Avelumab with axitinib for untreated advanced renal cell carcinoma (MA review of TA645)

Technology appraisal committee C [09 April 2025]

Part 1
For Screen / Public [REDACTED]

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Company: Merck Serono

Avelumab with axitinib for untreated advanced renal cell carcinoma

- ✓ **Background**
- ❑ Treatment pathway
- ❑ Key issues
- ❑ Cost-effectiveness results

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Background on untreated advanced renal cell carcinoma

Causes

- Main cause of renal cell carcinoma (RCC*) is unknown

Epidemiology

- 10,193 new kidney cancer diagnoses in England in 2021
- 80% of all kidney cancer cases are RCC
- 70% to 80% of RCC is clear cell. Other subtypes are heterogeneous and include papillary, chromophobe, and collecting duct - collectively known as non-clear cell RCC
- RCC risk status defined by International Metastatic RCC Database Consortium
    - At diagnosis an estimated 16.1% are favourable risk and 80.8% intermediate/poor risk

Diagnosis and classification

- RCC is categorised into stages 1 to 4.
- Stage 1 and 2: tumour is localised to the kidney. Stage 3: locally advanced and/or has spread to regional lymph nodes. Stage 4: Metastatic RCC.

Symptoms and prognosis

- Common symptoms: loss of appetite, fatigue, nausea, backpain or pressure and anaemia. Asymptomatic until advanced stage.
- 5-year kidney cancer survival rate in England is 66.6%

Abbreviations: RCC, renal cell carcinoma.
*Please note untreated advanced renal cell carcinoma will be referred to as RCC throughout this presentation

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Technology (Bavencio, Merck)

Marketing authorisation	• Avelumab with axitinib is indicated for the first-line treatment of adult patients with advanced renal cell carcinoma • Medicines and Healthcare Products Regulatory Agency (MHRA) marketing authorisation granted on 01/01/2021
Mechanism of action	• Avelumab: human immunoglobulin G1 monoclonal antibody against programmed cell death-ligand-1 (PD-L1) protein • Axitinib: tyrosine kinase inhibitors (TKI)
Administration	• Avelumab: Intravenous, 800mg every 2 weeks (Q2W) • Axitinib: oral, 5mg twice daily
Price	• Avelumab: £768 per 200 mg vial. Existing simple patient access scheme (PAS) discount available • Axitinib: £3,517 for 5 mg pack of 56 tablets. Existing simple PAS discount available [redacted]

Abbreviations: kg, kilogram; mg, milligram; PAS, Patient access scheme; q2, every 2 weeks

Summary of original appraisal (TA645)

1st committee meeting January 2020 → Guidance published September 2020 → CDF data collection July 2020 – February 2024 → Managed access review meeting

TA645 recommended avelumab with axitinib for use in CDF for full marketing authorisation population

Key uncertainties in TA645:

- immature overall survival data and company's approach to modelling long term overall survival
- company's methods for adjusting costs and benefits of subsequent treatments to reflect NHS practice
- lack of effectiveness data for non-clear cell disease

ID6294: Review of TA645

- JAVELIN RENAL 101 FAC data cut-off August 2023
- SACT (CDF and EAMS) data cut-off February 2024

Abbreviations: CDF: Cancer drugs fund, EAMS, Early Access to Medicines Scheme; SACT, Systemic Anti-Cancer Cancer Therapy

Patient perspectives

Submissions from Action Kidney Cancer, Kidney cancer UK and patient expert

Living with RCC

- People with kidney cancer feel anxious, emotionally low, abandoned after surgery and scared about the cancer returning
- Range of symptoms include fatigue, depression, weight loss, anorexia, anaemia and pain (pain severity varies and depends on stage of cancer)

Unmet need

- Unmet need in first-line RCC. Wider range of treatments with improved overall survival and quality of life with fewer side effects needed.
- Non-clear cell and clear cell RCC have similar treatment options. Non-clear cell RCC subtypes do not respond well to current treatments. Prognosis is poor.

Avelumab with axitinib

- Access for this treatment is considered invaluable, good response rates observed. Should be available to those who need it and would benefit from it.
- Key disadvantages are the side effects with some becoming long term/chronic due to the nature of immunotherapy

"The success of this combination has been well above my expectation, and I feel very lucky to have been involved from an early stage"
Patient expert

"The only disadvantages I can see are the side effects…I feel that the side effects could have been much worse and that I have been lucky in my responses to the treatment."
Action Kidney Cancer participant

Clinical perspectives

Submissions from British Uro-Oncology, and 2 clinical experts

Aim of treatment

- Early control of disease to improve outcomes and quality of life
- Durable treatment response that may cure approximately 20% with first line immunotherapy (IO)

Unmet need and current treatment options

- Unmet need in first line RCC and favourable risk group is partially addressed by availability of avelumab with axitinib. The technology is the only IO available for favourable risk group.
- Limited data in non-clear cell RCC. IO/tyrosine kinase inhibitor (TKIs) have shown some activity in non-clear cell. Some IO/TKI combinations are superior to single agent TKI in non-clear cell RCC. IO/TKIs considered less efficacious against non-clear compared with clear cell RCC.

Avelumab with axitinib

- Quality of life benefits and side-effect profile similar to other options available
- Manageable toxicity profile

"RCC is a heterogeneous disease, clinically and biologically, even within risk groups" Clinical expert 1

"Patients who do not receive immunotherapy in the first line face the prospect of dying without ever having received checkpoint Inhibitor Immunotherapy" Clinical expert 2

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Abbreviations: IO, immunotherapy; TKI, tyrosine kinase inhibitor

Equality considerations

Scope consultation: it was noted that the scope should address equity of access to avelumab with axitinib on the NHS regardless of where the person lives, for people with all subtypes of RCC, including RCC with sarcomatoid and rhabdoid features, and RCC brain metastases.

Company: important to consider equity of access to treatments across IMDC risk groups. Presently, no IO containing regimens are routinely recommended by NICE for first-line treatment in favourable risk patients, only in intermediate-/poor-risk patients.

Clinical and patient experts: unmet need in first line RCC and favourable risk group. Avelumab with axitinib will be the only IO available for the favourable risk group.

Are there any equality issues relevant to the potential recommendations?

Abbreviations: IMDC, International Metastatic RCC Database Consortium; IO, immunotherapy

Avelumab with axitinib for untreated advanced renal cell carcinoma

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- ✓ **Treatment pathway**
- ❑ Key issues
- ❑ Cost-effectiveness results

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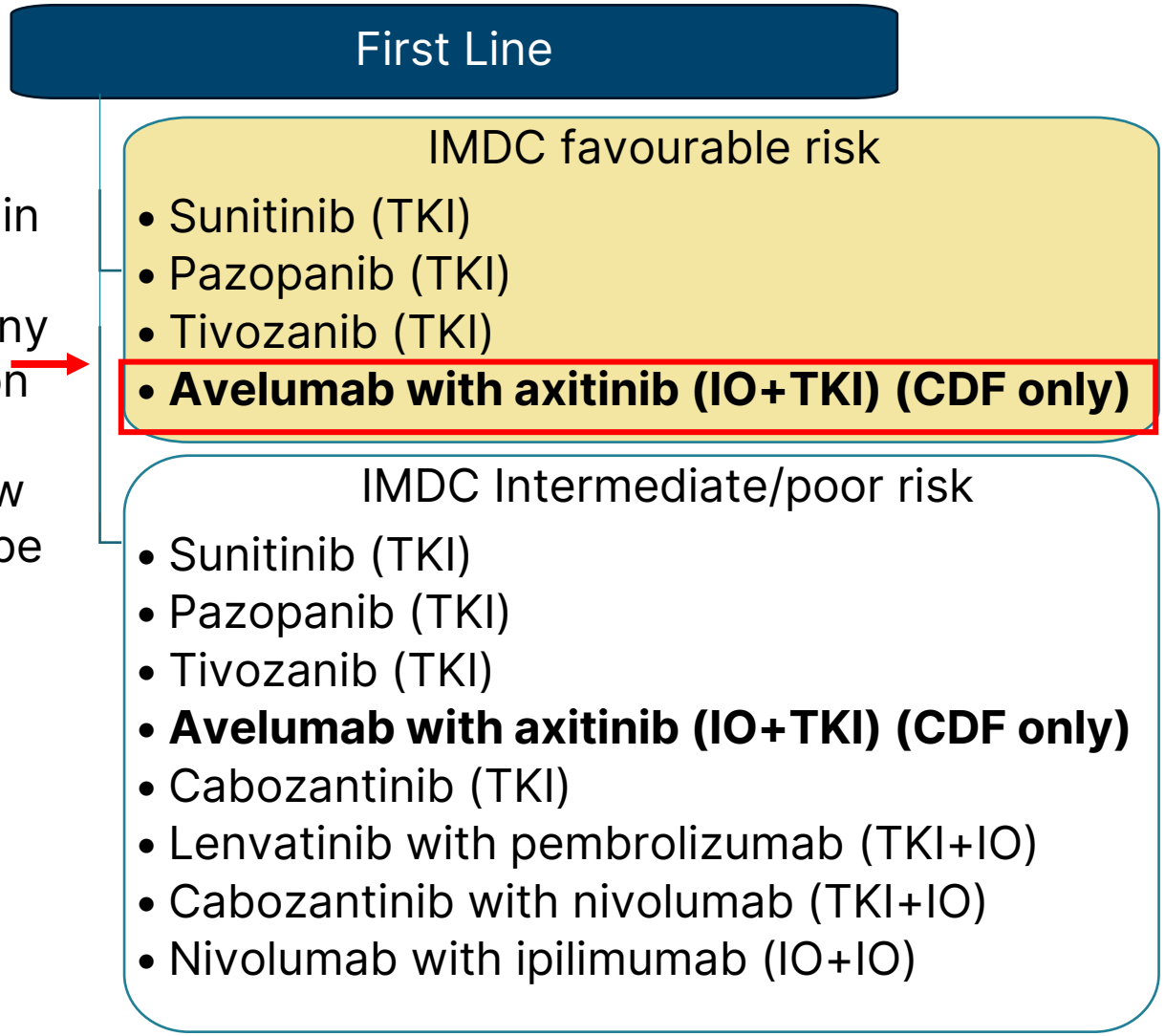
Treatment pathway presented by company

Company position in favourable risk population. Company said this population reflects greatest unmet need in new treatment landscape

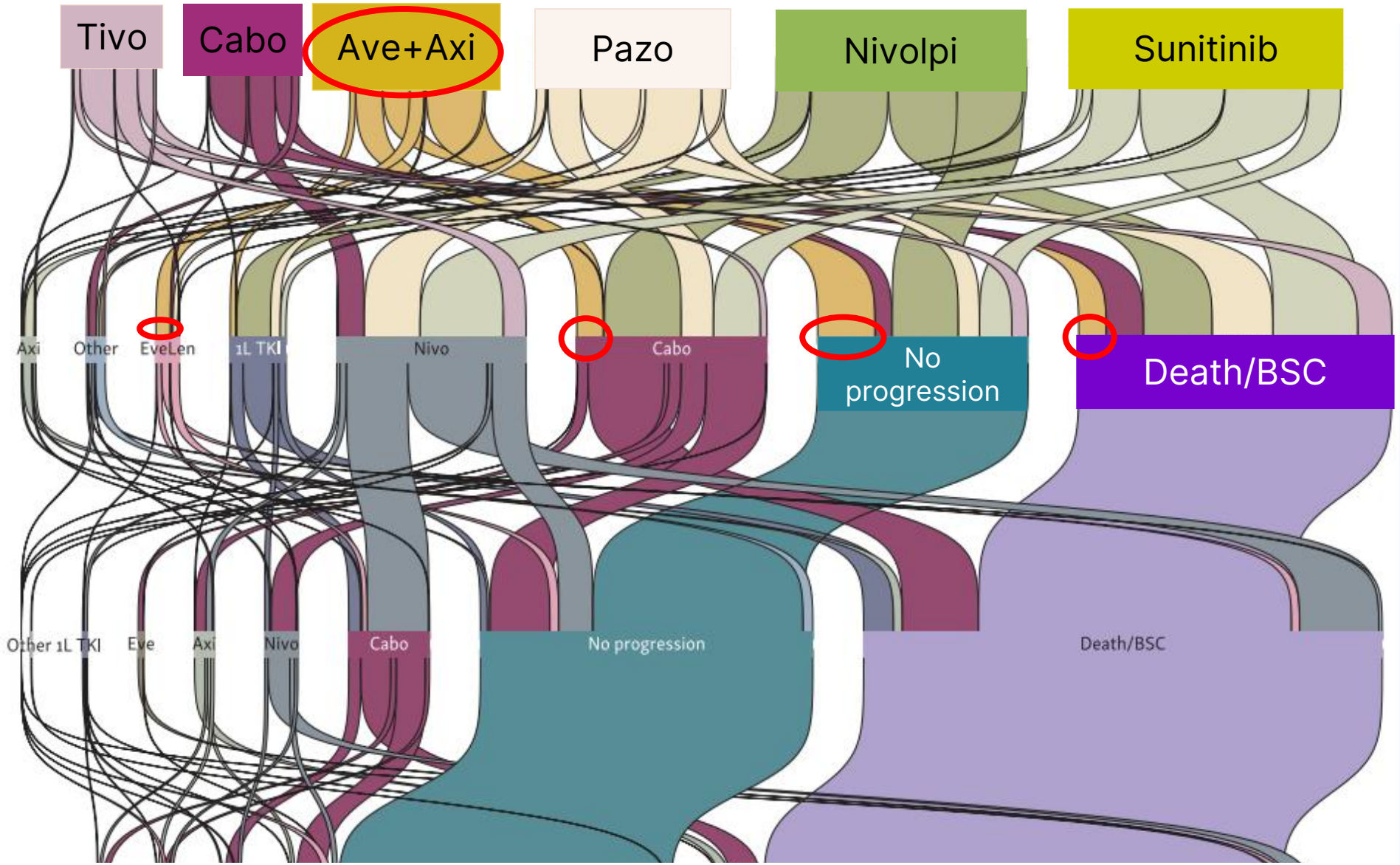


Clinical expert: The technology will be the only IO available for favourable risk. Less than 70% of people with favourable risk move to second line after censoring for people remaining on first line due to response

Abbreviations: CDF: Cancer drugs fund; IMDC, International Metastatic RCC Database Consortium; IO, Immunotherapy; SACT, systemic anti-cancer treatment TKI, Tyrosine kinase inhibitor

UK real-world treatment patterns for RCC

- Majority of people offered sunitinib as first line
- After first line avelumab with axitinib majority go on to either no progression or death /best supportive care.



Frazer, R. et al 2024. Ave+Axi, avelumab with axitinib; Axi, axitinib; BSC, best supportive care; Cabo, cabozantinib; Eve, everolimus; EveLen, everolimus with lenvatinib; 1L, first line; Nivo, nivolumab; Nivolpi, nivolumab with ipilimumab; Paz, pazopanib; Sun, sunitinib; Tiv, tivozanib; TKI, tyrosine kinase inhibitor.

Sankey diagram showing percentage of people offered treatment per line of therapy and how treatment in previous lines impacts choice of subsequent treatments

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Key issues

Issue	Resolved?	ICER impact
Uncertainty around comparators and comparative effectiveness of avelumab with axitinib: • Appropriateness of comparators included in the economic model for clear cell and non-clear cell RCC • Efficacy of avelumab with axitinib versus comparators in people with non-clear cell RCC	No – for discussion	Unknown 
Uncertainty about overall survival for avelumab with axitinib: • Avelumab with axitinib has non-significant difference in overall survival compared with sunitinib • Overall survival curve fittings and long-term projections using the JAVELIN Renal 101 trial data	No – for discussion	Large 

Abbreviations: ICER, Incremental cost-effectiveness ratio

Key issue: Comparators for clear cell and non-clear cell RCC

Background: Majority of RCC is categorised as clear cell. Treatment pathway within clear cell RCC usually split by IMDC risk groups (favourable, intermediate/poor). Non-clear cell RCC is a heterogenous group of conditions - treatment pathway split by its subtypes: papillary, chromophobe, or collecting duct.

Company: RCC treatment pathway and International guidelines were updated since original submission (September 2020). No UK-specific clinical guidelines, clinical practice in England and Wales reflect international guidelines and NICE technology appraisal recommendations. UK RWE shows three most common TKIs used in first-line for favourable risk group were sunitinib (50.5%), pazopanib (31.6%) and tivozanib (15%).

EAG comments: Comparators match those specified in the NICE scope. For the base case favourable risk population, comparators are sunitinib, tivozanib and pazopanib. Lack of comparator data for non-clear cell RCC from trials and UK RWE including SACT dataset.

NICE tech team considerations:

- ESMO and EAU guidelines split treatment of clear cell RCC by IMDC risk group and non-clear cell RCC by the distinct subtypes. EAU guideline suggest moving away from 'non-clear cell' terminology and prefer reference to distinct subtypes of non-clear cell RCC. *See appendix - ESMO treatment guideline for non-clear cell RCC

Is committee content to consider sunitinib, pazopanib and tivozanib as comparators for both clear cell RCC and non-clear cell RCC populations?

Abbreviations: CDF: Cancer drugs fund; EAU, European association of Urology; ESMO, European Society For Medical Oncology; IMDC, International Metastatic RCC Database Consortium; IO, Immunotherapy; OS, Overall survival; RWE, Real world evidence; SACT, systemic anti-cancer treatment TKI, Tyrosine kinase inhibitor

JAVELIN Renal 101 trial design and ITT key results

Phase 3, multinational, multicentre, open-label, parallel two-arm, randomised study

Participants
- 18 years and over
- Advanced or metastatic RCC with clear cell component
- Treatment-naive
- ECOG performance status 0 or 1
- Adequate renal, cardiac, hepatic function
- No brain metastases

n=442 → **Avelumab** 10mg/kg IV Q2W in a 6-week cycle + **axitinib** 5mg oral twice daily

n=444 → **Sunitinib** 50 mg oral daily for 4 weeks, followed by 2-week break

- Participants allowed to stop avelumab or axitinib
- No crossover allowed

Treat to progression or toxicity

All risks group results from latest data cut	Avelumab + axitinib (n=442)	Sunitinib (n=444)
PFS in the overall population		
Median follow-up, months (95% CI)	Not reported	Not reported
Median PFS, months (95% CI)	13.9 (11.1, 16.6)	8.5 (8.2, 9.7)
HR (95% CI); 1-sided p-value	0.66 (0.565, 0.768) <0.0001	
OS in the overall population		
Median follow-up, months (95% CI)	73.7 (72.3, 74.6)	73.6 (72.0, 75.5)
Deaths, n (%)	283 (64.0)	295 (66.4)
Median OS, months (95% CI)	44.8 (39.7, 51.1)	38.9 (31.4, 45.2)
HR (95% CI); 1-sided p-value	0.88 (0.749, 1.039) 0.0669	

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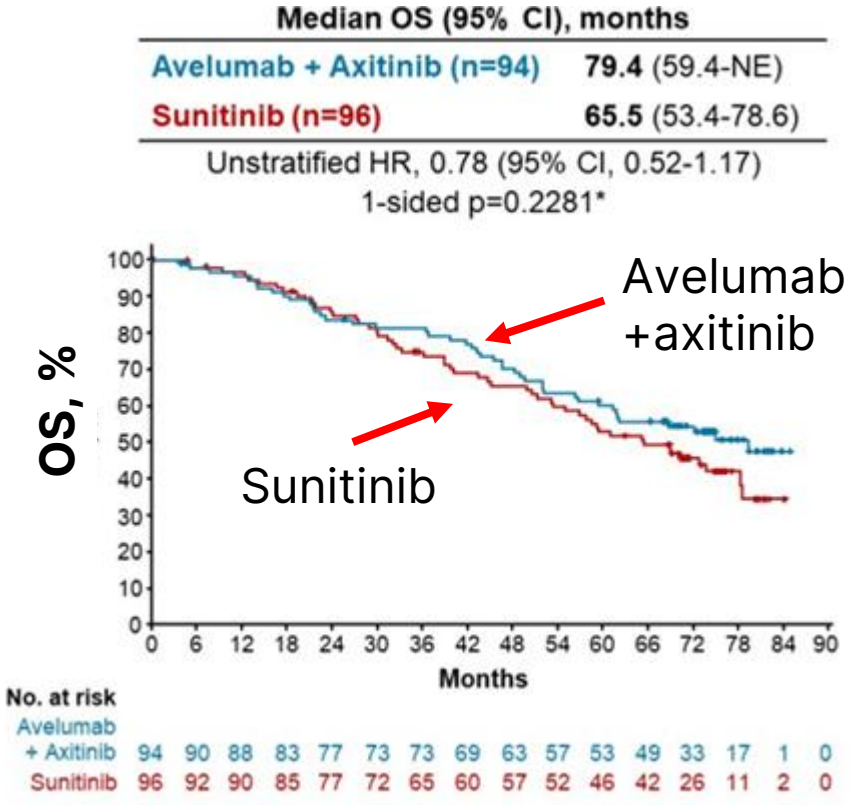
Abbreviations: CI, Confidence interval ; ECOG, Eastern Cooperative Oncology Group ; HR, Hazard ratio ; ITT, Intention to treat; IV, Intravenous; kg, kilogram; mg, milligram; PFS, Progression free survival ; Q2W: every two weeks; OS, Overall survival

Key clinical trial results: Favourable risk

Trial not powered to determine statistical significance within IMDC subgroups.

Sample size	Avelumab + axitinib	Sunitinib
ITT full analysis set	442	444
Favourable risk	94	96

Avelumab with Axitinib versus sunitinib: OS
Stratified HR (95% CI): 0.73 (0.48-1.10), p-value: 0.13

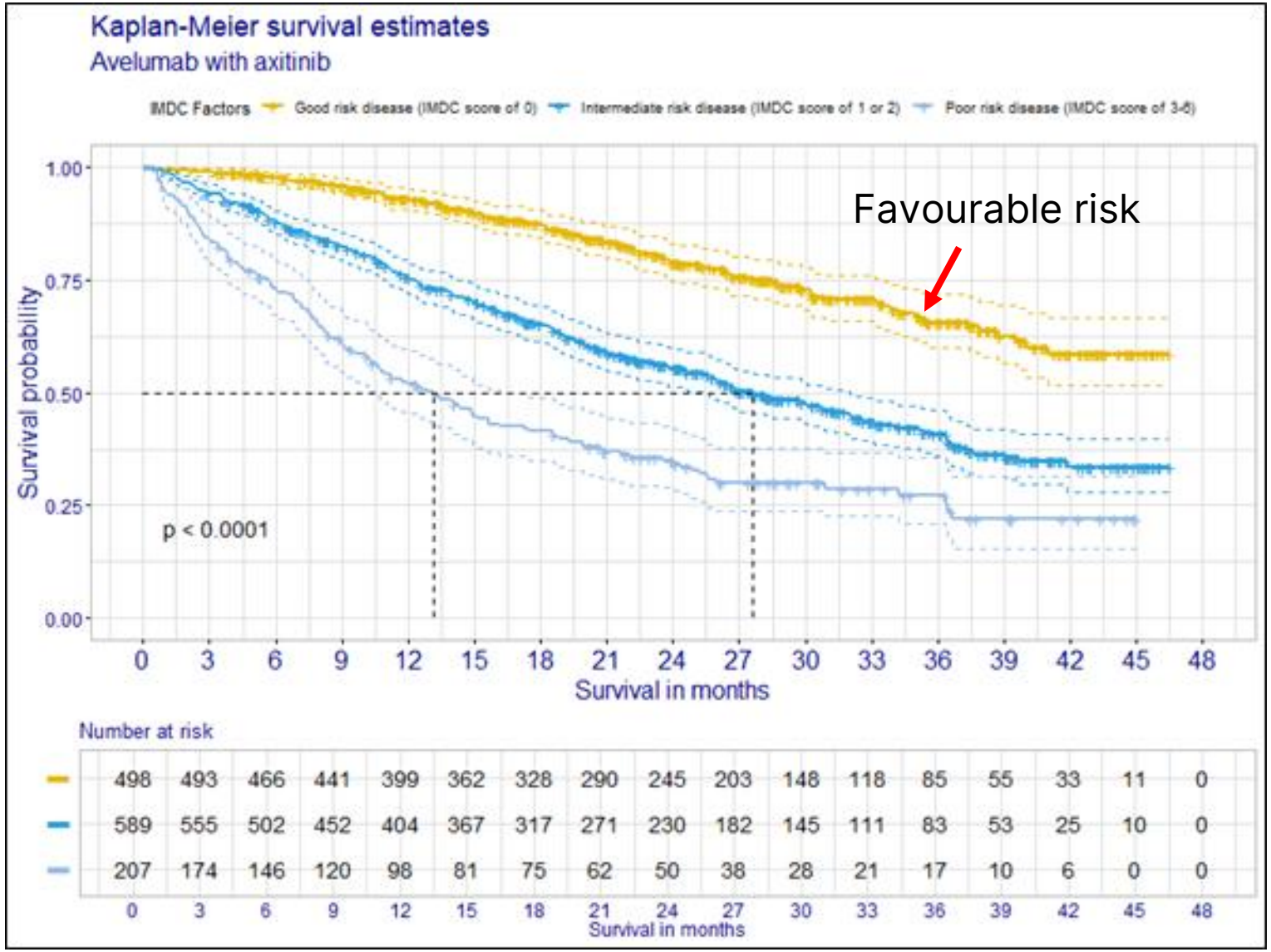


Avelumab with Axitinib versus sunitinib: PFS
Stratified HR (95% CI): 0.75 (0.53-1.07), p-value: 0.11

	Median PFS (95% CI) Months
Avelumab + axitinib (n=94)	20.7 (16.6-26.2)
Sunitinib (n=96)	13.8 (11.1-23.5)

Abbreviations: CI, Confidence interval; : IMDC, International Metastatic RCC Database Consortium; ITT, Intention to treat; HR, Hazard ratio; OS, Overall survival; PFS, Progression free survival

CDF dataset: Avelumab with axitinib Kaplan-Meier overall survival plot by IMDC risk group



Favourable risk

- Median OS **not reached**
- In comparison the median OS for favourable risk patients in JAVELIN Renal 101 was 79.4 months
- No CDF data on comparators
- Difference in OS statistically significant between intermediate risk and poor risk group.

Abbreviations: CDF: Cancer drugs fund; IMDC, International Metastatic RCC Database Consortium; OS, Overall survival

Key issue: Uncertainty in long term overall survival

Background: JAVELIN Renal 101 provides median OS follow-up of 6 years (~5 years of additional follow-up compared with datacut used in TA645). Equal efficacy assumed for sunitinib, pazopanib and tivozanib based on TA645 and past RCC NICE committee conclusions.

Company:

- JAVELIN Renal 101 provides the longest follow-up for an IO+TKI combination treatment from a RCC trial.
- Median OS 14 months longer in avelumab with axitinib arm than sunitinib arm. Clear separation of survival curves from approximately 30 months, which continued to end of follow-up

EAG comments:

- Trial was not powered to determine statistical significance within IMDC subgroups. Confidence intervals for OS are wider for favourable risk subgroup compared with ITT population because of small sample size resulting in more uncertainty in median OS estimates.

Note: OS statistical significance also not reached in larger ITT population. Hazard ratio (95% CI) 0.88 (0.749, 1.039); p-value 0.0669

Question for Committee
Has the uncertainty arising from the immature survival data presented for TA645 been resolved?

Abbreviations: CI, Confidence interval; IMDC, International Metastatic RCC Database Consortium; IO, Immunotherapy; ITT, Intention to treat; OS, Overall survival; TKI, Tyrosine kinase inhibitor

Key issue: Efficacy in non-clear cell RCC

Background: No head-to-head trials comparing avelumab with axitinib to comparators other than sunitinib in clear cell. SACT evidence (CDF) available for avelumab with axitinib split by non-clear cell and clear cell RCC. But does not include comparators or proportion with IMDC favourable risk for non-clear cell RCC. Equal efficacy assumed for sunitinib, pazopanib and tivozanib based on TA645 and past RCC NICE committee conclusions.

Company: JAVELIN Renal 101 excluded non-clear cell subtypes. Clinical experts note real-world data supports avelumab with axitinib in non-clear cell: UK early access to medicines scheme data show median OS = 21.5 months, Japan RWE shows median OS not reached in non-clear cell RCC treated with avelumab with axitinib.

EAG comments: Greater disease burden observed in people with non-clear cell RCC. CDF shows non-clear cell has shorter OS and treatment duration compared with clear cell RCC. Comparative effectiveness not available for this subtype from JAVELIN Renal 101 or UK real world evidence.

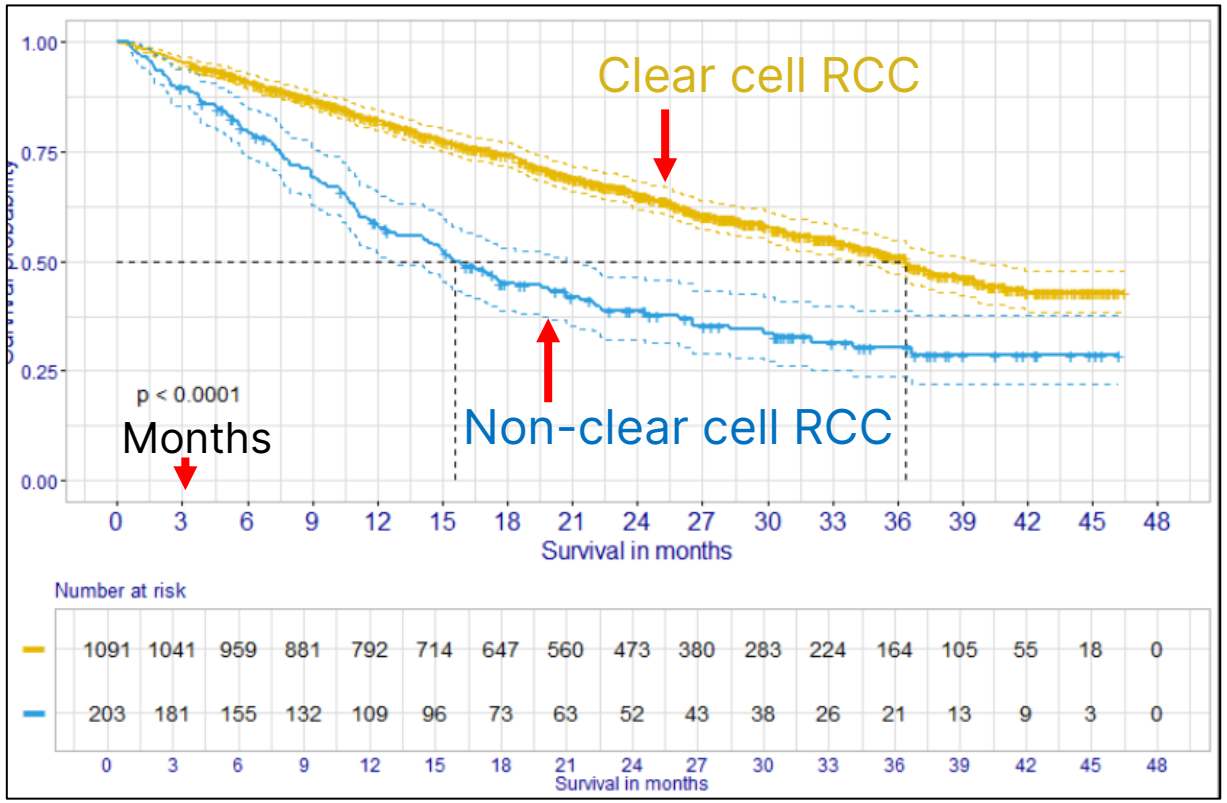
Other considerations: Clinical expert has experience of using avelumab with axitinib in non-clear cell RCC with good efficacy and tolerability. ESMO guidelines flag limited quality data to guide recommendations. Single agent TKIs, IOs/TKI combinations included in pathway but recommendation varies by subtype.*

*See appendix - ESMO treatment guideline for non-clear cell RCC

Questions for Committee:

1. In the absence of clinical effectiveness data is it reasonable to generalise the JAVELIN Renal 101 data on clear cell RCC for non-clear cell subtypes?
2. Is it reasonable to assume equal efficacy between the three comparators?

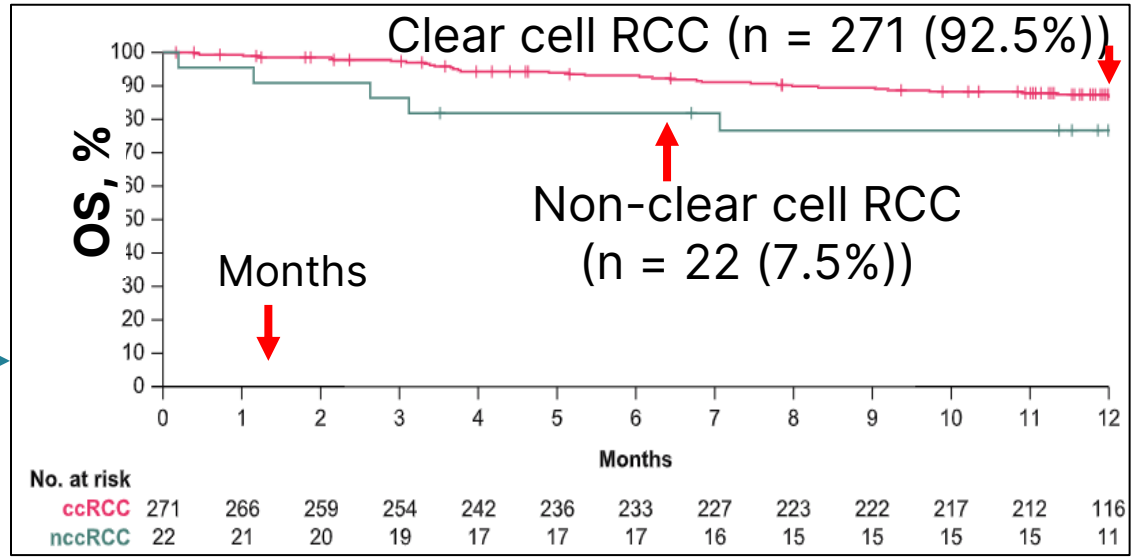
CDF and Japanese RWE: Avelumab with axitinib Kaplan-Meier overall survival plots by RCC histology



CDF dataset (Figure 10 SACT report): Shorter* median OS statistically significantly difference for non-clear cell compared with clear cell group

- Clear cell RCC: n = 1,091 (84%), median OS (95% CI): **36.4 months (33.9, 39.6)**
- Non-clear cell RCC**: n = 203 (16%), median OS (95% CI): **15.6 months (12.6, 20.7)**

*Hazard ratio and confidence interval for statistical difference in median OS for non-clear vs clear cell RCC not presented in SACT report. **Includes Unclassified RCC (n = 99 (8%)) and not captured (n = 2 (less than 1%))



Nonomura 2024: Japan RWE for curatively unresectable or metastatic RCC. Median OS not reached in clear cell or non-clear cell subgroups.

- 6-month OS rates were **93.1% and 81.8%**
- 12-month OS rates were **86.8% and 76.7%**

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Abbreviation: CDF, Cancer Drugs Fund; IMDC, International Metastatic RCC Database Consortium; IO, Immunotherapy; OS, Overall survival; RWE, Real world evidence

Key issue: Overall survival curve fittings and long-term projections

Background: Model uses parametric curves fitted to data for OS from JAVELIN Renal 101 for avelumab with axitinib and for sunitinib. OS for tivozanib and pazopanib are assumed equal to sunitinib.
EAG agrees with company's OS extrapolation curve selection with caveat that evidence/expert opinion is needed to inform the curve choice beyond 10 years.

Company:

- Proportional hazards assumption not met and independent parametric survival models fitted to trial OS data.
- Survival estimates remain similar between curves in initial 5 years, with wider spread observed at 10 years (avelumab with axitinib: ranging from 22.7% to 36.7% alive; sunitinib: 8.2% to 28.6% alive).
- Curves selected by statistical goodness-of-fit and long-term survival projections aligned with clinical expert opinion.

EAG comments:

- Company provided OS hazards plots on a log-cumulative scale*. Need OS hazard functions that plot mortality hazard against time on the hazard scale (**TSD21) for treatments in JAVELIN Renal 101 to visualise whether and how hazards change over time.
- AIC/BIC scores show similar statistical fits for log-logistic, Weibull and log-normal for avelumab with axitinib and for sunitinib, log-logistic, Weibull and log-normal have similar fits.
- RCC pathways pilot model (Lee 2023) used exponential distribution for sunitinib arm in favourable risk group but for JAVELIN Renal 101 trial this was a poor statistical fit.

Abbreviations: CI, Confidence interval; IMDC, International Metastatic RCC Database Consortium; IO, Immunotherapy; ITT, Intention to treat; OS, Overall survival; TKI, Tyrosine kinase inhibitor
*See appendix for plots provided by company - Exploratory analyses for JAVELIN Renal 101 (FA) – Overall...
**NICE Decision Support Unit technical support document 21: Flexible Methods for Survival Analysis

Overall survival extrapolations: Favourable risk (1/2)

Company and EAG use same extrapolations

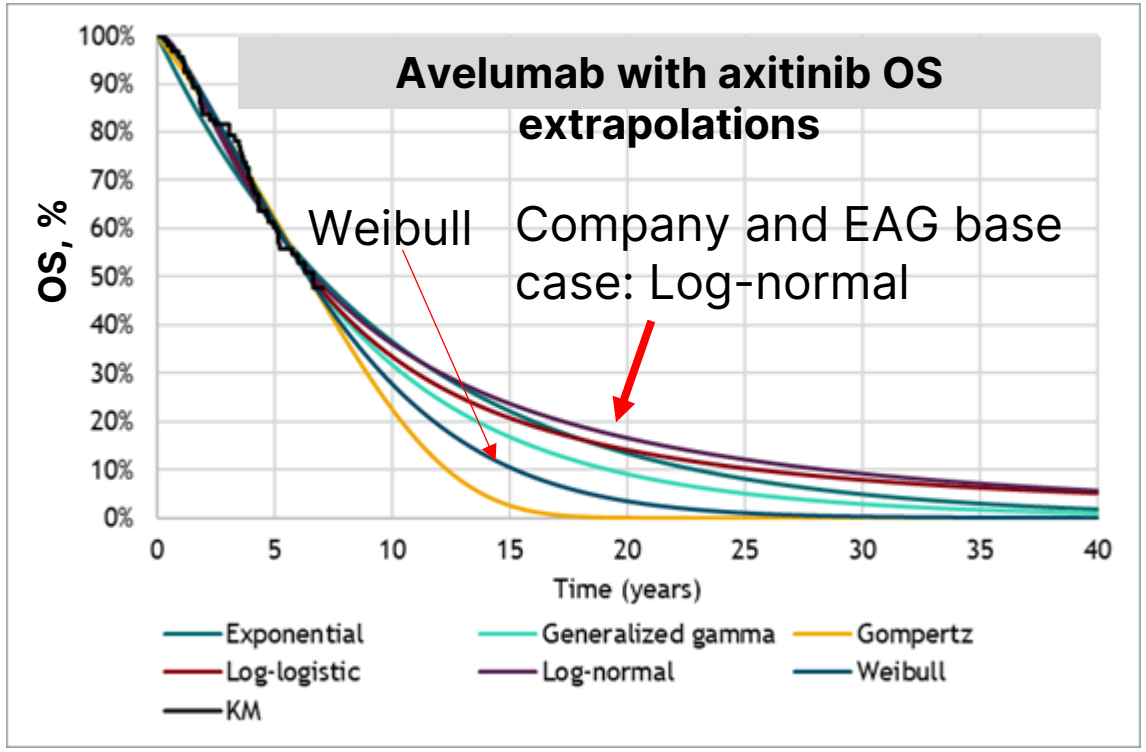
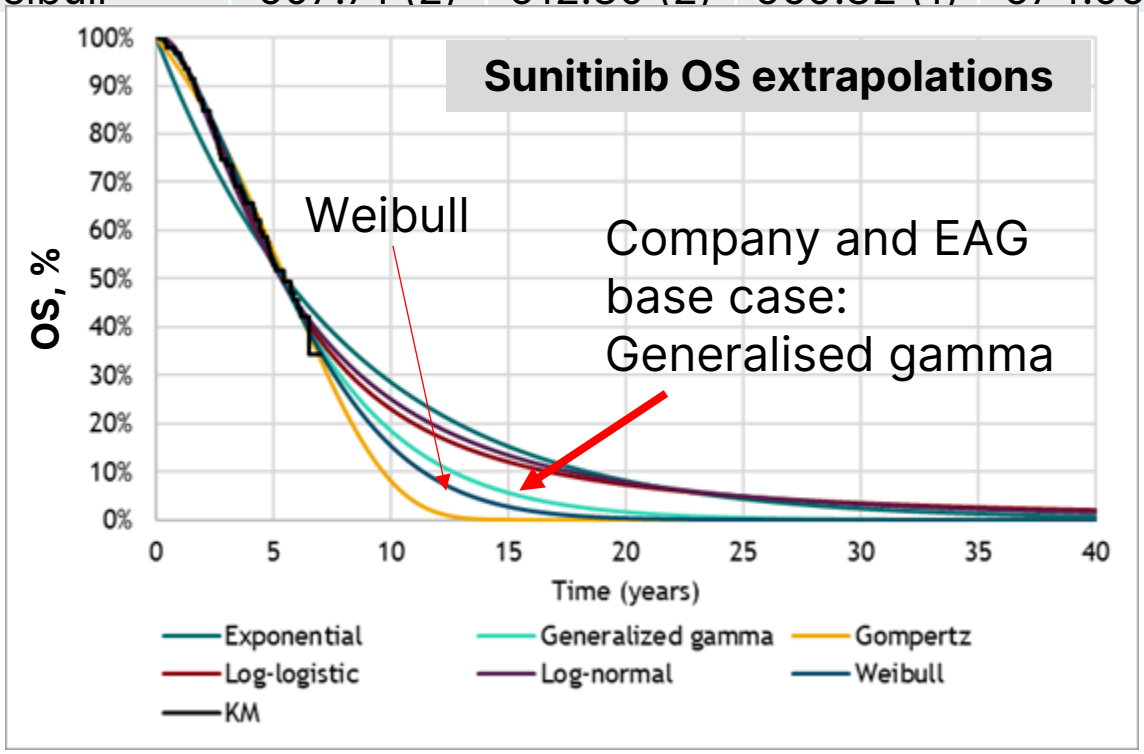


Table: Statistical goodness-of-fit scores for OS extrapolations

	Ave+Axi OS		Sunitinib OS	
Parametric function	AIC (Rank)	BIC (Rank)	AIC (Rank)	BIC (Rank)
Exponential	510.82(6)	513.36 (4)	580.32 (6)	582.88 (6)
Gen gamma	509.36 (4)	516.99 (6)	**571.59 (4)**	**579.28 (5)**
Gompertz	509.43 (5)	514.52 (5)	572.61 (5)	577.73 (4)
Log-logistic	507.57 (1)	512.65 (1)	570.12 (2)	575.25 (2)
Log-normal	**508.01 (3)**	**513.10 (3)**	571.12 (3)	576.25 (3)
Weibull	507.71 (2)	512.80 (2)	569.82 (1)	574.95 (1)



Abbreviations: AIC, Akaike information criterion; Ave+Axe, Avelumab with axitinib; BIC, Bayesian information criterion; KM, Kaplan-Meier; OS, overall survival

Overall survival extrapolations: Favourable risk (2/2)

Overall survival estimates from extrapolations adjusted for general population mortality

Parametric function	Avelumab + axitinib Estimated survival				
	5 years	10 years	20 years	30 years	40 years
Exponential	60.5%	36.6%	13.4%	3.9%	0.0%
Generalised gamma	60.6%	31.7%	9.1%	2.4%	0.0%
Gompertz	62.1%	22.5%	0.0%	0.0%	0.0%
Log-logistic	60.6%	33.4%	14.1%	4.5%	0.0%
★ Log-normal	60.1%	36.0%	16.6%	5.3%	0.0%
Weibull	61.4%	27.7%	3.5%	0.3%	0.0%

★→ EAG and company base case

Parametric function	Sunitinib Estimated survival				
	5 years	10 years	20 years	30 years	40 years
Exponential	53.4%	28.5%	8.1%	2.1%	0.0%
★ Generalised gamma	53.4%	18.5%	1.6%	0.1%	0.0%
Gompertz	55.6%	8.0%	0.0%	0.0%	0.0%
Log-logistic	53.0%	22.9%	7.3%	2.3%	0.0%
Log-normal	52.7%	25.0%	7.8%	2.3%	0.0%
Weibull	54.1%	15.3%	0.3%	0.0%	0.0%

Does the committee agree with the EAG and company's selection of curves?

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Recap: Key issues and questions for committee

Issue	Questions for committee
Uncertainty around comparators and comparative effectiveness of avelumab with axitinib: a) Appropriateness of comparators included in the economic model for clear cell and non-clear cell RCC b) Avelumab with axitinib efficacy versus comparators in people with non-clear cell RCC	1. Is committee content to consider sunitinib, pazopanib and tivozanib as comparators for both clear cell RCC and non-clear cell RCC populations? 2. In the absence of clinical effectiveness data is it reasonable to generalise the JAVELIN Renal 101 data on clear cell RCC to non-clear cell subtypes? 3. Is it reasonable to assume equal efficacy between the three comparators?
Uncertainty surrounding overall survival for avelumab with axitinib: a) Avelumab with axitinib has non-significant difference in overall survival compared with sunitinib b) Overall survival curve fittings and long-term projections using the JAVELIN Renal 101 trial data	1. Has the uncertainty arising from the immature survival data presented for TA645 been resolved? 2. Does the committee agree with the EAG and company's selection of curves?

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Key cost-effectiveness results summary

- Detailed results shown in part 2 only because of confidential prices for comparators
- All ICERs versus sunitinib >£30,000. Alternative overall survival distributions had greatest impact on ICER

No.	Scenario (applied to company base case)	ICER (£/QALY) versus Sunitinib	ICER (£/QALY) versus Tivozanib	ICER (£/QALY) versus Pazopanib
1	**Company and EAG base case**	Over £30,000	Dominated by sunitinib	Dominated by sunitinib
2-4	OS extrapolation (Avelumab with axitinib) • Exponential • Generalised gamma • Log-logistic	Over £30,000	Dominated by sunitinib	Dominated by sunitinib
5	OS extrapolation (Sunitinib) • Weibull	Over £30,000	Dominated by sunitinib	Dominated by sunitinib
6-7	OS extrapolation (Sunitinib) • Exponential • Log-logistic	Over £30,000	Dominated by sunitinib	Dominated by sunitinib

Appendix

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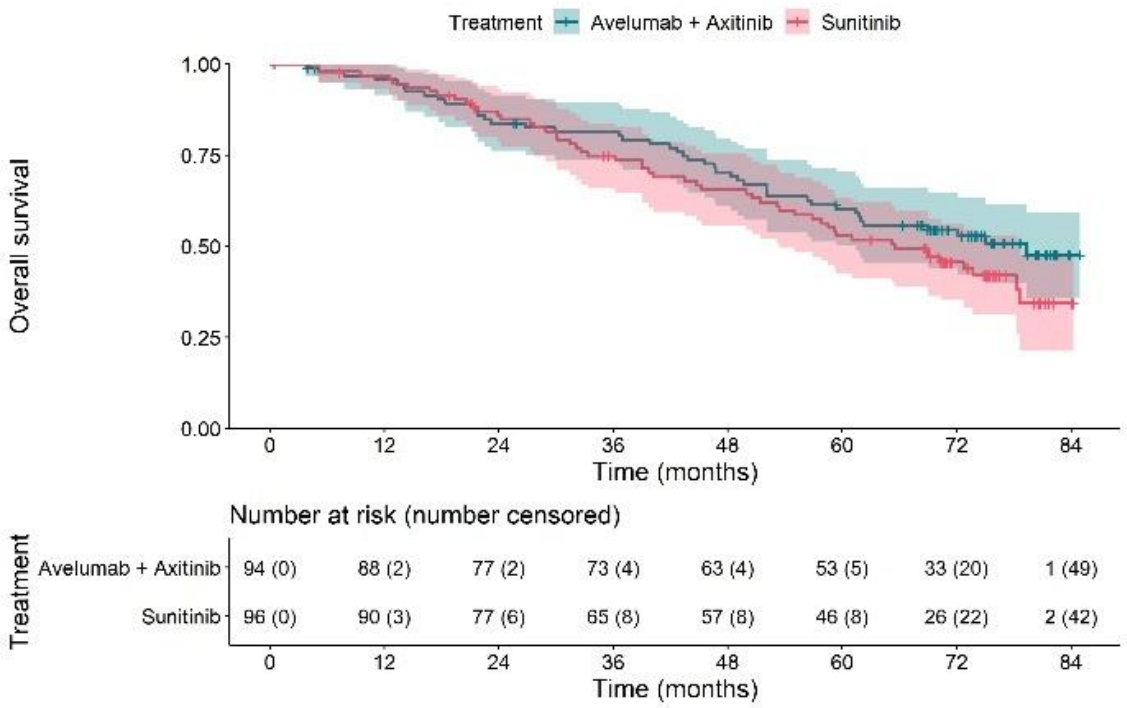
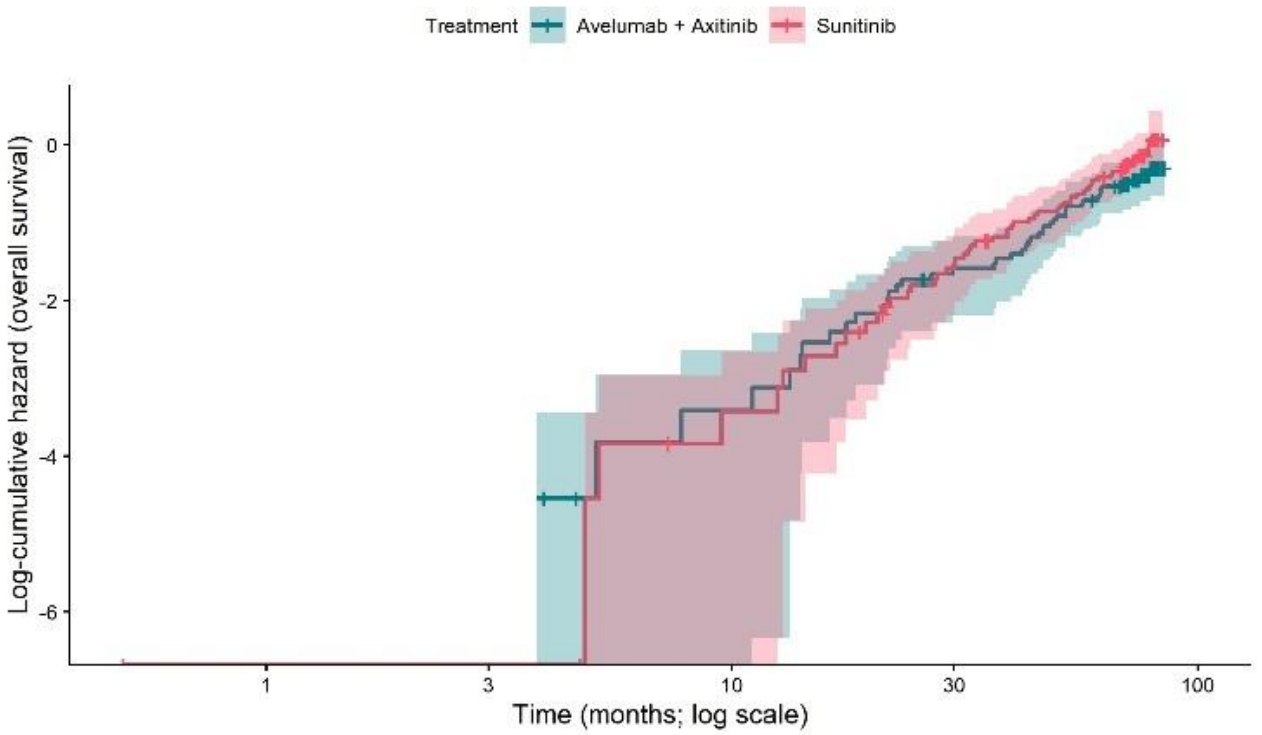
Exploratory analyses for JAVELIN Renal 101 (Final Analysis) – Overall survival (favourable risk)

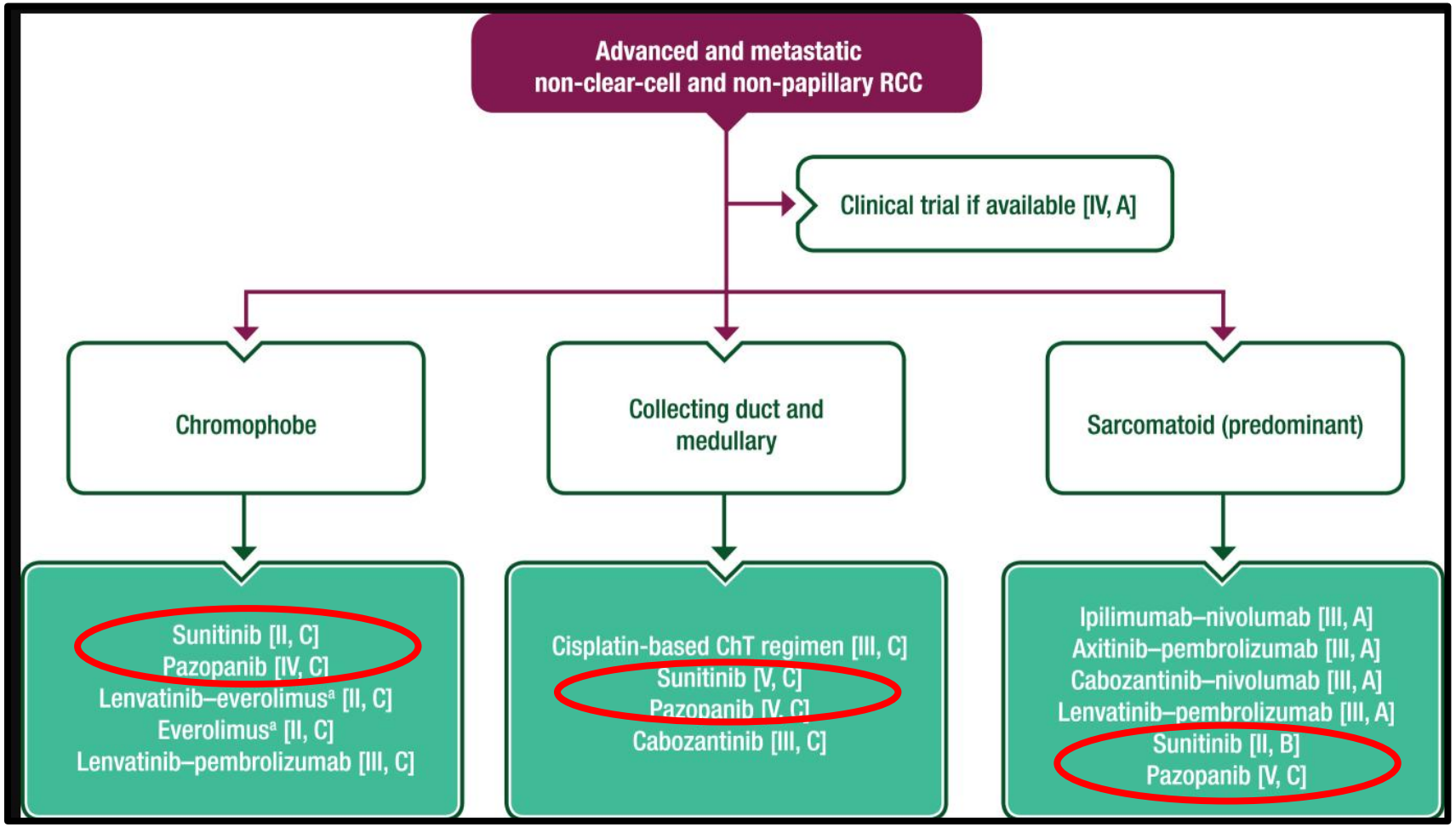


Kaplan-Meier plot



Log-cumulative hazard plot

ESMO treatment guideline for Non-clear cell RCC



"There is a paucity of robust data to guide management of non-clear cell, non-papillary RCC histologies"

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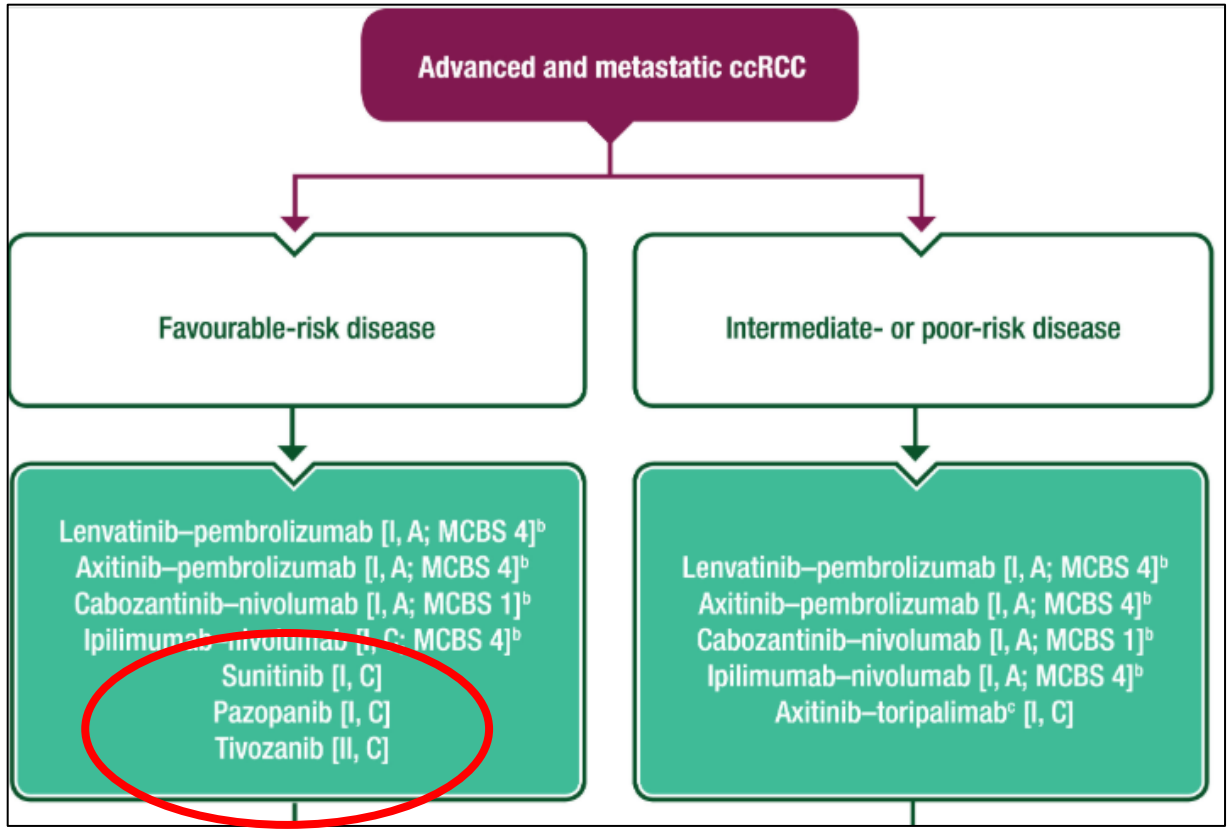
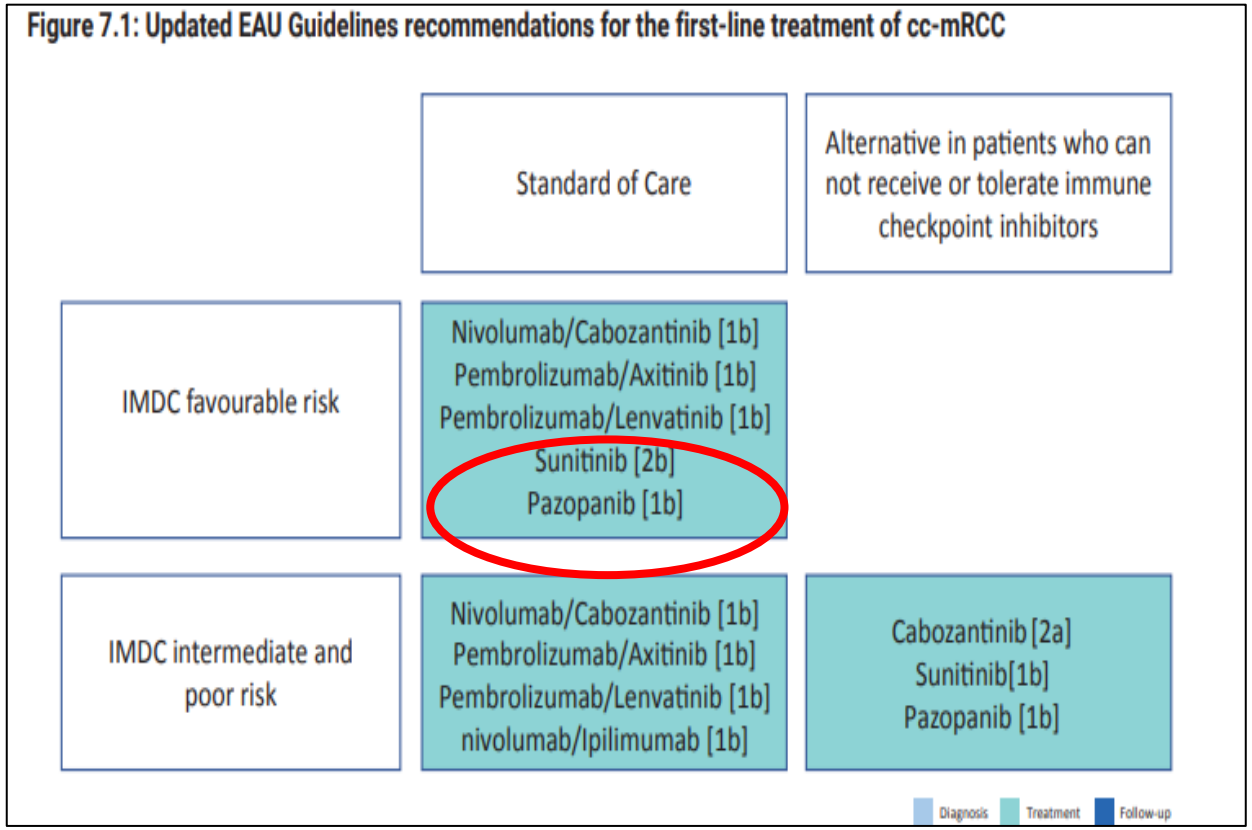
Renal cell carcinoma: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up Powles, T. et al. Annals of Oncology, Volume 35, Issue 8, 692 - 706

ESMO and EAU treatment guideline for Clear cell RCC



ESMO guidelines



EAU guidelines