizumab retreatment
- Discontinuation rates (ITT):
  - Pembrolizumab + axitinib: [redacted] (complete response [redacted], death [redacted])
  - Sunitinib: [redacted] (death [redacted])

Though retreatment permitted in KEYNOTE-426, company discourage modelling:

- Insufficient evidence to support, explore and justify assumptions
- No robust statistical methods to adjust for introduced biases / confounders

Scenario 2: Retreatment

Company	ERG
Scenario uses pembrolizumab retreatment rate pooled from two phase 3 RCTs: - **KEYNOTE-006** (1L-2L advanced melanoma) - **KEYNOTE-010** (≥3L advanced non-small cell lung cancer) Retreatment cost applied to **14.3%** of those with disease progression at 2 years (4.8% of ITT)	Limited generalisability of KEYNOTE-006 and -010: • Different indication • Unknown clinical heterogeneity • Pembrolizumab monotherapy: different method of action *Rate of retreatment may not be comparable – interpret with caution*

⊙ *Is company's retreatment rate generalisable to the population in this appraisal?*

Health related quality of life

ACD: The committee concluded that using values from the published literature for the progressed health state would be preferable to using the trial data

Company

Maintain time-to-death approach

Trial HRQoL data included in model for all other pembrolizumab indications:

- Same EQ-5D distribution post progression

Other sources considered but committee preferred utility unclear: paucity of post-progression data in RCC, trial data most valid.

Technical team

Committee preferred utility source not included in company's new analyses

RCC appraisals:

TA215 (pazopanib): post-progression utilities from health preference study

TA512 (tivozanib): TIVO-1 results–1st EQ-5D score for subsequent treatment

TA542 (cabozantinib): TA512 utilities

Pembrolizumab appraisals:

- Post-progression values consistent area of uncertainty
- Concerns with time-to death approach
- General preference for progression-state utilities

⊙ *Which utility source is most appropriate for decision making?*

Company's new evidence
Poor/Intermediate IMDC risk subgroup

ACD: Overall, the committee considered that the evidence base for the intermediate and poor-risk subgroup was weak.

Company

- Acknowledge small size of CARBOSAN trial
- NMA as robust as possible due to:
  - Lack of direct evidence
  - Comparable populations in network (minor heterogeneity in ethnicity)

No further analyses submitted in the poor/intermediate IMDC risk subgroup

Technical team

Relevant subgroup:

- Cabozantinib recommended only in poor/intermediate IMDC risk patients

Analyses in poor/intermediate risk population requested from ERG

⊙ *Should ICERs be considered separately for the high/intermediate IMDC risk subgroup versus cabozantinib?*

Cancer drugs fund (CDF)

Company

Willing to [redacted] to address uncertainty on overall survival, duration of response and retreatment with pembrolizumab

ERG

Inclusion in CDF would allow further data collection on retreatment rates

Technical team

- Further data cuts unlikely to reduce uncertainty on overall survival
- When commercial arrangements are considered, none of the analyses presented by the company are under £30,000 per QALY gained.

Cost effectiveness in routine commissioning unlikely

TA581 nivolumab + ipilimumab:

Recommended for CDF - data collection:

- Checkmate 214 overall survival, SACT database, new regulatory study.

Plausible ICERs £20,000 - 30,000/QALY gained

Pembrolizumab TAs:

TA519, TA522, TA531, TA540, TA553, TA557 and TA600 currently recommended for CDF

Cost-effectiveness results

Cost effectiveness results

Company's base case - deterministic

Company response to ACD, Table 2: Deterministic results for original company base case, log-logistic distribution for pembrolizumab + axitinib OS, adjusted for ERG preferences (based on list prices)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER
Pembrolizumab + axitinib	[redacted]	[redacted]	[redacted]	-	-	-
Sunitinib	[redacted]	[redacted]	[redacted]	144,723	2.320	**62,390**
Tivozanib	[redacted]	[redacted]	[redacted]	138,995	2.320	**59,921**
Pazopanib	[redacted]	[redacted]	[redacted]	141,163	2.320	**60,855**

Company response to ACD, Table 3: Deterministic results for new company base case using the exponential curve for both groups (based on list prices)

Technologies	Total costs	Total LYG	Total QALYs	Incremental costs	Incremental QALYs	ICER
Pembrolizumab + axitinib	[redacted]	[redacted]	[redacted]	-	-	-
Sunitinib	[redacted]	[redacted]	[redacted]	143,209	1.861	**76,972**
Tivozanib	[redacted]	[redacted]	[redacted]	137,481	1.861	**73,893**
Pazopanib	[redacted]	[redacted]	[redacted]	139,649	1.861	**75,058**

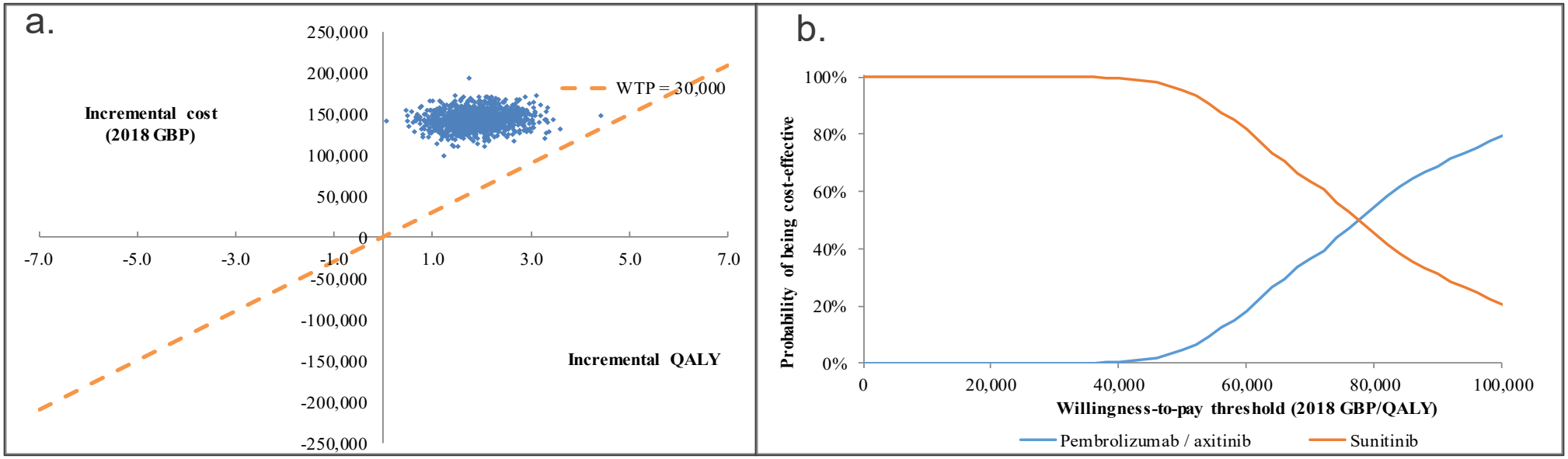
Cost effectiveness results

Company's base case - probabilistic

Company response to ACD, Table 4: Probabilistic results for company new base case using the exponential curve for both groups (based on list prices)

Technologies	Total costs (£)	Total QALYs	Incremental costs	Incremental QALYs	ICER
Pembrolizumab + axitinib	[redacted]	[redacted]	-	-	-
Sunitinib	[redacted]	[redacted]	143,075	1.88	**76,222**

Company response to ACD, Figure 4 and 5: a. scatterplot of PSA results (1,000 simulations) and b. cost-effectiveness acceptability curve. Results versus sunitinib for company new base case using the exponential curve for both groups



Cost-effectiveness results

Scenarios - ITT population

Scenario	Adjustment	Scenario	Incremental costs	Incremental QALYs	ICER
Base case ACM1	No ICER available using committee preferred assumptions				**59,292 - 150,257**
Original Base Case Log-logistic for pembro' + axitinib, adjusted for ERG preferences	Base case	Company	144,723	2.320	**62,390**
	Treatment waning effect applied to non-responders	Company	141,822	2.150	**65,963**
	Treatment waning effect applied to all	ERG	141,347	1.273	**111,064**
	Retreatment	Company	147,136	2.320	**63,430**
New Base Case Exponential distribution for both groups	Base case	Company	143,209	1.861	**76,972**
	Treatment waning effect applied to non-responders	Company	140,572	1.772	**79,333**
	Treatment waning effect applied to all	ERG	141,467	1.314	**107,693**
	Retreatment	Company	145,616	1.861	**78,266**

Cost-effectiveness results

Base case - Poor/intermediate IMDC risk subgroup

ERG report, Table 3: Deterministic results for updated company base case (list price) for the poor / intermediate RCC risk population, log-logistic distribution for pembrolizumab + axitinib OS, adjusted for ERG preferences (ERG replication)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Pembrolizumab + axitinib	[redacted]	[redacted]	[redacted]	-	-	-
Cabozantinib	[redacted]	[redacted]	[redacted]	46,040	1.543	**29,835**

ERG report, Table 4: Deterministic results for updated company base case (list price) for the poor / intermediate RCC risk population using the exponential curve for both groups (ERG replication)

Technologies	Total costs (£)	Total LYs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Pembrolizumab + axitinib	[redacted]	[redacted]	[redacted]	-	-	-
Cabozantinib	[redacted]	[redacted]	[redacted]	46,146	1.203	**38,346**

Cost-effectiveness results

Scenarios – Poor/intermediate IMDC risk

Scenario	Adjustment	Scenario	Incremental costs	Incremental QALYs	ICER
Base case ACM1	No ICER available using committee preferred assumptions				**21,452 – 75,589**
Original Base Case Log-logistic for pembro' + axitinib, adjusted for ERG preferences	Base case	Company	46,040	1.543	**29,835**
	Treatment waning effect applied to non-responders	Company	43,471	1.388	**31,321**
	Treatment waning effect applied to all	ERG	40,896	0.585	**69,910**
	Retreatment	Company	48,112	1.543	**31,178**
New Base Case Exponential distribution for both groups	Base case	Company	46,146	1.203	**38,346**
	Treatment waning effect applied to non-responders	Company	43,883	1.143	**38,410**
	Treatment waning effect applied to all	ERG	42,891	0.827	**51,836**
	Retreatment	Company	46,144	1.203	**38,344**

Key issues for consideration

= Model driver

Survival extrapolation: What is the most clinically plausible distribution for pembrolizumab + axitinib?

Treatment effect duration: What method should be used to model treatment effect waning in the pembrolizumab + axitinib group?

Retreatment with pembrolizumab: What proportion of people in clinical practice would be retreated after discontinuation?

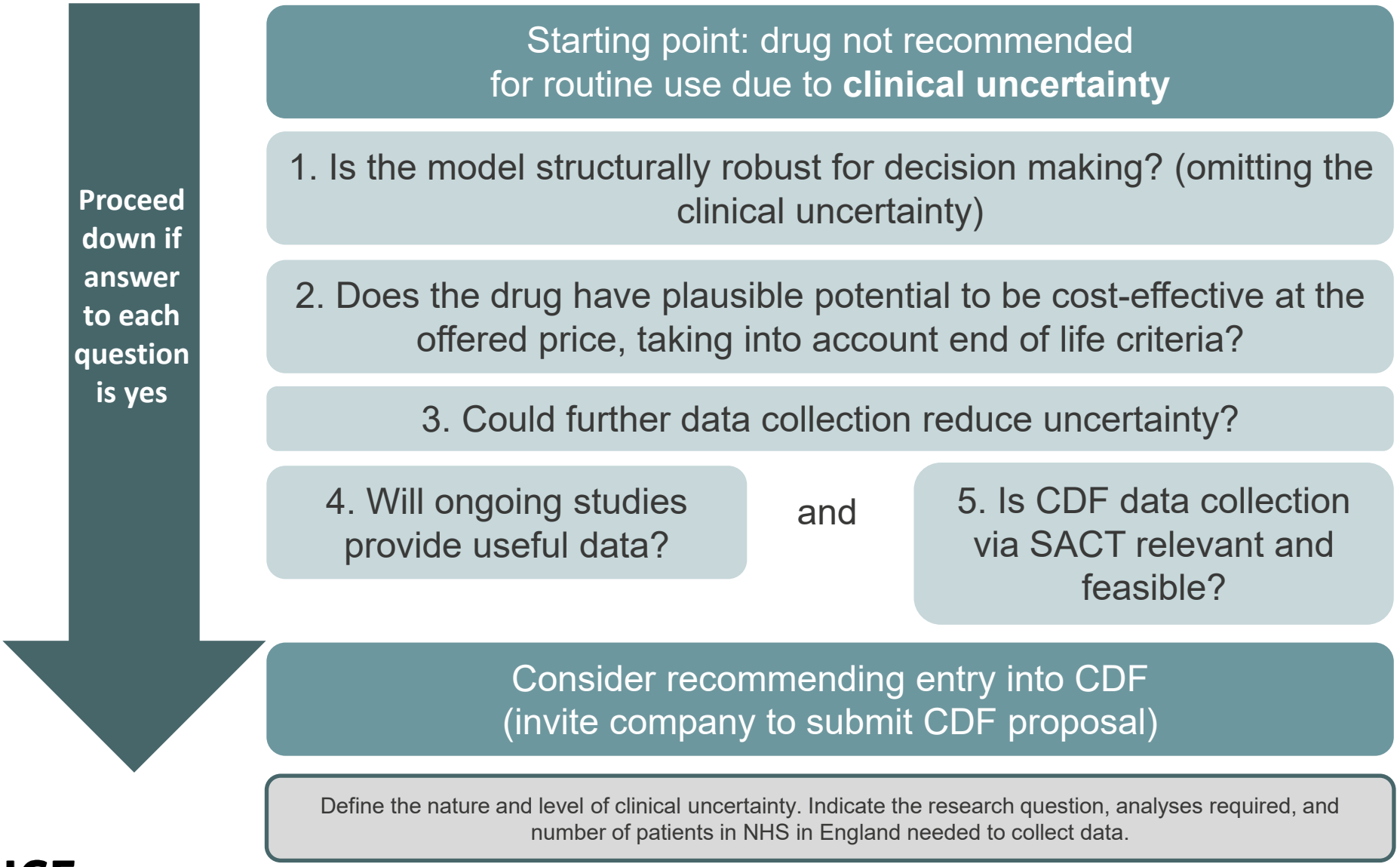
Health-related quality of life: What is the most appropriate source for post-progression utility values?

Poor/intermediate IMDC risk subgroup: Should the subgroup ICERs be considered separately?

Cancer Drug Fund: Could uncertainty be resolved within the proposed timeframe? Is there plausible potential to be cost-effective for routine commissioning?

Cancer drug fund (CDF)

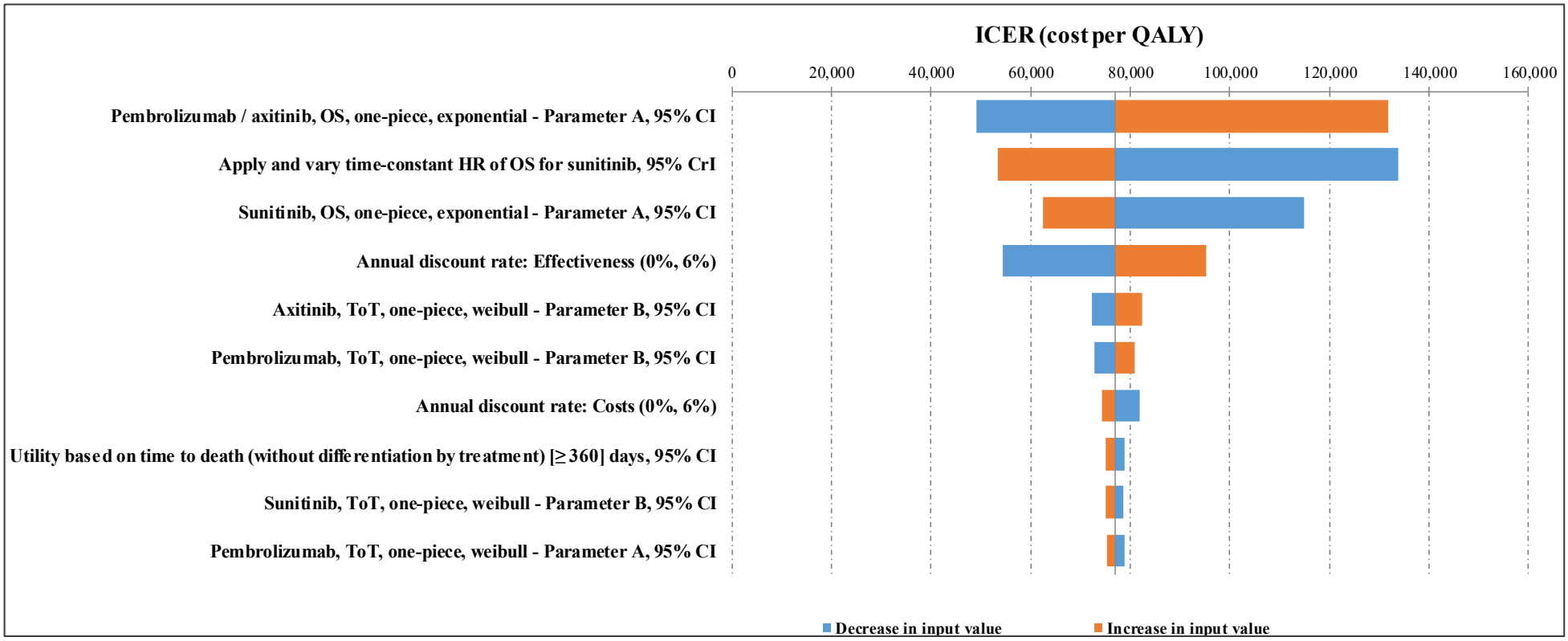
Committee decision making criteria:



NICE

Amended base case 2

Exponential distribution for overall survival



Company response to ACD: Figure 6. Tornado diagram presenting the results of the deterministic sensitivity analysis for the 10 most sensitive variables versus sunitinib (all drugs at list price)