NICE National Institute for Health and Care Excellence

PART 1

Public observer slides

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

Lead team presentation

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Company: Merck Sharp and Dohme

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Key Issues

- **Survival estimates from different modelling approaches:** What is the most appropriate survival model? [Issue 1]
- **Treatment effect duration:** What is the most appropriate time duration of treatment effect to model pembrolizumab combination therapy? [Issue 2]
- **Health-related quality of life:** What method is most appropriate to capture changes in health-related quality of life? [Issue 5]
- **End of life:** Does pembrolizumab combination therapy meet NICE's end of life criteria for the intermediate/poor IMDC subgroup? [Issue 7]
- **Cancer Drugs Fund:** Does pembrolizumab combination therapy meet the criteria for inclusion in the CDF? [Issue 8]
- **Pembrolizumab 2-year stopping rule:** Are treatment stopping rules appropriate in the treatment of RCC? [*New* Issue 9]

[redacted]

Renal cell carcinoma (RCC)

- In the UK, ~12,600 new cases of kidney cancer and 4,500 deaths due to kidney cancer annually
- RCC accounts for 80% of kidney cancer cases, is more common in people over 60 years old and males
- The International Metastatic Renal Cell Carcinoma Database Consortium (IMDC) criteria classifies people with metastatic RCC that receive systemic treatment in terms of favourable, intermediate or poor risk
- Prognosis is linked to stage of cancer at diagnosis:
  - ~ 44% presented at stage III or IV of disease
  - five year survival estimated at 83% and 6% for stage I and IV respectively

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 £XXXX over a patient's life time (£XXXX and £XXXX for drug acquisition and administration cost respectively)*

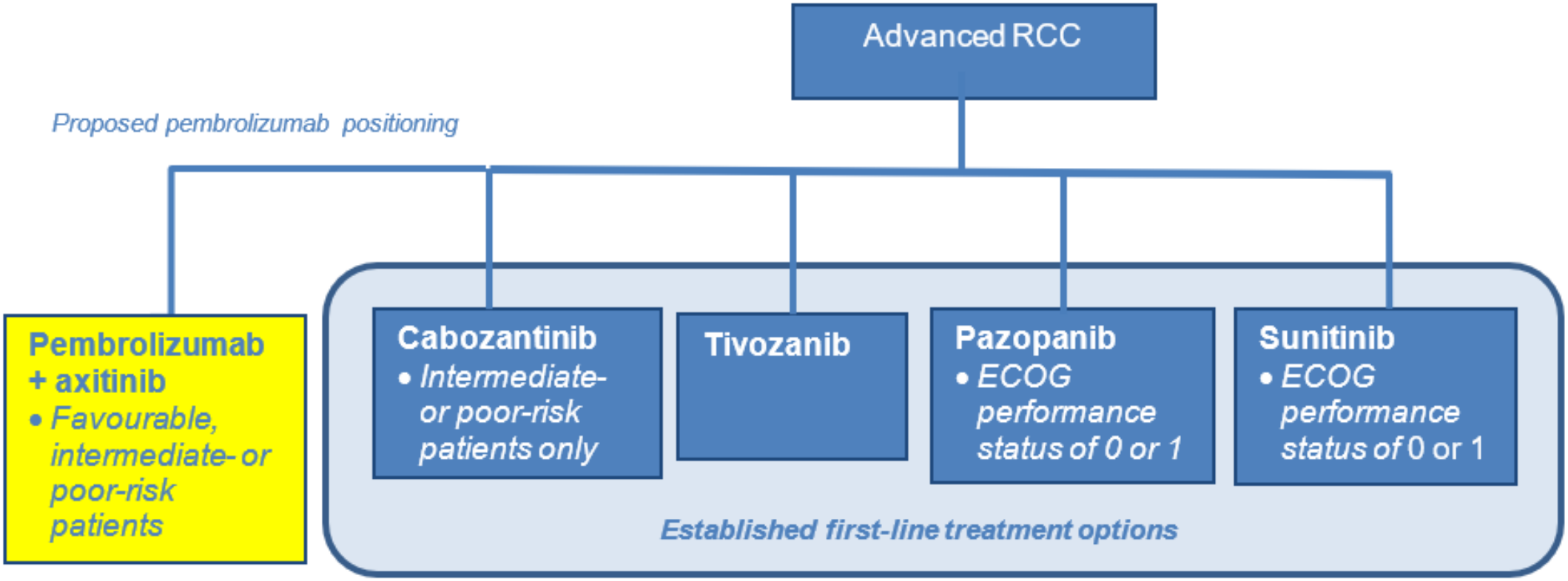
[redacted]

VEGFR = vascular endothelial growth factor receptor; PDGFR = platelet-derived growth factor receptor

*Company base case analysis, a 2-year stopping rule for pembrolizumab applied

Treatment pathway (1)

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*

[redacted]

Treatment pathway (2)

Clinical experts estimated that:

- 70% to 80% of people would get second-line treatment after pembrolizumab with axitinib
- 60% to 80% of people get second line therapy after sunitinib
- 40% to 60% of people who have pembrolizumab with axitinib would have cabozantinib as a second-line therapy

NICE guidance states that options for **second line** treatment of RCC include:

- **Lenvatinib plus everolimus** [TA498] after 1 previous VEGF-targeted therapy and ECOG performance status score is 0 or 1
- **Cabozantinib** [TA463] after VEGF-targeted therapy
- **Everolimus** [TA432] for advanced RCC that has progressed during or after treatment with VEGF-targeted therapy,
- **Nivolumab** [TA417] for previously treated RCC
- **Axitinib** [TA333] after failure of treatment with a first-line tyrosine kinase inhibitor or a cytokine
  - At time of publication (Feb 2015) need to gain consent and follow guidance by GMC if considered after any other first line treatments. DoH remit only included adults who had been previously treated with sunitinib, use of after other TKI treatment is not subject to statutory funding

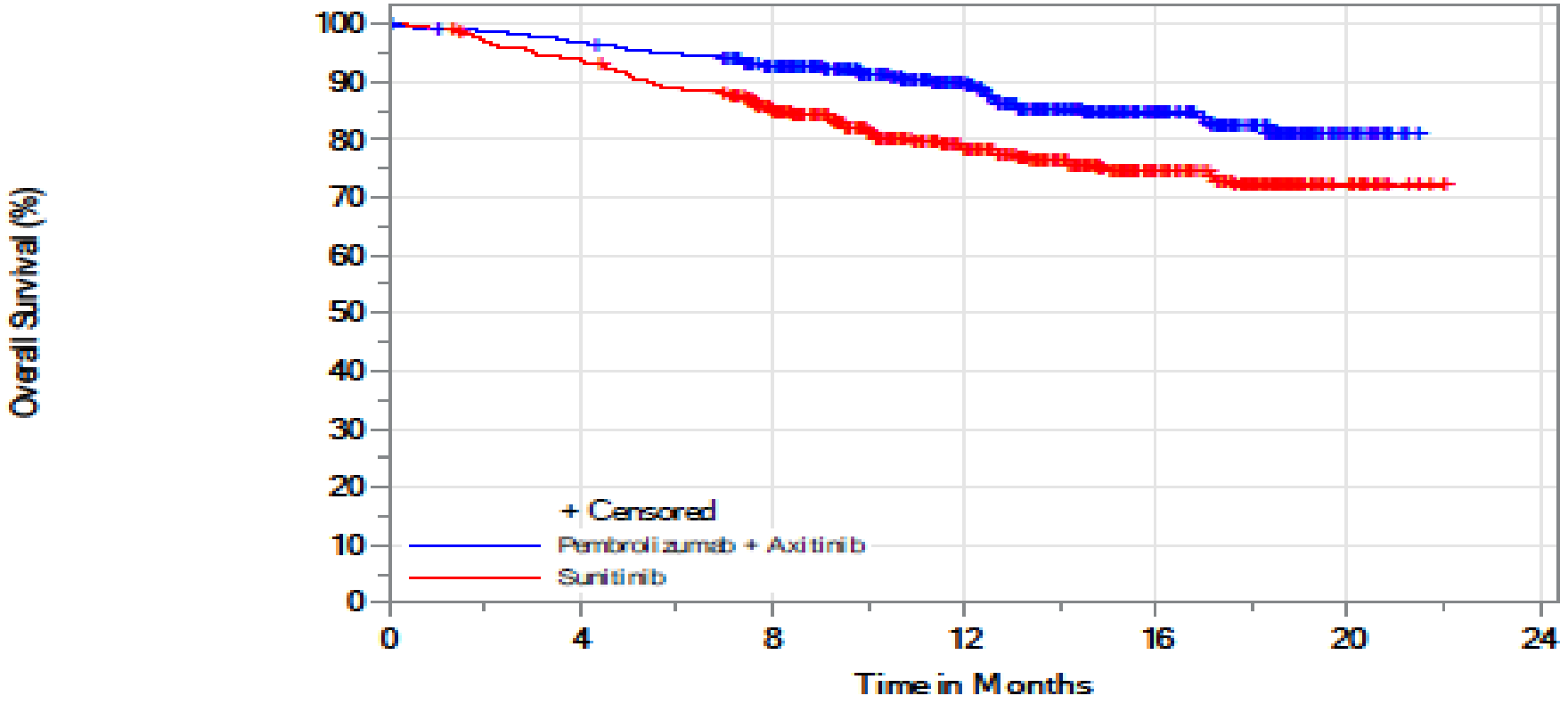
Background (2)

Comparators	Sunitinib monotherapy (50 mg orally once daily for 4 weeks and then off treatment for 2 weeks) Tivozanib and pazopanib were assumed to have equal efficacy and safety to sunitinib*
Subgroups	Intermediate/poor IMDC risk group – informed by NMA in the model
Key clinical trial	KEYNOTE 426: a phase III randomised, open-label study
Key results **(August 2018 data cut)**	OS HR: 0.53 (95% CI: 0.38, 0.74; p=0.00005). PFS HR: 0.69 (95% CI: 0.57, 0.84; p=0.00014). ORR: Difference of 23.6% (95% CI: 17.2, 29.9; p<0.0001). EQ-5D-VAS change from baseline to Week 30: The company report no clinically meaningful difference
Key result	Median OS was not reached in either group
Model	Partitioned survival model - based on three health states: Progression free, progressed disease and death
Company base-case ICER	Versus sunitinib: **£59,292** (scenarios: £50,436 to £86,712) Versus pazopanib: £57,540; Versus tivozanib: £56,648
Technical team preferred ICER	Versus sunitinib: **£150,257** Versus pazopanib: £144,425; Versus tivozanib: £146,638

*Equal efficacy assumption in line with TA215, TA512, TA542, TA581

[redacted]

Key clinical trial results – KEYNOTE 426



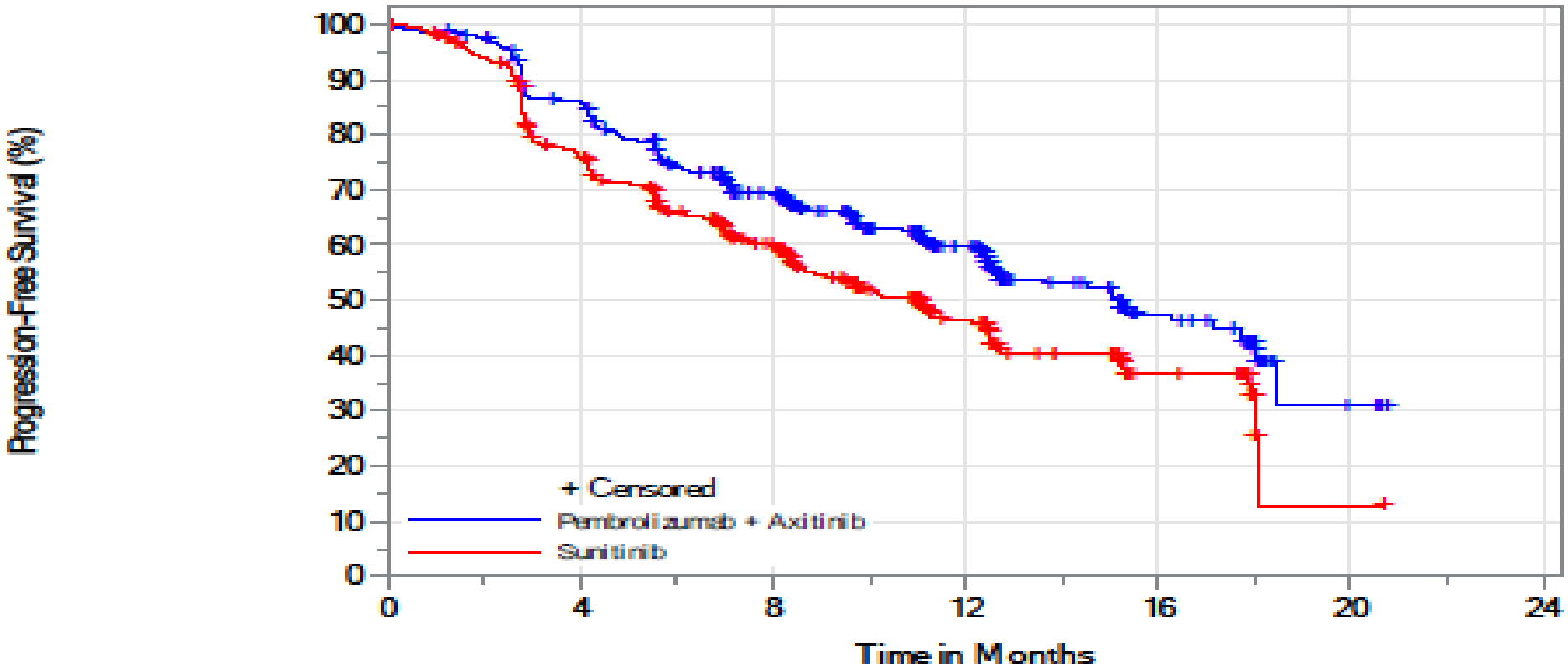
Number of subjects at risk

Pembrolizumab + Axitinib	432	417	378	256	136	18	0
Sunitinib	429	401	341	211	110	20	0

Company Submission Figure 5: KM Estimates of OS (ITT); IA1 August 2018 data-cut

[redacted]

Key clinical trial results – KEYNOTE 426



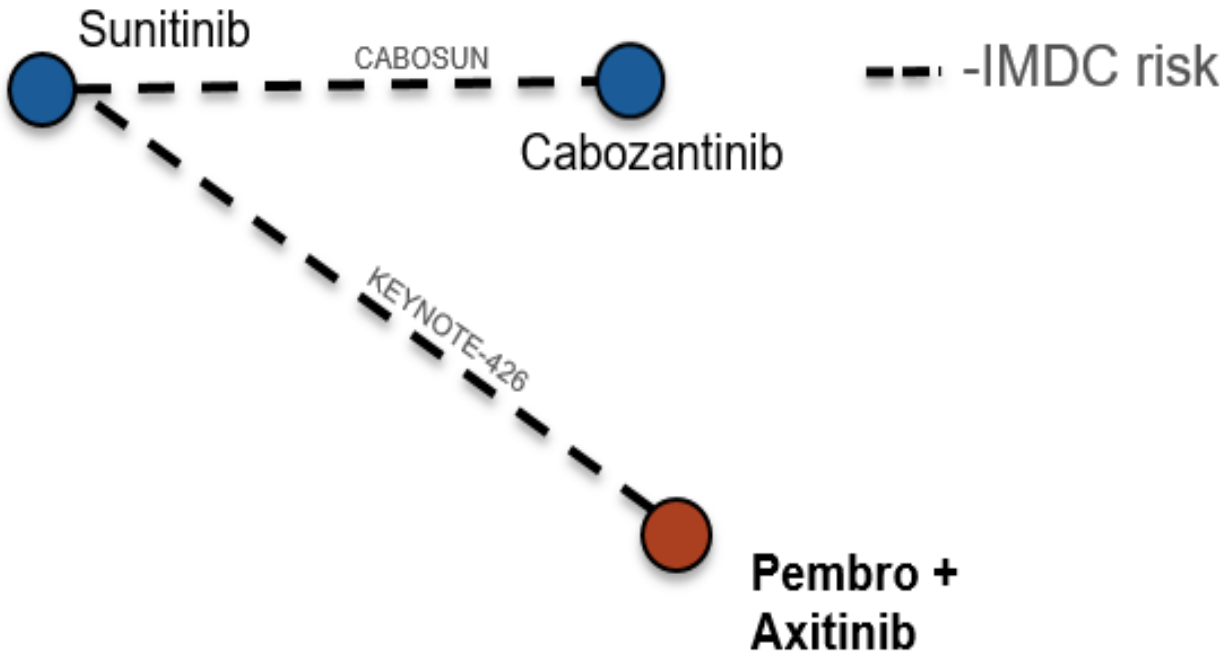
Number of subjects at risk

Pembrolizumab + Axitinib	432	357	251	140	42	3	0
Sunitinib	429	302	193	89	29	1	0

Company Submission Figure 6. KM Estimates of PFS (Primary Censoring Rule) Based on BICR Assessment per RECIST 1.1 (ITT): IA1 August 2018 data-cut

[redacted]

NMA for intermediate-poor IMDC risk group



Company Submission: Figure 13 and 14: Network of evidence for 1L RCC used for OS and PFS for the intermediate/poor risk subgroup;

CABOSUN: randomized phase II trial of cabozantinib (n = 79) versus sunitinib (n = 78)

[redacted]

NMA for intermediate/poor IMDC risk group

Company submission: Table 27. HRs estimated from fixed-effects constant hazard NMA of PFS; intermediate/poor risk subgroup

Sunitinib	XXXX (XXXX, XXXX)	XXXX (XXXX, XXXX)
XXXX (XXXX, XXXX)	Cabozantinib	XXXX (XXXX, XXXX)
XXXX (XXXX, XXXX)	XXXX (XXXX, XXXX)	Pembrolizumab + axitinib

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically meaningful at the 0.05 significance level. DIC: 3.38; Deviance: 1.38

Company submission: Table 29. HRs estimated from fixed-effects constant hazard NMA of OS; intermediate/poor risk subgroup

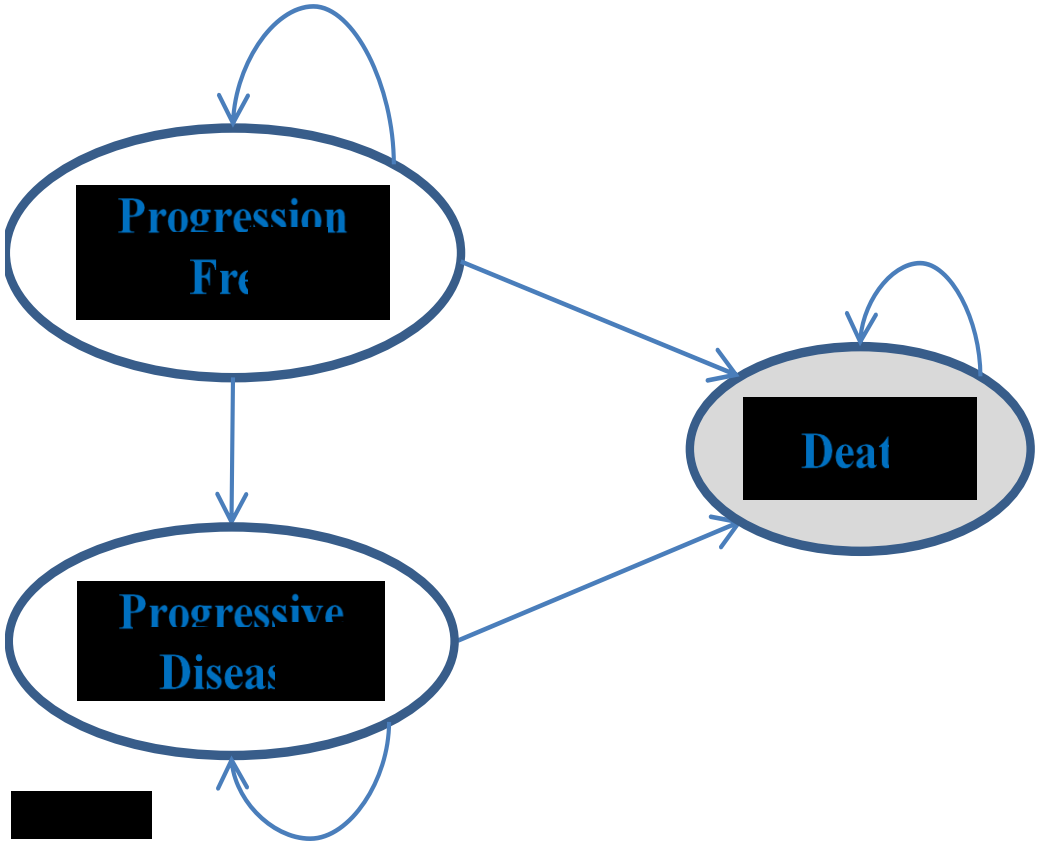
Sunitinib	XXXX (XXXX, XXXX)	XXXX (XXXX, XXXX)
XXXX (XXXX, XXXX)	**Cabozantinib**	XXXX (XXXX, XXXX)
XXXX (XXXX, XXXX)	XXXX (XXXX, XXXX)	**Pembrolizumab + axitinib**

Note: Each cell represents the comparison (hazard ratio and 95% CrI) of the row treatment versus the column treatment. All bolded values are statistically meaningful at the 0.05 significance level. DIC: 3.37; Deviance: 1.37

[redacted]

Background (3)

- Partitioned survival model with 3 health states and weekly cycle length.
- In company base case health related quality of life (HRQoL) is applied via time to death approach rather than via health state.
- ERG has commented that the model structure is reasonable



	Pooled (N=532), number of observations: 2,704		
	Estimate	SE	95% confidence interval
≥360 days	XXXX	XXXX	(XXXX, XXXX)
180 to 360 days	XXXX	XXXX	(XXXX, XXXX)
90 to 180 days	XXXX	XXXX	(XXXX, XXXX)
30 to 90 days	XXXX	XXXX	(XXXX, XXXX)
0 to 30 days	XXXX	XXXX	(XXXX, XXXX)
AE disutility		XXXX	

Patient and carer perspectives (1)

Comments: Kidney Cancer UK, Kidney Cancer Support Network, 1 patient

Unmet need

- Kidney cancer is not a homogenous disease.
- Effective first line treatment which would give a durable response with a good quality of life whilst on treatment, with manageable side effects.
- Systemic treatment for brain metastases is a concern.
- Psychological and emotional support (for patient and families); management of side effects of treatment.

Current treatment options

- Treatment options are expanding – which give patients more hope plus the potential to enable patients and clinicians to tailor care plans to suit individual patient needs.

Key outcomes for patients

- To achieve no evidence of disease (a cure).
- Tumour shrinkage or disease stability.
- Quality of life is also an important consideration for many patients.

"…….has enabled me to enjoy every day, do 3 or 4 days voluntary work a week and to care for my elderly parents. The side effects for me have been milder than many people but the fear of diarrhoea striking all through the day makes travelling and working very difficult. I would like a treatment without digestive effects, little fatigue and control of growths……".

Patient and carer perspectives (2)

Key concerns

- Persistent adverse events (diarrhoea, hypertension, skin changes, mucosal inflammation and many more) substantially impact quality of life; many require additional medicines.
- Transport to hospital may have financial and time burden on patients and carers, which may impact people with multiple morbidity and disability more.
- High cost of treatment for the NHS.

Key benefits

- Reassurance that as much as possibly can be done to stop spread of cancer and possibility of complete response.
- Short infusion time; contact with others and support whilst in hospital.
- May provide enhanced benefit through complementary mechanisms of action.
- Greater median progression free survival and overall survival, relative toxicity improves quality of life in comparison to other first line treatments.
- Patient testimonies are indicating with this drug combination they are having a greater initial reduction in their tumour and subsequent scans.
- They believe that due to being given the opportunity of having this treatment it has extended their life expectancy beyond that which was expected
- *"…a few of the patients we talked to, who were on this treatment, at presentation to the oncology team were intermediate risk. Therefore, predicted life expectancy is 22.5 months, yet 36 months later they are still doing well and have a good outlook"*

Clinician perspectives

Submissions: two clinical experts

- **High unmet need** for both patients and healthcare professionals in the setting of metastatic RCC and a **significant unmet need in the treatment of non-clear cell RCC**
- General expectation of a **durable effect** ('tail of the curve' effect) **and longer survival trajectory** associated with pembrolizumab with axitinib, compared to single agent or sunitinib, based on expected mode of action
- ~15% of patients will achieve long term durable remission / cure with use of pembrolizumab plus axitinib
- Recognise that data is **still immature**
- Adding pembrolizumab plus axitinib as a choice in the first-line enables patients and clinicians to **individualise treatment plans** to better control this disease and maintain a high quality of life
- The pembrolizumab plus axitinib combination is **well tolerated/**has a **manageable adverse event profile**

2L therapy	Pembro' + Axitinib	Sunitinib
Best supportive care	20% to 30%	20% to 40%
Lenvatinib / everolimus	5% to 30%	0% to 10%
Cabozantinib	40% to 60%	10% to 20%
Nivolumab	0%	30% to 40%
Sunitinib	0% to 15%	0%
Axitinib	0%	0% to 10%

[redacted]

CDF clinical lead perspective (1)

General comments

- Likely enthusiasm for this type of 1st line combination therapy which incorporates both a VEGF inhibitor and a checkpoint inhibitor
- Removes concern that patients might miss out on one important type of 2nd line therapy if they receive the other important type as 1st line treatment (2nd line treatment rate is currently approximately 50-60%)

IMDC poor risk subgroup

- Data on benefit could be considered more compelling for the use of the combination of nivolumab and ipilimumab (available via the CDF and thus not a comparator) in the poor risk group.
- IMDC poor prognosis group are underrepresented in the Keynote 426 trial (13% of patients rather than the expected 25%, probably due to use of the nivolumab/ipilimumab combination).

[redacted]

CDF clinical lead perspective (2)

2 year stopping rule

- Mismatch between maturation of data from a clinical trial with a re-treatment option and collecting data on company's base case with a 2 year treatment duration cap for pembrolizumab.
- Keynote 426 trial allowed:
  - A maximum initial treatment duration for the pembrolizumab part of the duo of a duration of 35 cycles (in effect after 2 years)
  - Patients in complete remission could stop the pembrolizumab after less than 2 years of treatment. In such patients who stopped at 35 cycles and in those patients who discontinued pembrolizumab due to complete remission, the Keynote 426 trial allowed these patients at subsequent relapse to re-start the pembolizumab for a further 17 cycles.
- In similar previous NICE appraisals of checkpoint inhibitors in which treatment durations were capped at 2 years. NICE committees:
  - did not assume lifetime treatment benefit for therapy which has stopped at 2 years.
  - examined analyses of treatment benefit waning effects that have benefit waned within 1 year and 3 years of stopping treatment (the '2+1' and '2+3' analyses in terms of time since starting treatment).

- In the absence of any robust outcome data as to the impact of a 2 year stopping rule of at least checkpoint inhibitor therapy in RCC, an open treatment duration is currently preferred.
  - If the only option was capped treatment duration for pembrolizumab and no re-starts, then clinicians would still wish to use the combination of a VEGF inhibitor and a checkpoint inhibitor as 1st line treatment (noting caveat regarding poor risk group in previous slide).

[redacted]

CDF clinical lead perspective (3)

If NICE recommendation caps treatment with pembrolizumab with axitinib on the basis of cost effectiveness at 2 years and no re-treatment at relapse, then NHS England will:

- commission a maximum treatment duration at 2 years and no allowed re-treatment
- commission its 1st line use in patients with locally advanced or metastatic papillary RCC (noting Keynote 426 trial was only performed in patients with RCC with a clear cell component).
- no commissioning of 2nd line therapy with nivolumab in patients previously treated with pembrolizumab plus axitinib.

Further data collection considerations:

- Due to short follow up of KEYNOTE 426, NHS England would to have some information on or incorporated (by assumptions) into the economic modelling for the following :
  - The number of patients completing 2 years of therapy or discontinuing on account of attaining a complete remission;
  - The proportion of these 2 groups that relapse and when they do;
  - The response to re-treatment.
- The two pembrolizumab plus axitinib and avelumab plus axitinib combinations when compared with the same sunitinib comparator look very similar. Any clinically significant difference between pembrolizumab (anti-PD-1 mode of action) vs avelumab (anti-PD-L1 mode of action) in RCC is highly speculative without at least longer term follow up data of these 2 trials

[redacted]

CDF clinical lead perspective (4)

If NICE recommends treatment of all RCC risk categories (favourable, intermediate and poor), this will have a substantial effect on the treatment pathway:

First line:

- It is pazopanib that has the largest market share as a 1st line tyrosine kinase inhibitor that can be potentially used in all IMDC prognostic groups
- Whilst displacement of current 1st line tyrosine kinase inhibitor (TKI) options to 2nd line would be possible, it is more likely that 2nd line treatment options would be considered from a combination of displaced current 1st line options and current 2nd line options

Second line:

- 2nd line nivolumab and 2nd line axitinib would not be commissioned as patients have been previously treated with a checkpoint inhibitor and axitinib.
- Most 2nd line treatment would be with a 'dirty' TKI (one which has many potential modes of action) such as cabozantinib. Other treatment options inline with current NICE-recommended 2nd line options (lenvatinib plus everolimus, everolimus monotherapy) and use of displaced current 1st line sunitinib (on label) or pazopanib (off label).
- NHS England does not consider tivozanib (off label) as such an appropriate displaced current 1st line option after failure of pembrolizumab plus axitinib as tivozanib's mode of action is 'cleaner'.

Key issues	Status
1 – Survival extrapolation	
Is there sufficient justification to utilise different distributions for the two arms?	For discussion
What is the most appropriate survival model?	For discussion
2 – Treatment effect duration – *What is the most plausible duration of treatment effect?*	For discussion
3 – Time horizon of 40 years is appropriate	Resolved
4 – Subsequent treatments: the ERG base case assumptions are reasonable	Resolved
5 – Health related quality of life	
Should a time to death approach be used?	For discussion
Should there be an age decrement in the model?	For discussion
6 – Method of NMA: The subgroup analysis for the intermediate/poor IMDC risk group should be informed by the constant hazard approach.	Resolved
7 – End of Life: *Does pembrolizumab with axitinib meet NICE's end of life criteria for the poor risk group?*	For discussion
8 – Cancer Drug's Fund: *Does pembrolizumab combination therapy meet the criteria for inclusion in the Cancer Drugs Fund?*	For discussion
9 – Stopping rules: *NEW ISSUE* *Are treatment stopping rules appropriate in the treatment of RCC? Would the 2-year stopping rule for pembrolizumab be implemented in clinical practice for RCC?*	For discussion

[redacted]

Issues resolved after technical engagement

	Summary	Stakeholder responses	Technical team consideration
3	The time horizon should be used to capture all relevant benefits and costs that arise as a result of treatment for untreated metastatic renal cell carcinoma (RCC).	Technical experts and company agree that a 40 year horizon should be utilized.	A 40-year horizon should be used in the technical team base case, however, a 20 year horizon could be a plausible scenario
4	Second-line treatments (including best supportive care) should be represented appropriately in the model.	The company agrees that approach used in the ERG base case (which includes cabozantinib as a second line treatment) is reasonable.	The scenario regarding second line treatments proposed in the ERG base case holds as a preferred assumption.
6	The method of undertaking the subgroup NMA was questioned given potential for unstable results.	Technical experts agreed that a constant hazard ratio NMA was reasonable and that the fractional polynomial model produced unstable results.	The subgroup analysis for the intermediate/poor IMDC risk group should be informed by the constant hazard approach.

Outstanding issues after technical engagement

- Issue 1: Extrapolating overall survival
- Issue 2: Treatment effect duration
- Issue 5: Health-related quality of life measurement
- Issue 7: End of life criteria
- Issue 8: Cancer Drugs Fund
- Issue 9 *new issue*: treatment stopping rules in RCC

[redacted]

Issue 1: Extrapolating overall survival

Background:

- **The NICE DSU** technical support document 14 advises that both arms should have the same extrapolation distribution applied unless substantial justification is given.
- **The company** used a log-logistic distribution for pembrolizumab with axitinib, and an exponential distribution for sunitinib to model OS.
- **The ERG and technical team** proposed that the Weibull distribution should be used for both the intervention and comparator extrapolation of OS.
- **Clinical experts** commented that a "tail of the curve" effect is likely to be observed for survival curves for combination immunotherapy and implied that long time survival trajectories (i.e. beyond 3 years) are not expected to be similar for people treated with combination immunotherapy compared to those having a single treatment (e.g. sunitinib only).

- There is uncertainty regarding the best distribution due to the immaturity of the data.
- The expected duration of treatment effect (issue 2) is closely linked to this issue.

[redacted]

KEY QUESTION: What is the most appropriate survival model?

Issue 1: Extrapolating overall survival

OS predictions of pembrolizumab with axitinib

	Potentially credible			Clinical experts		
Yr	Exponential	Weibull	Log-logistic	Company	ERG	Technical team
1	88.3%	88.6%	88.5%			
2	78.0%	76.2%	76.8%			
5	53.5%	44.9%	51.9%	50%	50% is optimistic	30%
10	28.7%	16.5%	31.6%			25%
20	8.2%	1.7%	16.5%			25%

Adapted from CS Appendix P Table 3

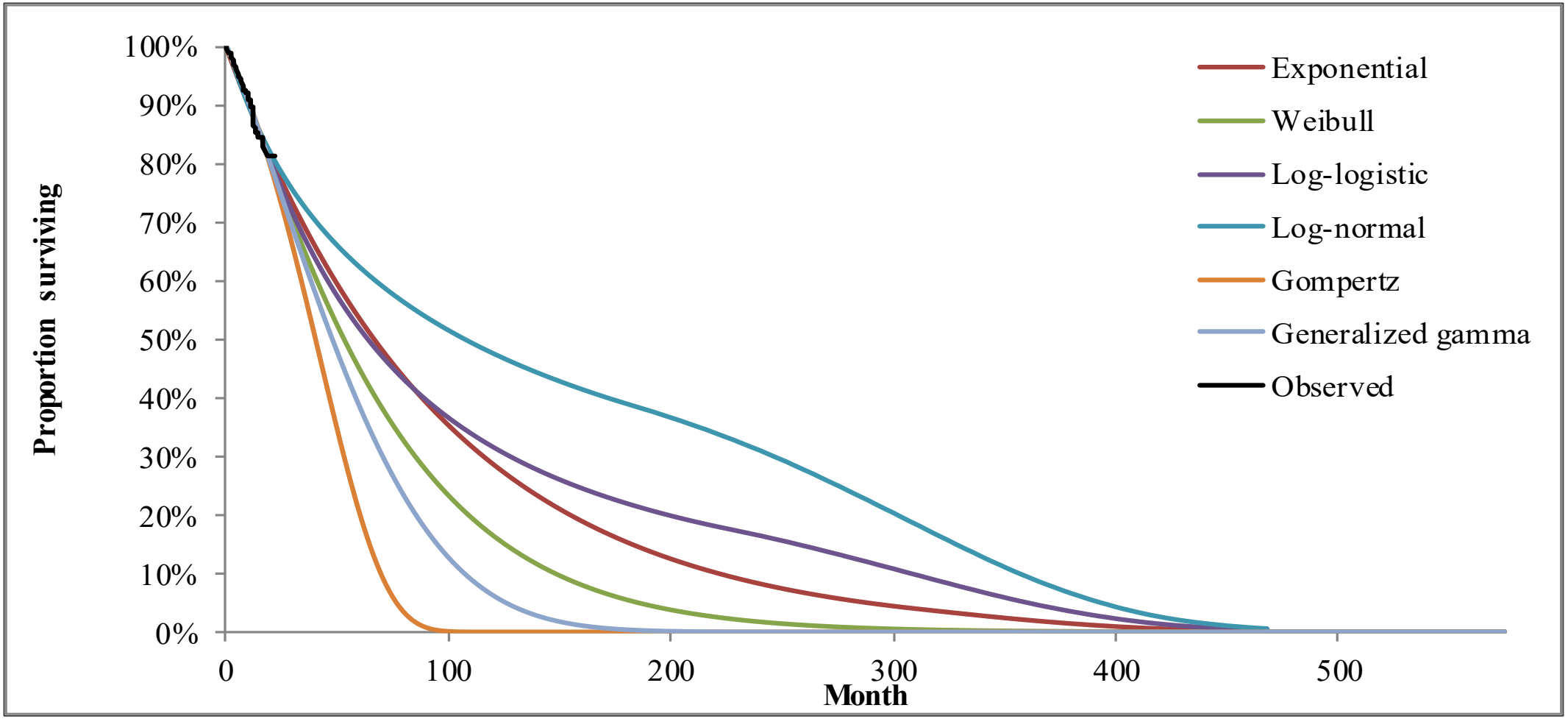
OS predictions of sunitinib

	Potentially credible			Clinical experts		
Yr	Exponential	Weibull	Log-logistic	Company	ERG	Technical team
1	79.9%	80.1%	79.7%			
2	63.9%	62.6%	63.6%			
5	32.5%	28.2%	37.3%	20-25%		
10	10.6%	6.9%	20.9%	10-15%		
20	1.1%	0.3%	10.5%			

Adapted from CS Appendix P Table 4

[redacted]

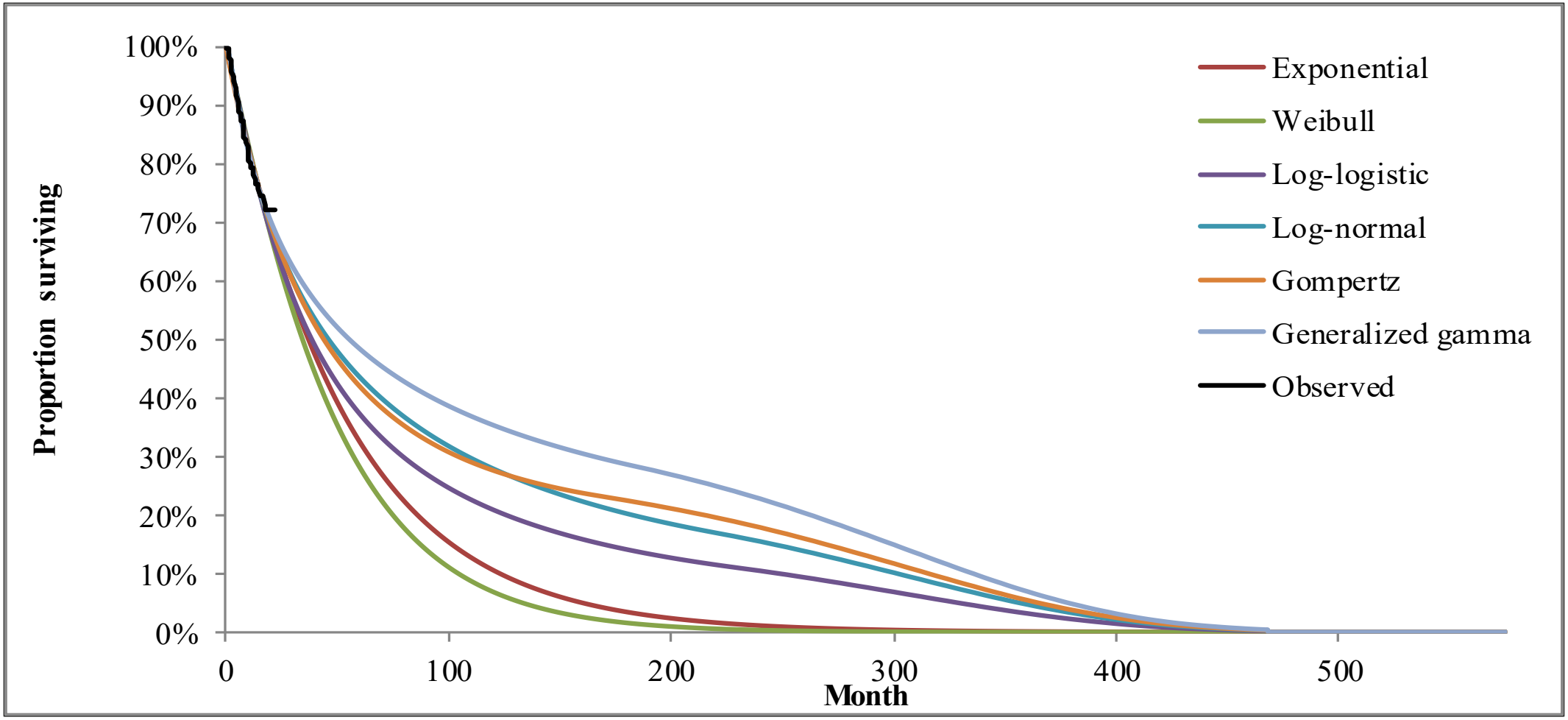
Issue 1: Extrapolating overall survival



Company submission: Figure 21. OS KM curve vs fitted one-piece model for **pembrolizumab + axitinib** based on KEYNOTE-426

[redacted]

Issue 1: Extrapolating overall survival



Company submission: Figure 22. OS KM curve vs fitted one-piece model for **sunitinib** based on KEYNOTE-426

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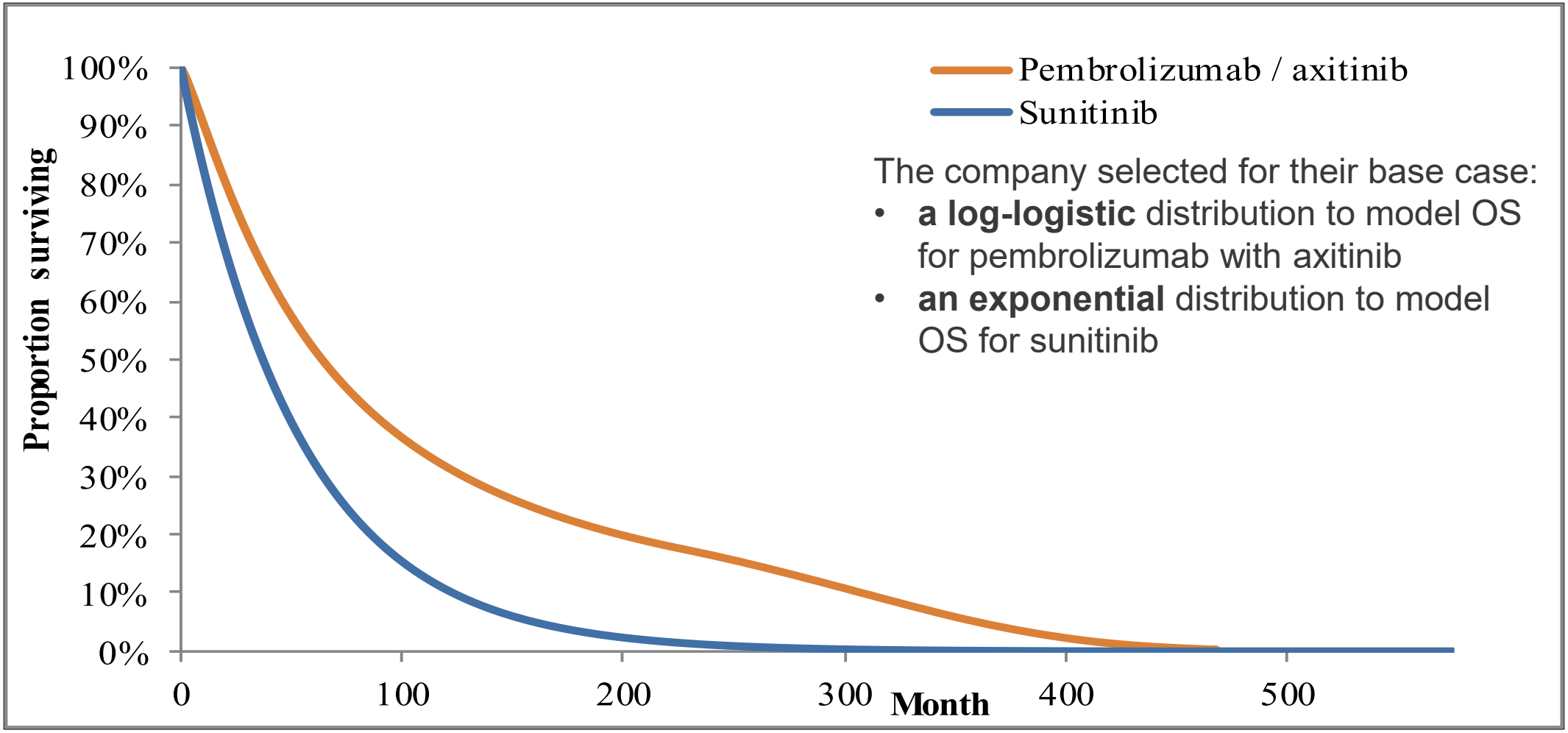
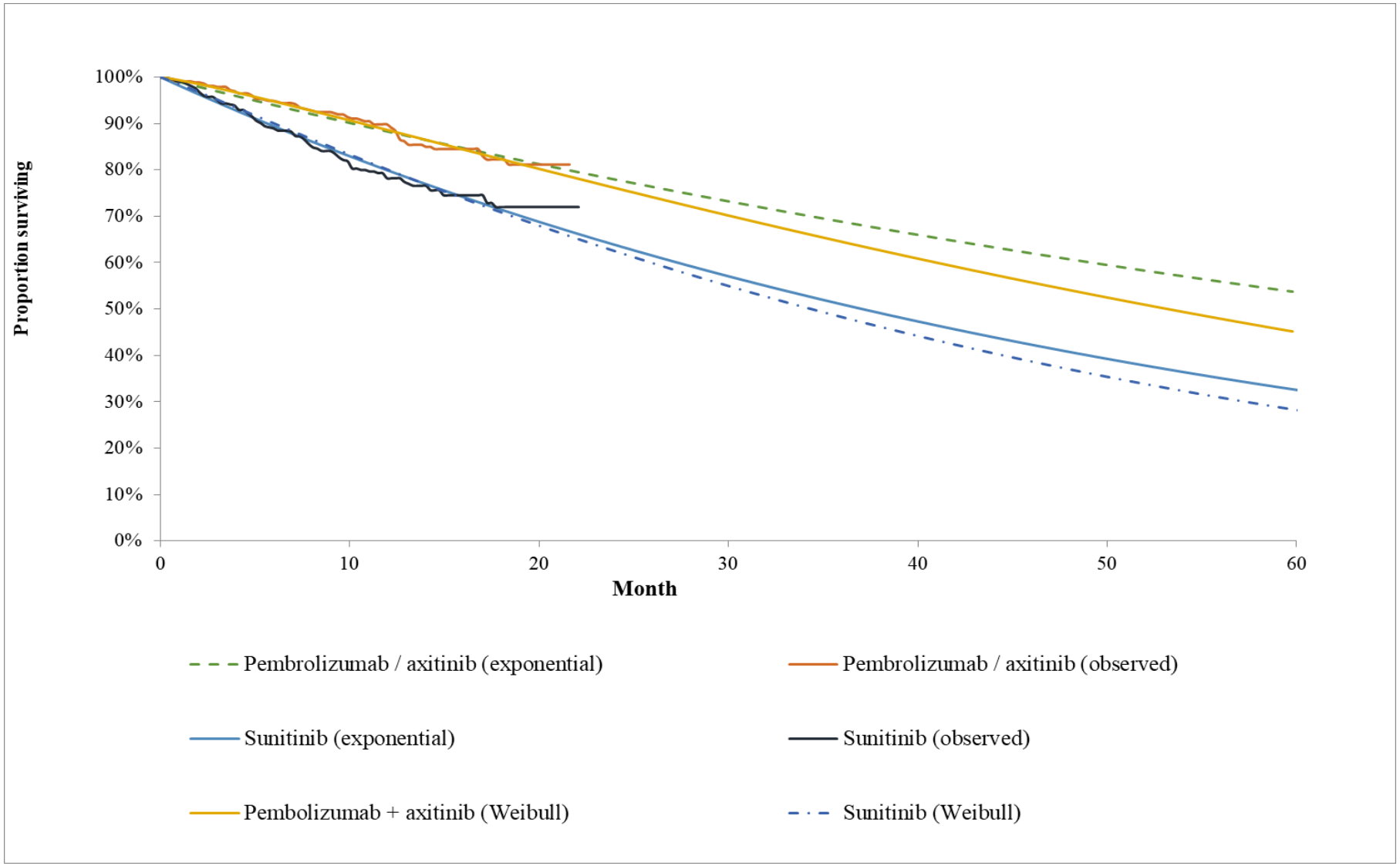
Issue 1: Extrapolating overall survival



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

[redacted]

Issue 1: Extrapolating overall survival



OS from KEYNOTE–426 compared to fitted curves for the exponential and Weibull distributions. Figure 4, ERG report post FAC page 86

[redacted]

Issue 1: Extrapolating overall survival

Company response to engagement:	ERG critique of company response
Distributions selected for company base case have good visual and statistical fit of observed data: • Fit expert opinion of OS at 10 years. • In KEYNOTE 426 89.9% of patients are still alive at 1 year • A 5-year 50% OS is plausible; agree with clinical experts' estimation of a survival plateau • TA581 (nivolumab with ipilimumab) considered a 5-year overall survival of 43.6% as clinically plausible in intermediate/poor-risk patients	5-year OS clinical estimates for pembrolizumab with axitinib clinical experts vary between 30-50%. TA581 appraised a combination of two immunotherapies where: • treatment could continue for up to 5 years; • not a combined immune checkpoint inhibitor and TKI tyrosine-kinase inhibitor (TKI) therapy where pembrolizumab is stopped after 2 years.
Long term survival of sunitinib may be underestimated: • the COMPARZ trial has poor applicability of second line treatments to current UK practice: • CHECKMATE-025: 30.0% of patients treated with nivolumab 2L are alive at 4 years. • CHECKMATE-214: sunitinib median OS at 37.9 months in the ITT population.	OS estimates may be underestimated: • unclear how much higher the 5-year survival would be with increased use of nivolumab as a subsequent-line treatment.

Issue 1: Extrapolating overall survival

Company response to engagement:	ERG critique of company response
Different distributions to extrapolate OS for separate arms is **"substantially justifiable":** • Editorials/reviews support the clinical rationale for the different mechanisms of action.	• No available robust evidence currently showing a difference in the underlying hazards for OS to support the use of different survival distributions • KEYNOTE-426 trial overall survival data are immature.
Weibull curve not appropriate: • poor AIC/BIC fit and poor visual fit. • underestimates OS of the comparator • CHECKMATE-214 estimated sunitinib OS at 37.9 months in the ITT population versus an estimated median 34.2 months	**The Weibull distribution provides:** • Closest fit to the COMPARZ trial data for sunitinib (allowing that few patients received nivolumab as a subsequent-line treatment) • 5-year OS (45%) for patients treated with pembrolizumab with axitinib is within 30%-50% range estimated by clinical experts. • Weibull and exponential have good visual fit to the KEYNOTE-426 trial data on inspection • Statistical fit is less important than validation against long-term data

[redacted]

Issue 1: Extrapolating overall survival

Company response to engagement:	ERG critique of company response
The company claim the survival estimates predicted from **scenario analyses 1 and 3 are similar to, and validate, the company base case** (in contrast to survival estimates produced using the Weibull distribution). Requested further consideration to scenario analysis 1 if the use of separate distributions to each arm is not accepted.	Noted the comparison of estimates of the Weibull against estimates of 2 scenario analysis, no further comment on whether the comparison with the selected scenarios validated the base case assumptions.

Final technical report judgement:

- Recognise that uncertainty regarding the best distribution will remain due to the immaturity of the data.
- **The preferred assumption is to use Weibull distribution for the extrapolation of OS for both pembrolizumab with axitinib, and sunitinib.**

[redacted]

Issue 1: Company scenario analyses

Table 1 from company response: Overall survival estimates using alternative approaches.

Years	Base Case		Scenario 1: Landmark		Scenario 3: L-L, NMA		Weibull curve	
	P+A	S	P+A	S	P+A	S	P+A	S
1	88.50%	79.90%	88.00%	79.80%	88.50%	79.60%	88.60%	80.10%
2	76.80%	63.90%	78.00%	64.70%	76.80%	60.90%	76.20%	62.60%
5	51.90%	32.50%	57.90%	37.30%	51.90%	29.10%	44.90%	28.20%
10	31.60%	10.60%	37.20%	16.20%	31.60%	11.50%	16.50%	6.90%
20	16.50%	1.10%	15.60%	3.10%	16.50%	3.40%	1.70%	0.30%

Issue 1: Company scenario 1

Figure 1. Verification of modeled vs. observed OS within the trial period under the landmark analysis scenario

Figure 2. Long-term extrapolation of OS under the landmark analysis scenario

- The modelled OS curves under the landmark approach achieved a close visual fit to observed data within the trial timeframe (Figure 1).
- Long-term extrapolations of OS from this scenario analysis are presented in Figure 2.
- At 5 years, predicted OS was 37.3% and 16.2% in the pembrolizumab/axitinib and sunitinib arms, respectively.
- The landmark response models of OS implied an increasing HR of death for sunitinib relative to pembrolizumab/axitinib over most of the modelled time horizon.
- Consistent with the expected immunotherapeutic survival benefit of pembrolizumab/axitinib.

Issue 1: Company scenario 1

Figure 1. Verification of modeled vs. observed OS within the trial period under the landmark analysis scenario

Figure 2. Long-term extrapolation of OS under the landmark analysis scenario

Long term OS predictions of pembrolizumab with axitinib (Table 3 of appendix P, company submission)

Yr	Exponential	Weibull	Log-logistic	Log-normal	Gompertz	Generalized Gamma
1	88.3%	88.6%	88.5%	88.3%	88.9%	88.7%
2	78.0%	76.2%	76.8%	79.2%	74.4%	75.6%
5	53.5%	44.9%	51.9%	62.4%	20.3%	38.5%
10	28.7%	16.5%	31.6%	47.6%	0.0%	6.2%
20	8.2%	1.7%	16.5%	31.0%	0.0%	0.0%

Long term OS predictions of sunitinib (Table 4 of appendix P, company submission)

Yr	Exponential	Weibull	Log-logistic	Log-normal	Gompertz	Generalized Gamma
1	79.9%	80.1%	79.7%	79.5%	79.7%	79.3%
2	63.9%	62.6%	63.6%	65.5%	65.5%	66.8%
5	32.5%	28.2%	37.3%	43.6%	42.0%	48.4%
10	10.6%	6.9%	20.9%	27.9%	27.6%	35.4%
20	1.1%	0.3%	10.5%	15.5%	17.9%	22.8%

Issue 2: Treatment effect duration

Background:

- **The company** base case has not included the assumption of treatment effect waning (reducing). It believes a proportion of patients would derive a long-term survival benefit from the combination of an immunotherapy with a TKI.
- **The ERG** does not include treatment waning in base case due to immaturity of data. It notes impact of second-line treatment after disease progression and survival. Some patients would receive nivolumab as second-line therapy and OS for patients receiving second-line treatment may be similar between treatment arms.
- **Clinical experts** "tail of the curve" effect is likely and could suggest a long duration of treatment effect, ranging from beyond the duration of therapy to potentially life long. in patients achieving long-term control.
- **Technical team** note that duration of treatment effect has been a key issue in several previous appraisals, and a lifetime duration of effect has not been accepted in similar appraisals.

- Previous NSCLC and RCC appraisals assumed 3 to 5 year treatment effect duration.
- There is uncertainty due to the immaturity of the data.
- The expected overall survival (issue 1) is closely linked to this issue.

[redacted]

KEY QUESTION: What is the most plausible duration of treatment effect?

Issue 2: Treatment effect duration

Company response:

- A lifetime treatment effect should be considered as plausible, supported by:
  - Clinical opinion that there will be no loss of treatment effect post discontinuation with pembrolizumab after 2 years, and a lifetime treatment effect is plausible
  - publications regarding the biochemical mode of action of the intervention
- Requested consistency of approach with the appraisals of nivolumab with ipilimumab for untreated advanced RCC (TA581) and nivolumab for previously treated advanced RCC (TA417) where no treatment waning effect imposed on the intervention
- Request for cost-effectiveness analyses exploring a treatment effect lasting until 2 years (when pembrolizumab treatment stops) and 3 years (treatment effect ends 1 year after stopping pembrolizumab treatment) was inappropriate, citing that survival estimates indicated such analyses would be clinically implausible (please see below table):

Years	Base Case		2-year treatment waning, base-case curve selection		3-year treatment waning, base-case curve selection		2-year treatment waning, ERG base-case curve selection		3-year treatment waning, ERG base-case curve selection	
	P+A	S	P+A	S	P+A	S	P+A	S	P+A	S
1	88.5%	79.9%	88.5%	79.9%	88.5%	79.9%	88.6%	80.1%	88.6%	80.1%
2	76.8%	63.9%	76.7%	63.9%	76.8%	63.9%	76.0%	62.6%	76.2%	62.6%
5	51.9%	32.5%	39.0%	32.5%	42.6%	32.5%	34.2%	28.2%	37.6%	28.2%
10	31.6%	10.6%	12.7%	10.6%	13.8%	10.6%	8.3%	6.9%	9.2%	6.9%
20	16.5%	1.1%	1.3%	1.1%	1.5%	1.1%	0.4%	0.3%	0.5%	0.3%

[redacted]

Issue 2: Treatment effect duration

ERG comments:

- The immaturity of data means that the long-term treatment effect of the drug is unclear.
- Focus should be on keeping consistency with appraisals for IO therapies in renal cell carcinoma and there is not a rationale for maintaining consistency with approaches adopted in appraisals concerning different indications.
- No treatment effect waning in the ERG base case is in line with NICE TA581 where no reduction in treatment effect was included.
- When the company survival estimates was ran through the economic model, the ICERs varied between £184,983 per QALY and £269,968 per QALY.

Final technical report judgement:

- Absence of mature data to substantiate a lifetime treatment effect.
- TA581: did not have a 2-year stopping rule and evaluated combined immunologics which could have an alternative mechanism of action.
- TA417: previously treated population and median stopping time was under one year (estimated by parametric modelling); treatment effect duration was not a key issue.
- **The preferred assumption is to use a treatment waning effect of 5 years and present the ERG and company analyses as alternative scenarios.**

[redacted]

Issue 5: Health related quality of life (1)

Background – <u>time to death versus health state approach</u> in estimating health related quality of life (HRQoL):

- **The company** base case uses a time to death approach
- **The ERG:** a health state or a time to death (ERG base case) approach is appropriate. Disease progression may not fully capture all predictive factors of patient utility and time to death provides a reasonable fit to patient data.
- **Clinical experts** commented that both control of disease and time until death were important factors in determining HRQoL. One expert concluded that HRQoL is most associated with the patient's disease status. When disease progression begins to occur, patients move closer to death and may experience stepwise deterioration as the time period shortens (unless subsequent therapy is again able to achieve good disease control).
- **The technical team** team recognized that time to death may be an appropriate approach, however, preferred to use pooled health state utilities due to a concern the approach may not have clinical plausibility when applied in a model with a time horizon longer than the trial.

[redacted]

KEY QUESTION: What is the most appropriate method of estimating HRQoL?

Issue 5: Health related quality of life (1)

Company Submission: Table 48. EQ-5D health utility scores by progression status (pooled)

	Pooled (N=810), number of observations: 7,119		
	Estimate	SE	95% confidence interval
Progression-free (Intercept)	XXXX	XXXX	(XXXX, XXXX)
Progressive disease	XXXX	XXXX	(XXXX, XXXX)
AE disutility	XXXX		

Company Submission: Table 49.
EQ-5D health utility scores by progression status (differentiated by treatment)

	Pembrolizumab+axitinib (N=X), number of observations:			Sunitinib (N=X), number of observations:		
	Estimate	SE	95% CI	Estimate	SE	95% CI
Progression-free (Intercept)	XXXX	XXXX	(XXXX, XXXX)	XXXX	XXXX	(XXXX, XXXX)
Progressive disease	XXXX	XXXX	(XXXX, XXXX)	XXXX	XXXX	(XXXX, XXXX)
AE disutility	XXXX					

Company Submission: Table 50. EQ-5D health utility scores by time-to-death

	Pooled (N=532), number of observations: 2,704		
	Estimate	SE	95% confidence interval
≥360 days	XXXX	XXXX	(XXXX, XXXX)
180 to 360 days	XXXX	XXXX	(XXXX, XXXX)
90 to 180 days	XXXX	XXXX	(XXXX, XXXX)
30 to 90 days	XXXX	XXXX	(XXXX, XXXX)
0 to 30 days	XXXX	XXXX	(XXXX, XXXX)
AE disutility	XXXX		

[redacted]

Issue 5: Health related quality of life (1)

Company response regarding time to death approach:

- Only one EQ-5D questionnaire was administered per patient, 30 days after disease progression, limiting post-progression.
- Patients who were ≥360 days from death were in a stable state.
- Conducted a 'hybrid' approach combining time-to-death with health-state based utilities (technical team agree with company this approach adds complexity and uncertainty).
- Recommended time to death approach because it utilised more health states than the model based on progression status, and captured most of the variance in the data.

ERG comments regarding time to death approach:

- A time to death approach is reasonable (inclusion of the disease progression state may not fully capture all predictive factors of patient utility and time-to-death provides a good fit to patient data).
- Little change in HRQoL when patients were ≥360 days from death in KEYNOTE-426
- Noted the company did not give a rationale for the hybrid analysis.

Final technical report judgement regarding time to death approach:

- The technical team prefer to present pooled health state utilities to
  - Keep consistency with the three health state modelling approach.
  - Provide a valid alternative scenario for committee consideration
- Agree with the ERG that either method may be valid and recognise limitations with pooled health state approach. Therefore, a time to death scenario analysis should be considered.
- **The preferred assumption is to use pooled health state utilities as base case alongside consideration of the time to death approach in scenario analysis.**

Issue 5: Health related quality of life (2)

Background: Application of age decrements when estimating HRQoL:

- **The company** base case uses an age decrement (as per NICE DSU 12)
- **The ERG:** utility values derived from the trial data were not associated with age and therefore an age decrement should not be applied.
- **Clinical experts** indicated that performance and control of disease would be a better indicator of HRQoL than age. One expert commented that the effect of age over a median survival period of 2-3 years is negligible.
- **The technical team** noted that age may have greater impact on HRQoL if people with RCC are expected to have a longer life expectancy due to new treatment. Therefore, propose that an age-related utility decrement is used

Company response to technical engagement:

- Plausible to remove age-adjusted utility from the base-case assumption

ERG technical engagement comments:

- No correlation between age and baseline utility assessment in the KEYNOTE-426 trial, it was unnecessary to include age-related utility.

Final technical report judgement:

- The technical team agrees with the approach in the company submission base case, therefore, **the preferred assumption is to adjust HRQoL with age in the economic model.**

[redacted]

KEY QUESTION: What is the most appropriate method of estimating HRQoL?

Issue 7: End of Life (EoL)

Background:

- **General agreement** that the overall population does not meet EoL criteria
- **The technical team** believes that the treatment offers an extension to life of at least an additional 3 months, compared to current NHS treatments for the poor/intermediate risk group. However, there is no supportive evidence presented that the first criterion is met in this subgroup for whom cabozantinib is the recommended first-line treatment.
- **The committee for TA581** (nivolumab with ipilimumab for untreated advanced renal cell carcinoma) considered that the end of life criteria in the intermediate-poor risk group had not been met because the median overall survival in the sunitinib arm of CheckMate 214 was 25.9 months.
- **The ERG** had concerns that the company appears to have used sunitinib as the standard of care arm instead of cabozantinib. The ERG noted that no rationale was provided by the company as to why the poor risk subgroup was chosen, when in their assessment of clinical and cost-effectiveness, the subgroup considered is intermediate/poor risk. The ERG was unable to generate modelled estimates of OS for the poor risk subgroup patients to inform end of life assessment.
- **The ERG** disagreed with the company that pembrolizumab with axitinib meets the first end of life criterion (treatment is indicated in patients with a short life expectancy, normally less than 24 months) in the poor risk RCC subgroup.

[redacted]

KEY QUESTION: Does pembrolizumab with axitinib meet NICE's end of life criteria for the poor risk group?

Issue 7: IMDC risk calculation

Variable	Points
<1 year from time of diagnosis to systemic therapy	1
Karnofsky performance status <80%	1
Hemoglobin < lower limit of normal (usually ~120 g/L or 12 g/dL)	1
Corrected calcium > upper limit of normal (usually ~8.5-10.2 mg/dL)	1
Neutrophils > upper limit of normal (usually ~2.0-7.0×10^9/L)	1
Platelets > upper limit of normal (usually ~150,000-400,000 cells/μL)	1

IMDC Risk Score	Risk group	Median survival
0	Favorable	43.2 months
1-2	Intermediate	22.5 months
≥3	Poor	7.8 months

Source: https://www.mdcalc.com/imdc-international-metastatic-rcc-database-consortium-risk-model-metastatic-renal-cell-carcinoma#evidence

[redacted]

KEY QUESTION: Does pembrolizumab with axitinib meet NICE's end of life criteria for the poor risk group?

Issue 7: End of Life (EoL)

Background:

- **The company** presented the following evidence in support that **the poor risk group** met criterion one :
  - Median OS of 21.8 months with 1L sunitinib and 30.3 months with 1L cabozantinib (a randomised, open label phase II trial (Choueiri et al 2017)).
  - Median OS was reported for the all-comer population of 18.7 months (noting some patients had prior therapy). The subpopulations stratified by risk group of favourable, intermediate and poor reported median OS of 56.5 months, 20.0 months and 9.1 months, respectively (Gore et al 2015).

Company response:

- The company reiterated its argument made in the main submission.
- Final results from an extended follow-up of a global, expanded-access trial that, prior to regulatory approval, provided sunitinib to metastatic renal cell carcinoma patients, ineligible for registration-directed trials.
- As per the company submission, patients with IMDC poor risk subgroup RCC meet the end of life criteria

[redacted]

KEY QUESTION: Does pembrolizumab with axitinib meet NICE's end of life criteria for the poor risk group?

Issue 7: End of Life (EoL)

Commentator response:

- lack of direct comparative data between 'pembrolizumab with axitinib' and cabozantinib in the poor risk group.
- Gore et al (2015) has issues in specification of baseline characteristics and applicability of findings to the present day.
- CABOSUN trial was not powered for OS and included few poor-risk patients (15 cabozantinib, 15 sunitinib), which was noted by both the ERG and the Committee during the appraisal TA542.

ERG comments:

- Company did not provide further data or justification for meeting the first or second end of life criterion
- Disagreed with the company that pembrolizumab with axitinib meets the first end of life criterion in the poor RCC risk subgroup, because the overall survival of 30.3 months for intermediate / poor risk patients in the CABOSUN trial of cabozantinib exceeds the end of life criterion of less than 24 months life expectancy.
- Modelled estimates of OS for poor risk subgroup not possible using current economic model.

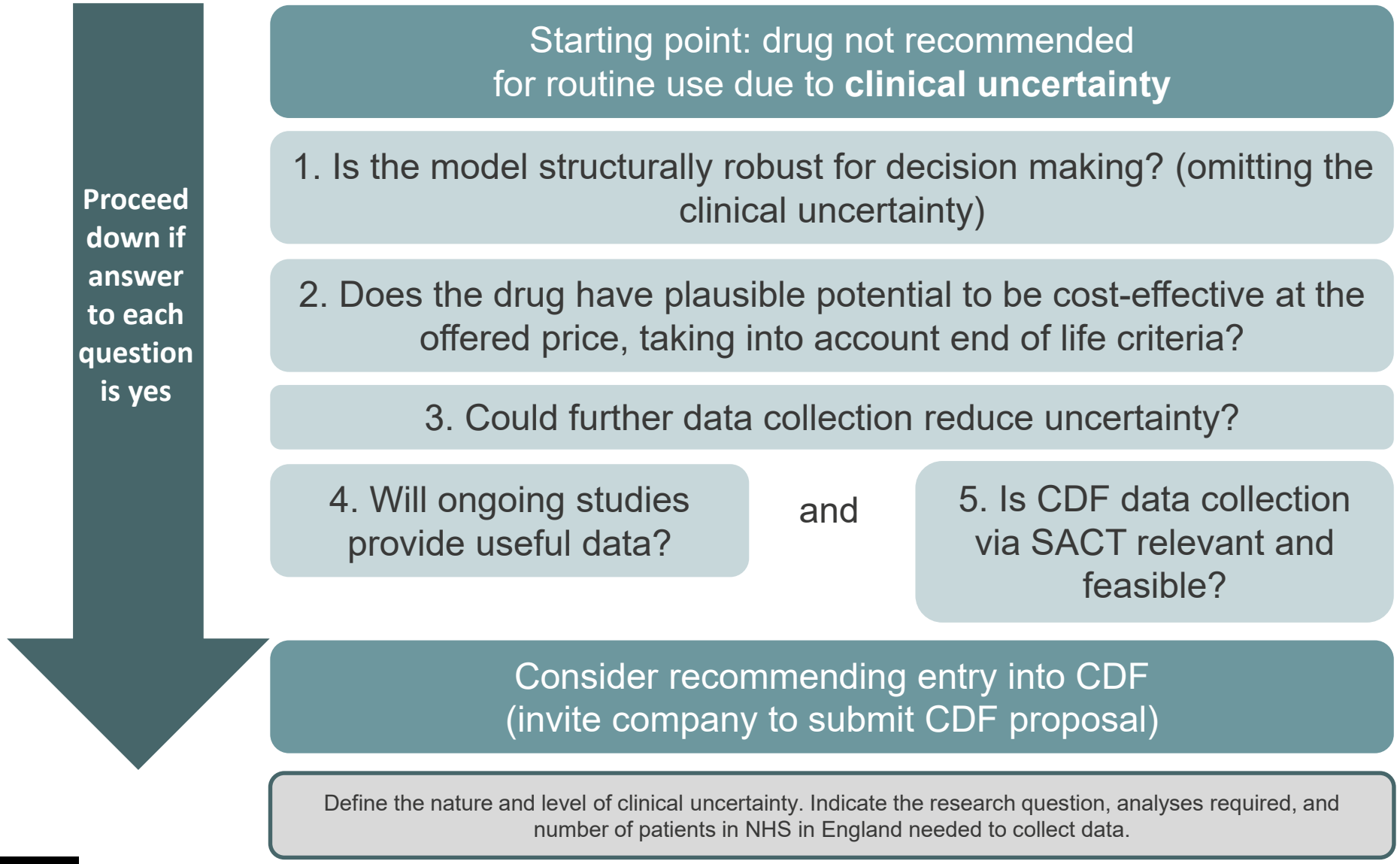
Final technical report judgement:

- It is unlikely that the end of life criteria is met for this indication in the poor risk subgroup, the intermediate/poor risk subgroup or in the general population of metastatic RCC.

[redacted]

Issue 8: Cancer drug fund (CDF)

Committee decision making criteria:



Issue 8: Cancer drug fund (CDF)

Background:

- There is high level of uncertainty resulting from the immature data presented from the KEYNOTE-426 trial.
- Further data may reduce uncertainty on overall survival estimates and whether there is a sustained treatment effect (taking into account the potential impact of stopping pembrolizumab after 2 years).

Company response:

- Considers pembrolizumab combination suitable for the Cancer Drugs Fund
  - Data from the final analysis of KEYNOTE-426 expected to be available in XXXX
- Expect to receive a Clinical Study Report for KEYNOTE-426 around XXXX

The ERG had no additional comments to those stated for other key issues in relation to uncertainties around clinical effectiveness and cost-effectiveness.
A patient representative commented that the cancer drug fund would be a good choice for this technology while the clinical trial data matures.

Final technical report judgement:

- At the current value proposition and using the technical team's preferred assumptions, pembrolizumab with axitinib does not appear to have plausible potential for cost-effectiveness with ICERs all above the £20,000–£30,000 per QALY gained range (when commercial arrangements are considered). It is therefore unlikely to meet the criteria for inclusion in the Cancer Drugs Fund

[redacted]

KEY QUESTION: Does pembrolizumab combination therapy meet the criteria for inclusion in the Cancer Drugs Fund?

Issue 9: Pembrolizumab 2-year stopping rule

Background:

- **New issue** arising post technical engagement.
- It was questioned whether a 2-year stopping rule for pembrolizumab may be clinically inappropriate when used with axitinib for untreated metastatic RCC
- KEYNOTE-426 protocol prescribes a 35-dose stopping rule for pembrolizumab
- The company economic model applies a 2-year stopping rule for pembrolizumab
- Clinical opinion noted the company stopping rule after 35 infusions, and following a very good response then pembrolizumab and axitinib could be stopped after 2 years of therapy
- TA581 (nivolumab with ipilimumab for untreated advanced renal cell carcinoma) did not support a stopping rule (of 5 years) – pivotal trial did not have a stopping rule
- Removal of the 2-year stopping rule within the economic model is likely to increase the ICER

Preliminary technical report judgement:

The stopping rule for pembrolizumab is appropriately applied within the company economic model, in line with KEYNOTE-426 protocol. No cost-effectiveness evidence was submitted without the stopping rule for pembrolizumab; cost-effectiveness of this scenario is not known.

KEY QUESTIONS:

- Are treatment stopping rules appropriate in the treatment of RCC?
- Would the 2-year stopping rule for pembrolizumab be implemented in clinical practice for RCC?

[redacted]

Cost-effectiveness results: Company base case

Base case cost effectiveness results for the overall patient population

Adapted from company submission Table 64 and CS Table 65

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline
Pembrolizumab + axitinib	[redacted]	6.887	[redacted]	-	-	-
Sunitinib	[redacted]	3.864	[redacted]	£137,537	2.320	**£ 59,292**
Pazopanib	[redacted]	3.864	[redacted]	£133,472	2.320	**£ 57,540**
Tivozanib	[redacted]	3.864	[redacted]	£131,402	2.320	**£ 56,648**

Base case cost effectiveness results for the intermediate/poor IMDC patient population

Adapted from company submission Table 70

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline
Pembrolizumab + axitinib	[redacted]	5.878	[redacted]	-	-	-
Cabozantinib	[redacted]	3.885	[redacted]	£33,103	1.543	**£21,452**

[redacted]

Company Scenarios (list price)

Adapted from company submission, Table 67. Results from the scenario analyses versus sunitinib

	Description of scenario	Inc. costs	Inc. QALYs	ICER (£)
	Base Case	£ 137,537	2.320	£59,292
1	Landmark Modelling approach	£ 137,249	2.237	£61,341
2	Fully parametric exponential OS extrapolation	£ 135,994	1.861	£73,094
3	Fully parametric log-logistic OS extrapolation for pembrolizumab + axitinib, time-constant HR for sunitinib	£ 137,497	2.318	£59,310
4	Fully parametric log-logistic OS extrapolation for pembrolizumab + axitinib, time-varying HR for sunitinib	£ 135,616	1.720	£78,854
5	Treatment waning after 10 years	£ 134,833	1.555	£86,712
6	Alternative modelling approach of PFS and ToT	£ 182,710	2.320	£78,767
7	Health state-based utilities (pooled)	£ 137,537	2.169	£63,400
8	Health state-based utilities (treatment specific)	£ 137,537	2.259	£60,876
9	Removing age-related disutilities	£ 137,537	2.499	£55,045
10	Sunitinib dose intensity = 86% (TA169)	£ 133,690	2.320	£57,634
11	Removing AE disutilities	£ 137,537	2.319	£59,300
12	Trial-based subsequent therapy distribution	£ 141,482	2.320	£60,993
13	Axitinib 2 year stopping rule	£ 116,994	2.320	£50,436
14	Remove half-cycle correction	£ 137,537	2.320	£59,289

Cost-effectiveness results

Reproduced from company submission, Table 67. Results from the scenario analyses versus sunitinib (list price)

Scenario No.	Description	Pembrolizumab + axitinib			Sunitinib			Pembrolizumab + axitinib vs Sunitinib		
		Total costs (£)	Total LYs	Total QALYs	Total costs (£)	Total LYs	Total QALYs	Inc. costs (£)	Inc. QALYs	ICER (£)
Base Case	-	£XXXX	6.887	XXXX	£XXXX	3.864	XXXX	£ 137,537	2.320	£59,292
Scenario 1	Landmark Modelling approach	£XXXX	7.350	XXXX	£XXXX	4.448	XXXX	£ 137,249	2.237	£61,341
Scenario 2	Fully parametric exponential OS extrapolation	£XXXX	6.251	XXXX	£XXXX	3.864	XXXX	£ 135,994	1.861	£73,094
Scenario 3	Fully parametric log-logistic OS extrapolation for pembrolizumab + axitinib, time-constant HR for sunitinib	£XXXX	6.887	XXXX	£XXXX	3.882	XXXX	£ 137,497	2.318	£59,310
Scenario 4	Fully parametric log-logistic OS extrapolation for pembrolizumab + axitinib, time-varying HR for sunitinib	£XXXX	6.887	XXXX	£XXXX	4.654	XXXX	£ 135,616	1.720	£78,854
Scenario 5	Treatment waning after 10 years	£XXXX	5.836	XXXX	£XXXX	3.864	XXXX	£ 134,833	1.555	£86,712
Scenario 6	Alternative modelling approach of PFS and ToT	£XXXX	6.887	XXXX	£XXXX	3.864	XXXX	£ 182,710	2.320	£78,767
Scenario 7	Health state-based utilities (pooled)	£XXXX	6.887	XXXX	£XXXX	3.864	XXXX	£ 137,537	2.169	£63,400
Scenario 8	Health state-based utilities (treatment specific)	£XXXX	6.887	XXXX	£XXXX	3.864	XXXX	£ 137,537	2.259	£60,876
Scenario 9	Removing age-related disutilities	£XXXX	6.887	XXXX	£XXXX	3.864	XXXX	£ 137,537	2.499	£55,045
Scenario 10	Sunitinib dose intensity = 86% (TA169)	£XXXX	6.887	XXXX	£XXXX	3.864	XXXX	£ 133,690	2.320	£57,634
Scenario 11	Removing AE disutilities	£XXXX	6.887	XXXX	£XXXX	3.864	XXXX	£ 137,537	2.319	£59,300
Scenario 12	Trial-based subsequent therapy distribution	£XXXX	6.887	XXXX	£XXXX	3.864	XXXX	£ 141,482	2.320	£60,993
Scenario 13	Axitinib 2 year stopping rule	£XXXX	6.887	XXXX	£XXXX	3.864	XXXX	£ 116,994	2.320	£50,436
Scenario 14	Remove half-cycle correction	£XXXX	6.896	XXXX	£XXXX	3.873	XXXX	£ 137,537	2.320	£59,289

Cost-effectiveness results: ERG base case (list price)

Table 48, ERG report: ERG base case for pembrolizumab with axitinib versus comparators in the overall population (pairwise comparisons)

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Pembro' + axitinib	£XXXX	XXXX	-	-	-
Sunitinib	£XXXX	XXXX	£140,895	1.170	£120,455
Tivozanib	£XXXX	XXXX	£135,168	1.170	£115,558
Pazopanib	£XXXX	XXXX	£137,335	1.170	£117,411

Table 50, ERG report: ERG base case for pembrolizumab with axitinib versus comparators in the intermediate / poor risk population (pairwise comparisons)

	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Pembro' + axitinib	£XXXX	XXXX	-	-	-
Sunitinib	£XXXX	XXXX	£141,941	1.010	£140,481
Tivozanib	£XXXX	XXXX	£137,480	1.010	£136,065
Pazopanib	£XXXX	XXXX	£139,200	1.010	£137,768
Cabozantinib	£XXXX	XXXX	£44,012	0.909	£48,424

Cost-effectiveness results: ERG scenarios (list price)

Adapted from Table 49, ERG report: ERG scenario analyses for pembrolizumab + axitinib versus sunitinib in the overall population

Scenario	Scenarios	Incremental costs	Incremental QALYs	ICER (£/QALY)
Base case		**£140,895**	**1.170**	**£120,455**
Time horizon	20 years	£140,779	1.149	£122,498
OS curves	Exponential	£143,209	1.973	£72,591
	Log-logistic	£141,615	1.419	£99,790
PFS curves	Weibull	£140,996	1.170	£120,541
	Log-logistic	£141,019	1.170	£120,561
ToT curves	Exponential	£141,627	1.170	£121,080
	Log-logistic	£166,512	1.170	£142,356
Persistence of OS benefit	Waning effect after 5 years	£137,625	0.847	£162,424
	Waning effect after 10 years	£140,534	1.086	£129,368
Time varying HR for PFS and OS	Company best fitting FP model	£140,784	1.162	£121,183
	Company 2nd best fitting FP model[a]	£140,569	1.074	£130,897
Health state utilities	Utilities from Tivozanib TA512;	£140,895	0.953	£147,873
	Utilities from pazopanib TA215	£140,895	0.883	£159,484
Population norms utility	Utility set at 0.775 for time to death > 360 days	£140,895	1.100	£128,044
Age-adjusted utility	Use age-adjusted utility	£140,895	1.124	£125,389
Subsequent treatment costs	ERG scenario analysis (see Table 47)	£138,591	1.170	£118,485
Administration costs	Oral treatments: administration cost of £131.61;	£140,527	1.170	£120,140

[a] fractional polynomial NMA 2nd best fitting model (company clarification response document appendix Table 43, 44).

Cost-effectiveness results: ERG scenarios (list price)

Adapted from Table 51, ERG report: Scenario analyses for pembrolizumab + axitinib versus cabozantinib in the intermediate / poor risk population

Scenario	Scenarios	Incremental costs	Incremental QALYs	ICER (£/QALY)
ERG base case		£44,012	0.909	£48,424
Time horizon	20 years	£43,989	0.904	£48,645
OS curves	Exponential	£46,146	1.265	£36,489
	Log-logistic	£46,040	1.651	£27,892
PFS curves	Weibull	£59,261	0.909	£65,201
	Log-logistic			Implausible
ToT curves	Exponential	£40,397	0.909	£44,447
	Log-logistic	£83,907	0.909	£92,318
Persistence of OS benefit	Waning effect after 5 years	£50,525	0.689	£73,290
	Waning effect after 10 years	£44,651	0.872	£51,223
Time varying HR for PFS and OS	Best-fitting FP model	£38,473	0.258	£149,347
	3rd best-fitting FP model[a]	£42,805	0.365	£117,279
Health state utilities	Utilities from tivozanib TA512;	£44,012	0.673	£65,401
	Utilities from pazopanib TA215	£44,012	0.591	£74,530
Population norms utility	Utility set at 0.775 for time to death > 360 days	£44,012	0.855	£51,469
Age-adjusted utility	Use age-adjusted utility	£44,012	0.878	£50,108
Subsequent treatment costs	ERG scenario analysis (see Table 47)	£45,862	0.909	£50,460
Administration costs	Oral treatments: administration cost of 131.61.	£41,639	0.909	£45,813

[b] OS only, company clarification question response appendix Table 129, Table 130. PFS uses constant HR

Cost effectiveness results: Technical team preferred ICERs, versus sunitinib (list price)

Overall RCC population

Analysis	Total Costs	Incremental costs	Total QALYs	Incremental QALYs	ICER (£/LY)*	ICER (£/QALY)**
Technical team base case	£XXXX	£137,102	XXXX	0.782	£133,470*	£175,316
Scenario analyses						
20 year horizon	£XXXX	£137,087	XXXX	0.780	£133,844	£175,736
Exponential for OS	£XXXX	£137,812	XXXX	0.999	£104,048	£137,964
Landmark OS	£XXXX	£138,188	XXXX	1.107	£93,324	£124,777
Time to death utilities	£XXXX	£137,102	XXXX	0.823	£133,470	£166,578
10 year waning	£XXXX	£140,011	XXXX	0.992	£106,395	£141,135
No waning effect	£XXXX	£140,373	XXXX	1.062	£99,085	£132,214

Technical team preferred assumptions: (1) Weibull distribution to model overall survival (OS); (2) treatment waning effect of 5 years; (3) subsequent treatment = ERG assumption; (4) age adjusted pooled health state utilities; (5) Weibull distribution to model time to treatment; (6) cost of terminal care: £8073; (7) administration costs of oral treatment set to £0. *Content updated, corrected due to cell mis-reference (previously reported £150,257). **additional content added to display cost per QALY

Cost effectiveness results: Technical team preferred ICERs, vs. cabozantinib (list price)

Intermediate / poor IMDC risk group

Analysis	Total Costs	Incremental costs	Total QALYs	Incremental QALYs	ICER (£/QALY)
Technical team base case	£XXXX	£50,525	XXXX	0.613	£82,488*
Scenario analyses					
20 year horizon	£XXXX	£50,521	XXXX	0.612	£82,538
Exponential for OS	£XXXX	£51,670	XXXX	0.655	£78,869
Landmark OS	NA				
Time to death utilities	£XXXX	£50,525	XXXX	0.672	£75,223
10 year waning	£XXXX	£44,651	XXXX	0.771	£57,895
No waning effect	£XXXX	£44,012	XXXX	0.802	£54,846

Technical team preferred assumptions: (1) Weibull distribution to model overall survival (OS); (2) treatment waning effect of 5 years; (3) subsequent treatment = ERG assumption; (4) age adjusted pooled health state utilities; (5) Weibull distribution to model time to treatment; (6) cost of terminal care: £8073; (7) administration costs of oral treatment set to £0. *Updated content, corrected due to cell mis-reference (previously reported £75,589).

Cost effectiveness results: analyses in response to technical engagement (list price)

Table 1: Treatment effect waning scenario analyses for treatment with pembrolizumab with axitinib compared to sunitinib.

Scenario	Incremental costs	Incremental QALYs	ICER (£/QALY)
Company base case	£137,537	2.32	£59,292
2-year treatment effect	£116,835	0.495	£236,229
3-year treatment effect[a]	£123,483	0.668	£184,983
ERG Base case	£140,895	1.170	£120,455
2-year treatment effect [b]	£125,895	0.466	£269,968
3-year treatment effect [b]	£131,854	0.626	£210,586
Technical team base case [c] (5-year treatment effect)	£137,102	0.782	£175,316*

Notes:
- Timeframe is from treatment initiation. For example:
  - For a 2-year treatment effect, no effect after stopping pembrolizumab at 2 years.
  - For 3-year treatment effect, there is 1 year of effect after stopping pembrolizumab at 2 years
  - For a 5-year treatment effect, there is 3 years of effect after stopping pembrolizumab at 2 years
- Company and ERG base case use a lifetime treatment effect

[a] Using the company's base case fitted parametric survival curves (provided by ERG in response to engagement),
[b] Using the ERG's base case fitted parametric survival curves (provided by ERG in response to engagement),
[c] Using the technical team's preferred assumptions (inclusive of ERG's base case fitted parametric survival curves).
*Updated: Previously read cost per life year of £133,470

Key Issues

- **Survival estimates from different modelling approaches:** What is the most appropriate survival model? [Issue 1]
- **Treatment effect duration:** What is the most appropriate time duration of treatment effect to model pembrolizumab combination therapy? [Issue 2]
- **Health-related quality of life:** What method is most appropriate to capture changes in health-related quality of life? [Issue 5]
- **End of life:** Does pembrolizumab combination therapy meet NICE's end of life criteria for the intermediate/poor IMDC subgroup? [Issue 7]
- **Cancer Drugs Fund:** Does pembrolizumab combination therapy meet the criteria for inclusion in the CDF? [Issue 8]
- **Pembrolizumab 2-year stopping rule:** Are treatment stopping rules appropriate in the treatment of RCC? [*New* Issue 9]

[redacted]