Public observer

NICE National Institute for Health and Care Excellence

Avelumab in combination with axitinib for advanced renal cell carcinoma

Lead Team Presentation

1st appraisal committee B meeting

Chair: Amanda Adler

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Company: Merck

ERG:Liverpool Reviews & Implementation Group (LRiG)

15 January 2020

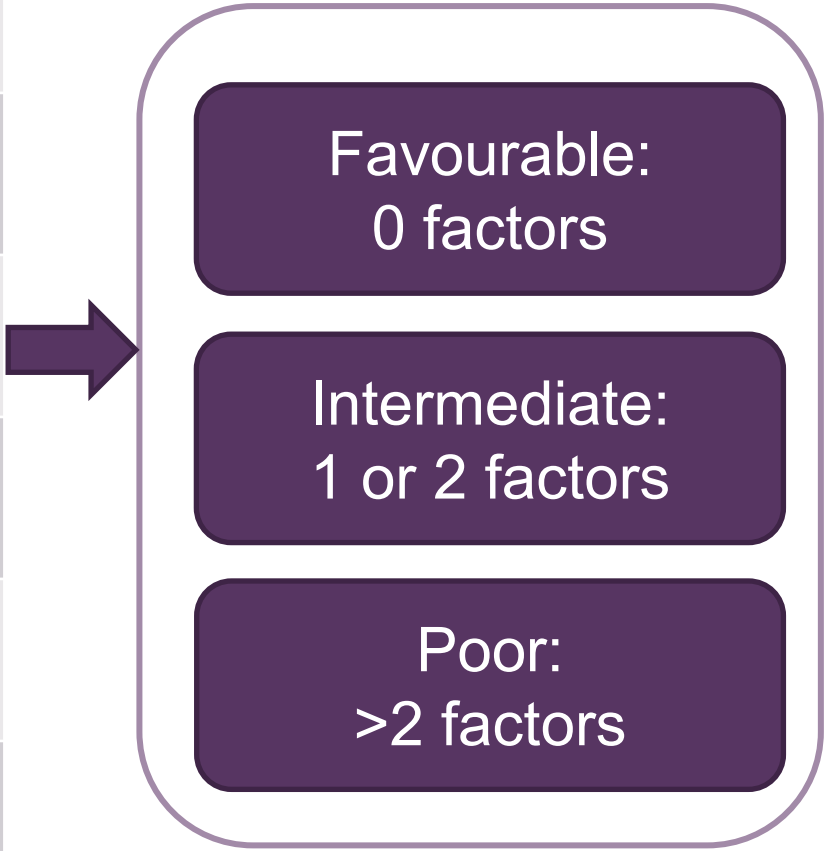
Background: renal cell carcinoma (RCC)

- Company defines ‘advanced’ as stage III and IV which includes locally advanced and metastatic RCC (aRCC).
- Survival rates associated with stage at diagnosis are:
  - Stage III: 90% (1 year) and 67% (5 year)
  - Stage IV: 37% (1 year) and 11% (5 year)
- Some trialists and clinicians use risk scores to predict survival categorising into favourable-, intermediate- and poor-risk and include:
  - Memorial Sloan Kettering Cancer Center (MKSCC) classification
  - International Metastatic Renal Cell Carcinoma Database (IMDC)
    - *Used in this appraisal*
    - Both use prognostic factors e.g. Karnofsky performance status, time from diagnosis to treatment, haemoglobin and corrected serum calcium concentration

IMDC risk categories

International Metastatic Renal Cell Carcinoma (IMDC) risk score 2013	
Factor	**Poor prognostic factor**
Karnofsky Performance Status	Less than 80%
Time from diagnosis to treatment	Less than 12 months
Anaemia	Haemoglobin below normal range
Hypercalcemia	Corrected serum calcium above normal range
Neutrophilia	Neutrophil count above normal range
Thrombocytosis	Platelet count greater than normal range

Risk categories by score



Patient and carer perspectives

- People want therapy that extends life, with few adverse effects:
  - Adverse effects of current treatments include, among others, extreme fatigue, itching, nausea, vomiting, diarrhoea, back pain, anaemia, high blood pressure
  - These may require additional medicines
- People value a choice of therapies that maintain quality of life, and hope of cure
- People with good prognosis do not currently receive immunotherapy 1st line
- People would require more hospital visits for intravenous avelumab + axitinib than for oral treatments, but balanced against this extra travel and time is an improved side effect profile and enhanced quality of life
  - Kidney Cancer Support Network: ‘Half a day in hospital is preferable to the debilitating side effects of VEGFR inhibitors’
- Location of specialist centres may create issues accessing treatment especially in patients with multiple comorbidities

Avelumab and axitinib for untreated advanced RCC

Mechanism	• Avelumab: human immunoglobulin G1 monoclonal antibody against programmed cell death-ligand-1 (PD-L1) protein • Axitinib: tyrosine kinase inhibitors (TKI)
Market Authorisation	• *Avelumab with axitinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma*
Administration and dose	• Avelumab: Intravenous, **flat dosing** schedule 800mg every 2 weeks (q2 weeks). Licensed dose used in cost-effectiveness analyses. • Note: Main trials was **weight-based** 10mg/kg q2 weeks e.g. doses for female weighing 70 kg would be 700 mg q2 weeks • Axitinib oral, 5mg twice daily • Marketing authorisation and trials did not have stopping rules
List price	• Avelumab: £768 per 200 mg vial • Axitinib: £3,517 for 5 mg pack of 56 tablets. • Existing patient access scheme discount for axitinib
Other NICE recom-mendations	• Avelumab for metastatic Merkel cell carcinoma (Cancer Drugs Fund, CDF, TA517) • Axitinib 2nd line or later for advanced RCC (recommended, TA333)

Decision problem

	Final scope issued by NICE	Company submission
Population	Adults with untreated advanced or metastatic renal cell carcinoma	Per scope, but key trial limited to clear cell histology
Intervention	Avelumab with axitinib	
Comparator	1. Pazopanib 2. Sunitinib 3. Tivozanib 4. Cabozantinib only for intermediate/poor risk (as defined in the International Metastatic Renal Cell Carcinoma Database Consortium criteria) • *Note*: nivolumab+ipilimumab for intermediate/poor risk (TA581), in CDF so not a comparator	
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	
Subgroups	None	Avelumab+axitinib vs. cabozantinib restricted to intermediate/poor risk status per cabozantinib licence

Treatment pathway

1st line	**Avelumab + axitinib**	Sunitinib *Comparator in main trial*	Pazopanib	Tivozanib	Cabozantinib *Intermediate or high risk*	Nivolumab + ipilimumab CDF
2nd line 3rd line	Axitinib	Nivolumab	Cabozantinib	Lenvatinib + everolimus		
4th line	Everolimus					

⊙ Would having avelumab + axitinib have an impact on the treatment options at later lines?

Clinical effectiveness

Company's clinical evidence

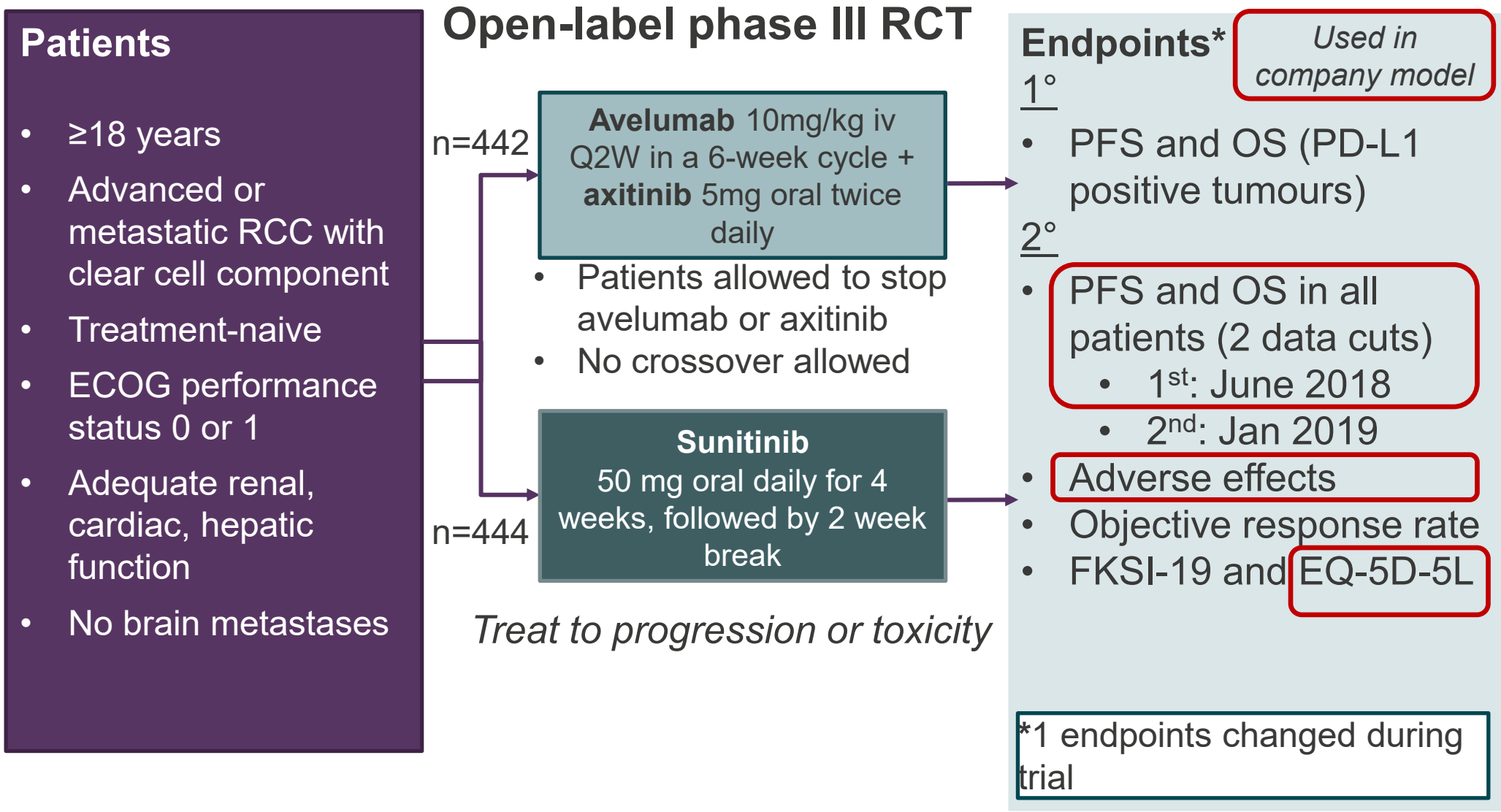
Data source, avelumab+axitinib vs treatment

- versus **sunitinib**:
  - JAVELIN Renal 101
  - Open-label randomised controlled trial, 1st line, advanced RCC
- versus **tivozanib**
  - Network meta-analyses in same population as in Javelin Renal 101 trial
  - ITCs on OS and PFS included 6 trials
- versus **pazopanib**
  - assumed equivalent to sunitinib in line with TA512 [ivozanib], TA581[Nivolumab with ipilimumab]
- versus **cabozantinib**:
  - Network meta-analyses in subpopulation of patients with intermediate- or poor-risk risk status (ie excluding favourable-risk status patients) in line with licence and TA542 [Cabozantinib].
  - Network meta-analyses on PFS and OS included 2 trials

Abbreviations: aRCC=advanced renal cell carcinoma, IMDC=International Metastatic Renal Cell Carcinoma Database Consortium, PFS=progression free survival, OS=overall survival, ITC= Indirect treatment comparison

Company's clinical evidence

Avelumab+axitinib vs sunitinib: JAVELIN Renal 101 trial (n=886)



Abbreviations: RCC=renal cell carcinoma, Q2W: every two weeks, EQ-5D-5L=EuroQol 5-Dimension 5-Level, FKSI-19=Functional Assessment of Cancer Therapy-Kidney Symptom Index-19, PFS=progression free survival, OS=overall survival, ECOG=Eastern Cooperative Oncology Group

Company's clinical evidence

JAVELIN trial: Primary analysis protocol amendment

Original 1◦ objective

- Population: all patients - irrespective of PD-L1 expression
- Superiority vs sunitinib in PFS (blinded central review)

New 1◦ objective following protocol amendment June 2017

- Rationale: New external evidence suggested overall survival benefit
- Population: among patients with PD-L1–positive tumours
- Superiority vs sunitinib 'independent 1◦ endpoints PFS and OS'
  - Events: for PFS estimated 336 events would provide 90% power to detect a HR of 0.65 1 -sided log-rank. test p of 0.004
  - Events: for OS estimated 368 deaths would provide 90% power to detect a hazard ratio of. 0.70 1 -sided log-rank test p of 0.021
  - Results from 2nd interim analysis (Jan 19) for OS available but company did not use them in model
- Marketing authorisation and submission to NICE for the overall population
  - Does **not** restrict to PD-L1 expression

⊙ Is the data generalisable to the whole population (i.e. those without PD-L1 positive tumours)?

JAVELIN Renal 101 trial: External validity and key baseline characteristics

Dosing differs evidence and licence, included only clear cell histology and good performance

Demographic/baseline characteristic	Total (n=886)
Mean age (SD), years	[redacted]
Prior nephrectomy	80%
Histopathology	
Clear cell only	[redacted]
Eastern Cooperative Oncology Group ECOG performance	
0	[redacted]
1	[redacted]
IMDC prognostic criteria*	
Favourable	21%
Intermediate	62%
Poor	16%
PD-L1 status*	
Positive	63%
Negative	[redacted]
Unknown	[redacted]

Clinical input: Did not include people with poor performance status. Baseline characteristics in trial reflect NHS practice

Avelumab: flat 800mg IV dose licensed but weight-based dose used in trial (10mg/kg of body weight)

- Based on pharmacokinetic modelling and simulation studies
- Accepted by regulators

Abbreviations: ECOG = Eastern Cooperative Oncology Group; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; PD-L1 = programmed death-ligand 1; PS = performance status; SD = standard deviation; RCC= Renal Cell Carcinoma *adds to 99% because of rounding

Generalisability JAVELIN trial

Technical issue

- Dose differs in trial (weight based) vs license (flat 800mg)
- Clear cell histology only
- Trial excluded patients with ECOG performance status ≥2 and people with some comorbidities, these patients may require treatment in practice

Comments from company:

- Between different dosages, modelling analyses demonstrated similar safety, efficacy & pharmacokinetics, accepted by licence regulators. Less waste
- Company's clinical expert: unclear whether works for non-clear cell
- Baseline characteristics in trial reflect NHS practice
- Licence includes all advanced RCC patients
- Trial patients could have tumours with non-clear cell components
- Sunitinib recommended for all patients (TA169) based on clear cell trial, and avelumab + axitinib has shown clinical benefit vs sunitinib in similar cohort
- No reason patients with ECOG score 2 would not benefit from treatment

Abbreviations: ECOG = Eastern Cooperative Oncology Group; IMDC = International Metastatic Renal Cell Carcinoma Database Consortium; PD-L1 = programmed death-ligand 1; PS = performance status; SD = standard deviation; aRCC= advanced Renal Cell Carcinoma

Generalisability continued

Comments received from professional organisation:

- Trial generalisable to NHS practice or people with poor performance status
- Both ways of dosing equally active, evidence from similar treatment demonstrates this
- Activity in non-clear cell RCC unknown. Equivalent activity should not be assumed
- Non-clear cell RCC is an area of significant clinical need. Need evidence

Comments received from patient organisation:

- Trial generalisable to NHS practice, but not to patients with poor performance status
- Not appropriate to extrapolate JAVELIN Renal 101 results to non-clear cell RCC
- Trial included some patients with sarcomatoid element to their clear cell RCC, these patients had PFS benefit vs sunitinib

Technical team judgement after engagement :

- On dosing, trial likely generalisable. Similar situation with nivolumab
- On clear-cell and performance status, uncertainty remains

⊙ ***Is it appropriate to generalise on dosing, histology, performance status? Is this population likely to generate a different relative effectiveness? Different baseline risk?***

JAVELIN results progression free survival independent review

Data monitoring committee after 1st data collection 'efficacy boundaries for progression-free survival… in the overall population had been crossed. Trial continued to evaluate overall survival.'

	1st data cut off 20 June 2018		2nd data cut-off 28 Jan 2019	
	Avelumab+ axitinib (N=442)	Sunitinib (N=444)	Avelumab+ axitinib (N=442)	Sunitinib (N=444)
Median follow-up time (95% CI), months	10.8 ([redacted])	8.6 ([redacted])	[redacted]	[redacted]
Events, n (%) [disease progression or death]	180 (40.7)	216 (48.6)	229 (51.8)	258 (58.1)
Censored*, n (%)	262 (59.3)	228 (51.4)	[redacted]	[redacted]
Ongoing without disease progression, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median PFS (95% CI), months	13.8 (11.1 to NE)	8.4 (6.9 to 11.1)	**13.3** (11.1 to 15.3)	**8.0** (6.7 to 9.8)
HR (95% CI)	**0.69 (0.56 to 0.84)**		**0.69 (0.57 to 0.83)**	

*patients whose disease has not progressed, lost to follow up, withdrawal of consent, no adequate baseline assessment, start of new anti-cancer therapy

Abbreviations: IA=interim analysis, CI=confidence interval, HR=hazard ratio, PFS= progression free survival, FAS=full analysis set, BICR=blinded independent central review, NE=not estimable, RECIST=Response Evaluation Criteria in Solid Tumors.

JAVELIN key results

Progression free survival chart – Interim analysis 2

- ***Why the 2nd interim analysis?***
- ***Is avelumab + axitinib more effective than sunitinib?***

Abbreviations: IA=interim analysis, CI=confidence interval, HR=hazard ratio, PFS= progression free survival, FAS=full analysis set, BICR=blinded independent central review, NE=not estimable, RECIST=Response Evaluation Criteria in Solid Tumors.

JAVELIN key results: Overall Survival

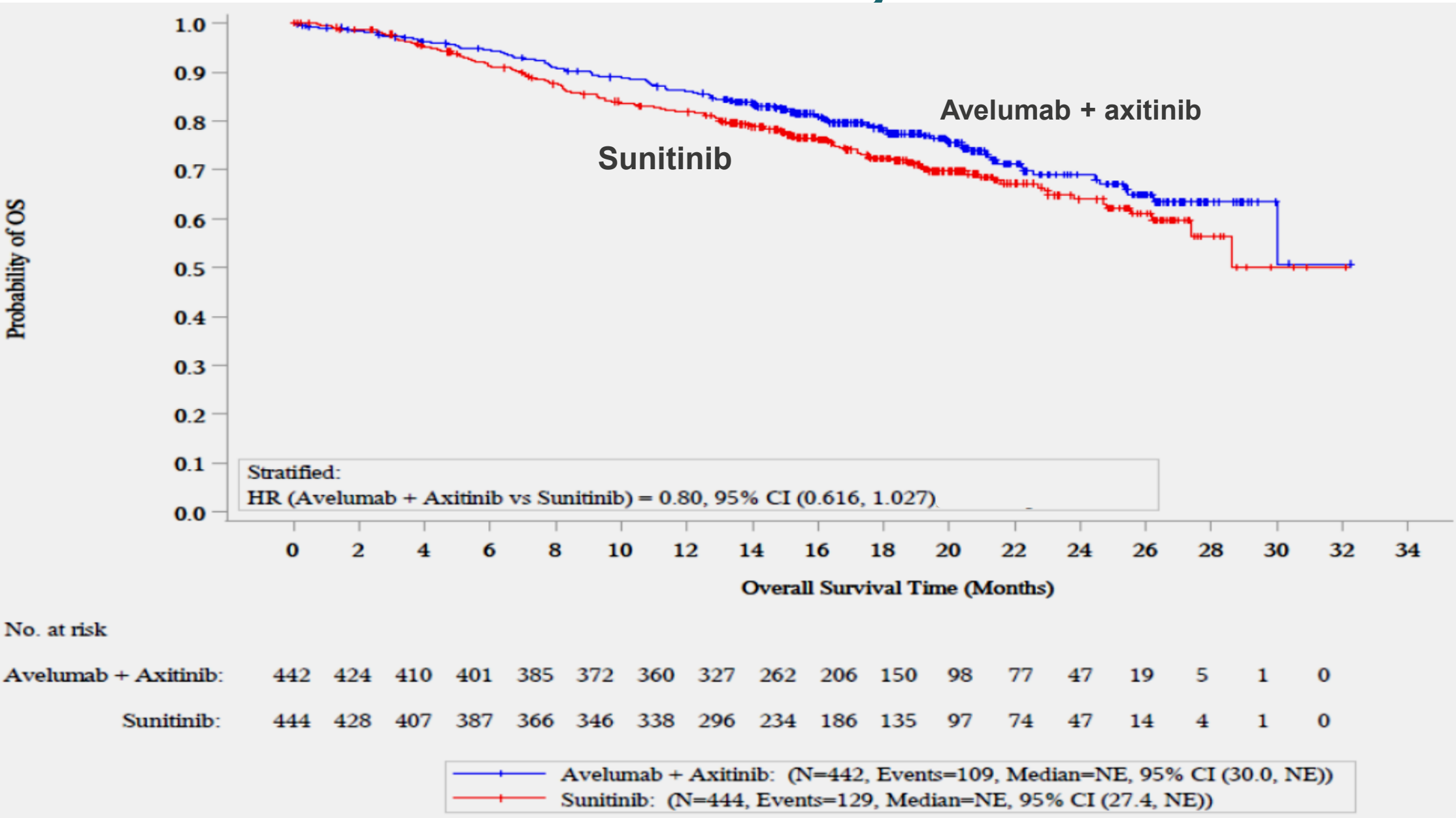
At 2nd analysis 45% of 535 deaths required for final analysis due May 2020
Company used 1st not 2nd interim analyses in base-case results
Company wishes NHS to fund drug

	1st data cut off 20 June 2018		2nd data cut-off 28 Jan 2019	
	Avelumab+ axitinib (N=442)	Sunitinib (N=444)	Avelumab+ axitinib (N=442)	Sunitinib (N=444)
Median follow-up time (95% CI), months	12.0 [redacted]	11.5 [redacted]	[redacted]	[redacted]
Deaths, n (%)	63 (14.3)	75 (16.9)	109 (24.7)	129 (29.1)
Censored*, n (%)	379 (85.7)	369 (83.1)	[redacted]	[redacted]
Ongoing without event, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Median OS (95% CI), months	NE [redacted]	NE [redacted]	NE (30.0 to NE)	NE (27.4 to NE)
HR (95% CI)	**0.78 (0.55 to 1.08)**		**0.80 (0.62 to 1.03)**	

*patients alive, lost to follow up, withdrawal of consent

Abbreviations: IA=interim analysis, CI=confidence interval, HR=hazard ratio, PFS= progression free survival, FAS=full analysis set, BICR=blinded independent central review, NE=not estimable, RECIST=Response Evaluation Criteria in Solid Tumors.

JAVELIN key results
Overall survival chart – Interim analysis 2



*Source: CHMP assessment report, European Medicines Agency (modified).

Abbreviations: IA=interim analysis, CI=confidence interval, HR=hazard ratio, PFS= progression free survival, FAS=full analysis set, BICR=blinded independent central review, NE=not estimable, CHMP=Committee for Medicinal Products for Human Use.

JAVELIN immature data on overall survival

Number deaths for final analysis not yet met; company models benefit

Comments from company:

- Acknowledges immature data, but considers results promising
- Avelumab+axitinib combines immune-oncology drug + tyrosine kinase inhibitor; thus must have better overall survival vs TKI monotherapy
- In TA542 (cabozantinib), non-statistically significant overall survival from CABOSUN trial vs sunitinib used to model OS difference in favour of cabozantinib
- **Clinical input:**
  - Pembrolizumab+axitinib vs sunitinib 'statistically significant' overall survival
  - So, should model a survival difference in this appraisal
- **Patient organisation**:
  - Clear benefit on progression, but no clear benefit on death yet
- **Tech team post engagement conclusion:**
  - Results look promising, but trial has not yet demonstrated an overall survival benefit therefore uncertainty remains
  - Should explore impact of no benefit in scenario analyses

⊙ ***What value of hazard ratio about overall survival benefit of avelumab+axitinib versus sunitinib/ pazopanib should the model include?***

Javelin 2nd line treatments and beyond

Affect hazard ratio for OS and should reflect NHS practice

Subsequent therapy received by >10 patients	JAVELIN subsequent therapy received (n patients)	
	Avelumab + Axitinib	Sunitinib
Cabozantinib	42	28
Everolimus	8	3
Axitinib	15	17
Sunitinib	15	23
Nivolumab	**14**	**107**
Lenvatinib + everolimus*	11	16
Pazopanib	**7**	**12**

Company:

- Subsequent therapies in trial broadly in line with what clinical experts 'would expect' in NHS
- Follow-on treatments biased against intervention. Proportion of patients receiving checkpoint inhibitor 2nd line between arms [redacted] vs [redacted] sunitinib
- Usage of 2nd line checkpoint inhibitor in sunitinib arm [redacted] higher than expected in UK ([redacted] (Systematic Anti-Cancer Therapy SACT data 2013-2018)
- Company adjusted results using rank preserving structural failure time (RPSFT) analysis used to explore impact, HR [redacted] (bootstrap 95% CI [redacted]
  - ERG: RPSFT is for adjusting for crossover, not for the effect of next treatments. Company does not provide its methods for RPSFT

⊙ *Why reports data for >10 patients only? What hazard ratio should the model include? 2nd analysis? A value of 1.0? Should it be adjusted for subsequent treatments? If so, did the company do this adequately? Do NHS patients get a checkpoint inhibitor twice?*

Javelin 2nd line treatments and beyond

Affect costs

Subsequent therapy received by >10 patients	JAVELIN subsequent therapy received (n patients)	
	Avelumab + Axitinib	Sunitinib
Cabozantinib	42	28
Everolimus	8	3
Axitinib	15	17
Sunitinib	15	23
Nivolumab	**14**	**107**
Lenvatinib + everolimus*	11	16
Pazopanib	**7**	**12**

- Subsequent therapies received by >10 of people in either treatment arm of the JAVELIN Renal 101 trial were accounted for in the economic model.
- Subsequent therapies received by ≤ 10 people in the JAVELIN Renal 101 trial were proportionally distributed across the included subsequent therapies.
- Subsequent treatments in other comparators modelled as in sunitinib
- Cost of subsequent therapies was applied as a one-off cost upon progression

⊙ *Do NHS patients get a checkpoint inhibitor twice? If not, should the model reflect that?*

Abbreviations: IA=interim analysis, CI=confidence interval, HR=hazard ratio, PFS= progression free survival, FAS=full analysis set, BICR=blinded independent central review, NE=not estimable, RECIST=Response Evaluation Criteria in Solid Tumors,

JAVELIN intermediate OR poor risk subgroup key results 1st analysis

Relevant for comparing avelumab+ axitinib to cabozantinib

78% trial population intermediate- and poor-risk

	Risk subgroup	N	Progression-free survival		Overall survival	
			Median (95% CI), months	HR (95% CI)	Median (95% CI), months	HR (95% CI)
Avelumab+ axitinib	Intermediate risk	271	13.8 (9.7-NE)	0.74 (0.57-0.95)	[redacted]	[redacted]
Sunitinib	Intermediate risk	276	8.4 (7-11.2)		[redacted]	
Avelumab+ axitinib	Poor risk	72	6 (3.6-8.7)	0.57 (0.375-0.88)	[redacted]	[redacted]
Sunitinib	Poor risk	71	2.9 (2.7-5.5)		[redacted]	

⊙ *Is there an interaction by risk level? Is it appropriate to use a different hazard ratio?*

Abbreviations: aRCC=advanced renal cell carcinoma, IMDC=International Metastatic Renal Cell Carcinoma Database Consortium, PFS=progression free survival, OS=overall survival, HR= hazard ratio, NE=not estimable

Appropriate estimates for intermediate/poor risk subgroup

Comments received from company:

- **Poor-risk** subgroup **alone** showed statistically significant OS at interim analysis 2: [redacted]
- 78% trial pop intermediate- and poor-risk
- CABOSUN much smaller, and OS KM curves crossed multiple times, unlike JAVELIN trial, and OS HR confidence intervals for JAVELIN (upper CI 1.03) narrower than cabozantinib (upper CI 1.21)

Patient and professionals

- Not enough data for firm conclusions

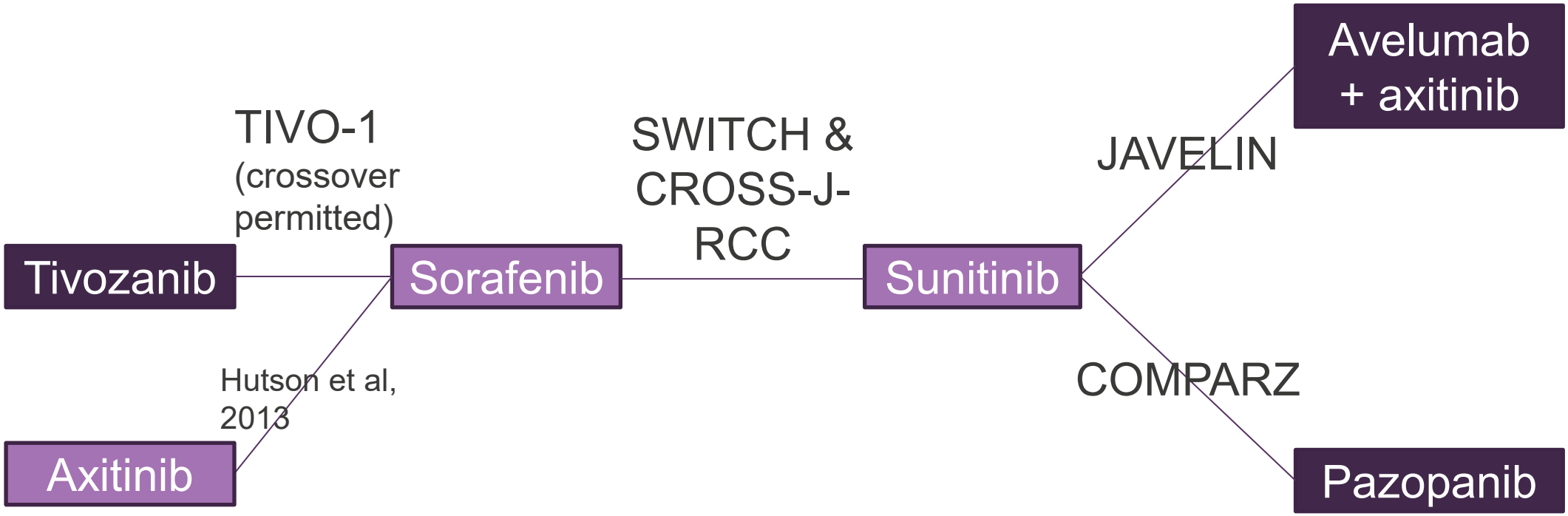
Technical team post engagement conclusion:

- Result in poor-risk subgroup alone cannot be used intermediate/ poor risk
- Need to explore impact of uncertainty

⊙ *What is the appropriate hazard ratio for PFS for these subgroups? For OS – same as for overall group? 1.0?*

Indirect comparisons: to pazopanib and tivozanib

All levels of risk, 6 trials, 1 permitted cross-over



- Networks for both PFS and OS
- Although pazopanib in the indirect comparison, pazopanib assumed equivalent to sunitinib in economic model in line with TA512, TA581
- In all networks , data from JAVELIN 1st interim analysis used

⊙ *Why does the company not use least immature data for OS? Should network account for cross-over?*

Indirect comparisons: to cabozantinib

- Vs **cabozantinib**: Network meta-analyses
  - in subpopulation of intermediate- or poor-risk risk in line with cabozantinib licence and TA542
  - For OS and PFS included 2 trials with common comparator (sunitinib)
- In all network, company used data from JAVELIN 1st interim analysis

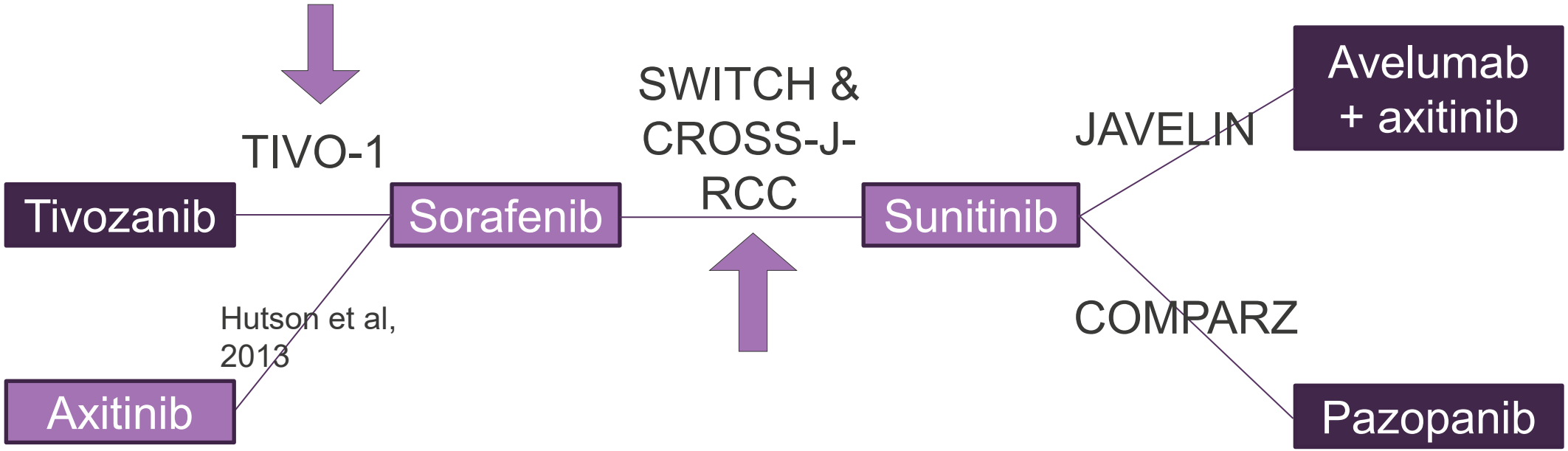
⊙ *Should there be a separate network for intermediate/high risk? Again, which data cut for PFS? For OS?*

Comparing avelumab+axitinib to tivozanib for overall survival

Problems comparing sorafenib to sunitinib and tivozanib to sorafenib

Technical issue:

- Sunitinib vs sorafenib trials (SWITCH and CROSS-J-RCC) designed for sorafenib to follow sunitinib, or vice-versa; OS data reported only at end. No OS comparison of sorafenib vs sunitinib. Not a comparator but a 'link'
- In TIVO-1 61% who progressed on sorafenib crossed over to tivozanib
- In all trials in both networks between 18% to 65% received ≥1 follow-on therapy
- Risk status varied between trials
- ERG and technical team: network not valid.
  - Should assume effect of tivozanib and sunitinib on overall survival same



Abbreviations: MSKCC=Memorial Sloan Kettering Cancer Center, PFS=progression free survival, OS=overall survival

Comparing avelumab+axitinib to tivozanib for overall survival

Comments received from company:

- Network meta-analysis appropriate
- Provides sensitivity analyses assuming same survival for sorafenib and sunitinib and TIVO-1 adjusted for crossover
- Clinicians perceive tivozanib as similar, but not necessarily equivalent to sunitinib
- NICE (TA512) recognised tivozanib likely less effective than sunitinib and pazopanib

Clinical input:

- Unlikely to be clinically meaningful differences between sunitinib and tivozanib

Comments received from patient organisations:

- Tivozanib should not be considered equivalent to sunitinib for overall survival

Technical team post engagement conclusion:

- Network for OS not valid because of trials comparing sunitinib with sorafenib
- Should explore alternative network or assume overall survival associated with tivozanib and sunitinib are the same

⊙ ***How should model address effect on overall survival of avelumab+axitinib vs tivozanib?***

Network meta-analyses

Proportional hazards may not hold for either PFS or OS

Company did 2 network meta-analyses:

- Proportional hazards: Bayesian
  - Avelumab+axitinib vs sunitinib or pazopanib reduces ~~PFS~~ progression hazard in fixed effects model
  - All other results (i.e. vs tivozanib or cabozantinib for PFS, all random effects results, and all OS results) no statistically significant differences
- Non-proportional hazards
  - Used in the economic model (company base case)
  - Results as probabilities of survival at 1, 2 and 10 years
    - PFS probabilities in all risk status population generally higher for avelumab+axitinib vs all of comparators at 1, 2 and 10 years
    - OS probabilities similar across all treatments at 1 and 2 years
    - PFS and OS probabilities for IMDC intermediate/poor risk status population are similar for avelumab+axitinib and cabozantinib at 1, 2 and 10 years
    - Results at 10 years based on extrapolation rather than trial data
- ERG overall satisfied with methods but has concerns with results

Abbreviations: NMA= Network meta-analysis, PH= proportional hazards,

Network meta-analyses key conclusions

Avelumab+axitinib clearly better than sunitinib or pazopanib for PFS; other endpoints and comparisons unclear

PFS:

- Both proportional and non-proportional hazards networks results show treatment with avelumab+axitinib improves PFS vs **sunitinib or pazopanib** (although magnitude of benefit uncertain)
- Vs tivozanib or cabozantinib - uncertain

OS:

- Versus all comparators - uncertain
- ERG emphasises concerns with both PH and non-PH validity due to inclusion of trials of randomised sequential design, treatment crossover and differences in subsequent therapies

⊙ ***What should provide the estimates of avelumab+axitinib versus tivozanib and cabozantinib in the economic model?***

Abbreviations: NMA= Network meta-analysis, PH= proportional hazards, OS=overall survival; PFS=progression-free survival; PH=proportional hazards

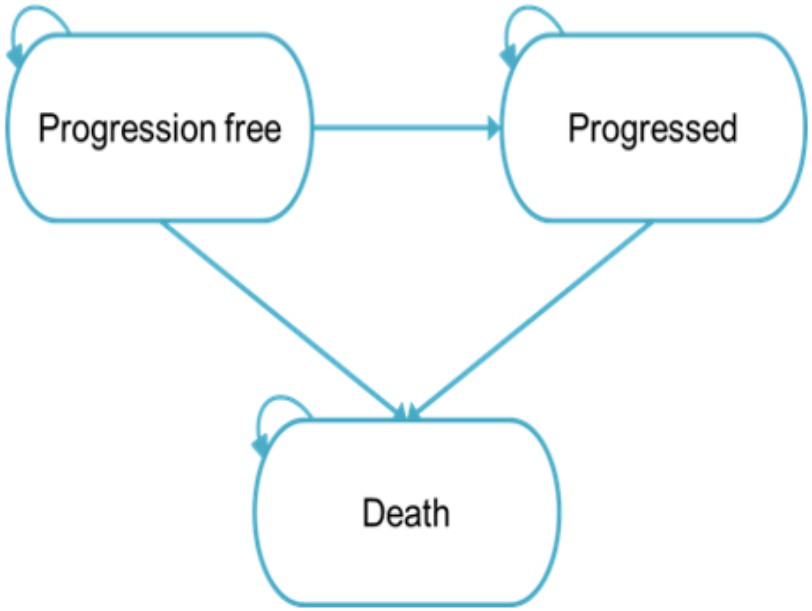
Cost effectiveness

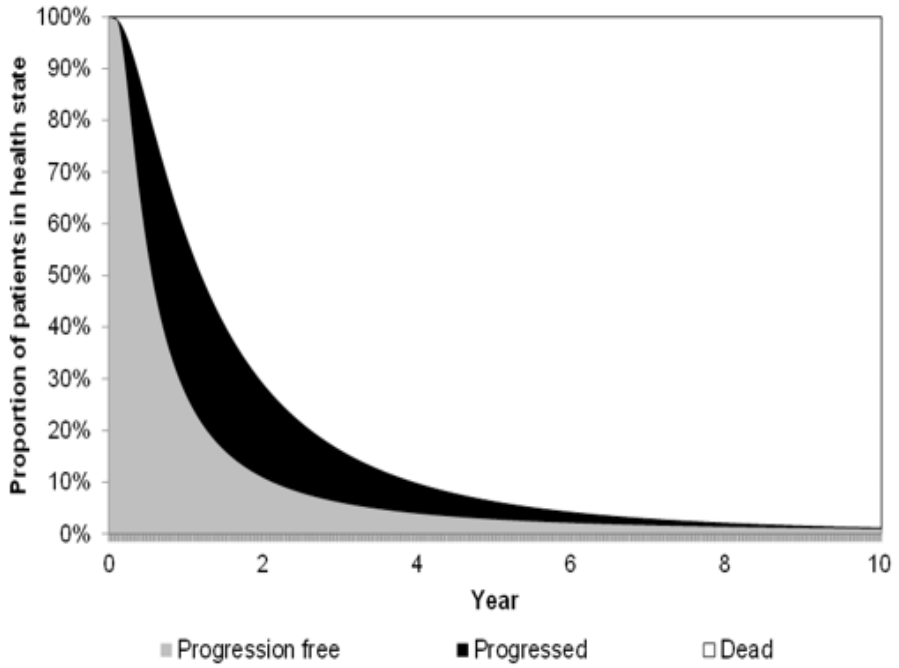
Key issues

- What are the most plausible long term survival estimates for avelumab+axitinib?
- Should model include a stopping rule?
- Should data sources and parametric models for avelumab+axitinib differ by comparator?
- Is avelumab+axitinib innovative?

Abbreviations: IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; NMA=network meta-analysis; PH=proportional hazard; OS=overall survival; ToT=time on treatment

Company's model – partitioned survival

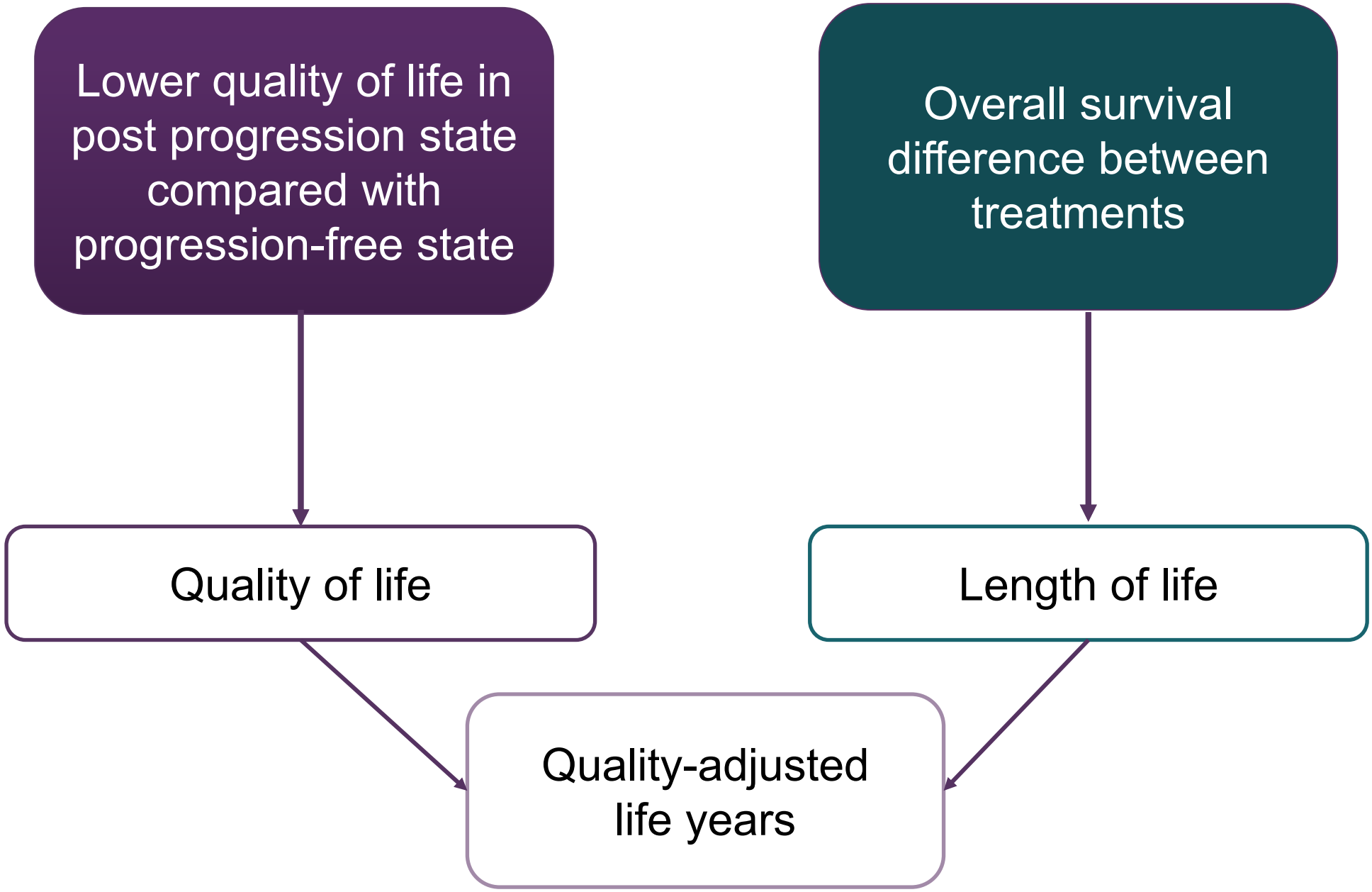




- Estimated proportions in each health state based on parametric survival curves fitted to clinical trial data for PFS and OS
- Time horizon: 40 years
- Cycle length: 1 week
- Model structure consistent with previous NICE appraisals of aRCC: pazopanib (TA215), tivozanib (TA512), cabozantinib (TA542) and nivolumab (TA581)

Abbreviations:OS=overall survival; ToT=time on treatment, PFS=progression-free survival, aRCC=advanced renal cell carcinoma

Overview - how quality-adjusted life years accrue



Company's model and key assumptions overview

Key assumptions overview	
2 populations	• All risk status (vs sunitinib, pazopanib and tivozanib) • Intermediate/poor risk status (vs cabozantinib, per licence)
Parametric distributions	• Used for OS, PFS and time on treatment • Choice based on statistical tests, visual inspection and expert opinion • Survival curves adjusted for general population mortality risk • OS, PFS and time on treatment estimates for sunitinib used also for pazopanib (in line with TA581)
Stopping rule and treatment effect waning	• Company included 2-year stopping rule for avelumab and axitinib even if progression has not occurred • After stopping treatment 33% of patients will adopt the PFS and OS hazards associated with treatment with sunitinib within a two year period • 67% of patients will continue to accrue the modelled survival benefit without receiving avelumab+axitinib • Not reflected in evidence • Not previously accepted for nivolumab with ipilimumab [TA581]

Abbreviations:OS=overall survival; ToT=time on treatment, PFS=progression-free survival, aRCC=advanced renal cell carcinoma

Extrapolating OS: avelumab+axitinib vs sunitinib/ pazopanib

Choice of curve key to survival and cost effectiveness

ERG feels company's choice of log-logistic implausible – better survival than general population

Clinical input at 5 years 20% of patients will be alive and at 10 years 15%

NICE

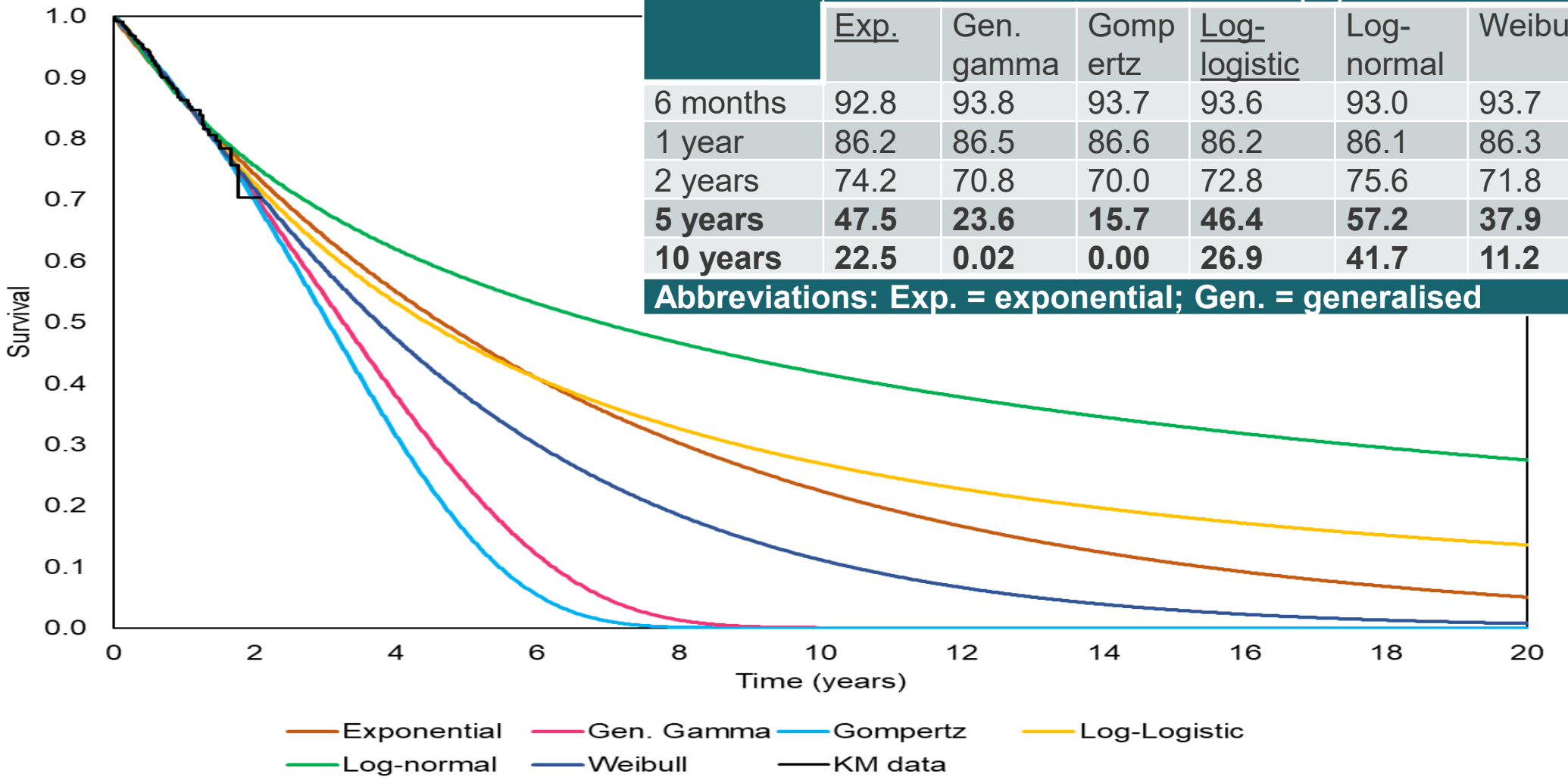
Abbreviations: OS=overall survival, PFS=progression-free survival, KM= Kaplan–Meier,

Extrapolating OS: avelumab + axitinib only

Company feels exponential inappropriate as: does not allow for decreasing mortality; mortality rates below general population after 30 years; expect flattening of OS curve

Time	OS estimate (%)					
	Exp.	Gen. gamma	Gompertz	Log-logistic	Log-normal	Weibull
6 months	92.8	93.8	93.7	93.6	93.0	93.7
1 year	86.2	86.5	86.6	86.2	86.1	86.3
2 years	74.2	70.8	70.0	72.8	75.6	71.8
5 years	**47.5**	**23.6**	**15.7**	**46.4**	**57.2**	**37.9**
10 years	**22.5**	**0.02**	**0.00**	**26.9**	**41.7**	**11.2**

Abbreviations: Exp. = exponential; Gen. = generalised



⊙ *Which curve should be used to extrapolate overall survival? For both arms?*

Abbreviations: OS=overall survival, PFS=progression-free survival, KM= Kaplan–Meier, AA=Avelumab+axitinib

Extrapolating OS and PFS: avelumab+axitinib vs tivozanib 'all risk' population

Should avelumab + axitinib be modelled differently in the same population?
ERG notes avelumab+axitinib should not be modelled differently in same population and questions output from network with non-proportional hazards

	Ave + axi versus sunitinib, pazopanib		Avelumab+axitinib versus tivozanib		Comments
	PFS	OS	PFS	OS	
Company	JAVELIN trial/ generalised gamma function	JAVELIN trial/ log-logistic function	Non-PH NMA / generalised gamma	Non-PH NMA / generalised gamma	
ERG	JAVELIN trial/ generalised gamma function	JAVELIN trial/ exponential function	JAVELIN trial/ generalised gamma function	JAVELIN trial/ exponential function	ERG prefers same representations of the effect of avelumab+ axitinib on PFS and OS

Comparison to tivozanib 'all risk' population

Should avelumab + axitinib be modelled differently in the same population?

ERG notes avelumab+axitinib should not be modelled differently in same population and questions output from network with non-proportional hazards

⊙ *Which approach to modelling?*

Abbreviations: AIC=Akaike Information Criterion, BIC-=Bayesian Information Criterion, OS=overall survival; ToT=time on treatment, PFS=progression-free survival

Stopping rule and treatment effect waning: Company's base case

Costs lower, but effectiveness still based on trial without stopping rule

- At 2 years patients stop avelumab and axitinib but treatment benefit continues
- Company argues for immune-modifying effect on the basis of:
  - avelumab's mechanism of action
  - Comparing PFS results of nivolumab+ipilimumab with avelumab+axitinib
    - N.b. not a comparator
  - an acceptance by SMC of a stopping rule for nivolumab+ipilimumab
  - evidence with pembrolizumab in patients with melanoma suggesting sustained response after stopping treatment
    - N.b. not the same indication
  - convenience, lower costs and safety advantages of stopping rule
  - previous NICE appraisals in lung cancer, head and neck cancer and urothelial carcinoma (TA484, TA490, TA520, TA525) in which 2-year stopping rule accepted, despite lack of a stopping rule in relevant trials or licenses.
    - N.b. committee did not accept stopping rule for nivolumab and ipilimumab in same indication

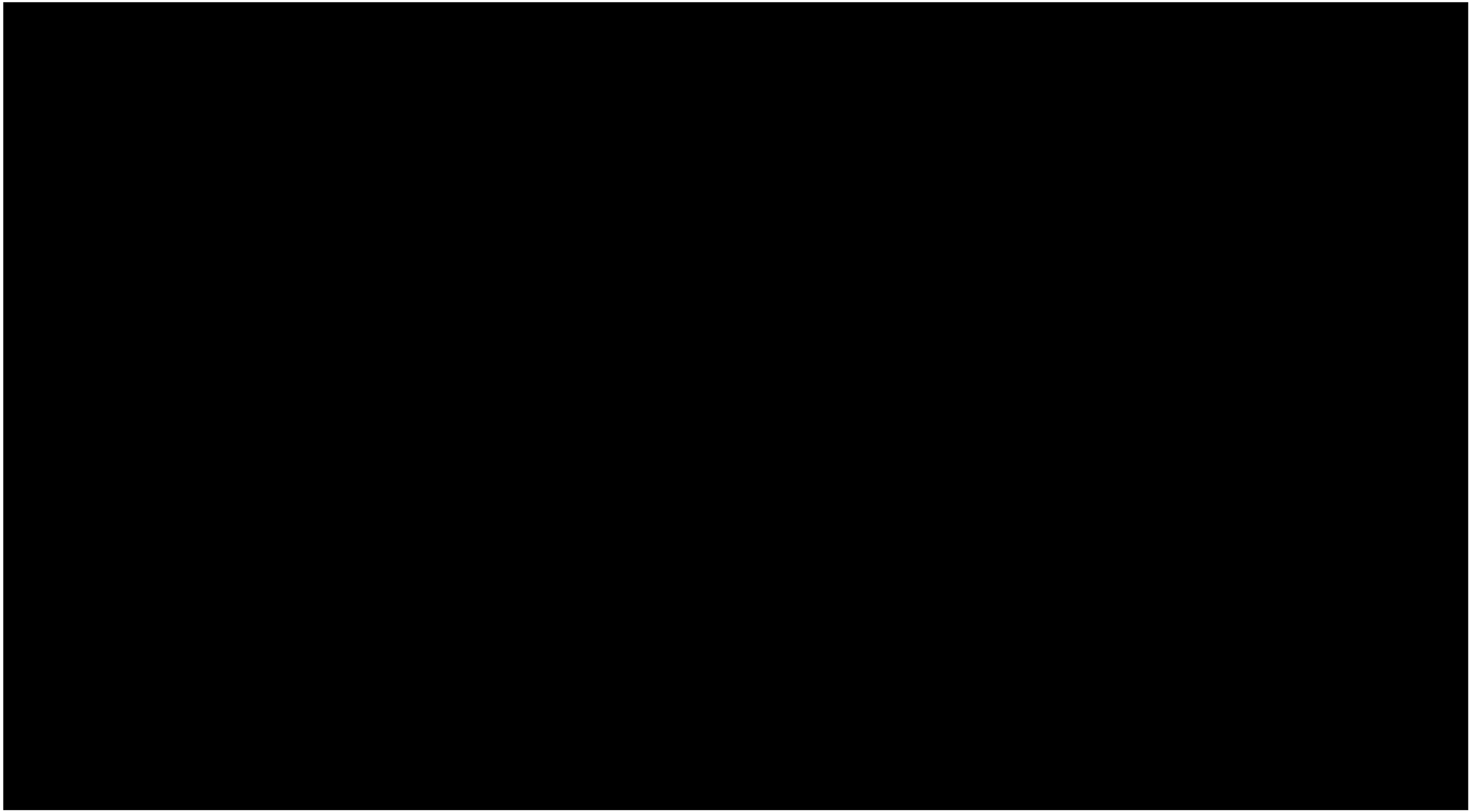
Abbreviations: IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; NMA=network meta-analysis; PH=proportional hazard; OS=overall survival; SMC=Scottish Medicines Consortium; ToT=time on treatment

Stopping rule and treatment effect waning: Company's base case (cont)

- To account for uncertainty of immune-modifying effect, company assumed after stopping avelumab+axitinib 33% of patients will, over 2 years, follow progression and mortality hazards of treatment with sunitinib.
  - 33% chosen as clinical input ranged from 20%-50%
  - 67% modelled to have lifetime benefit after stopping treatment
- At technical engagement, company consulted 5 clinicians
  - estimates of proportion of patients who stopped treatment, and then progressed after:
    - 1 year: 5 – 60%
    - 2 years: 10 – 80%
  - in company base case modelled estimate of 22% (1 year) and 38% (2 years) post stopping is within these ranges

Abbreviations: IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; NMA=network meta-analysis; PH=proportional hazard; OS=overall survival; ToT=time on treatment

Company proposes stopping rule and treatment waning: effect on model avelumab + axitinib versus sunitinib – company base case



Abbreviations: IMDC=International Metastatic Renal Cell Carcinoma Database Consortium; NMA=network meta-analysis; PH=proportional hazard; OS=overall survival; ToT=time on treatment

Stopping rule and treatment effect waning

ERG:

- Stopping rule not in avelumab+axitinib trials or in license
- JAVELIN can never answer question about stopping rule

Clinical input:

- Stopping rule at 2 years reasonable assuming patients who relapse after stopping would be able to **re-access** the combination upon relapse
  - *not modelled in company base case*
- Following stopping treatment, there will be 2 groups of patients, those who never relapse after stopping and those who do. No data to inform the proportions of these groups. Reasonable and conservative to assume 50:50 split.

Comments received from patient organisations:

- No clinical evidence to support stopping rule
- Will patients stop treatment before 2 years? What is the benefit to patients after 2 years? Will patients continue with treatment until they are unable to tolerate the drugs? Will patients benefit from treatment breaks?

Technical team

- Wide range of estimates (10%-80%) in clinical input on proportion expected to progress after stopping treatment
- No evidence

⊙ *Should a stopping rule be applied for both avelumab and axitinib?*

Cost-effectiveness results

All ICERs are reported in PART 2 slides because they include confidential PAS discounts for comparators

Equality considerations and innovation

- No equality issues related to the use of avelumab + axitinib to treat patients with advanced RCC were identified
- Company considers avelumab+axitinib innovative because:
  - 1st combination of immuno-oncology agent + tyrosine kinase inhibitor licensed for use in 1st-line advanced RCC
  - 'step-change' in the management of the condition due to complementary mechanisms of action
  - Promising Innovative Medicine (PIM) status designation in January 2019
  - Early access to medicines scheme (EAMS) positive scientific opinion in July 2019

⊙ ***Is avelumab+axitinib a 'step change' in the treatment of RCC?***
⊙ ***Are there benefits not included in model?***

Consideration for the Cancer drugs Fund (CDF)

Technical engagement issue:

- Overall survival data immature and trial ongoing. Company argues entry into CDF will allow patients access to treatment and data will be sufficiently mature to reassess following the final analysis.

Comments received from company:

- By 2023 the JAVELIN Renal 101 study will have 5 years of follow-up data
- Avelumab+axitinib can be cost-effective

Clinical input:

- Current modelling is highly flawed if only based on assumptions of equivalent overall survival between TKIs and avelumab with axitinib

Comments received from patient organisations:

- As the overall survival data from JAVELIN Renal 101 matures and ongoing data collection from the Early Access to Medicine Scheme (EAMS) continues, we are confident that this will be sufficient to show an overall survival benefit

Tech team post engagement conclusion:

- Ongoing data collection in the Javelin 101 trial would address a key uncertainty

Committee decision-making: CDF recommendation criteria

Proceed down if answer to each question is yes

Starting point: drug not recommended for routine use due to clinical uncertainty

TBD in Part 2

1. Is the model structurally robust for decision making? (omitting the clinical uncertainty)

⊙ *Agree?*

2. Does the drug have plausible potential to be cost-effective at the offered price, taking into account end of life criteria?

TBD in Part 2

3. Could further data collection reduce uncertainty?

4. Will ongoing studies provide useful data?

and

5. Is CDF data collection via SACT relevant and feasible?

⊙ *JAVELIN Renal 101? Other sources?*

Consider recommending entry into CDF (invite company to submit CDF proposal)

TBD in Part 2

Define the nature and level of clinical uncertainty. Indicate the research question, analyses required , and number of patients in NHS in England needed to collect data.

⊙ ***Will data from CDF diminish uncertainty?***

Minor amendments post committee

- Please note the following amendments for clarity have been made to the slides originally presented to committee:
  - Slide 5 updated 15/06/20 to clarify existing PAS scheme is for axitinib. Original text presented to committee stated: “Existing patient access scheme”.
  - Slide 45 updated 15/06/20 to provide a more detailed summary for clinical input comments. Original text presented to committee stated “Current modelling is highly flawed”.