Treatments for renal cell carcinoma

Contains AIC information, CIC and cPAS redacted

Technology appraisal committee B [26 October 2023]

Chair: Charles Crawley

Lead team: Gabriel Rogers, David McAllister, Nigel Westwood

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Technical team: Lewis Ralph, Hannah Nicholas, Elizabeth Bell, Jasdeep Hayre

Company: Ipsen

Pathway approach to technology appraisal

Introduction to the pilot process

NICE National Institute for Health and Care Excellence

Proportionate Approach To Technology appraisals (PATT)

Supporting access	NICE appraises all new medicines and indications
Increasing demand	98 appraisals per year Anticipated to grow
Capacity constraints	Across patient and carer groups, academic groups and committees, clinicians, industry and NICE
Complexity	How can we best use our time, and our stakeholders' time, to support rapid access to innovative medicines?

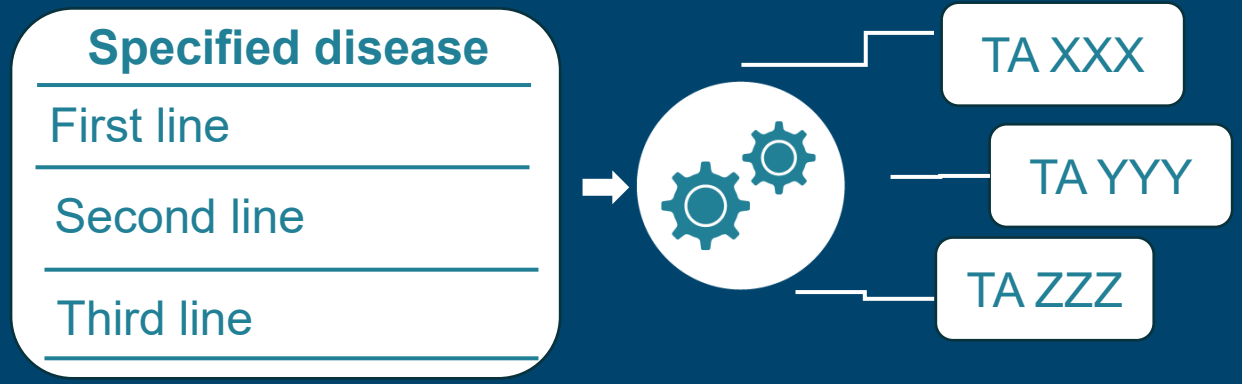
Pathway approach

Challenges

- Increasing number of appraisals in the same disease area
- Appraisals consider a single point in the pathway at a single point in time
- Creating complex pathways and multiple sequential decisions
- Repetition in appraisals and inconsistent inputs

Solutions

A core model, spanning a disease pathway to **efficiently** assess multiple technologies across decision spaces



Provide **useful and useable advice,** aligning access decisions in the care pathway

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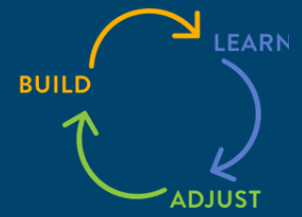
Pathway aims



Pathway approach

- **Improve efficiency**, assessing multiple technologies in a disease pathway
- **Inform robust decisions** by building an evolving model for a disease area
- Create more **cohesive guidance** about treatment options in the pathway
- Provide a **platform for monitoring and updating** the disease pathway in the future

- The first pilot for 'Pathway approach' is Renal Cell Carcinoma (RCC) [ID6186]
  - One technology, sponsored by Ipsen: cabozantinib with nivolumab at first line
  - A transparent model, developed by an EAG, that, if NICE implements the pathway approach, will form the basis of decision making for current and future RCC appraisals
    - RCC model programmed in R
    - Code published on GitHub for transparency and internal/external validation
  - Evidence collected for each decision point in the pathway and results used in committee decision making

NICE

Abbreviations: EAG, external assessment group; RCC, renal cell carcinoma.

Evaluation process

Phase 1 - Scope development and preparatory work

- NICE team developed and engaged on an RCC pathway scope, outlining the care pathway in a scoping workshop **[Completed]**

Phase 2 - Academic evidence synthesis and modelling work

- NICE commissioned the modelling work from an academic group, starting with model conceptualisation and analysis plan and culminating in an external assessment report and model **[Completed]**

Phase 3 - Evaluation and decision-making

- Company evidence submission incorporated into the Phase 2 model, engagement between EAG and company on model assumptions **[Completed]**
- ***Committee presented with base cases and scenarios to sign off assumptions***

Phase 4 – Maintenance phase

- If NICE implements the pathway approach:
- New treatments entering the pathway
- Final model updates before open-source release
- Triggers for model and evidence update (i.e., safety review, patent expiry, service provision change etc.)

NICE

Abbreviations: EAG, external assessment group; RCC, renal cell carcinoma.

Committee

Outputs

1

Pathways conclusions

- Committee conclusions on:
  - Model structure
  - Likely treatment pathway
  - Source to estimate absolute event rates
  - Utilities
  - Resource costs
  - Severity at different decision nodes
  - No consideration of optimal sequencing of treatments

2

Guidance recommendation

- Committee conclusions on cabozantinib and nivolumab
  - Clinical-effectiveness
  - Cost-effectiveness
  - Specific value proposition (uncaptured benefits etc.)
  - Considerations of uncertainty
- No recommendations on optimal sequencing of treatments

- Committee consider both elements today
- Committee will not be making recommendations about any other interventions, but these are incorporated in the clinical and cost-effectiveness analyses

Abbreviations: ACM, appraisal committee meeting; CABO+NIVO, cabozantinib plus nivolumab.

Treatments for renal cell carcinoma

Background information

NICE National Institute for Health and Care Excellence

Background on renal cell carcinoma

Advanced RCC associated with poor survival outcomes

Causes

- RCC is a cancer that usually originates in the lining of the tubules of the kidney

Epidemiology

- RCC is the most common type of kidney cancer, accounting for more than 80% of cases
- Occurs 1.7 times more in men than in women; 25% diagnosed aged 60 to 69 years, 50% ≥70 years
- There are several types of RCC, with clear cell accounting for 75% of cases

Diagnosis and classification

- Treatment depends on the location and stage
    - Stage 1 and 2 – early stage where tumour is localised in the kidney
    - Stage 3 – locally advanced stage with possible spread to regional lymph nodes
    - Stage 4 – advanced, metastatic stage where tumour has spread to other parts of the body
- Risk status classified by IMDC risk score; used to stratify patients in trials and guide treatment decisions
- Majority of patients with RCC in the UK are classified as intermediate or poor risk

Symptoms and prognosis

- 5-year survival rate: Stage 1, 86.8%; Stage 2, 76.6%, Stage 3, 74.2% and Stage 4, 12.4%

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Abbreviations: IMDC, International Metastatic RCC Database Consortium; RCC, renal cell carcinoma; UK, United Kingdom.

Patient perspectives

Advanced RCC has a big impact on daily life and is currently incurable

Submissions from Action Kidney Cancer, Kidney Cancer UK and the BAUS

- Advanced/metastatic RCC is devastating and currently incurable
- Most forced to give up work due to symptoms or toxicity of treatment
- This brings financial pressures for patients and their families, can result in psychosocial problems, depression and loss of confidence and self-worth
- Treatment side effects severely affect quality of life, and impact the lives of family
- Treatments have improved, but RCC is still clearly well behind other cancer treatments and more needs to be done

Treatment does not necessarily put you free from the condition. I have received news of a recurrence and so the fear and worries start again after 5 years

I was advised about the difficulty of my treatment; I realised there may be things after it I may not ever be able to do the same

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Abbreviations: BAUS, British Association of Urological Surgeons; RCC, renal cell carcinoma.

Cabozantinib (Cabometyx, Ipsen) plus nivolumab (Opdivo, BMS)

Marketing authorisation	• Combination was granted approval for the first-line treatment of adults with advanced RCC • Granted by MHRA on 13 May 2021
Mechanism of action	• Cabozantinib: multiple receptor TKI • Nivolumab: PD-1 inhibitor
Administration	• Cabozantinib orally at a dose of 40 mg once daily • Nivolumab intravenously at either 240 mg every 2 weeks or 480mg every 4 weeks
Price	• Cabozantinib: £5,143 per 30 x 40 mg capsule pack (list price) • Nivolumab: £439 per 40 mg; £1,097 per 100 mg; £2,633 per 240 mg vial (list price) • Approved commercial arrangements (commercial in confidence)

Abbreviations: BMS, Bristol Myers Squibb; mg, milligram; MHRA, Medicines and Healthcare products Regulatory Agency; PD, programmed death; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor.

Decision problem

	Final scope	Decision problem addressed by EAG
Population	People with untreated advanced or metastatic RCC	Per the scope, all evidence identified was for adults
Intervention	Cabozantinib plus nivolumab	Per the scope
Comparators	• Pazopanib • Tivozanib • Sunitinib • Cabozantinib (int-/poor-risk only) • Nivolumab plus ipilimumab (int-/poor-risk only) • Lenvatinib plus pembrolizumab (int-/poor-risk only) • Active surveillance	In line with the scope, except active surveillance has not been included Considered to happen prior to the decision node at which this model starts
Outcomes	• Overall survival • Progression-free survival • Response rates • Duration of response • Time on treatment/time to next treatment • Adverse effects of treatment • Health-related quality of life	Per the scope dependent upon data availability; limited data are available for time on treatment and time to next treatment within published literature
Subgroups	If evidence allows: • Int-/poor-risk advanced metastatic RCC as defined in the IMDC criteria • prior treatment	• Int-/poor-risk advanced metastatic RCC defined by IMDC criteria • Favourable-risk advanced metastatic RCC defined by IMDC criteria

Abbreviations: EAG, external assessment group; IMDC, International Metastatic RCC Database Consortium; int, intermediate; RCC, renal cell carcinoma.

Key questions for committee: decision problem

Category	Question
Comparators	Is tivozanib a relevant comparator?
Risk groups	Should cabo + nivo be assessed in different risk groups (all, favourable and intermediate/poor)?
Subsequent treatments	Does the EAG's understanding of the clinical pathway and treatment sequencing match NHS practice?
	How could inclusion of nivo+cabo change the pathway?
	Are the proportions of subsequent treatments from the RWE reflective of clinical practice?

Abbreviations: cabo+nivo, cabozantinib plus nivolumab; EAG, external assessment group; NHS, National Health Service; RWE, real-world evidence.

Comparators

EAG excludes avelumab plus axitinib but includes tivozanib as comparators

Background

- EAG excluded ave+axi as only available in CDF; included tivozanib as is used by a reasonable proportion of patients and has been recommended for routine commissioning by NICE

Company

- Note the value of ave+axi and propose it is a relevant comparator, as it is available at first line in England
- Disagree that tivozanib is frequently used in first line as uptake data suggests differently
- Including tivozanib in the NMAs increases uncertainty as TIVO-1 did not include any poor risk patients

EAG comments

- Only comparators included in the final decision problem have been considered by the EAG
- Ave+axi data have still been included in the analysis model for completeness, and for the long-term goal of the pathways approach but not for economic analyses for this appraisal (ID6186)
- Acknowledge limitations with tivozanib data, but included as tivozanib is a recommended option
  - Sensitivity analysis excluding tivozanib showed minimal difference to NMA outputs

NICE position

- Ave+axi is not a relevant comparator as it is only available through the CDF, and not established practice
- It is up to the committee to conclude is tivozanib is a relevant comparator for advanced RCC

Is tivozanib a relevant treatment for the pathway? Is tivozanib a relevant comparator for cabo+nivo?

Abbreviations: Ave+axi, avelumab plus axitinib; cabo+nivo, cabozantinib plus nivolumab; CDF, Cancer Drugs Fund; EAG, external assessment group; NMA, network meta-analysis; RCC, renal cell carcinoma.

Subgroups (1)

EAG presents results for risk subgroups separately

Background

- Risk status has been important in prior NICE RCC appraisals
- Some treatments have received optimised recommendations by risk-group (TA542, TA780, TA858)

Company

- Expect that cabo+nivo should be assessed in the all-risk group
- No novel therapies available in 1L all-risk (except ave+axi, not available in routine commissioning)
- Modelling in an all-risk population requires the fewest assumptions

EAG comments

- Acknowledges there is evidence for cabo+nivo in the pooled population but observes that prior NICE appraisals have considered risk subgroups when making recommendations
- Majority of UK patients fall into the intermediate-/poor-risk group; all-risk comparison could be misleading as it would exclude all other novel therapies
- CheckMate 9ER data and subgroup-specific NMAs show differences in effect by risk group
- Present results for all-risk and risk subgroups separately, reflecting prior appraisals for RCC

Other considerations (clinical and patient expert comments)

- Include cost effectiveness in all risk, as well as intermediate/poor and favourable risk separately

NICE **Abbreviations:** ave+axi, avelumab plus axitinib; cabo+nivo, cabozantinib plus nivolumab; EAG, external assessment group; NMA, network meta-analysis; RCC, renal cell carcinoma; TA, technology appraisal; UK, United Kingdom.

Subgroups (2) – Risk stratification

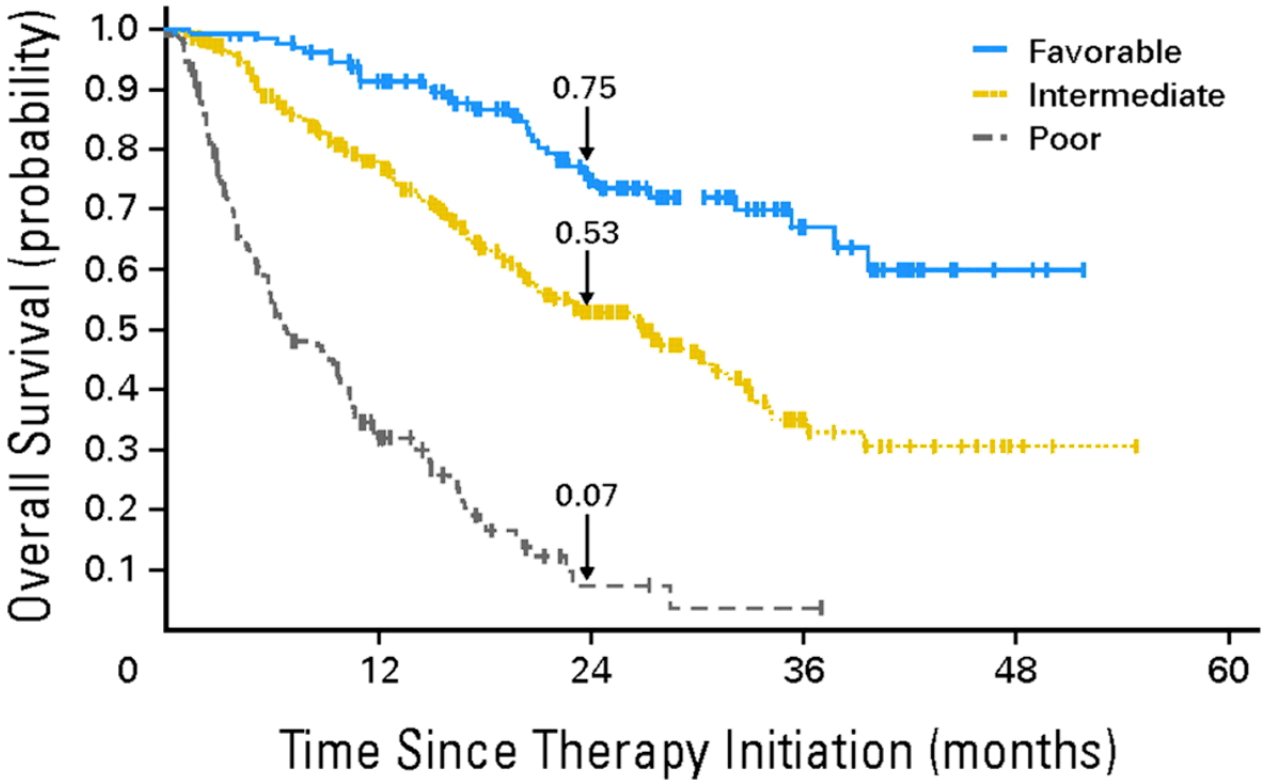
International Metastatic Renal Cell Carcinoma Database Consortium (IMDC)

Risk factors

- Karnofsky performance status < 80%
- Time from diagnosis to treatment < 1 year
- Decreased haemoglobin
- Elevated calcium
- Neutrophilia
- Thrombocytosis

Score

- Favourable **0** risk factors
- Intermediate **1–2** risk factors
- Poor **≥3** risk factors



No. of events/No. at risk					
Favorable	11/133	16/110	4/62	2/22	0/3
Intermediate	61/301	50/182	17/82	2/18	0/3
Poor	94/152	19/36	1/3	0/1	0/0

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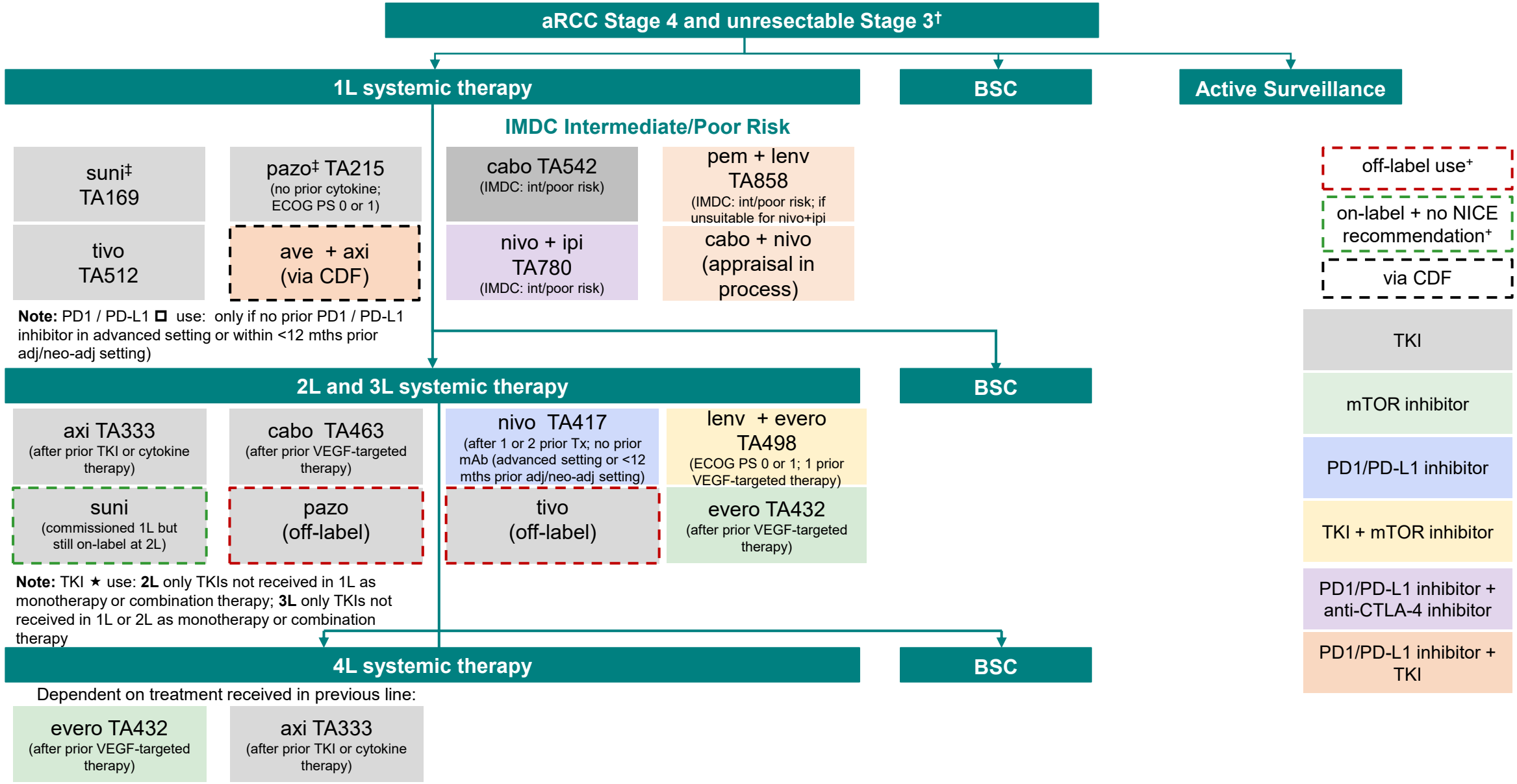
https://doi.org/10.1200/jco.2008.21.4809

Treatment pathway: overview



Notes: +, off-label use commissioned through NHSE blueteq;
BSC focuses on monitoring disease progression, symptom control, and palliative care without active treatment.

Treatment pathway: possible sequences

1L systemic therapy	2L and 3L systemic therapy			4L systemic therapy
TKI monotherapy Sunitinib TA169 Pazopanib TA215 Tivozanib TA512 Cabozantinib TA542*	cabo TA463* after prior VEGF-targeted Tx	lenv + evero TA498 ECOG PS 0 or 1; 1 prior VEGF-targeted therapy	evero TA432 after prior VEGF-targeted Tx	Dependent on treatment received in previous line: evero TA432 after prior VEGF-targeted Tx axi TA333 after prior TKI or cytokine Tx
	axi TA333 after prior TKI or cytokine Tx	nivo TA417 after 1 or 2 prior Tx; no prior mAb		
nivo + ipi TA780 IMDC: int/poor risk	cabo off-label	tivo off-label	lenv + evero TA498 ECOG PS 0 or 1; 1 prior VEGF-targeted therapy	Dependent on treatment received in previous line: evero TA432 after prior VEGF-targeted Tx axi TA333 after prior TKI or cytokine Tx
	suni commissioned 1L but still on-label at 2L	pazo off-label		
pem + lenv TA858 IMDC: int/poor risk; unsuitable for nivo+ipi	axi TA333 after prior TKI or cytokine Tx	cabo TA463 after prior VEGF-targeted Tx	evero TA432 after prior VEGF-targeted Tx	Dependent on treatment received in previous line: evero TA432 after prior VEGF-targeted Tx axi TA333 after prior TKI or cytokine Tx
	suni commissioned 1L but still on-label at 2L	pazo off-label	tivo off-label	
cabo + nivo (appraisal in process)	axi TA333 after prior TKI or cytokine Tx	lenv + evero TA498 ECOG PS 0 or 1; 1 prior VEGF-targeted therapy	evero TA432 after prior VEGF-targeted Tx	Dependent on treatment received in previous line: evero TA432 after prior VEGF-targeted Tx axi TA333 after prior TKI or cytokine Tx
	suni commissioned 1L but still on-label at 2L	pazo off-label	tivo off-label	

off-label use+

on-label + no NICE recommendation+

via CDF

TKI

mTOR inhibitor

PD1/PD-L1 inhibitor

TKI + mTOR inhibitor

PD1/PD-L1 inhibitor + anti-CTLA-4 inhibitor

PD1/PD-L1 inhibitor + TKI

NICE

Notes: *, only if not after cabozantinib at first line; +, off-label use commissioned through NHSE blueteq.

Sequence of treatments at later lines

Capturing the optimal treatment pathway is challenging

Background

- The most cost-effective sequence of treatments to use is not considered in this appraisal
- NICE have future work planned to investigate how treatment sequences can be considered in appraisals
- However, still need to understand plausible sequences as pathway model needs to reflect clinical practice

EAG

- Optimal treatment sequencing following novel treatments at first line (i.e. IO/IO or IO/TKI combinations) remains an area of uncertainty; optimal treatment pattern in favourable patients remains an area of debate
- Received clinical advice on most likely sequences and implements treatment rules in the analysis

Company

- Capturing and modelling the optimal treatment sequencing pathway is challenging
- There has been variability in subsequent treatments in prior NICE RCC TAs, demonstrating the difficulty in accurately defining treatment sequencing in RCC

NICE comments

- It is expected that the distribution of subsequent treatments would vary across appraisals as they were conducted at different time points where treatments available differed
- An aim of the pathways approach is to promote more cohesive guidance across appraisals

NICE

Abbreviations: EAG, external assessment group; IO, immune-oncology; RCC, renal cell carcinoma; TA, technology appraisal; TKI, tyrosine kinase inhibitor.

Key real-world evidence (1) – Treatment sequence

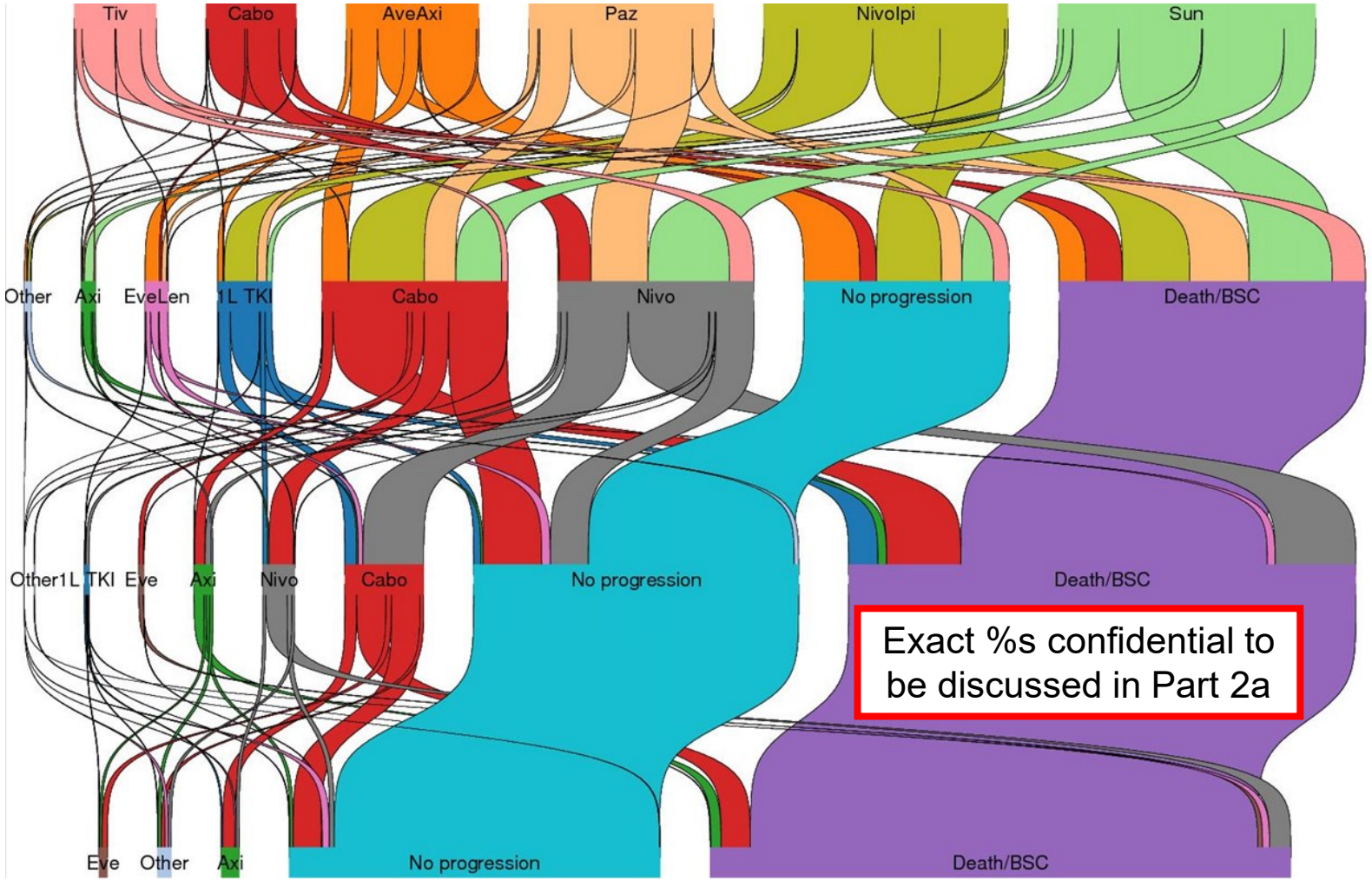
EAG analysis of UK RWE indicates the pathway of care from 1st to 4th line treatment

Background

UK RWE included a wide range of treatments used in UK clinical practice.

- Consecutive case series of 1,319 RCC participants from 15 UK centres who had SACT June 2018-Aug 2022
- Used to inform treatment sequences, baseline characteristics and baseline risk

RWE methods described in later slides



Exact %s confidential to be discussed in Part 2a

Does the pathway match clinical expectations? Would pathway look similar with len+pem? How would the addition of cabo+nivo change the pathway?

Abbreviations: Ave, avelumab; axi, axitinib; cabo, cabozantinib; EAG, external assessment group; eve, everolimus; ipi, ipilimumab; len, lenvatinib; N, number; nivo, nivolumab; paz, pazopanib; pem, pembrolizumab; RCC, renal cell carcinoma; RWE, real-world evidence; SACT, systemic anti-cancer therapy; sora, sorafenib; sun, sunitinib; tivo, tivozanib.

Clinical effectiveness

NICE National Institute for Health and Care Excellence

Key questions for committee: clinical

Category	Question
Clinical data	Is the sample from the RWE likely to be reflective of NHS practice?
	Do baseline characteristics reflect NHS practice?
NMA	How should the cabozantinib data from CABOSUN be interpreted?
	Which NMA is preferred – fractional polynomial or proportional hazards?
	Is it appropriate to use a proportional hazards NMA for pem+len, and a fractional polynomial NMA for all other treatments?

Abbreviations: NHS, National Health Service; NMA, network meta-analysis; pem+len, pembrolizumab plus lenvatinib; RWE, real-world data.

Key clinical trial of cabo+nivo

Cabo+nivo assessed against sunitinib in CheckMate 9ER

	CheckMate 9ER (N=651)
Design	Phase 3, multi-centre, single blind
Population	Previously untreated renal cell carcinoma
Intervention	Cabozantinib plus nivolumab
Comparator(s)	Sunitinib
Duration	Final follow up: 44 months
Primary outcome	PFS, by BICR
Key secondary outcomes	OS, ORR, and safety. HRQL as exploratory end point.
Locations	UK (N=21), USA, Europe, Rest of World
Used in model?	Yes, through NMA

Abbreviations: BICR, blinded independent central review; CABO+NIVO, cabozantinib plus nivolumab; HRQL, health-related quality of life; N, number; NMA, network meta-analysis; ORR, objective response rate; OS, overall survival, PFS, progression-free survival; UK, United Kingdom; USA, United States of America.

CheckMate-9ER – Key results by risk group

Relative effect of cabo+nivo versus sunitinib differs by risk group

	Outcome	Cabo+nivo	Sunitinib
All-risk	PFS, m (95% CI)	16.56 (12.75, 19.48)	8.38 (6.97, 9.69)
	HR (95% CI)	0.59 (0.49, 0.71)	
	OS, m (95% CI)	49.48 (40.31, NE)	35.52 (29.24, 42.25)
	HR (95% CI)	0.70 (0.56, 0.87)	
Favourable	PFS, m (95% CI)	21.42 (13.08, 24.71)	13.86 (9.56, 16.66)
	HR (95% CI)	0.72 (0.49, 1.05)	
	OS, m (95% CI)	NE (40.67, NE)	47.61 (43.63, NE)
	HR (95% CI)	1.07 (0.63, 1.79)	
Int-/poor-	PFS, m (95% CI)	15.61 (11.17, 19.15)	7.05 (5.68, 8.90)
	HR (95% CI)	0.56 (0.46, 0.69)	
	OS, m (95% CI)	49.5 (34.9, NE)	29.2 (23.7, 36.0)
	HR (95% CI)	0.65 (0.51, 0.83)	

Key results

- Median follow-up was 44 months (36.5–56.5)
- Median DOT was 21.8 months for cabo+nivo and 8.9 months for sunitinib
- 35.9% of people receiving cabo+nivo received subsequent therapy compared to 45.1% on sunitinib

Company

- Reiterates cabo+nivo best appraised in an all-risk population

EAG comments

- Evidence of effect modification by risk group for OS and PFS
- Reinforces value of risk as key consideration
- Similar pattern seen for other IO / TKIs

Should cabo+nivo be assessed in different risk groups?

NICE

Abbreviations: CI, confidence interval; HR, hazard ratio; IMDC, International mRCC Database Consortium; int, intermediate; IO, immuno-oncology; m, month; n, number; NE, not estimable; OS, overall survival; PD-L1, programmed death ligand 1; PFS, progression-free survival TKI, tyrosine kinase inhibitor.

Key real-world evidence (2)

UK RWE used as baseline data source for EAG pathway model

Background

- SLR of RWE conducted to identify evidence of pathway, natural history and characteristics
- Following quality assessment, concluded UK RWE dataset (Challapalli et el.) most robust and relevant
- 25 centres from UK locations were approach and 17 responded
- Consecutive case series of 1,319 RCC participants from 15 UK centres who had SACT June 2018-Aug 2022
- Includes patients from all regions of the UK; a mix of secondary/tertiary centres and urban/rural geographies
- Used to inform treatment sequences and generate sunitinib curves for “backbone” of model

Company

- Concerned that the RWE conflicts with the EAG’s own structured expert elicitation
- Was also concerned with external validity of the RWE and how this was assessed
- Key RWE information in the model is dummy data due to confidentiality restrictions

EAG response

- EAG regards it is for the committee to determine what the appropriate baseline data are for natural history
  - EAG proposes that these are from RWE
  - RWE has an important part in understanding the likely distribution of characteristics in clinical practice

NICE **Abbreviations:** EAG, external assessment group; RCC, renal cell carcinoma; RWE, real-world evidence; SACT, systemic anti-cancer therapy; SLR, systematic literature review; UK, United Kingdom.

Baseline characteristics

	CM9ER – CABO+NIVO	CM9ER - Sunitinib	UK RWE
N	323	328	1,319
Age years (range)	Median: 62.0 (29, 90)	Median: 61.0 (28, 86)	Mean: 64.4 (21, 90)
Male (%)	249 (77.1%)	232 (70.7%)	936 (71%)
Maximum number of lines of treatment received	NR	NR	1L: 687 (48%); 2L: 415 (35%); 3L: 168 (16%); 4L: 42 (%); 5L: 7 (%)
IMDC (fav; int; poor), n (%)	Fav: 74 (22.9%) Int: 188 (58.2%) Poor: 61 (18.9%) *Int/Poor: 249 (71.1%)*	Fav: 72 (22.0%) Int: 188 (57.3%) Poor: 68 (20.7%) *Int/Poor: 256 (78.0%)*	Fav: 294 (22.3%) Int/Poor: 1,016 (77.0%) Missing: 9 (<1%)
ECOG-PS	≥1: 83 (25.7%) <1: 240 (74.3%)	≥1: 83 (25.3%) <1: 245 (74.7%)	NR
Clear cell (%)	323 (100%)	328 (100%)	1,092 (82.8%)
Prior nephrectomy, n (%)	222 (68.7%)	233 (71.0%)	715 (54.2%)

EAG: Relatively small number of UK patients and higher rate of treatment post-progression in CM9ER

Is UK dataset reflective of NHS practice?

Abbreviations: CABO+NIVO, cabozantinib plus nivolumab; CM9ER, CheckMate 9ER; ECOG-PS, Eastern Cooperative Oncology Group performance score; fav, favourable; int, intermediate; L, line; N, number; NHS, National Health Service; NR, not reported; RWE, real-world evidence; UK, United Kingdom.

Evidence base: Systematic review and indirect comparison

EAG conducted SLRs to inform indirect comparisons between treatments

Systematic literature review

- EAG conducted SLRs to identify published evidence and real-world data sets in advanced RCC
- Existing SLRs published since 2020 included along with RCTs, extension studies and RWE
- Prioritised 17 trials for review
- Treatments included axitinib, ave+axi, cabozantinib, cabo+nivo, everolimus, eve+len, nivolumab, nivo+ipi, pazopanib, len+pem, sorafenib, sunitinib, tivozanib, and placebo
- Appraisal of evidence identified limitations in the quality of included trials, including CheckMate 9ER
  - 9/17 high risk of bias; 8/17 unclear risk of bias (including CheckMate 9ER)

Indirect comparisons

- Evidence networks for each outcome were formed by decision points on the pathway
- Second, third and fourth lines were combined as trials included general “previously treated” people
- NMAs were carried out for PFS and OS; insufficient studies available for TOT and TTNT
  - NMAs also conducted for ORR and AEs
- Separate networks were formed for 1st line treatment and or 2nd+ line treatment
  - First line treatment network was further stratified by IMDC risk subgroup
  - Second line+ associated with challenges constructing evidence network, leading to the exclusion axitinib and tivozanib in some second-line networks

Abbreviations: AEs, adverse events; EAG, external assessment group; HRQoL, health-related quality of life; ORR, objective response rate; OS, overall survival, PFS, progression-free survival; RCC, renal cell carcinoma; RCT, randomised controlled trial; RWE, real-world evidence; SLR, systematic literature review; TOT, time on treatment; TTNT, time to next treatment.

Evidence base: Indirect comparisons (1)

Reference treatments of sunitinib for first line and everolimus for second line plus

1st-line treatments

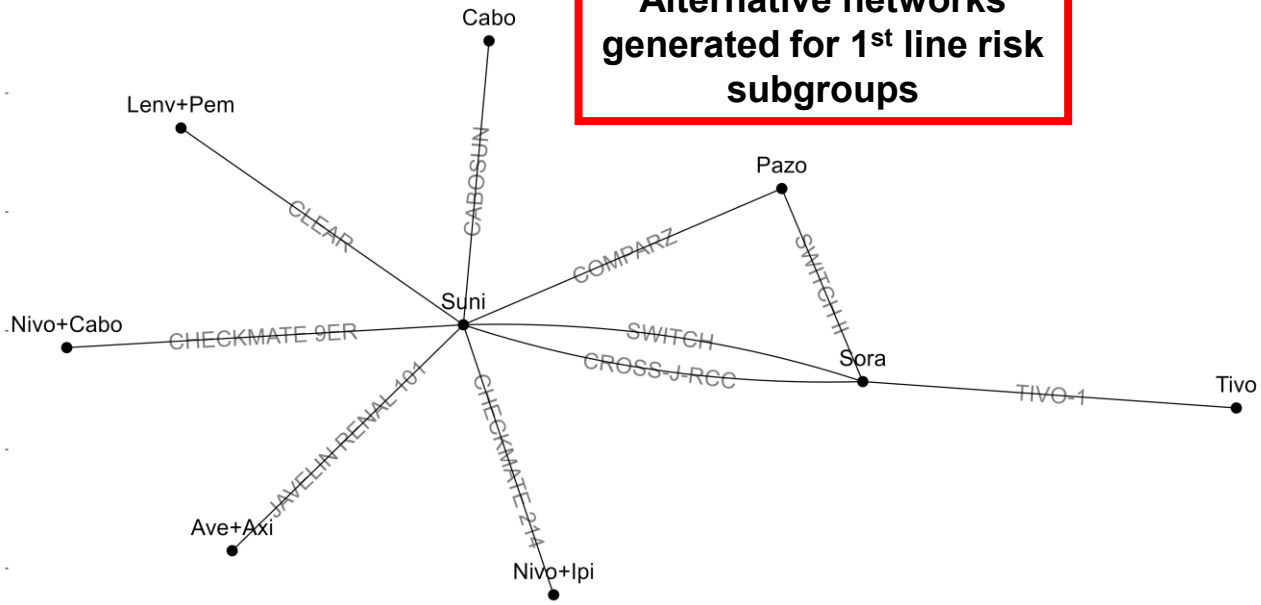
- Sunitinib acts as a central node for all comparators of interest, except tivozanib
- Therefore, sunitinib acts as reference treatment
- CheckMate 9ER acts as reference study, as considers CABO+NIVO

2nd-line+ treatments

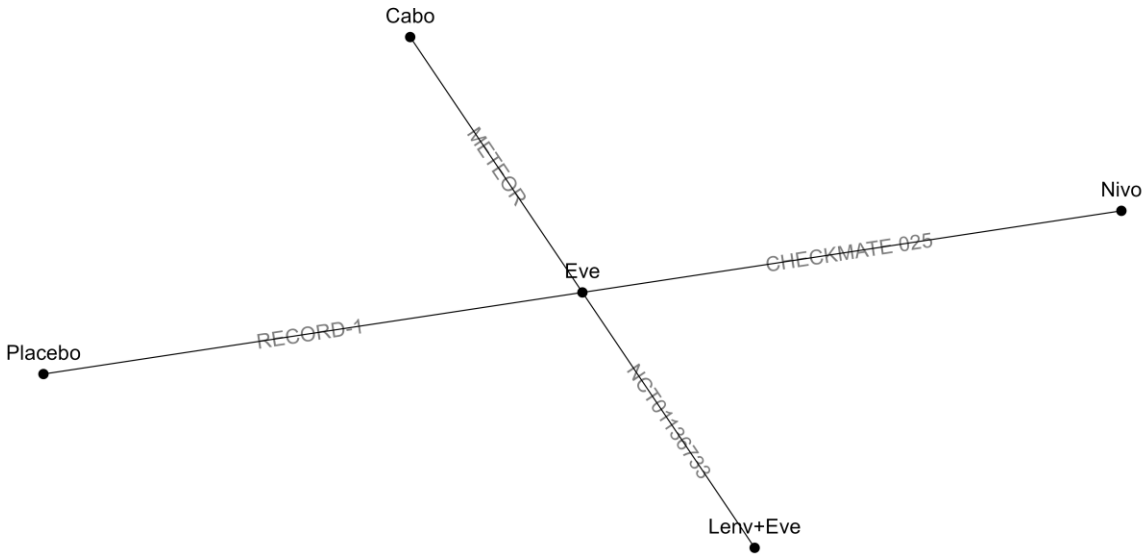
- Everolimus acts as a central node for all treatments of interest, except tivozanib
- Therefore, everolimus as reference treatment
- CheckMate 025 acts as reference study, as has the longest follow-up

1st line network diagram for PFS – all risk

Alternative networks generated for 1st line risk subgroups



2nd+ line network diagram for PFS – all risk



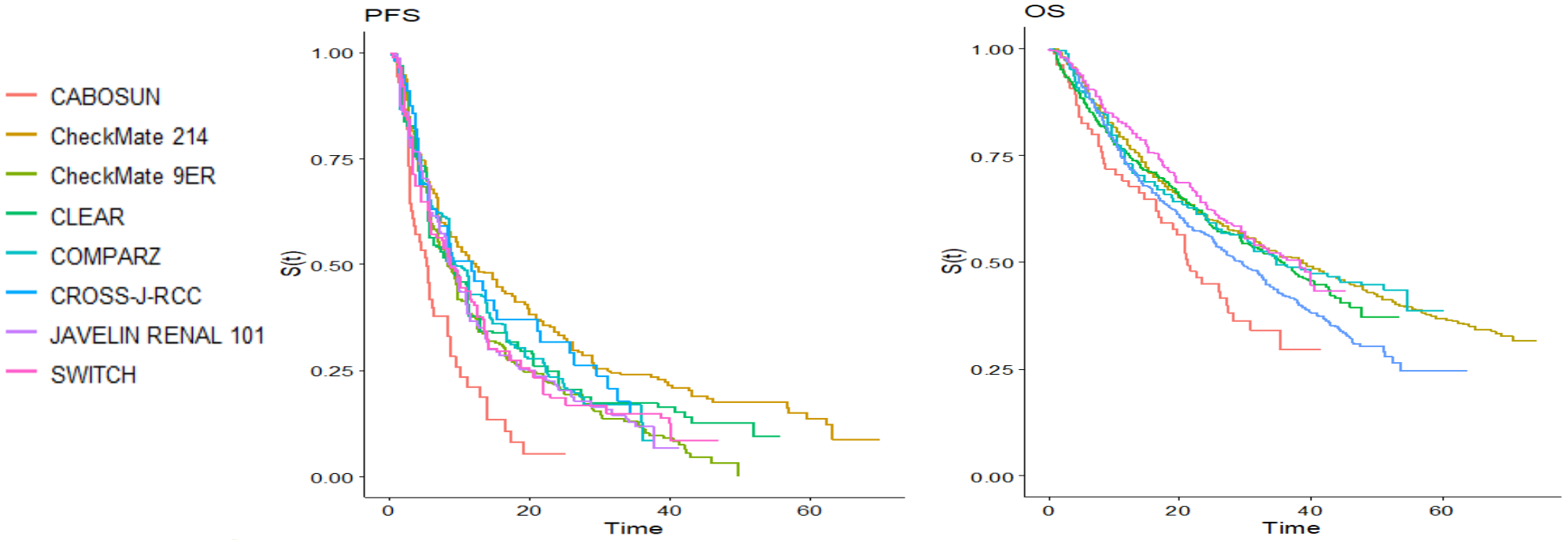
Abbreviations: CABO+NIVO, cabozantinib plus nivolumab; IMDC, international metastatic database consortium; OS, overall survival; PFS, progression-free survival.

Evidence base: Common treatment arm – 1st line

Reference common sunitinib arm – some variation in outcomes across trials

EAG

- Comparison of sunitinib across trials in the network shows largely consistent outcomes, with some variation
- No obvious explanation for anomalous PFS in the sunitinib arm of CheckMate214, likely chance observation or as CheckMate 214 was investigator assessed
- CABOSUN older study so no 2L IOs available, no fav risk patients and larger proportion bone metastases



How should we interpret cabozantinib data from CABOSUN for NMA?

Abbreviations: IO, immuno-oncology; L, line; OS, overall survival; PFS, progression-free survival.

Indirect comparisons (2)

Background

- PH NMAs require fewer assumptions but implausible when considering hazard changes over time
- FP NMAs have greater data requirements but can deal with complex hazards
- PH assumption not met in some prior appraisals and PH NMA still used in some cases
- Issues justifying PH for all endpoints; EAG used FP analysis for OS and PFS as hazards can vary over time
- EAG also conducted PH NMAs of survival outcomes (for scenario analysis), response rates, and safety
- NMAs (FP and PH) for all-risk PFS and OS suggest CABO+NIVO more effective than TKIs at first line

EAG

- Informed FP model selection was made combining statistical criteria with clinical or logical plausibility
  - Considered plausible models where RMST > threshold for every treatment curve with AIC difference ≤5
  - Plausible FP models best conforming to expert survival estimates at 5 years (conditional on surviving to 3) and 10 years (conditional on surviving to 5) selected by EAG at 1L (except len+pem)
- 2L/3L use PH NMA in preference to the FP NMA due to the sparsity of the available network

Company

- Although PH assumption was judged to be violated, the FP NMA is associated with limitations
- Choice of FP NMA inconsistent with previous submissions, even where PH assumption does not stand
- Inconsistent application of relative efficacy between comparators, lines of treatment, and prior appraisals
  - Applying PH NMA to pem+len only biases the analysis in favour of pem+len

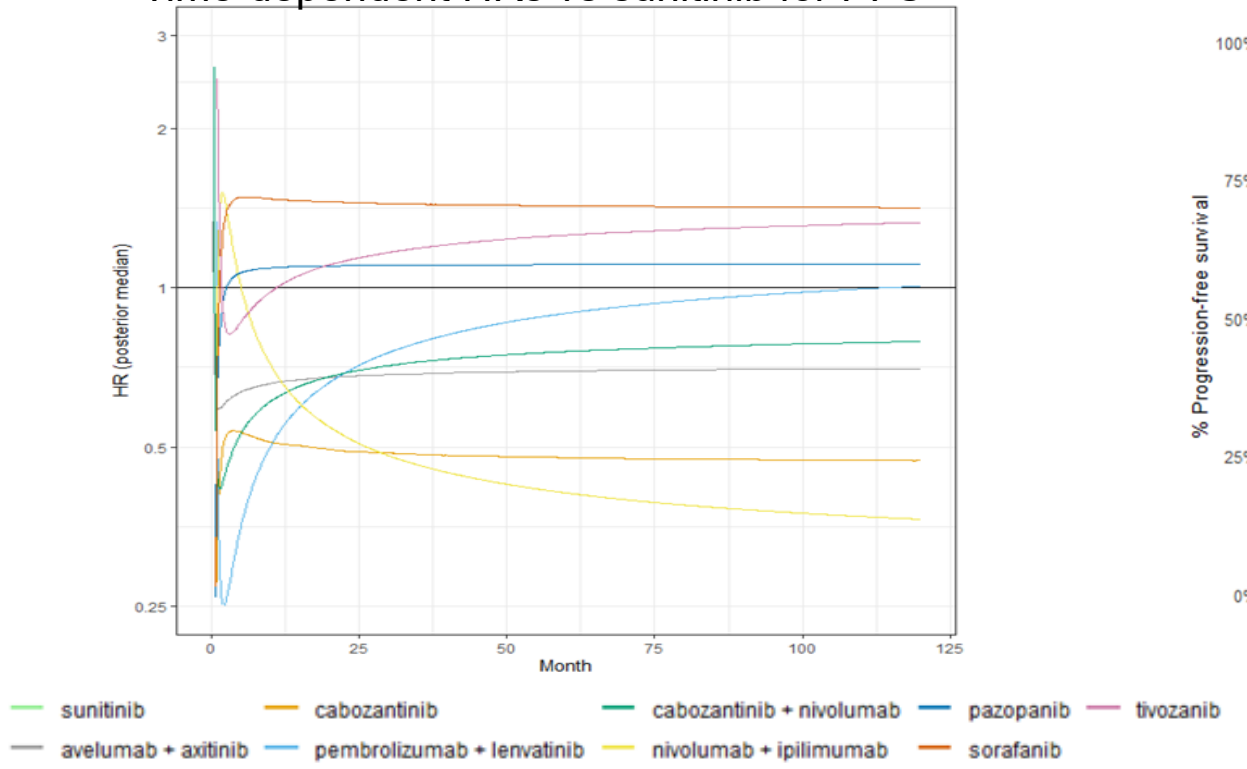
Which indirect treatment approach is preferred?

Abbreviations: AIC, Akaine information criteria; cabo+nivo; cabozantinib plus nivolumab; DIC, decision information criteria; EAG, external assessment group; FP, fractional polynomial; L, line; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; PH, proportional hazards; RMST, restricted mean survival time; TKI, tyrosine kinase inhibitor.

Evidence base: FP NMA results – 1L PFS

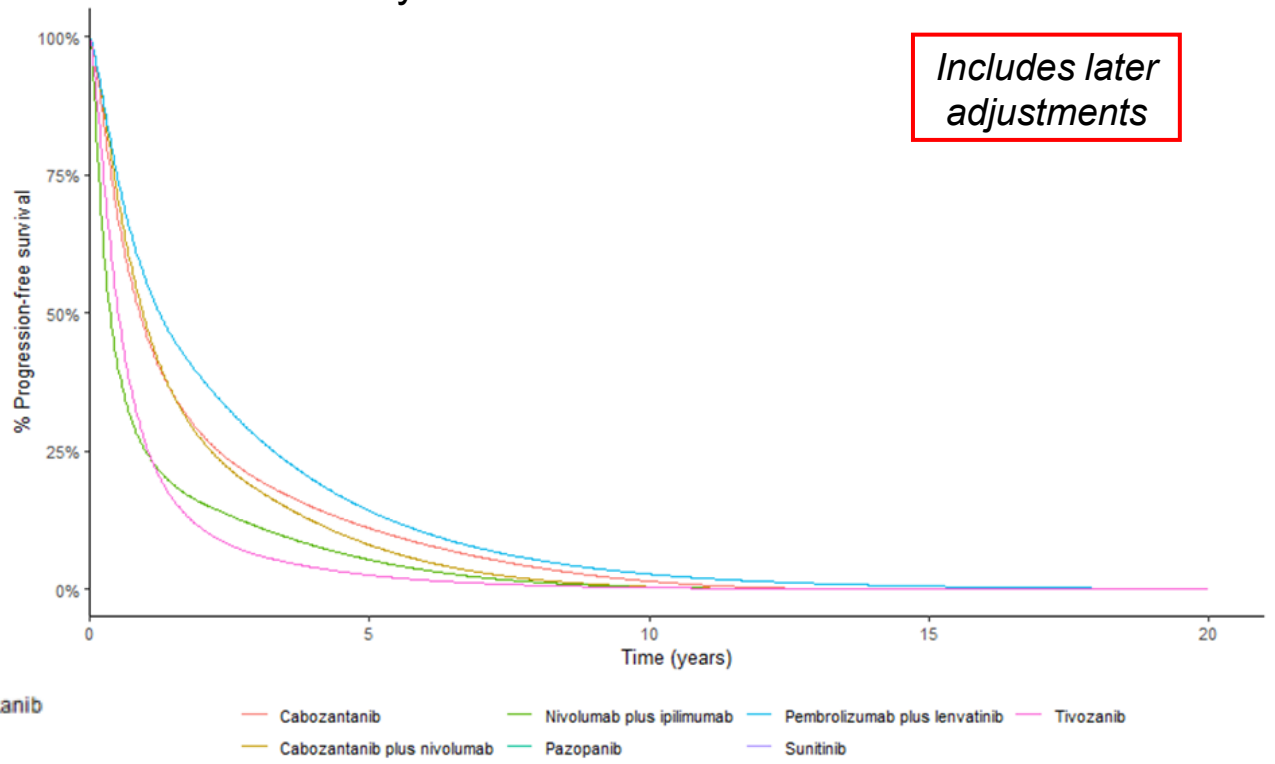
Time-dependent HRs applied to reference sunitinib curve to generate comparator survival estimates

Time-dependent HRs vs sunitinib for PFS



PFS curves by treatment from selected FP model

Includes later adjustments



EAG

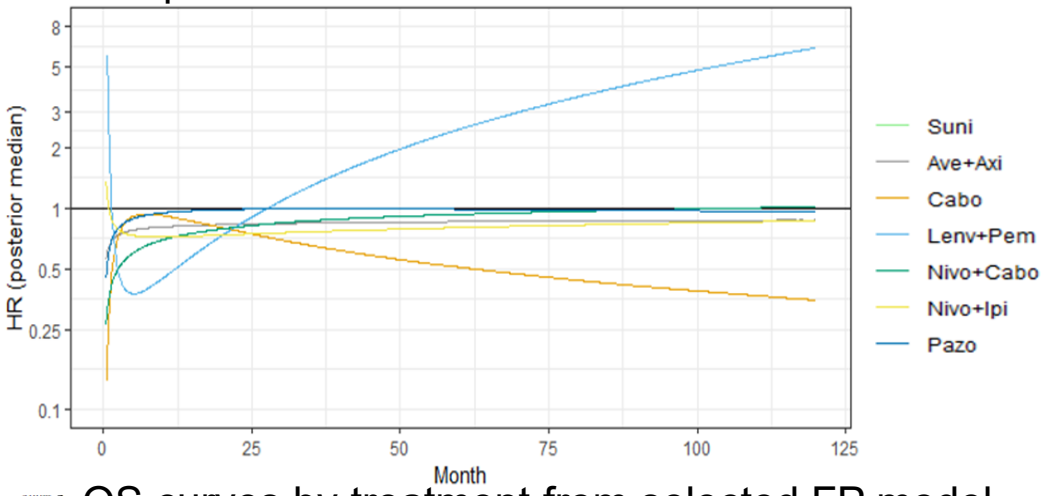
- Treatments with higher HRs than sunitinib are other TKIs; most others less than 1 over the time horizon
- CABO+NIVO: HR trends gradually upwards towards 1 after the end of data period but remains below 1
- Len+pem excluded in risk-specific FP NMAs due to redacting of data in TA858

Abbreviations: EAG, external assessment group; FP, fractional polynomial; HR, hazard ratio; NMA, network meta-analysis; PFS, progression-free survival; TA, technology appraisal; TKI, tyrosine kinase inhibitor.

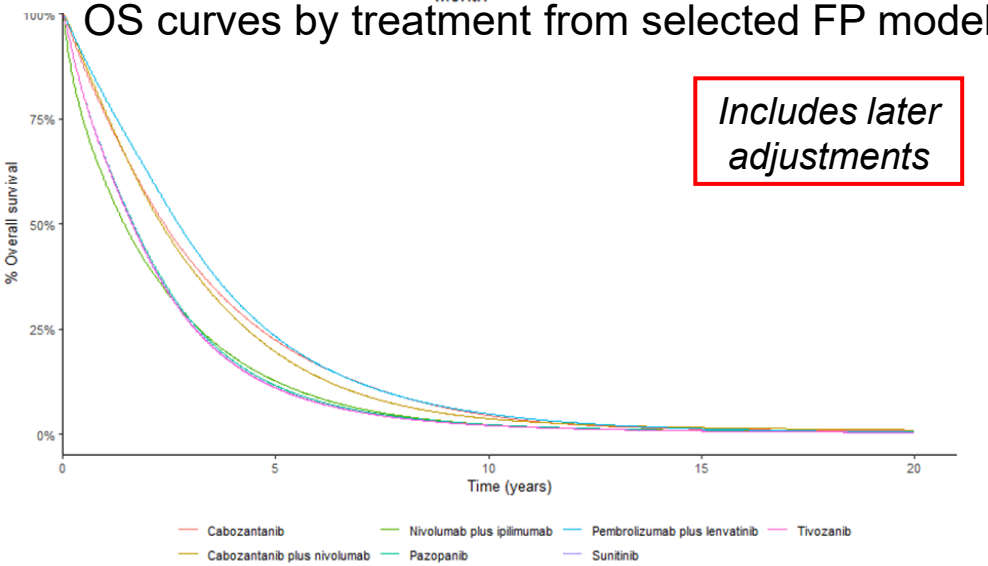
Evidence base: FP NMA results – 1L OS

Time-dependent HRs applied to reference sunitinib to generate comparator survival

Time-dependent HRs vs sunitinib for OS for 1L



OS curves by treatment from selected FP model



Includes later adjustments

OS NMA only used in PartSA model

EAG

- Unlike PFS, comparisons are much more similar in OS, only cabozantinib appears to have a long-term HR below 1
- Cabo+nivo: HR trends gradually upwards after the end of the observed data period coming close to 1
- Present results of both NMA approaches (FP and PH)

Company comments

- Limited discussion on poor face validity of some curves
- EAG used FP NMA to inform relative treatment efficacy, except for pem+len where PH NMA used; biases results in favour of pem+len
- Believes the PH NMA should be preferred in the base case, in line with prior technology appraisals

Abbreviations: CABO+NIVO, cabozantinib plus nivolumab; CI, confidence interval; EAG, external assessment group; FP, fractional polynomial; HR, hazard ratio; LEN+PEM, lenvainib plus pembrolizumab; NMA, network meta-analysis; OS, overall survival; PartSA, partitioned survival analysis; PFS, progression-free survival; PH, proportional hazards.

Evidence base: PH NMA results – 1L all-risk PFS

	AVE+AXI	CABO+NIVO	CABO	NIVO+IPI	PAZO	PEM+LENV	SORA	SUNI	TIVO
AVE+AXI	-	1.136 (0.888,1.46)	1.405 (0.879,2.216)	**0.78 (0.619,0.981)**	**0.668 (0.54,0.825)**	**1.425 (1.099,1.845)**	**0.491 (0.387,0.62)**	**0.671 (0.57,0.789)**	**0.65 (0.46,0.924)**
CABO+NIVO	0.880 (0.685,1.126)	-	1.237 (0.765,1.98)	**0.687 (0.538,0.882)**	**0.588 (0.467,0.742)**	1.254 (0.948,1.646)	**0.432 (0.336,0.557)**	**0.591 (0.49,0.711)**	**0.571 (0.401,0.825)**
CABO	0.712 (0.451,1.137)	0.809 (0.505,1.308)	-	**0.556 (0.352,0.882)**	**0.476 (0.304,0.755)**	1.012 (0.632,1.658)	**0.349 (0.22,0.56)**	**0.478 (0.311,0.739)**	**0.462 (0.27,0.793)**
NIVO+IPI	**1.283 (1.019,1.615)**	**1.456 (1.134,1.859)**	**1.800 (1.134,2.839)**	-	0.857 (0.693,1.053)	**1.826 (1.411,2.364)**	**0.628 (0.497,0.794)**	0.86 (0.732,1.009)	0.83 (0.586,1.185)
PAZO	**1.496 (1.212,1.852)**	**1.701 (1.348,2.139)**	**2.101 (1.325,3.289)**	1.167 (0.95,1.443)	-	**2.134 (1.67,2.716)**	**0.734 (0.614,0.874)**	1.005 (0.876,1.15)	0.974 (0.71,1.331)
PEM+LENV	**0.702 (0.542,0.91)**	0.797 (0.607,1.054)	0.989 (0.603,1.583)	**0.548 (0.423,0.709)**	**0.469 (0.368,0.599)**	-	**0.344 (0.265,0.45)**	**0.471 (0.387,0.577)**	**0.456 (0.315,0.665)**
SORA	**2.036 (1.613,2.583)**	**2.317 (1.796,2.979)**	**2.864 (1.785,4.553)**	**1.592 (1.259,2.013)**	**1.362 (1.144,1.628)**	**2.91 (2.223,3.773)**	-	**1.368 (1.153,1.62)**	**1.322 (1.014,1.72)**
SUNI	**1.49 (1.268,1.755)**	**1.692 (1.407,2.042)**	**2.092 (1.354,3.213)**	1.162 (0.991,1.365)	0.995 (0.87,1.141)	**2.124 (1.733,2.587)**	**0.731 (0.617,0.867)**	-	0.967 (0.709,1.321)
TIVO	**1.538 (1.083,2.176)**	**1.75 (1.212,2.494)**	**2.165 (1.261,3.699)**	1.205 (0.844,1.707)	1.027 (0.752,1.409)	**2.195 (1.505,3.174)**	**0.756 (0.581,0.986)**	1.034 (0.757,1.411)	-

Key: **Red cells** indicate option above is significantly better than option to left; **green cells** indicate option to left is significantly better than option above; **grey cells** show comparisons with options that are included in the network but not in the cabo+nivo decision problem
Abbreviations: CABO+NIVO, cabozantinib plus nivolumab; CI, confidence interval; EAG, external assessment group; FP, fractional polynomial; HR, hazard ratio; LEN+PEM, lenvainib plus pembrolizumab; NMA, network meta-analysis; PFS, progression-free survival.

NICE

Alternative NMAs for risk subgroups

Evidence base: PH NMA results – 1L all-risk OS

	AVE+AXI	CABO+NIVO	CABO	NIVO+IPI	PAZO	PEM+LENV	SUNI
AVE+AXI	-	1.128 (0.833,1.518)	0.984 (0.623,1.581)	1.096 (0.844,1.422)	0.859 (0.669,1.103)	0.999 (0.734,1.355)	**0.789 (0.644,0.97)**
CABO+NIVO	0.887 (0.659,1.2)	-	0.875 (0.552,1.404)	0.973 (0.744,1.278)	0.762 (0.585,1.001)	0.889 (0.641,1.215)	**0.007 (0.56,0.878)**
CABO	1.016 (0.632,1.605)	1.143 (0.712,1.813)	-	1.113 (0.713,1.74)	0.873 (0.558,1.357)	1.012 (0.635,1.628)	0.804 (0.529,1.214)
NIVO+IPI	0.912 (0.703,1.185)	1.028 (0.783,1.345)	0.898 (0.575,1.403)	-	**0.784 (0.631,0.973)**	0.913 (0.69,1.193)	**0.720 (0.614,0.843)**
PAZO	1.164 (0.907,1.494)	1.312 (0.999,1.708)	1.145 (0.737,1.791)	**1.276 (1.028,1.584)**	-	1.165 (0.885,1.522)	0.92 (0.792,1.063)
PEM+LENV	1.001 (0.738,1.363)	1.125 (0.823,1.559)	0.988 (0.614,1.575)	1.096 (0.838,1.449)	0.858 (0.657,1.13)	-	**0.789 (0.632,0.995)**
SUNI	**1.267 (1.031,1.554)**	**1.428 (1.14,1.785)**	1.243 (0.824,1.889)	**1.39 (1.186,1.628)**	1.087 (0.941,1.262)	**1.267 (1.005,1.582)**	-

Alternative NMAs for risk subgroups

OS NMAs only used in PartSA model

Key: **Red cells** indicate option above is significantly better than option to left; **green cells** indicate option to left is significantly better than option above; **grey cells** show comparisons with options that are included in the network but not in the cabo+nivo decision problem

Abbreviations: CABO+NIVO, cabozantinib plus nivolumab; CI, confidence interval; EAG, external assessment group; FP, fractional polynomial; HR, hazard ratio; LEN+PEM, lenvainib plus pembrolizumab; NMA, network meta-analysis; PFS, progression-free survival.

Key issues relating to the evidence base

EAG present results for all-risk and risk subgroups separately

Background

- EAG used systematic literature reviews to identify evidence base and form treatment networks for RCC
- Indirect comparisons used to generate relative effectiveness estimates for all treatments versus sunitinib

EAG issues with evidence base

- Limitations in quality of evidence; high risk of bias in 9/17 trials; Majority of comparisons were informed by only one trial, so comparisons between novel treatments were based on indirect evidence only
- Risk group-specific analyses drew on comparatively sparse data

Company comments on EAG analysis

- Presented a series of queries relating to the EAG's NMA; relating to
  - Lack of available of data for some treatments and risk groups
  - Need for simplifying assumptions
  - Application of relative treatment efficacy across comparators and lines of therapies

EAG response

- Agrees with the company about the broader limitations in the evidence base
- Used parallel analysis methods for survival outcomes, including fractional polynomial NMA and proportional hazards NMA to test the robustness of analyses to different assumptions (including relative efficacy)

Which indirect treatment approach is preferred?

How should we interpret cabozantinib for NMA?

Abbreviations: EAG, external assessment group; NMA, network meta-analysis; RCC, renal cell carcinoma.

Applicability across histologies and for adjuvant treatment

Adjuvant therapy use likely to affect treatment pathway

Background

- Included trials primarily restricted inclusion to patients with clear cell RCC
- Adjuvant pembrolizumab now available in routine practice, but not when any clinical trials were conducted

Company

- Presence of sarcomatoid differentiation is an indicator of an especially aggressive form of RCC
  - CheckMate 9ER included 11.95% of patients with sarcomatoid features, enhancing generalisability
- Adjuvant pembrolizumab expected to impact sequencing for a range of therapies, including 1L pem+len

EAG

- Clinical advice that adjuvant pembrolizumab may reduce subsequent effectiveness of IO treatments and improve prognosis for other types of treatment
- Could not address these issues due to sparsity of evidence but trials emerging in different RCC histologies
- As adjuvant pembrolizumab use increases, likely that IO effect will vary in practice compared to trials
  - May impact cost-effectiveness of 1L IO-based treatments; Exploratory scenario increased ICER
- Expect that adjuvant pembrolizumab use will impact all IO-based therapies, not just pem+len

Other considerations (clinical and patient expert comments)

- NHSE does not fund subsequent IO treatment if received adjuvant IO in the previous 12 months

NICE

Abbreviations: EAG, external assessment group; IO, immuno-oncology; NHSE, NHS England; RCC, renal cell carcinoma.

Cost effectiveness

NICE National Institute for Health and Care Excellence

Key questions for committee: cost effectiveness

Category	Question
Model structure	Which model structure is more appropriate – state transition or partitioned survival analysis?
	How many lines of treatment is it appropriate to model?
Modelled treatment effectiveness	Is the EAG's use of outcomes in the model appropriate? Should TTD be set as equal to PFS? Or is it more appropriate to apply HRs from the PFS NMAs to TTD and TTP curves?
	Is the EAG's 'down weighting' method appropriate to account for available later line treatments
Adverse events	Which approach to generating rates of Grade 3+ adverse events (NMA or naïve comparison between CheckMate 9ER and comparator trial) is most appropriate?
Utility values	Is the approach to capture utility used in the model appropriate?
	Does the published evidence from previous NICE appraisals, or CheckMate 9ER, better represent expectations for quality of life in advanced RCC?
Relative dose intensity	What proportion of people get each lenvatinib dose and is the lenvatinib titration reflective of NHS practice?
	Is the company or EAG's approach to calculating RDI most appropriate?
Severity	Which method for calculating a severity modifier is most appropriate?
	Does a severity modifier apply?

NICE **Abbreviations:** EAG, external assessment group; HR, hazard ratio; NMA, network meta-analysis; PFS, progression-free survival; RCC, renal cell carcinoma; RDI, relative dose intensity; TTD, time to discontinuation; TTP, time to progression.

Key model assumptions – model settings

	Assumption	Source
Perspective	• NHS and Personal Social Services	NICE reference case
Time horizon	• 40 years	TA858, TA780, TA650 and TA645
Cycle length	• Weekly	
Discounting	• Costs and outcomes were discounted at 3.5% per annum • All costs from 2022 price year	NICE manual
Baseline characteristics	• Informed by UK RWE population • *Scenarios investigate CheckMate 9ER population*	UK RWE
Model structure	• Hybrid state transition approach • Consider 5 lines (up to 4 active treatments followed by BSC) • Each line split by on- and off-treatment status • *Scenarios investigate PartSA model and fewer treatment lines*	Hybrid STM based on approach used in TA798
Disease progression	• Transitions between lines are driven by progression status • Transitions between the on and off treatment states driven by TTD	Based on approach to STM transitions in TA798

Abbreviations: BSC, best supportive care; NHS, National Health Service; PartSA, partitioned survival model; RWE, real-world evidence; STM, state transition model; TA, technology appraisal; TTD, time to discontinuation; UK, United Kingdom.

Key model assumptions – effectiveness

	Assumption	Source
Reference treatments	• Sunitinib 1L reference treatment as central node in 1L network • Everolimus 2L+ reference treatment as central node in 2L+ network	UK RWE
PFS (and TTP)	• UK RWE used to model relevant outcomes at each line for the reference treatment, log-logistic curve selected for PFS and TTP; scenarios test Weibull • *Scenarios investigate using CheckMate 9ER*	UK RWE
4L and PPS	• Log-normal curve selected; scenario tests exponential • 3L vs 4L HR used to down-weight survival in 4th line	
Comparative effectiveness	• 1L fractional polynomial NMA applied to generate outcomes for non-reference treatments; proportional hazards NMA applied to 2L reference outcomes • *Scenarios investigate proportional hazards NMA throughout*	
Surrogacy	• HRs from PFS NMA applied to TTD and TTP outcomes	Assumption
Treatment discontinuation	• TTD information from the reference curve for the UK RWE, log-logistic curve selected – HRs from PFS NMA applied to TTD • Stopping rules applied using no. doses received or after curves generated • *Scenarios investigate CheckMate 9ER*	UK RWE
Treatment effect waning	• Applies treatment effect waning at 5 years to all IO / TKI combinations based on hazards, all endpoints; *scenarios test no waning and alternative timepoints*	Assumption

Abbreviations: BSC, best supportive care; HR, hazard ratio; IO, immuno-oncology; L, line; NMA, network meta-analysis; PFS, progression-free survival; PPS, post-progression survival; RWE, real-world evidence; TA, technology appraisal; TKI, tyrosine kinase inhibitor; TTD, time to discontinuation; TTP, time to progression; UK, United Kingdom.

Key model assumptions – costs and benefits

	Assumption	Source
Treatment sequencing	Proportions from RWE; treatment rules limit available later lines treatments	NICE guidance, RWE, clinical input, BlueTeq
Adverse events	G3+ AE rates in >5% of patients taken from CheckMate 9ER for cabo+nivo and sunitinib, additional AEs of interest included on clinical advice For other treatments, NMA applied to reference sunitinib data *Scenarios investigate trial informed AE rates*	CheckMate 9ER data EAG SLR Clinical input
Utilities	Utility differs by progression status and line of therapy Use published utility values accepted in previous NICE TAs TA645 (1L PF/PD → 2L PF), TA498 % reduction applied for later lines *Scenarios investigate CM9ER proportional reduction applied to TA645*	TA645 (JAVELIN-RENAL 101) and TA498 (AXIS)
Costs	NHS Reference costs, PSSRU, Nuffield Trust, BNF, eMIT RDI from CheckMate 9ER and published sources *Scenarios investigate company alternative RDI estimates*	
Resource use	Based on NICE TA542, TA858 and Edwards 2018, complemented by clinical opinion	
Severity	EAG investigate full incremental analysis, pairwise analyses and market share analysis	

Abbreviations: AE, adverse event; BNF, British National Formulary; EAG, external assessment group; eMIT, electronic medicines information tool; G, grade; L, line; NHS, National Health Service; NMA, network meta-analysis; PD, progressed disease; PF, progression free; PSSRU, Personal Social Services Research Unit; RDI, relative dose intensity; RWE, real-world evidence; SLR, systematic literature review; TA, technology appraisal.

Key model assumptions – differences between risk groups

	All risk	Favourable risk	Intermediate/poor risk
Baseline characteristics	Risk specific baseline characteristics and treatment patterns	Risk specific baseline characteristics and treatment patterns	Risk specific baseline characteristics and treatment patterns
1L efficacy data	All-risk sunitinib 1L reference curves	Favourable-risk sunitinib 1L reference curves	Int/poor-risk sunitinib 1L reference curves
2L efficacy data	All-risk 2L cabozantinib reference curves		
Survival curve extrapolations	Consistent sunitinib parametric survival models chosen using UK RWE		
NMA 1st line	All-risk FP NMA for relevant comparators	Favourable-risk PH NMA	Int-/poor-risk FP NMA (PH NMA for pem+len)
NMA 2nd line onwards	All-risk PH NMA		
Subsequent treatments	Treatment rules applied based on 1L treatment received		
AEs	Assumed comparable across risk groups (all risk rates used)		
Utility	Assumed comparable across risk groups (all risk utilities used)		

NICE

Abbreviations: AE, adverse event; FP, fractional polynomials; int, intermediate; L, line; NMA, network meta-analysis; PH, proportional hazards.

EAG model conceptualisation (1)

Model to capture disease and treatment status along the treatment pathway

Disease background

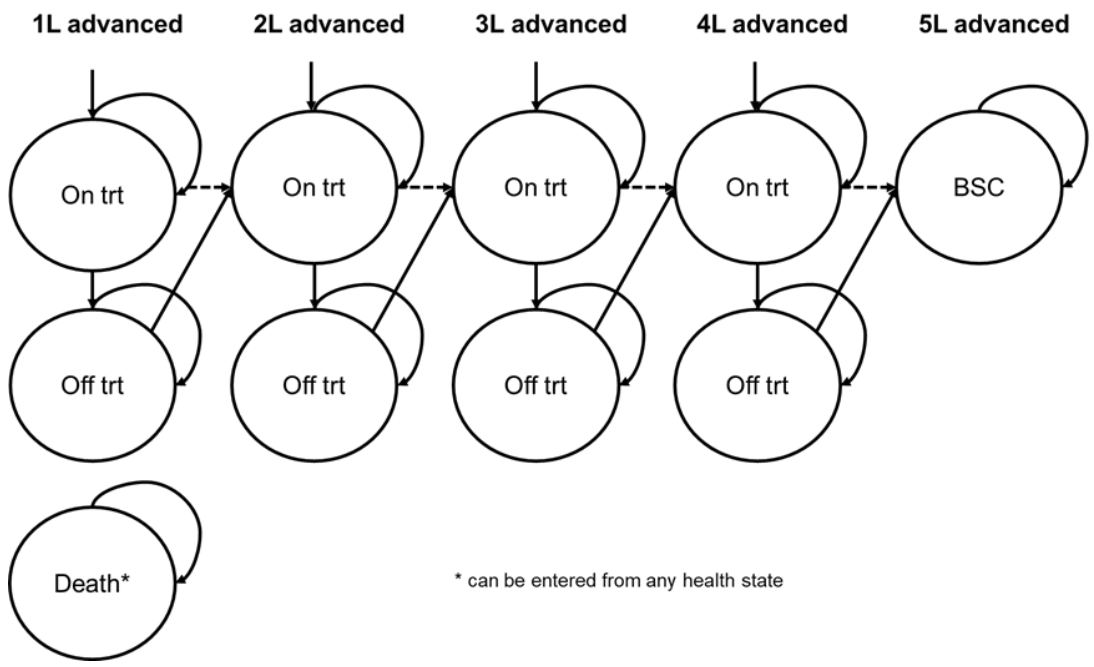
- Goal of RCC treatment is to extend life and delay progression
- People may get multiple lines of treatment – expert advice indicated maximum of 4 lines followed by BSC
- Improving HRQoL by relieving symptoms and tumour burden is also an important clinical outcome
  - Impacted by stage of disease and treatment received

Model concept

- EAG concept had to represent full disease pathway to meet aims of pathways approach
- Health states based on:
  - Disease status (treatment line and progression status)
  - Treatment received and treatment status (on/off)

Model perspective and settings

- NHS and PSS perspective
- Lifetime time horizon (40 years)
- Weekly cycle length, no half-cycle correction
- Costs and QALYs discounted at 3.5%



Abbreviations: BSC, best supportive care; EAG, external assessment group; HRQoL, health-related quality of life; L, line; NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life-years; RCC, renal cell carcinoma; trt, treatment.

Model structure (1)

Background

- Option to use a 4+ line state transition model (base case) or partitioned survival model (scenario analysis)
- Predicted life years and QALYs were generally higher when using a partitioned survival analysis

Company

- STM and PartSA model structures appear to give different results
- During consultation, recommended favouring the STM model with two lines of treatment

EAG

- Use STM approach; while both appropriate, it is for the committee to prefer one or the other

State transition	Partitioned survival
• OS dependent upon progression status and line of treatment; implies surrogacy between PFS and OS • Use of tunnel states allow flexibility to model future outcomes based on past events • However, limited clinical trial data available to define the split between progression and death events within PFS (UK RWE does provide this)	• Assumes OS, PFS and TTD are independent • *"The lack of structural link between endpoints in PartSA models may increase the potential for inappropriate extrapolation"* • Any differences between subsequent therapy mix in practice, CM9ER and other trials do not impact relative effectiveness (assumption used in prior PartSA models submitted to NICE)

Which model structure is more appropriate?

Abbreviations: CM9ER, CheckMate 9ER; OS, overall survival; PartSA, partitioned survival analysis; PFS, progression-free survival; QALY, quality-adjusted life-year; STM, state transition model; TTD, time to discontinuation.

Model structure (2) – number of lines

Background

- EAG developed model that could investigate explicitly modelling a number of lines of treatments
- EAG base case considers 4 lines of active treatment before BSC
- Scenarios investigate 2 or 3 lines of active treatment before BSC

Company

- EAG base case model structure and granularity in modelling four lines of treatment deviates from precedence, creating inconsistencies in decision making
- Majority of LYs and QALYs in the model are accumulated in the first two lines of treatment and scope of this appraisal focuses on evaluating cabo+nivo as a 1L treatment
- Prefer a model considering 2 lines of active therapy before BSC, in line with past appraisals

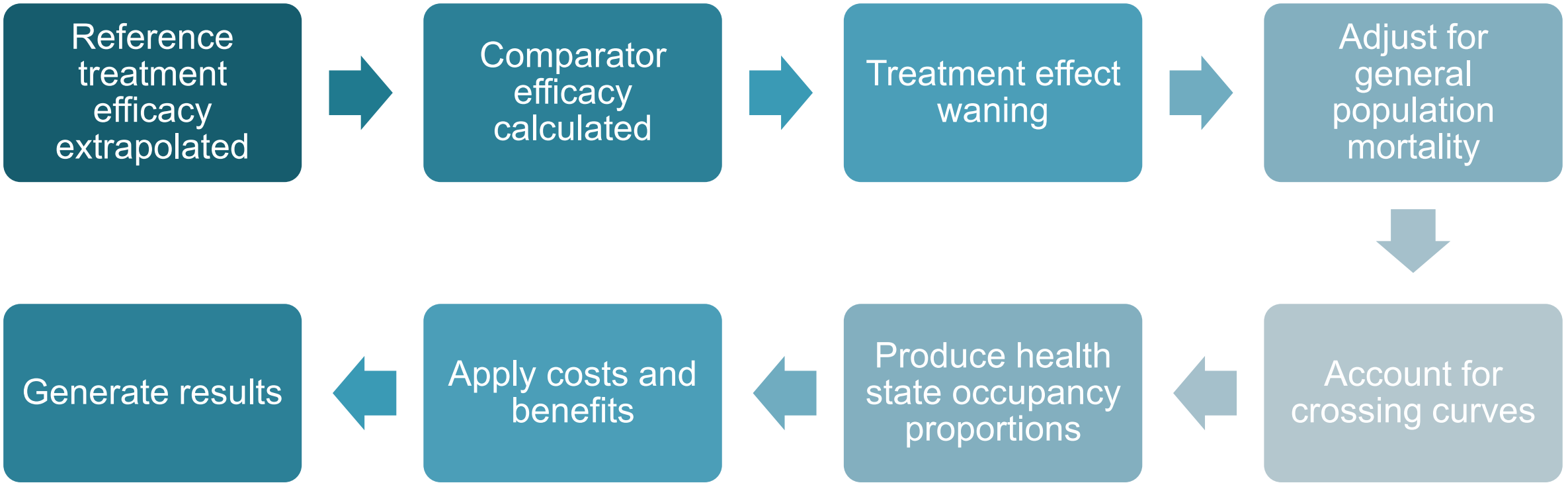
EAG and NICE comments

- Small proportion of time spent in 3L/4L which aligns with the low numbers observed in RWE
- As majority of LYs and QALYs accumulated in first two lines, 3L/4L assumptions have limited impact
- Past appraisals haven't explicitly considered modelling up to 4 lines, but intrinsically captured a range of lines in baskets applied after discontinuing 1L treatment – typically in a partitioned survival approach
- Strength of the analysis that we have the option to consider later lines more granularly until the time horizon

How many line of treatment is appropriate?

Abbreviations: BSC, best supportive care; EAG, external assessment group; L, line; LYs, life-years; OS, overall survival; PartSA, partitioned survival analysis; PFS, progression-free survival; QALY, quality-adjusted life-year; STM, state transition model; TTD, time to discontinuation.

EAG model flow



NICE

Abbreviations: EAG, external assessment group.

Reference treatment extrapolation (1)

EAG

- Modelling of treatment effectiveness in EAG base case STM requires extrapolation of 4 different curves for the reference treatment at each line in the model base case:

PFS	TTP	TTD	PPS
• Progression and death (events) • Informs pre-progression to death transition and PartSA	• Progression (event) and death (censor) • Informs transitions between treatment lines (1L PF to PD/2L PF)	• Discontinuation and death (events) • Informs on treatment to off treatment transitions	• Time from progression to death (event) • Informs progressed disease to death transition for BSC

- Scenario PartSA model uses only OS, PFS and TTD for the sunitinib reference curve at first line then applies the 1L OS and PFS NMAs to generate comparator effectiveness estimates
- **1L data source –** Base case: UK RWE sunitinib data; *Scenario analysis: CheckMate 9ER sunitinib data*

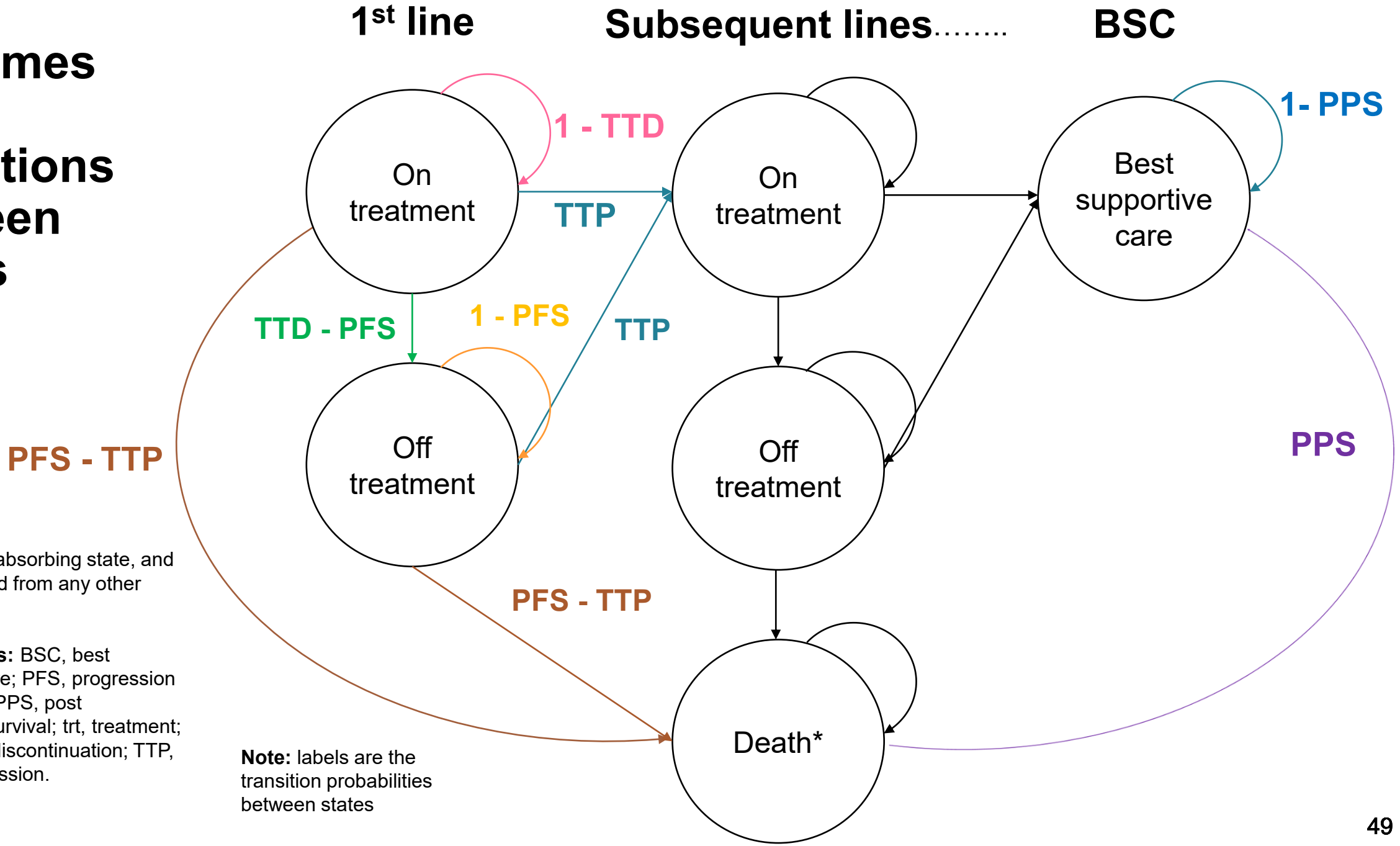
Company comments

- Company consider more simplified assumption that TTD equal to PFS more appropriate and consistent

Is EAG approach appropriate?

Abbreviations: EAG, external assessment group; OS, overall survival; PartSA, partitioned survival analysis; PFS, progression-free survival; PPS, post-progression survival; RWE, real-world evidence; STM, state transition model; TTD, time to discontinuation; TTP, time to progression; UK, United Kingdom.

How outcomes drive transitions between states



* Death is an absorbing state, and can be entered from any other model state.

Abbreviations: BSC, best supportive care; PFS, progression free survival; PPS, post progression survival; trt, treatment; TTD, time to discontinuation; TTP, time to progression.

Note: labels are the transition probabilities between states

NICE

Comparator efficacy (1)

Effectiveness for all other therapies calculated using EAG NMAs

EAG: FP NMA used to capture differences in hazards between treatments over time; long-term hazards outcomes for IO combinations and TKI monotherapies expected to be different so PH not appropriate

First-line therapy

- Model uses sunitinib as the reference treatment
- **Base case:**
  - Other treatment effectiveness derived from EAG 1L NMA
  - FPs/HRs used to generate other curves
  - Assumes PFS HR applies to TTD and TTP
- **Scenarios:** PH NMA, individually fitted curves to trial data, assuming len+pem equal to cabo+nivo

Second- and third-line therapy

- Model uses cabozantinib as reference
- **Base case:**
  - Other effectiveness derived from 2L+ NMA
  - HRs used to generate other curves
  - TTD data not available in RWE. So, HR: TTD vs PFS: 1.19 (1.15, 1.24) from 1L applied
- **Scenario:** FP NMA

Fourth-line therapy

- Apply HR from PH NMAs between pooled 3rd and 4th line outcomes from UK RWE to 'downweight' all treatments, then calculate TTP based upon its relationship to PFS at earlier lines
- 4th line OS HR 2.01 (1.45, 2.78); 4th line PFS HR 1.74 (1.21, 2.51); TTP HR to PFS: 0.82 (0.80, 0.84)

Are methods for comparators appropriate?

Is it appropriate to 'down-weight' outcomes at later lines?

Abbreviations: EAG, external assessment group; FP, fractional polynomial; HR, hazard ratio; IO, immuno-oncology; L, line; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; PH, proportional hazards; RWE, real-world evidence; TKI, tyrosine kinase inhibitor; TTD, time to discontinuation; TTP, time to progression.

Surrogacy between outcomes

EAG apply PFS NMA to other outcomes

Background

- In the EAG literature reviews, there was a lack of published TTP, TTNT and TTD data
- Targeted review conducted investigating surrogacy between different endpoints in advanced RCC
- Analysis from the UK real-world evidence dataset indicated a high level of correlation between TTD and PFS endpoints
- Clinical advice was that TTNT and PFS and TTD and PFS are well correlated and that TTNT is a reasonable proxy for PFS
- EAG apply outcomes from PFS NMAs to TTD and TTP in the absence of enough published data to form standalone networks

Company

- Company consider more simplified assumption that TTD equal to PFS more appropriate and consistent

Is the EAG's approach appropriate?

Abbreviations: EAG, external assessment group; NMA, network meta-analysis; PFS, progression-free survival; RWE, real-world evidence; TTD, time to discontinuation; TTNT, time to next treatment; TTP, time to progression; UK, United Kingdom.

Comparison of clinical endpoints CM9ER and RWE

[redacted]

[redacted]

Comparator efficacy (2)

Effectiveness for all other therapies calculated using EAG NMAs

1L	TTD	PFS	TTP	OS
Cabo+nivo	Rel. effect = PFS	**FP NMA**	Rel. effect = PFS	**FP NMA**
Nivo+ipi	Rel. effect = PFS	**FP NMA**	Rel. effect = PFS	**FP NMA**
Pem+len	Rel. effect = PFS	**FP NMA / PH NMA¥**	Rel. effect = PFS	**FP NMA**
Ave+axi	Rel. effect = PFS	**FP NMA**	Rel. effect = PFS	**PH NMA**
Suni	*Reference*	*Reference*	*Reference*	*Reference*
Pazo	Equal to suni*	Equal to suni+	Equal to suni*	Equal to suni+
Tivo	Equal to suni*	Equal to suni+	Equal to suni*	Equal to suni*
Cabo	Rel. effect = PFS	**FP NMA**	Rel. effect = PFS	**FP NMA**

Notes: *Data not available in either NMA; + PH NMA available but not used in base case; ¥ FP NMA only available for all risk population

2L/3L	TTD	PFS	TTP	OS
Nivo	HR to PFS	PH NMA	Rel. effect = PFS	PH NMA
Pazo	HR to PFS	Equal to tivo*	Rel. effect = PFS	Equal to tivo*
Tivo	HR to PFS	PH NMA	Rel. effect = PFS	PH NMA
Suni	HR to PFS	Equal to tivo*	Rel. effect = PFS	Equal to tivo*
Cabo	*HR to PFS*	*Reference*	*Reference*	*Reference*
Len+eve	HR to PFS	PH NMA	Rel. effect = PFS	PH NMA
Evero	HR to PFS	PH NMA	Rel. effect = PFS	PH NMA
Axi	HR to PFS	PH NMA	Rel. effect = PFS	PH NMA

Notes: *Data not available in either NMA; + PH NMA available but not used in base case; ¥ FP NMA only available for all risk population

Notes: Separate NMAs performed for favourable/all-risk and intermediate-/poor-risk groups
Only proportional hazards NMA available for favourable risk group
Fractional polynomials NMA only available for pem+len all-risk population, proportional hazards used in int-/poor-risk

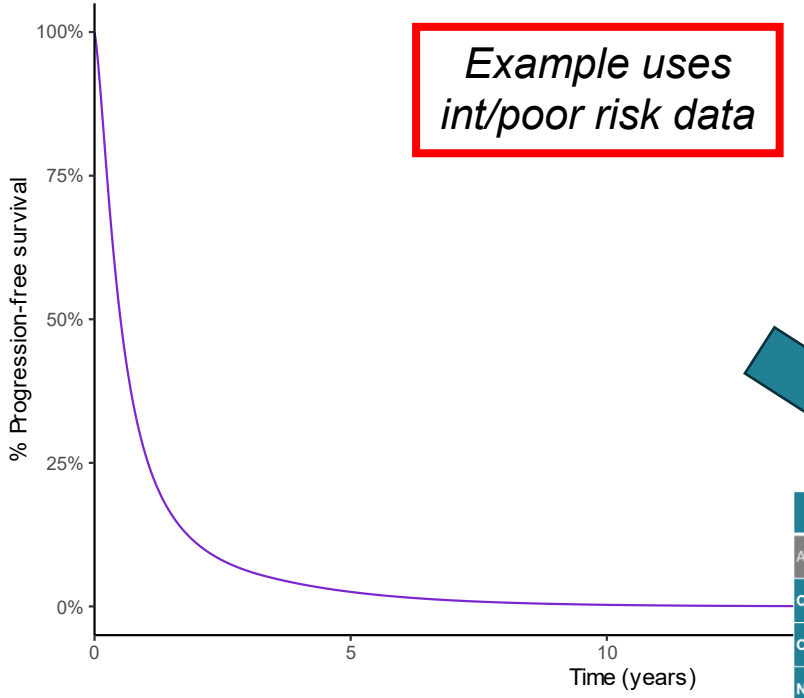
Is it appropriate to use PH NMA for pem+len and FP NMA for all other treatments?

NICE **Abbreviations:** 1L, first line; EAG, external assessment group; FP, fractional polynomial; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; PH, proportional hazards; TTD, time to discontinuation; TTP, time to progression; UK, United Kingdom.

Comparator efficacy (3) – proportional hazards NMA

Sunitinib reference treatment and time-**invariant** HRs applied for other treatments

Sunitinib RWE progression free survival extrapolation (reference curve)



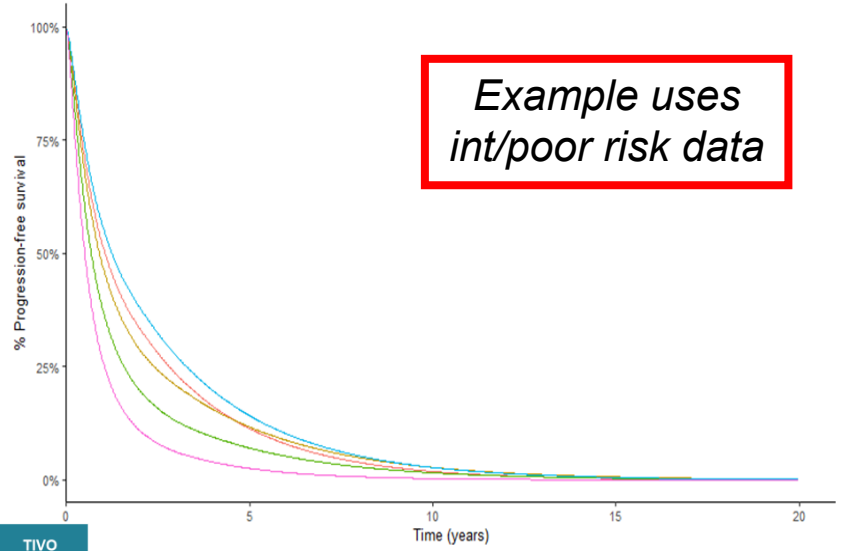
Example uses int/poor risk data

PH NMA applied

	AVE+AXI	CABO+NIVO	CABO	NIVO+IPI	PAZO	PEM+LENV	SORA	SUNI	TIVO
AVE+AXI	-	1.136 (0.888,1.46)	1.405 (0.879,2.216)	0.78 (0.619,0.981)	0.668 (0.54,0.825)	1.425 (1.099,1.845)	0.491 (0.387,0.62)	0.671 (0.57,0.789)	0.65 (0.46,0.924)
CABO+NIVO	0.880 (0.685,1.126)	-	1.237 (0.765,1.98)	**0.687 (0.538,0.882)**	**0.588 (0.467,0.742)**	1.254 (0.948,1.646)	0.432 (0.336,0.557)	**0.591 (0.49,0.711)**	**0.571 (0.401,0.825)**
CABO	0.712 (0.451,1.137)	0.809 (0.505,1.308)	-	**0.556 (0.352,0.882)**	**0.476 (0.304,0.755)**	1.012 (0.632,1.658)	0.349 (0.22,0.56)	**0.478 (0.311,0.739)**	**0.462 (0.27,0.793)**
NIVO+IPI	1.283 (1.019,1.615)	**1.456 (1.134,1.859)**	**1.800 (1.134,2.839)**	-	0.857 (0.693,1.053)	**1.826 (1.411,2.364)**	0.628 (0.497,0.794)	0.86 (0.732,1.009	0.83 (0.586,1.185)
PAZO	1.496 (1.212,1.852)	**1.701 (1.348,2.139)**	**2.101 (1.325,3.289)**	1.167 (0.95,1.443)	-	**2.134 (1.67,2.716)**	0.734 (0.614,0.874)	1.005 (0.876,1.15)	0.974 (0.71,1.331)
PEM+LENV	0.702 (0.542,0.91)	0.797 (0.607,1.054)	0.989 (0.603,1.583)	**0.548 (0.423,0.709)**	**0.469 (0.368,0.599)**	-	0.344 (0.265,0.45)	**0.471 (0.387,0.577**	**0.456 (0.315,0.665)**
SORA	2.036 (1.613,2.583)	2.317 (1.796,2.979)	2.864 (1.785,4.553)	1.592 (1.259,2.013)	1.362 (1.144,1.628)	2.91 (2.223,3.773)	-	1.368 (1.153,1.62)	1.322 (1.014,1.72)
SUNI	1.49 (1.268,1.755)	**1.692 (1.407,2.042)**	**2.092 (1.354,3.213)**	1.162 (0.991,1.365)	0.995 (0.87,1.141)	**2.124 (1.733,2.587)**	0.731 (0.617,0.867)	-	0.967 (0.709,1.321)
TIVO	1.538 (1.083,2.176)	**1.75 (1.212,2.494)**	**2.165 (1.261,3.699)**	1.205 (0.844,1.707)	1.027 (0.752,1.409)	**2.195 (1.505,3.174)**	0.756 (0.581,0.986)	1.034 (0.757,1.411	-

As seen on Slide 35

Comparator progression free survival



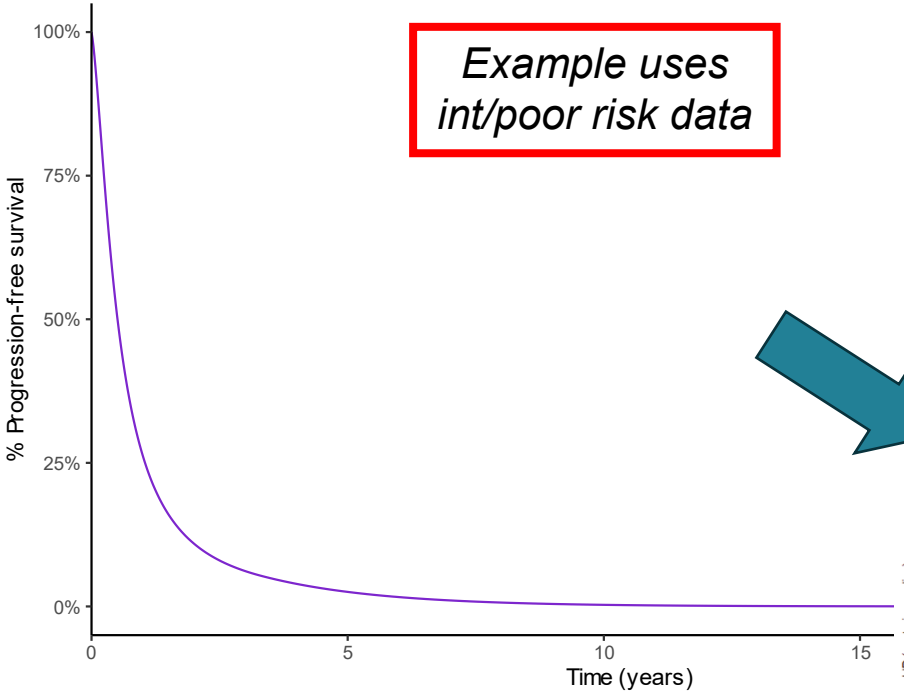
Example uses int/poor risk data

Abbreviations: HR, hazard ratio; int, intermediate; NMA, network meta-analysis; PFS, progression-free survival; PH, proportional hazards; RWE, real-world evidence.

Comparator efficacy (4) – fractional polynomial NMA

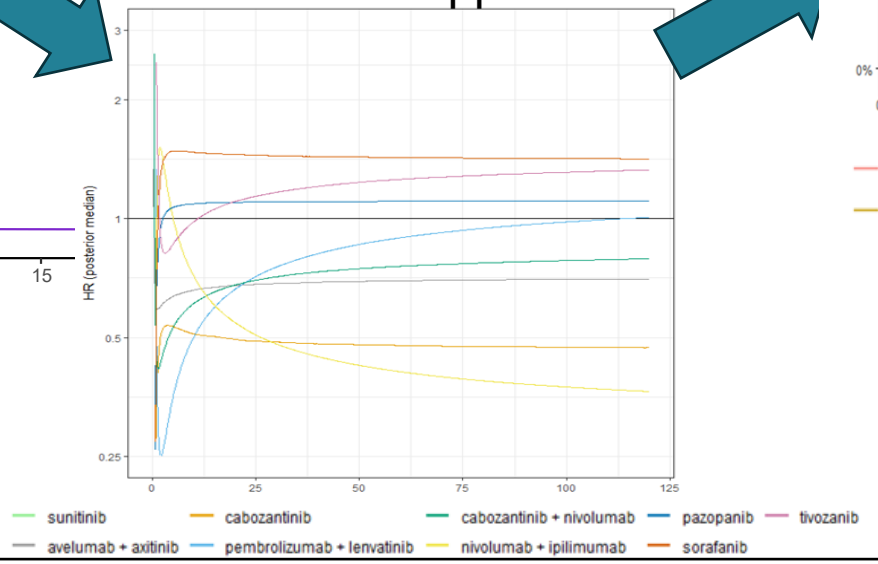
Sunitinib reference treatment and time-**variant** HRs applied for other treatments

Sunitinib RWE progression free survival extrapolation (reference curve)

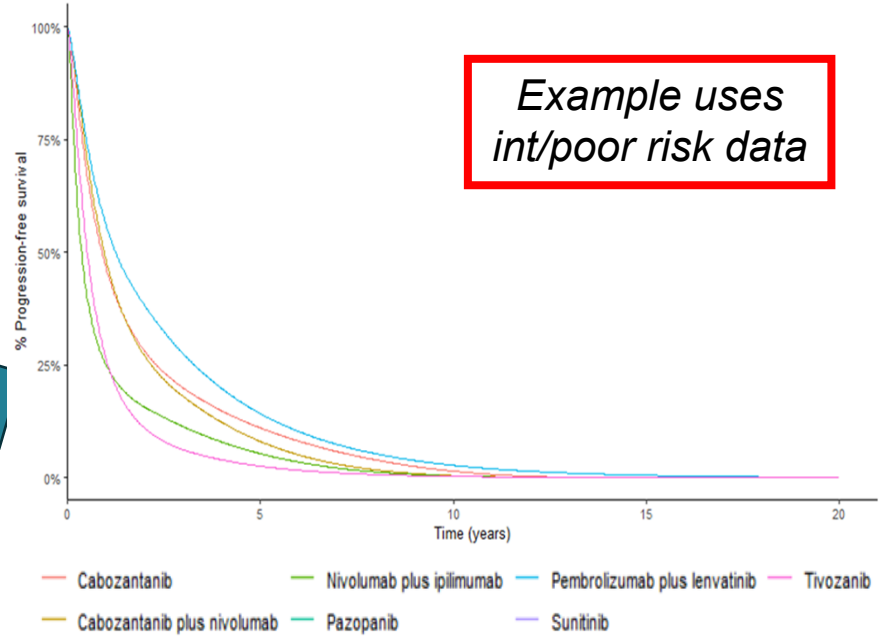


Example uses int/poor risk data

FP NMA applied



Comparator progression free survival



Example uses int/poor risk data

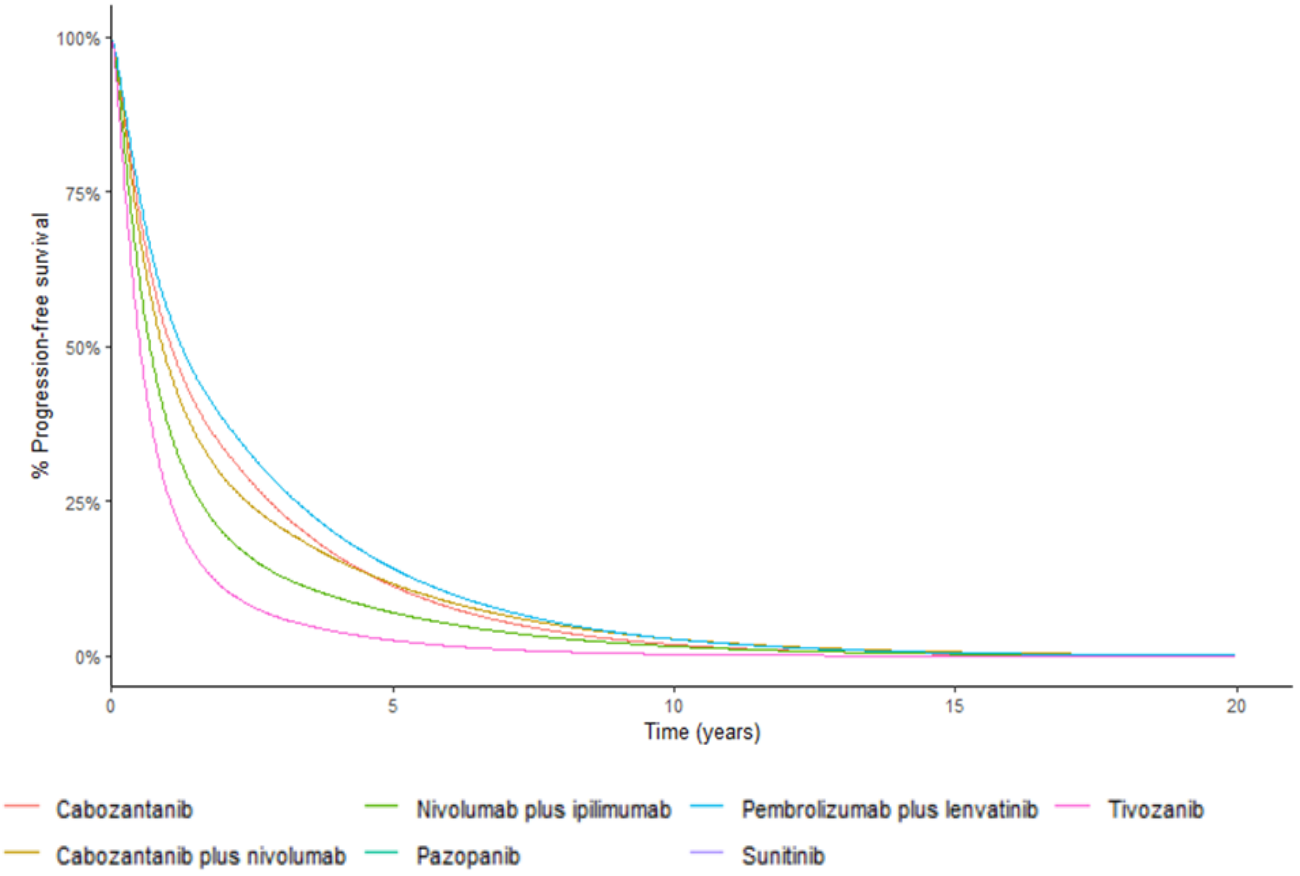
Note: *Pem+len uses PH model*

As seen on Slide 33

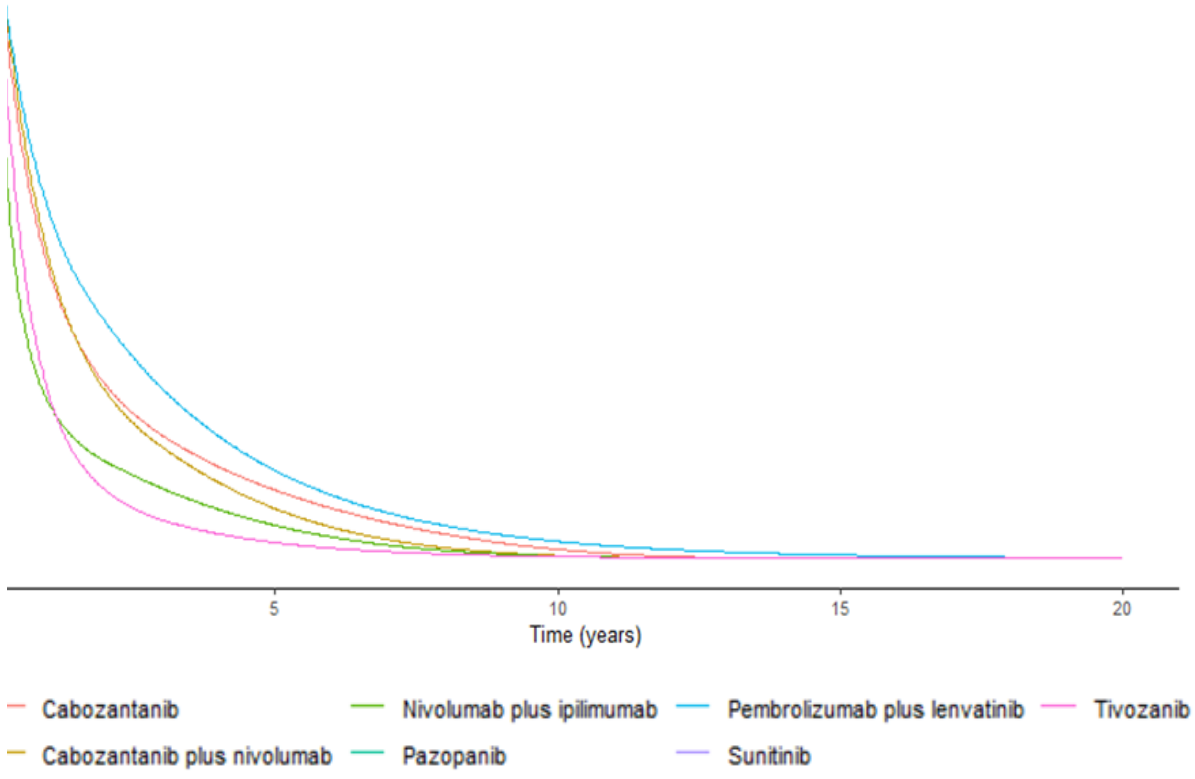
Abbreviations: FP, fractional polynomial; HR, hazard ratio; int, intermediate; NMA, network meta-analysis; PFS, progression-free survival; RWE, real-world evidence.

Extrapolation by treatment – Progression-free survival

STM predicted PFS using PH NMA, intermediate / poor risk population



STM predicted PFS using FP NMA, intermediate / poor risk population



Note: in the model base case pazopanib, sunitinib and tivozanib all have equal PFS; Pem+len uses PH model

Abbreviations: FP, fractional polynomials; NMA, network meta-analysis PH, proportional hazards; PFS, progression-free survival; STM, state transition model.

Treatment sequencing (1)

EAG implement subsequent treatment rules to reflect expectations

Background

- The most cost-effective sequence of treatments to use is not considered in this appraisal
- However, the model does consider the cost and impacts of subsequent treatments which is an important consideration for cost effectiveness in this appraisal
- NICE have future work planned to investigate how treatment sequences can be considered in appraisals

EAG

- The state-transition approach permits the exploration of subsequent treatments as the treatment pathway includes multiple options over multiple lines
- The EAG received clinical advice as to most likely treatment sequences and use RWE to inform likeliest subsequent treatment after each possible comparator
- Implemented rules to match expectations in clinical practice i.e. no repeated treatments (incl. IOs)
- Reweighted RWE proportions after eliminating implausible treatment patterns

Company

- The company agreed that treatment sequencing is a challenge in this appraisal
- Increased uncertainty with modelling subsequent lines of treatment serves as a source of bias in the results

Abbreviations: EAG, external assessment group; IO, immuno-oncology; RWE, real world evidence.

Treatment sequencing (2)

EAG implement subsequent treatment rules to reflect expectations

1L to 2L treatment rules

1L treatments	Subsequent 2L treatments, %								
	Axi	Cabo	Lenv+evero	Nivo	Pazo	Suni	Tivo	Evero	BSC
Cabo	X%		X%	X%	X%	X%	X%	X%	X%
Nivo+ipi	X%	X%			X%	X%	X%	X%	X%
Cabo+nivo	X%		X%		X%	X%	X%	X%	X%
Lenv+pem	X%	X%			X%	X%	X%	X%	X%
Pazo	X%	X%	X%	X%		X%	X%	X%	X%
Suni	X%	X%	X%	X%	X%		X%	X%	X%
Tivo	X%	X%	X%	X%	X%	X%		X%	X%

EAG

- At consultation, updated model to allow 2nd line cabozantinib treatment after nivolumab plus ipilimumab

Is EAG reweighting method appropriate to account for available later line treatments?

NICE

Abbreviations: BSC, best supportive care; EAG, external assessment group; L, line.

Treatment effect waning

EAG include treatment waning applied at 5 years to all IO/TKI combinations

EAG assessment of waning

- Waning assumptions included in previous RCC TAs (TA780, TA650, TA542)
- More recent, more mature datacuts for IO combinations increase the uncertainty of a durable long-term effect where stopping rules are in place – evidence of 'slippage' in OS and PFS outcomes
- EAG considered whether treatment waning is appropriate for IO/IO and IO/TKI combinations:
  - How long the treatment is given
  - Mechanism of action and biological plausibility informed by clinical expert advice
  - Trends seen within the trials and fitted FP NMA models
  - Consistency between treatments with similar mechanisms of action
  - Precedent in prior appraisals
- EAG base case applies treatment effect waning at 5 years to all IO / TKI combinations based on hazards
  - Five years longest timepoint data available for 1L combinations with a reasonable number at risk
- Scenarios more optimistic than previous TAs and have limited impact due to data maturity

EAG waning scenarios

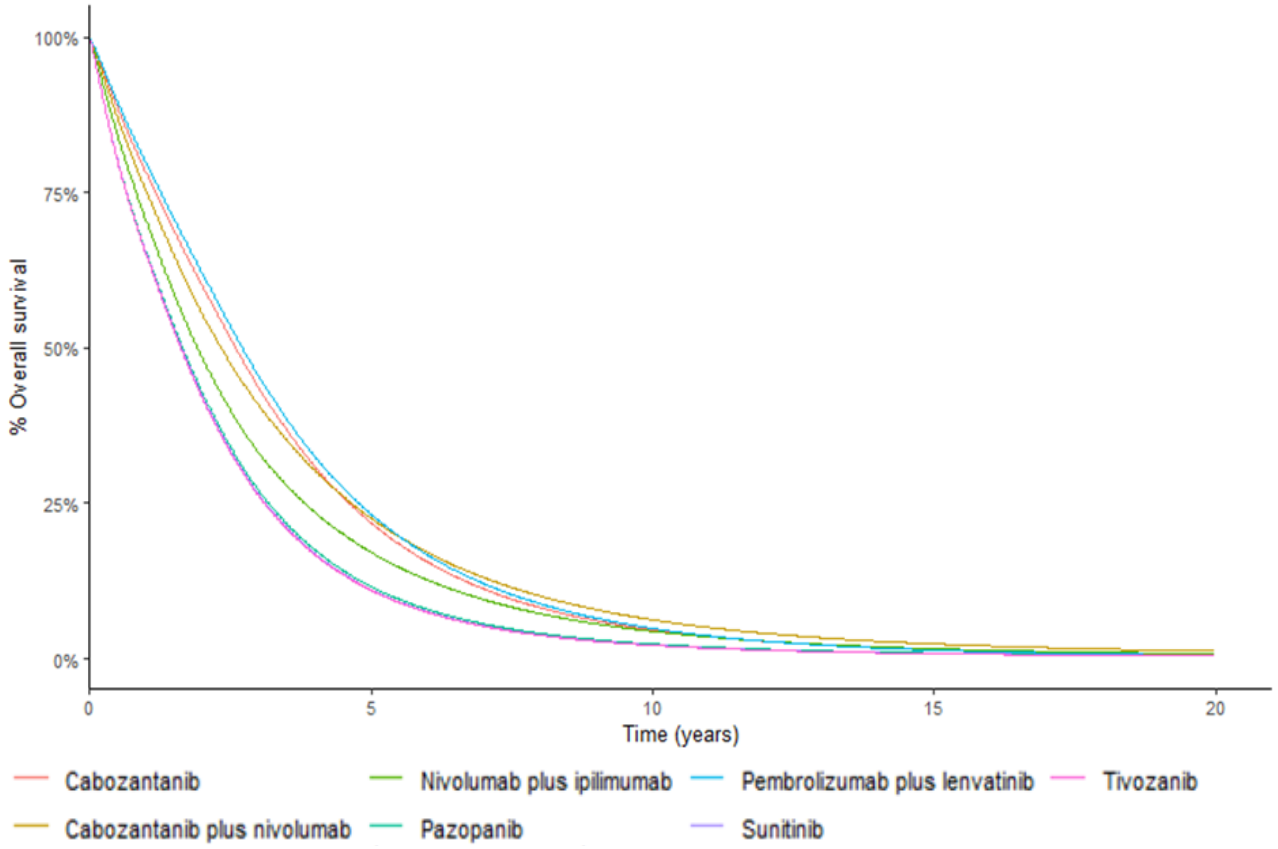
- Applied at 10 years to all IO/TKI combinations
- Applied at 10 years to all IO combinations
- Applied between five and 20 years to IO/TKI
- Applied between five and 20 years to all IO combo
- No treatment effect waning

Are EAG waning assumptions appropriate?

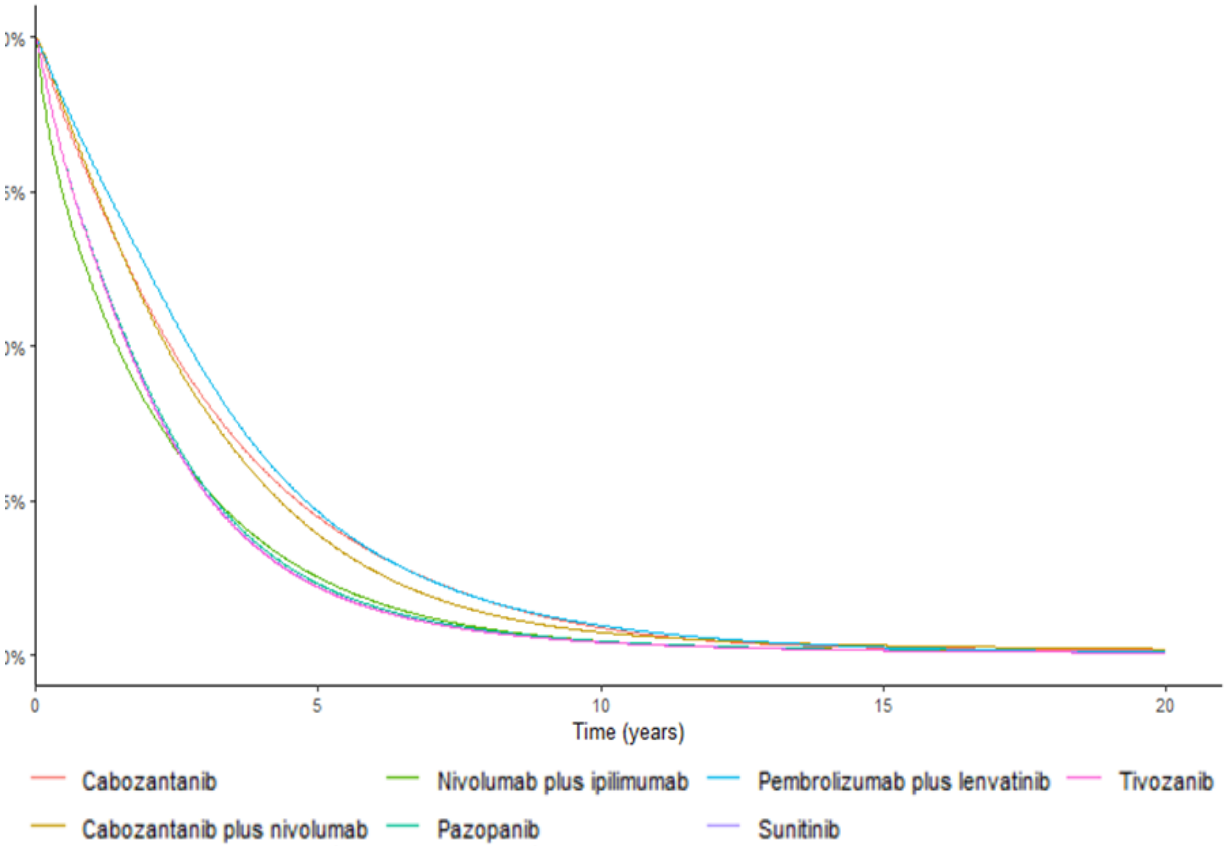
Abbreviations: EAG, external assessment group; FP, fractional polynomials; IO, immuno-oncology; NMA, network meta-analysis; RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor.

Extrapolation by treatment – Overall survival

STM predicted OS using PH NMA, intermediate / poor risk population

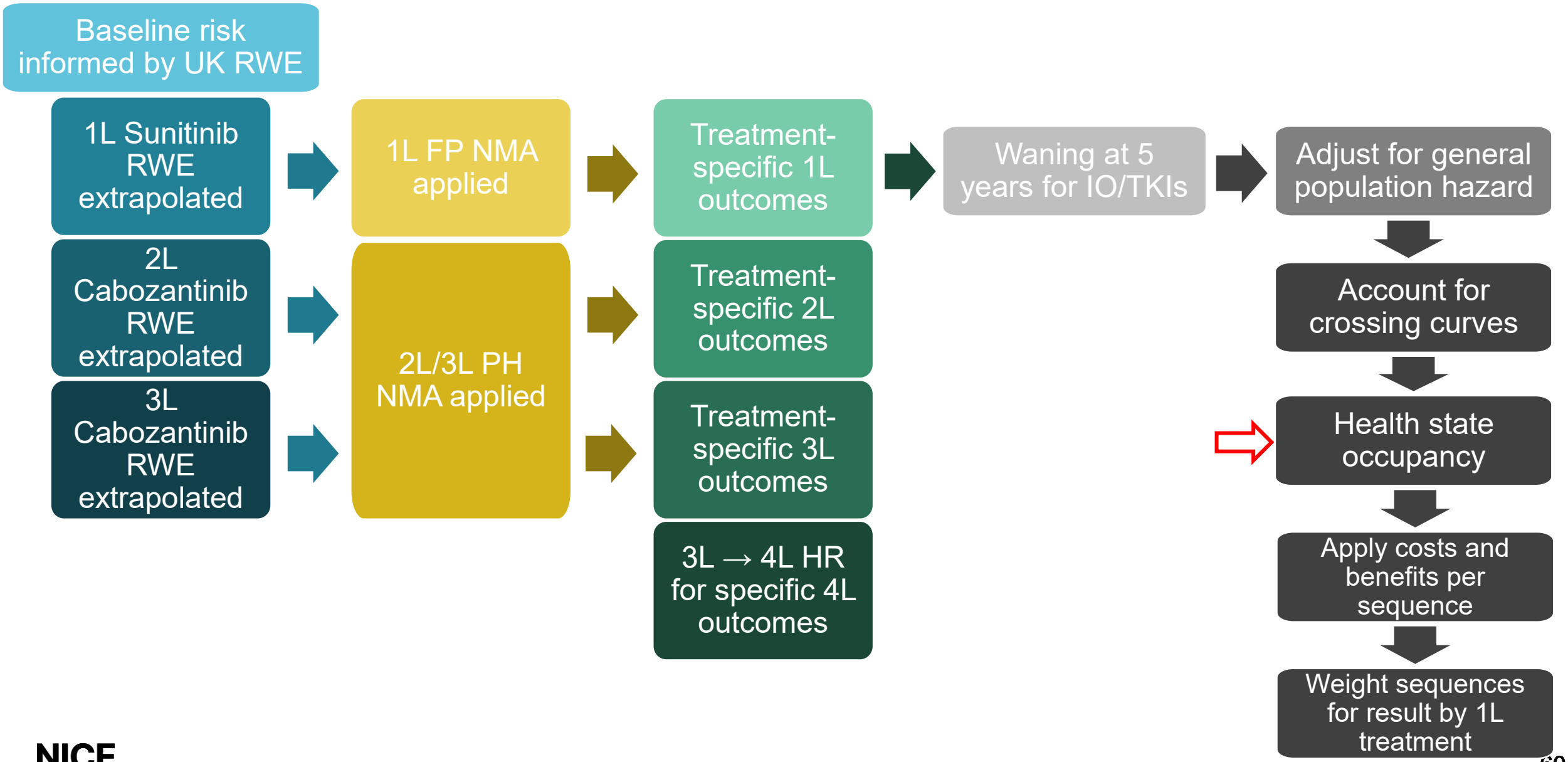


STM predicted OS using FP NMA, intermediate / poor risk population



Abbreviations: FP, fractional polynomials; NMA, network meta-analysis PH, proportional hazards; OS, overall survival; STM, state transition model.

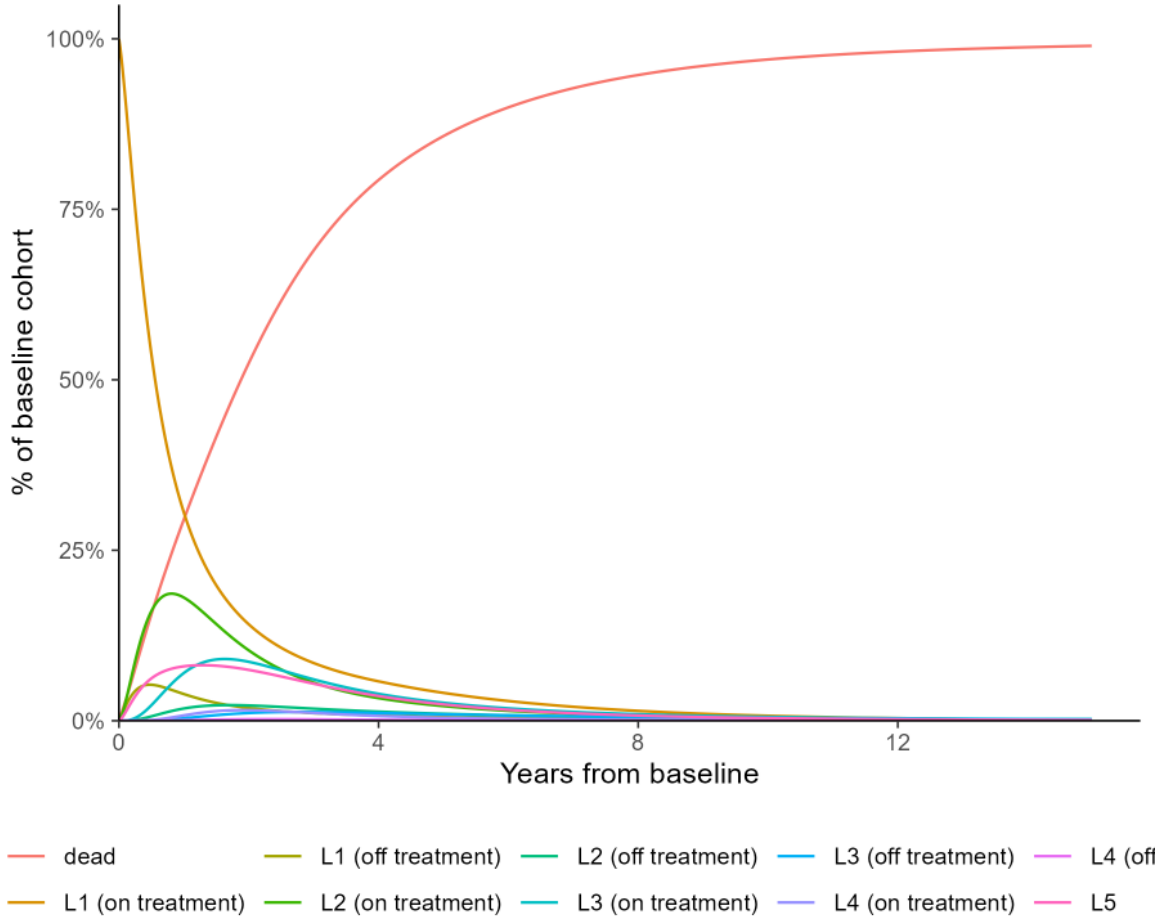
Final efficacy model flow



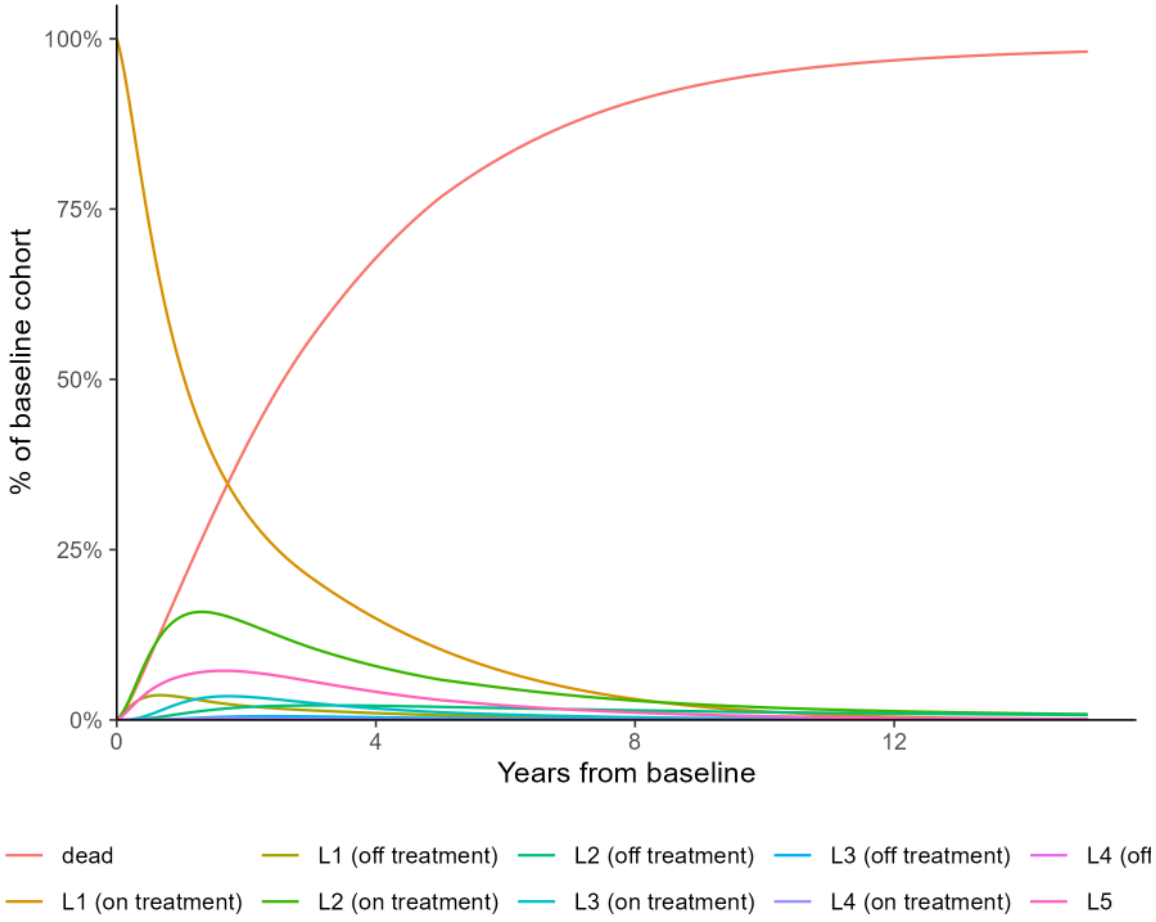
Abbreviations: FP, fractional polynomials; IO, immuno-oncology; L, line; PH, proportional hazards; RWE, real world evidence; TKI, tyrosine kinase inhibitor.

Final health state occupancy – all-risk

Markov trace (all risk groups): sunitinib



Markov trace (all risk groups): CABO+NIVO

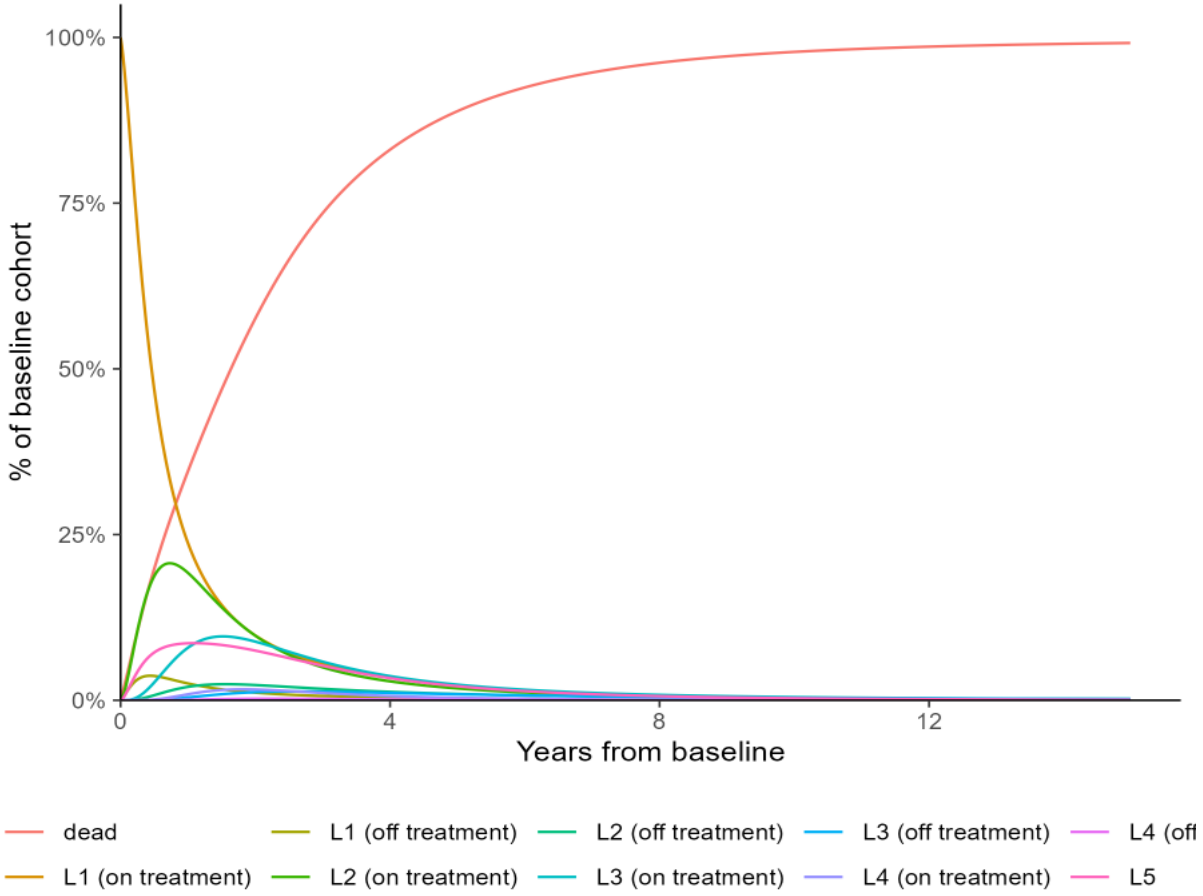


NICE

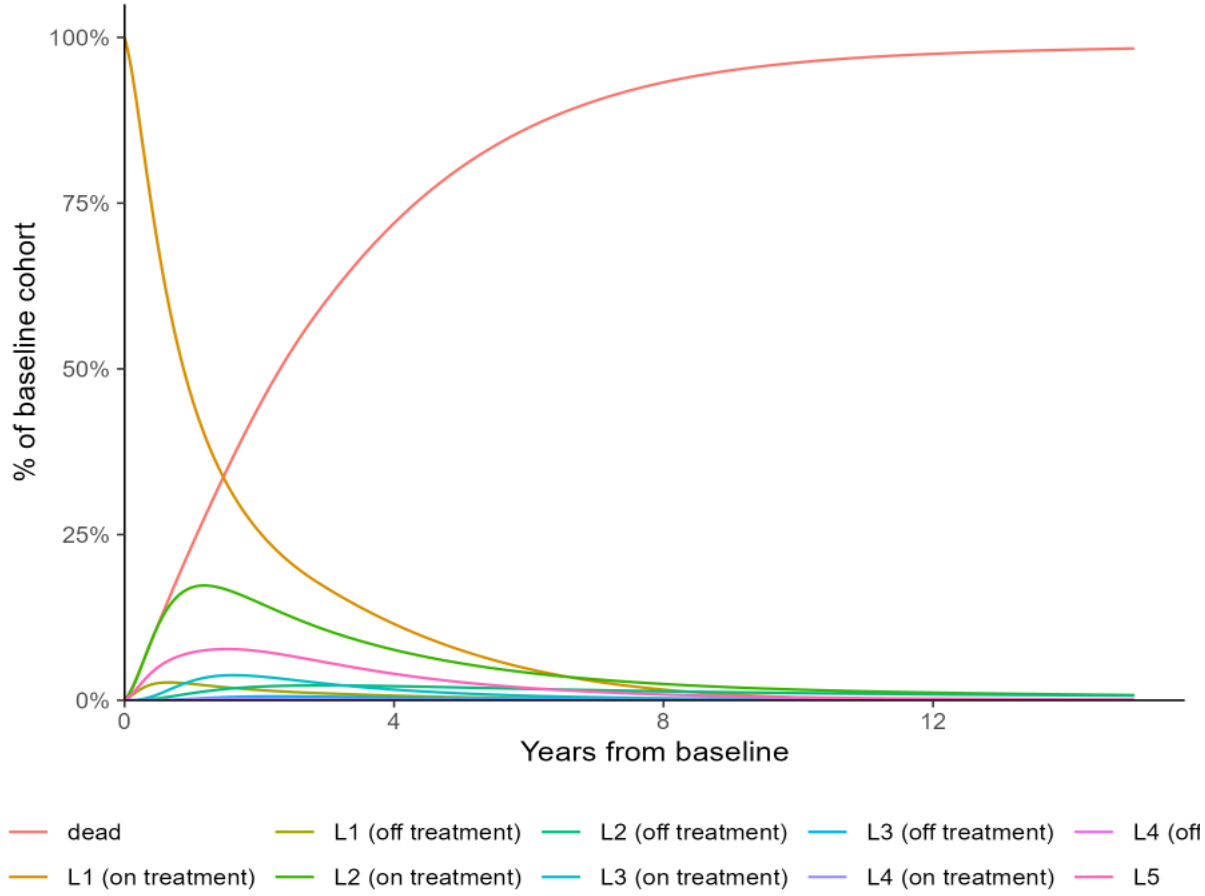
Abbreviations: CABO+NIVO, cabozantinib plus nivolumab; L, line.

Final health state occupancy – intermediate-/poor-risk

Markov trace (intermediate-/poor-risk group): sunitinib



Markov trace (intermediate-/poor-risk group): CABO+NIVO



NICE

Abbreviations: CABO+NIVO, cabozantinib plus nivolumab; L, line.

Validation of reference curve extrapolation

Overall survival fit to UK RWE sunitinib Kaplan–Meier data

[redacted]

[redacted]

Key:
A, All-risk group
B, Intermediate-/poor-risk group
C, Favourable-risk group

Model in A and B refers to OS calculated using STM

NICE

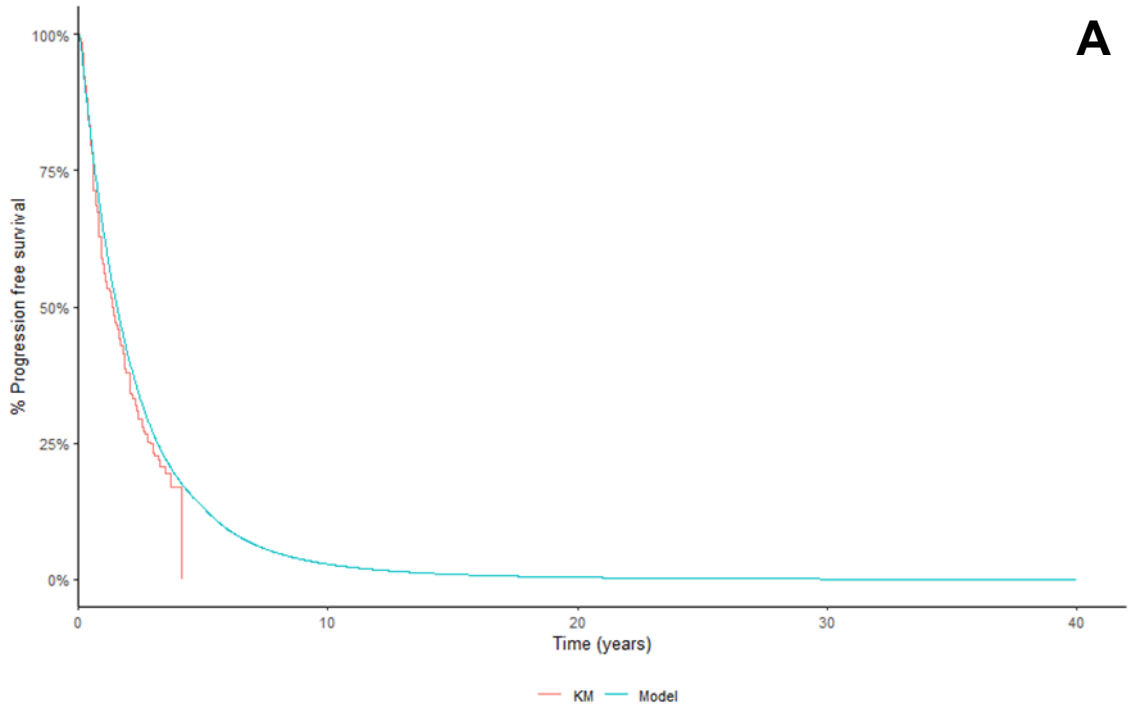
EAG

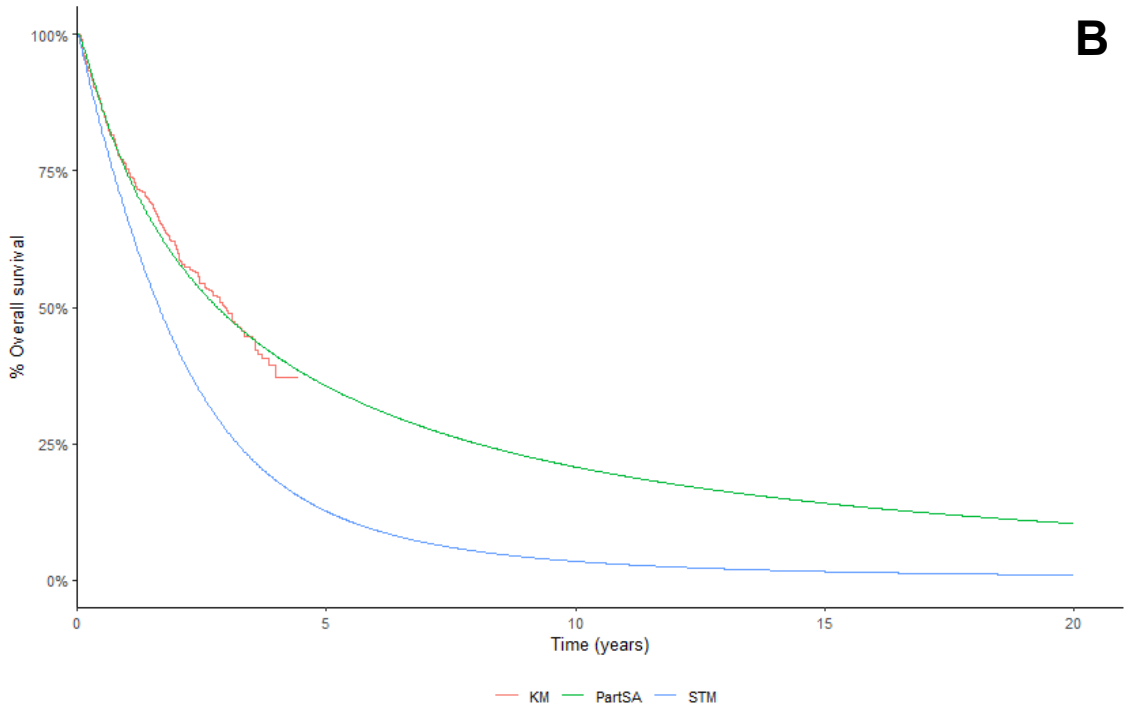
- Shows good fit to all- and intermediate-/-poor-risk groups, but an underprediction compared to the KM for favourable-risk
- Due to impact of risk score as a prognostic factor for later line outcomes

Abbreviations: KM, Kaplan–Meier; PartSA, partitioned survival analysis; RWE, real-world evidence; UK, United Kingdom.

Validation of reference curve extrapolation

Overall survival fit to CheckMate-9ER sunitinib Kaplan–Meier data





Key:
A, STM fit to cabo+nivo PFS when using sunitinib reference curve from CheckMate 9ER
B, Model fit to sunitinib OS when using sunitinib reference curve from CheckMate 9ER

Model in A refers to OS calculated using STM

EAG

A shows STM fits well to CM9ER KM
B shows PartSA using CM9ER data fits well to OS KM and STM underpredicts

- CM9ER includes subsequent therapy not used in UK practice
  - Potentiall under-reported 2L subsequent therapy
- CM9ER did not report 3/4L subsequent therapy so UK RWE used instead

STM is likely to present a more realistic projection of expected OS

Abbreviations: CM9ER, CheckMate-9ER; KM, Kaplan–Meier; L, line; OS, overall survival; PartSA, partitioned survival analysis; RWE, real-world evidence; STM state transition model; UK, United Kingdom.

Adverse events

EAG use CM9ER safety data and ITC for comparators

EAG approach

- Impact of toxicity on costs and HRQoL has been included in the economic analysis
- No AE data available in UK RWE
- For cabo+nivo and sunitinib, AE rates were taken from data supplied by Ipsen for CheckMate 9ER
  - Included G3+ AEs which occur in >5% of patients in any trial arm, aligns with TA858
  - In addition, hand-foot syndrome, diarrhoea and fatigue included at any grade from Cochrane review
- For other treatments, EAG G3+ NMA and published all-grade NMA applied to reference sunitinib
- Think that the impact of key AEs is likely to be underestimated due to selection bias within the trials
- *Scenarios investigate treatment naïve G3+ AEs from CM9ER or comparator trials; remove impact of AEs; increase disutility by 10%*

Costs and utility

- AEs may be applied per cycle or as a one-off cost and utility impact at the start of each treatment
- Clinical advice was that the majority of AEs occur within the first 6 months so base case applied as one-off
- Utility decrements sourced from CheckMate 9ER; costs sourced from NHS reference costs

Company

- Prefer using treatment naïve G3+ AE rates from CheckMate 9ER and comparator trial scenario

Which approach (NMA or naïve comparison) is most appropriate?

Abbreviations: AE, adverse event; CABO+NIVO, cabozantinib plus nivolumab; EAG, external assessment group; G3, grade 3; HRQoL, health-related quality of life; NHS, National Health Service; NMA, network meta-analysis; RWE, real world evidence; TA, technology appraisal; UK, United Kingdom.

Utility values (1)

CheckMate 9ER utility values higher than other appraisals

EAG

- Utility values used in the model differ by progression status and line of therapy
- HRQoL data supplied by the company did not have face validity compared to the general population
- Patient utility decrease as people progress and move onto later line therapy
- Utility estimates were higher across health states than for most other appraisals
- Base case uses an alternative source considered to have greater face validity:
  - Use published utility values accepted in previous NICE TAs for first and second line before assuming the percentage reduction from TA498 applies to later lines
- Scenarios investigate using CheckMate 9ER utility

Company

- Argue high utility values derived from CheckMate9ER are supported by other previously published studies of treatments with similar mechanisms of action
- Precedence in the literature for maintaining a high post-progression utility value
- Suggest a scenario applies the proportional utility reduction from the trial to UK RWE utility

Abbreviations: HRQoL, health-related quality of life; RWE, real-world evidence; TA, technology appraisal; UK, United Kingdom.

Utility values (2)

Comparison of EAG utility values and CheckMate 9ER

CheckMate 9ER utility

CheckMate 9ER	Progression free (mean)	Progressed disease (mean)
ITT	[redacted]	[redacted]
Favourable	[redacted]	[redacted]
Intermediate/poor	[redacted]	[redacted]

EAG approach using published utilities from past NICE TAs

Line	Utility	Source
1L	PF: 0.753 PD: 0.683	JAVELIN Renal 101 (TA645)
2L	PF: 0.683 PD: 0.616	PF utility assumed to reflect PD in 1L. PD value estimated based on % reduction from the AXIS trial (TA498)
3L	PF: 0.616 PD: 0.545	Estimated based on % reduction from the AXIS trial (TA498). Approach follows NICE DSU12 guidance
4L	PF: 0.545 PD: 0.482	Estimated based on % reduction from the AXIS trial (TA498). Approach follows NICE DSU12 guidance

Are utility values used in the model appropriate?
Which source better represents expectations for quality of life in advanced RCC?

Abbreviations: DSU, decision support unit; EAG, external assessment group; ITT, intention to treat; L, line; PD, progressed disease; PF, progression free; RCC, renal cell carcinoma; TA, technology appraisal.

Cost and resource use

EAG conducted literature review for cost and resource use data in RCC

Resource frequencies sourced from prior NICE TAs; costs from published sources (NHS refs, PSSRU)

- Applied weekly

End of life costs based on Nuffield trust report exploring the costs of care at the end of life

- Applied as one-off cost on death

Drug and administration frequency sourced from the summary of product characteristics

Drug costs sourced from the BNF or eMIT; confidential PASs applied where relevant

Subsequent therapy proportions informed by RWE, implausible patterns reweighted

- For STM, costs are calculated per line according to time spent in state
- For PartSA, applied as a one-off cost on entry into next line
- Costs of surgery and radiotherapy subsequent therapies are applied as a one off regardless of model structure

Adverse event costs sourced from NHS reference costs

- Applied as one-off cost

NICE comments

- Sunitinib now off patent so complex PAS no longer cheapest option (eMIT and CMU)

Abbreviations: BNF, British National Formulary; eMIT, electronic medicines information tool; NHS, National Health Service; PAS, patient access scheme; PSSRU, Personal Social Services Research Unit; RWE, real-world evidence; TA, technology appraisal.

Cost and resource use – relative dose intensity

RWE and trial dose intensity uncertain and alternatives investigated

Background

- RDIs appear lower in clinical practice (RWE) compared to trials; RDI commonly redacted from NICE TAs
- RDI for pem+lenv may be less reliable than others as it was estimated based on median no. infusions

Company

- RWE RDI can be helpful corroboration but requires accurate records to be meaningful
- Consistency deriving RDI is important – consider RDI from clinical trials more appropriate
- Suggested alternative dose intensities from clinical trials including [redacted]% nivolumab and [redacted]% cabozantinib
- Clinical feedback that lower dose intensities with pem and nivo when in combination with len and cabo

EAG

- Lower dose intensities of IOs impacted by toxicity of high dose of TKI (len given at max 20 mg dose CLEAR)
- For nivo+cabo, cabo given at 40 mg which is lower than monotherapy 60 mg dose – more tolerable
- Updated base case with new company data, but not company method, which double counts with TTD
- Len methodology updated at consultation to account for different pill sizes and titration regimen used in UK
  - As len pills are flat priced, important to accurately capture number of pills received
  - Start at 10mg for 2 weeks, then 75% get 14 mg for next 2 weeks, before 18% get 18 mg then 20 mg
  - Len (len+pem): 25% at 10 (1 pill), 57% at 14 (2 pills), 18% at 20 (2 pills)
- *Scenario analysis where all RDIs are set to 100% given the inconsistency in RDI methods*

What proportion of people get each lenvatinib dose? Is the titration reflective of NHS practice?

Abbreviations: BNF, British National Formulary; eMIT, electronic medicines information tool; mg, milligram; NHS, National Health Service; PAS, patient access scheme; PSSRU, Personal Social Services Research Unit; RDI, relative dose intensity; RWE, real-world evidence; TA, technology appraisal; TKI, tyrosine kinase inhibitor; UK, United Kingdom.

Severity (1)

Unclear how to apply severity modifiers in a multi-comparator decision space

EAG

- NICE manual is unclear as to how current practice should be defined in a multi-comparator decision space
- Three clear options to define current practice in these circumstances:
  1. Define common reference treatment to calculate severity modifiers for all treatments (EAG base case)
  2. Calculate the severity modifier based upon the market shares of all the comparators
  3. Calculate severity modifiers separately for pairwise comparisons
- Pairwise comparisons, whilst the simplest, inconsistent with the principle of fully incremental analysis

Company

- EAG applied the first approach and stated others inconsistent with fully incremental analysis
- However, EAG highlight that the application of severity modifiers is a key uncertainty due to lack of guidance
- Agrees whether a modifier should be applied in a fully incremental or a pairwise analysis is an academic debate; It is unlikely that this appraisal would reach a definitive answer to this question

NICE comments

- In TA927, severity was calculated separately for each comparator (like option 3 above)

Stakeholder comments

- Welcome clarity on how modifiers should be applied where probabilistic results indicate different modifiers

Abbreviations: EAG, external assessment group.

Severity (2)

Unclear how to apply severity modifiers in a multi-comparator decision space

1. Fully incremental analysis

- Cabo+nivo **unlikely to** qualify for a severity modifier using the EAG definition of standard of care
  - i.e. treatment with largest absolute QALYs not ruled out via dominance rules in incremental analysis
    - **All-/fav-risk:** only TKI monotherapies available via routine commissioning (SOC = pazopanib)
      - Note: proportionate shortfall of 0.85 close in the all-risk population
    - **Intermediate/poor risk:** novel combinations are available which increase the expected SOC QALYs (SOC = pem+lenv)

Risk	SOC QALYs	Gen pop QALYs	Abs SF	Prop SF	Modifier	Treatment considered SOC
All	1.695	10.382	8.687	0.837	1.0	Pazo
Fav	2.226	10.382	8.156	0.786	1.0	Pazo
Int/poor	2.229	10.382	8.153	0.785	1.0	Pem+lenv
Int/poor	1.485	10.382	8.897	0.857	1.2	Pazo
Int/poor	2.070	10.382	8.312	0.801	1.0	Cabo

All judgements here based on EAG base case and other analyses may provide different answers

What is appropriate standard of care in each population?

Abbreviations: Abs, absolute; cabo+nivo, cabozantinib plus nivolumab; fav, favourable; gen pop, general population; int, intermediate; pem+lenv, pembrolizumab plus lenvatinib; prop, proportionate; QALY, quality-adjusted life-year; SF, shortfall; SOC, standard of care; TKI, tyrosine kinase inhibitor.

Severity (3)

Unclear how to apply severity modifiers in a multi-comparator decision space

2. Pairwise analyses

- **All-/favourable risk:**
  - Cabo+nivo **unlikely to** qualify for a severity modifier versus any TKI treatment
- **Intermediate-/poor-risk:**
  - Cabo+nivo **likely to** qualify for a severity modifier (x1.2) versus sunitinib, pazopanib and tivozanib
  - Cabo+nivo **unlikely to** qualify for a severity modifier versus any IO combination or cabozantinib mono

EAG: pairwise analyses generally best avoided as excluding relevant comparators can lead to errors in interpretation (e.g. comparisons of interventions not on the efficient frontier)

3. Weighted market share analysis

- Most recent company market share data for the all-risk population indicate current practice is increasingly made up of other novel therapies
  - IO / TKI combos: [redacted], nivo+ipi: [redacted], cabo: [redacted], other TKIs: [redacted],
- Higher proportion of novel therapies lowers likelihood severity modifier is appropriate for nivo+cabo

All judgements here based on EAG base case and other analyses may provide different answers

Which approach is method to estimate the severity modifier (if any)?

Abbreviations: cabo+nivo, cabozantinib plus nivolumab; EAG, external assessment group; IO, immuno-oncology; QALY, quality-adjusted life-year; TKI, tyrosine kinase inhibitor.

Summary of company and EAG base case assumptions

All risk population and risk-subgroups

Assumptions in company and EAG base case

Assumption	EAG base case	Company base case	STM	PartSA
Model structure	STM	Both STM and PartSA base cases provided	▬	↑
Indirect comparison	FP NMA 1L; PH NMA 2L	PH NMA throughout	↓	↓
No. lines of treatment	4 lines of treatment then BSC	2 lines of treatment then BSC	↓	↑
Time to discontinuation	UK RWE for reference curve then PFS NMA applied for comparators	TTD equal to PFS	↑	↑
Adverse events	CM9ER for reference rates then AE NMA applied for comparators	Individual trials	↓	↓
Relative dose intensity	Company updated RDI data but recalculated nivo (nivo+cabo) and pem (pem+len)	Company analysis	↓	↓

What is the committee position on each key assumption?

Abbreviations: AE, adverse event; BSC, best supportive care; cabo, cabozantinib; EAG, external assessment group; FP, fractional polynomials; nivo, nivolumab; NMA, network meta-analysis; PartSA, partitioned survival analysis; PFS, progression-free survival; PH, proportional hazards; RDI, relative dose intensity; TTD, time to discontinuation.

Key questions for committee: decision problem

Category	Question
Comparators	Is tivozanib a relevant comparator?
Risk groups	Should cabo + nivo be assessed in different risk groups (all, favourable and intermediate/poor)?
Subsequent treatments	Does the EAG's understanding of the clinical pathway and treatment sequencing match NHS practice?
	How could inclusion of nivo+cabo change the pathway?
	Are the proportions of subsequent treatments from the RWE reflective of clinical practice?

Abbreviations: cabo+nivo, cabozantinib plus nivolumab; EAG, external assessment group; NHS, National Health Service; RWE, real-world evidence.

Key questions for committee: clinical

Category	Question
Clinical data	Is the sample from the RWE likely to be reflective of NHS practice?
	Do baseline characteristics reflect NHS practice?
NMA	How should the cabozantinib data from CABOSUN be interpreted?
	Which NMA is preferred – fractional polynomial or proportional hazards?
	Is it appropriate to use a proportional hazards NMA for pem+len, and a fractional polynomial NMA for all other treatments?

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Abbreviations: NHS, National Health Service; NMA, network meta-analysis; pem+len, pembrolizumab plus lenvatinib; RWE, real-world data.

Key questions for committee: cost effectiveness

Category	Question
Model structure	Which model structure is more appropriate – state transition or partitioned survival analysis?
	How many lines of treatment is it appropriate to model?
Modelled treatment effectiveness	Is the EAG's use of outcomes in the model appropriate? Should TTD be set as equal to PFS? Or is it more appropriate to apply HRs from the PFS NMAs to TTD and TTP curves?
	Is the EAG's 'down weighting' method appropriate to account for available later line treatments
Adverse events	Which approach to generating rates of Grade 3+ adverse events (NMA or naïve comparison between CheckMate 9ER and comparator trial) is most appropriate?
Utility values	Is the approach to capture utility used in the model appropriate?
	Does the published evidence from previous NICE appraisals, or CheckMate 9ER, better represent expectations for quality of life in advanced RCC?
Relative dose intensity	What proportion of people get each lenvatinib dose and is the lenvatinib titration reflective of NHS practice?
	Is the company or EAG's approach to calculating RDI most appropriate?
Severity	Which method for calculating a severity modifier is most appropriate?
	Does a severity modifier apply?

Abbreviations: EAG, external assessment group; HR, hazard ratio; NMA, network meta-analysis; PFS, progression-free survival; RCC, renal cell carcinoma; RDI, relative dose intensity; TTD, time to discontinuation; TTP, time to progression.

Summary of pairwise deterministic cost-effectiveness results

ICERs greater than £30,000 per QALY gained, apart from vs pem+lenv in intermediate/poor risk

All-/favourable-risk

- EAG base case:
  - Cabo+nivo ICER above £30,000 per QALY gained versus all comparators
- Company base cases:
  - Cabo+nivo ICER above £30,000 per QALY gained versus all comparators
- *EAG and company scenarios*
  - *ICERs >£30,000 per QALY gained or cabo + nivo dominated/extendedly dominated vs all comparators*

Intermediate-/poor-risk

- EAG base case:
  - Cabo+nivo ICER above £30,000 per QALY gained or dominated versus all comparators except:
    - South-west ICER above £30,000 saved per QALY lost versus pem+lenv
- Company base cases:
  - Cabo+nivo ICER above £30,000 per QALY or dominated versus all comparators except:
    - South-west ICER above £30,000 saved per QALY lost versus pem+lenv
- *EAG and company scenarios presented on next slides*

All results include confidential patient access scheme discounts for all applicable comparators. Detailed results, including ICERs, reported in PART 2 slides

NICE

Pairwise results reported here, however fully incremental results will also be available to committee in Part 2. Committee will decide most appropriate results to use for decision making. **Abbreviations:** Cabo+nivo, cabozantinib plus nivolumab; ICER, incremental cost-effectiveness ratio; PAS, patient access scheme; pem+lenv, pembrolizumab plus lenvatinib; QALY, quality-adjusted life-year.

EAG base case results

Explanation of EAG base case results

- Cabo+nivo dominated by cabo monotherapy in intermediate-/poor-risk population
  - Driven by unexpectedly good performance of cabo observed relative to suni CABOSUN
  - Neither pem+lenv or nivo+ipi cost-effective versus cabo monotherapy and other TKIs, aligns with TA858

Results versus other combinations

- When comparing to the two other novel combinations:
  - Cabo+nivo less effective and less expensive than pem+lenv (SW quadrant ICER of >£30,000)
    - Driven by higher effectiveness of pem+lenv by PH NMA and increased cost associated with reduced doses of pem+lenv being priced at the same cost (lenv pills flat pricing)
  - ICER vs nivo+ipi is >£30,000
    - Driven by a lower predicted TOT at 1L driven by lower expected PFS compared to other treatments

Abbreviations: Cabo+nivo, cabozantinib plus nivolumab; ICER, incremental cost-effectiveness ratio; L, line; NMA, network meta-analysis; pem+lenv, pembrolizumab plus lenvatinib; PFS, progression-free survival; PH, proportional hazards; QALY, quality-adjusted life-year; SW, southwest; TOT, time on treatment.

EAG scenarios in intermediate/poor risk population

ICERs > £30,000 / QALY or cabo+nivo dominated/extendedly dominated vs all comparators, except:

	Scenario (applied to EAG base case)	ICER (£/QALY)
	EAG base case	SW ICER >£30,000 vs pem+len
1	PartSA	SW ICER <£30,000 vs pem+len
3	State transition 2 lines	SW ICER >£30,000 vs pem+len
6	Trial-based analyses, state transition	<£30,000 vs nivo+ipi and SW ICER <£30,000 vs pem+len
7	Trial-based analyses, PartSA	SW ICER >£30,000 vs pem+len
11	Preferred 1L NMA, PH	SW ICER >£30,000 vs pem+len
21	PH NMA throughout, PartSA	Dominant vs pem+len
13	FP NMA for pem+lenv	<£30,000 vs pem+len
73	TTNT as a proxy for nivo+ipi PFS, PH NMA	<£30,000 vs nivo+ipi and SW ICER >£30,000 vs pem+len
74	TTD = PFS	<£30,000 vs nivo+ipi and SW ICER >£30,000 vs pem+len
75	NHSE input for lenv dosing within pem+lenv	SW ICER >£30,000 vs pem+len
20	Relative effectiveness for nivo + ipi from simple HR between PFS and TTD from CheckMate 214	Dominant versus nivo+ipi and SW ICER >£30,000 vs pem+len
24	Gradual TE waning between 5 and 20 years for IO/TKIs	SW ICER >£30,000 vs pem+len
26	No treatment effect waning	SW ICER >£30,000 vs pem+len
29	Weibull for 1L reference sunitinib	SW ICER >£30,000 vs pem+len
50	CheckMate 9ER utility for all lines	SW ICER >£30,000 vs pem+len
58	Individual trial AEs	SW ICER >£30,000 vs pem+len

Scenario results versus other combinations

- Nivo+ipi dominates nivo+cabo in int-/poor-risk population when trial data used in PartSA
- When PH NMA used within the STM the most effective treatment in the int-/poor-risk population is pem+lenv (2.23 QALYs) followed by cabo+nivo (2.16 QALYs) and then by nivo+ipi (1.82 QALYs)
- When PH NMA used within the PartSA the most effective treatment in the int-/poor-risk population is cabo+nivo (2.17 QALYs) followed by nivo+ipi (2.09 QALYs) and then pem+lenv (1.96 QALYs)
- When TTNT is used instead of PFS from CheckMate 214 within the FP NMA nivo+ipi remains predicted to be of lower effectiveness than cabo+nivo
  - this is due to the HR predicted being higher in the first year during which time many events have already occurred within the sunitinib RWE reference curve
- If all RDIs are set to 100% the costs associated with cabo+nivo substantially increase and at PAS prices the ICER vs pem+lev is SW quadrant <£30,000

Abbreviations: ICER, incremental cost-effectiveness ratio; int, intermediate; FP, fractional polynomials; L, line; NMA, network meta-analysis; PartSA, partitioned survival analysis; PAS, patient access scheme; PFS, progression-free survival; QALY, quality-adjusted life-year; RDI, relative dose intensity; STM, state transition model; SW, southwest; TOT, time on treatment.

Company scenario deterministic cost-effectiveness results

Company intermediate-/poor-risk scenario analyses – STM

- ICERs > £30,000 per QALY gained or cabo+nivo dominated/extendedly dominated versus next best comparator in all intermediate-/poor-risk stepwise scenarios
    - Note: All stepwise scenarios versus nivo+ipi >£30,000 and SW ICERs >£30,000 vs pem+len

Company intermediate-/poor-risk scenario analyses – PartSA

- ICERs > £30,000 per QALY gained or cabo+nivo extendedly dominated versus next best comparator in all intermediate-/poor-risk stepwise scenarios
    - Note: cabo+nivo is dominant or cost-effective vs pem+lenv in all scenarios except:
        - In final stepwise scenario in which the company RDI data is used where ICER <£30,000 (although EAG note this biases towards pem+len due to impact of lenvatinib pill prices)
    - Note: ICERs > £30,000 versus nivo+ipi except
        - In final stepwise scenario in which the company RDI used <£30,000 (although EAG argue this is incorrect and double counts TTD)

NICE **Abbreviations:** EAG, external assessment group; ICER, incremental cost-effectiveness ratio; PartSA, partitioned survival analysis; QALY, quality-adjusted life-year; RDI, relative dose intensity; STM, state transition model; SW, southwest; TTD, time to discontinuation.

Other considerations

Equality considerations

- Use of cabozantinib with nivolumab is not expected to raise any equalities issues

Managed access

- Ipsen does not expect cabozantinib with nivolumab to be a candidate for managed access given the relative maturity of the data available from the CheckMate 9ER trial

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Thank you.

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Back up slides

Previous NICE appraisals in advanced RCC

Previous RCC appraisals

TA	Year	Drug	Recommendation
TA858	2023	Lenvatinib with pembrolizumab for untreated aRCC	Recommended, only if intermediate-/poor-risk and if NIVO+IPI would have been offered
TA780	2022	Nivolumab with ipilimumab for untreated aRCC (review of TA581)	Recommended, only if intermediate-/poor-risk
TA650	2020	Pembrolizumab with axitinib for untreated aRCC	Not recommended
TA645	2020	Avelumab with axitinib for untreated aRCC	Recommended for use in the CDF
TA542	2018	Cabozantinib for untreated aRCC	Recommended, intermediate-/poor-risk only
TA512	2018	Tivozanib for treating aRCC	Recommended, only if no prior treatment
TA498	2018	Lenvatinib with everolimus for prev treated aRCC	Recommended after previous anti-VEGF
TA463	2017	Cabozantinib for previously treated aRCC	Recommended after previous anti-VEGF
TA432	2017	Everolimus for previously treated aRCC	Recommended after previous anti-VEGF
TA417	2016	Nivolumab for previously treated aRCC	Recommended after previous treatment
TA215	2011	Pazopinib for the first-line treatment of aRCC	Recommended first line
TA169	2009	Sunitinib for the first-line treatment of aRCC	Recommended first line

NICE **Abbreviations:** aRCC, advanced renal cell carcinoma; CDF, Cancer Drugs Fund; NIVO+IPI, nivolumab plus ipilimumab; RCC, renal cell carcinoma; TA, technology appraisal; VEGF, vascular endothelial growth factor.

Key issues – Decision problem

Unknown
Small
Large

Key issues

Issue	Resolved?	ICER impact
Relevant comparators *Company consider ave+axi a relevant comparator, but only available in CDF*	Yes	
Relevant subgroups *Risk status is prognostic and has been important in prior NICE RCC appraisals*	No	
Optimal sequencing of treatments *Treatment sequencing following first-line treatment remains an area of uncertainty*	No	

Key issues not presented here

Issue	Resolved?	ICER impact
Relevant outcomes *Time to next treatment data was unable to be included*	Yes	NA

Abbreviations: ave+axi, avelumab plus axitinib; CDF, Cancer Drugs Fund; ICER, incremental cost-effectiveness ratio; NA, not applicable; RCC, renal cell carcinoma.

Key issues – Clinical

Unknown
Small
Large

Key issues

Issue	Resolved?	ICER impact
CheckMate 9ER: Trial generalisability	Unresolvable	Unknown
CheckMate 9ER: Effect modification by risk groups	Yes	Large
Evidence base: quality and sufficiency of included randomised trials	No	Unknown
Evidence base: distribution of effect modifiers across evidence networks		
Evidence base: non-proportional hazards and slippage in survival outcomes		
Indirect treatment methods: proportional hazards or fractional polynomials	No	Large
Evidence base: unanswered questions relating to applicability across histologies and in a context of adjuvant treatment	No	Unknown

Key issues not presented here

Issue	Resolved?	ICER impact
CheckMate 9ER: Consistency of reporting	Unresolvable	NA

Key issues – Cost effectiveness

Unknown
Small
Large

Key issues

Issue	Resolved?	ICER impact
Inconsistency between prior appraisals	Unresolvable	?
Maturing data relating to IO/TKI combinations have magnified uncertainties relating to their long-term effectiveness	No	?
Impact of RDI and toxicity on economic case	No	large
Problems with the HRQoL data supplied by the company	No	small
Outstanding uncertainties in application of severity modifiers	No	?
Which choice of model structure is most appropriate?	No	large
How many lines of treatment should be modelled?	No	small

NICE

Abbreviations: .

EAG model development (2)

EAG model considered hybrid state transition model approach

Model structure

- State transition model with partitioned survival component – transitions applied to reference sunitinib
  - Scenarios investigate full partitioned survival model structure

TTP and PFS	Pre-progression survival (Pre-PS)	TTD	Treatment effects	Subsequent treatment
• UK RWE (base case) • CheckMate 9ER (scenario analysis)	• Difference between TTP and PFS	• UK RWE (base case) • CheckMate 9ER (scenario analysis) • Stopping rule and RDI considered	• Treatment effects for other treatments applied from NMA • Assume treatment effect for TTP and PFS is the same	• Effectiveness data, sequences and proportions taken from RWE • Relative effects based on NMA

Company comments

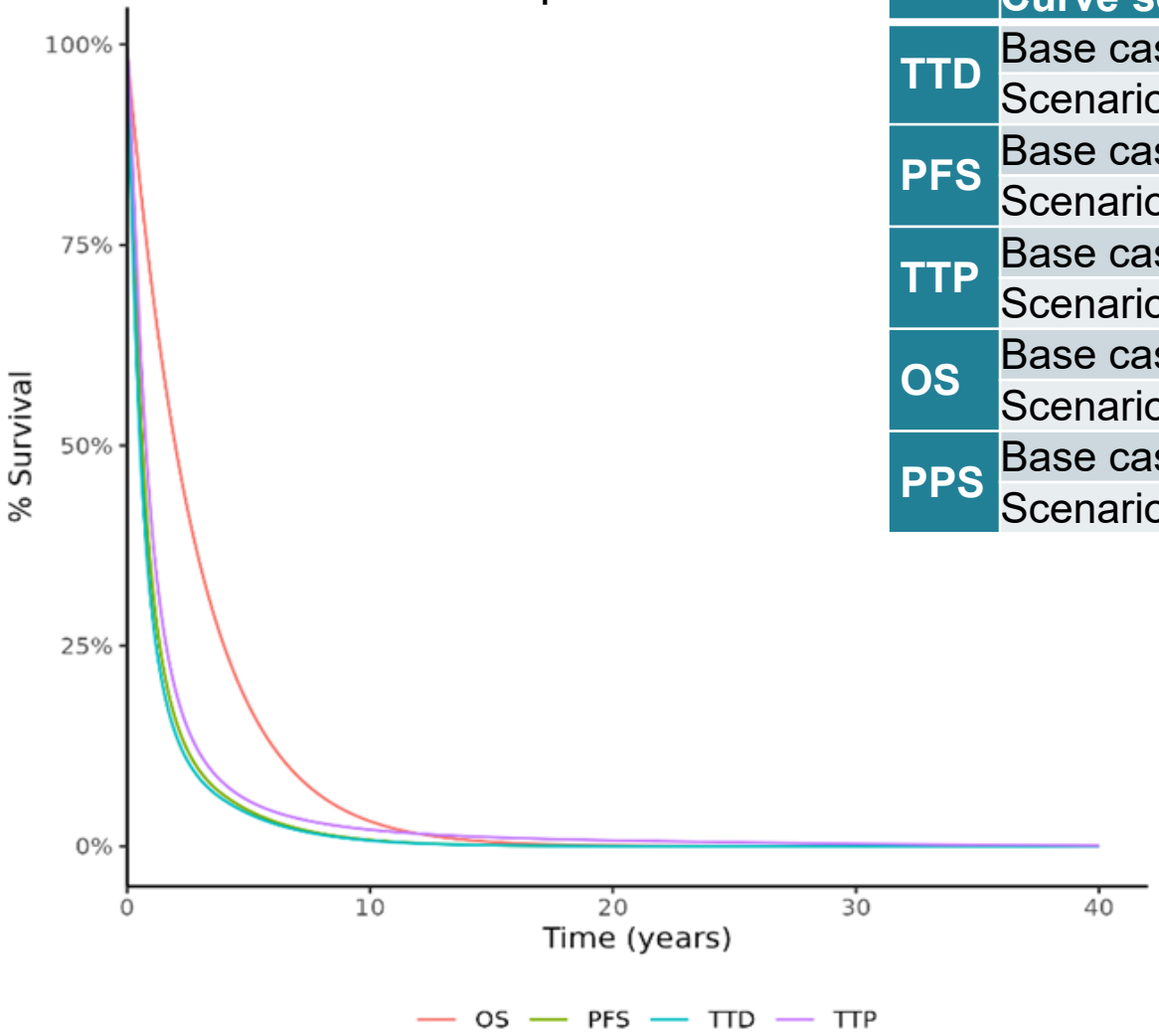
- Raised concerns related to model run time, the lack of presentation of all scenarios at the time of production of the EAG report and inability to reproduce EAG results due to redaction of RWE

Is EAG approach appropriate?

Abbreviations: EAG, external assessment group; NMA, network meta-analysis; PFS, progression-free survival; RWE, real-world evidence; TTP, time to progression; UK, United Kingdom.

Reference treatment extrapolation (2)

Curve selection example for sunitinib



	Curve selection	Rationale
TTD	Base case: Log-logistic	Statistical/ visual fit, consistent with CM214 and KN426
	Scenarios: Weibull	Consistent with PFS
PFS	Base case: Log-logistic	Statistical and visual fit. Broadly consistent with external data
	Scenarios: Weibull	
TTP	Base case: Log-logistic	Statistical and visual fit. Consistency with PFS selection
	Scenarios: Weibull	
OS	Base case: Exponential	Statistical and visual fit
	Scenarios: Weibull	Midrange within plausible curves
PPS	Base case: Exponential	All similar AUC due to maturity of KM
	Scenarios: Log-normal	Expert advice that outcomes are poor

- Majority of time is spent in 1L
  - Few patients making it to later lines
- Relatively high proportion of time in 1L spent off therapy
  - TTP curve has a longer tail than TTD or PFS
- Alternative curve selections tested in scenario analysis

Abbreviations: AUC, area under the curve; CM214, CheckMate-214; KM, Kaplan–Meier; OS, overall survival; PFS, progression-free survival; PPS, post-progression survival; TTD, time to discontinuation; TTP, time to progression.

Other efficacy adjustments

EAG implement limits on efficacy data to ensure face validity

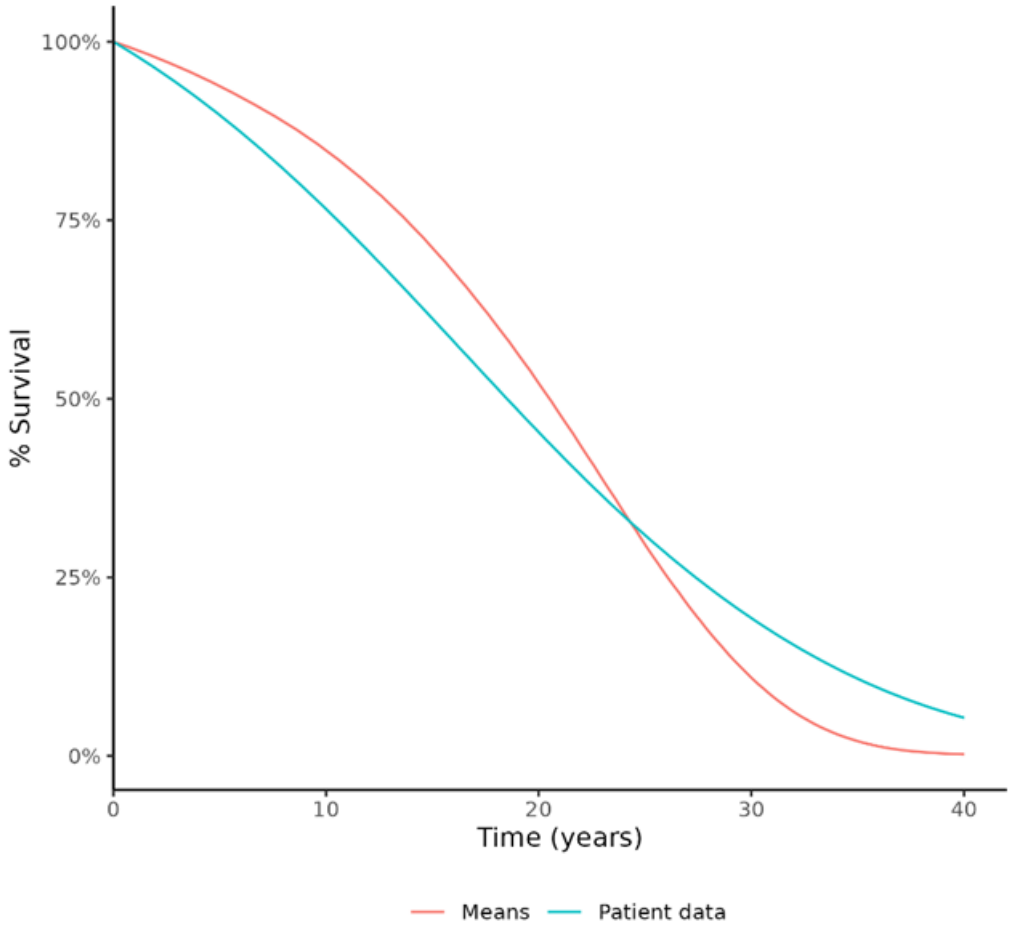
General population mortality

- Use UK RWE patient data in the base case
- ONS life tables used to calculate mortality for the general population with age/sex data for patients from UK RWE
- Figure demonstrates 40-year time horizon is appropriate
- Shows difference that the method for calculation of general population mortality makes
- Using full age and sex demographics produces steeper drop at the beginning of the curve and a longer tail than assuming all patients have the same mean age

Curves crossing

- Every effort has been made to ensure that curves do not cross during curve selection
- But this may be unavoidable when curves are close (e.g. TTP and PFS)
- Apply PFS <= TTP and PFS <= OS limits to remove any logical inconsistency

Expected general population survival: age-/sex-matched to UK RWE



Abbreviations: EAG, external assessment group; OS, overall survival; PFS, progression-free survival; RWE, real-world evidence; TTD, time to discontinuation; TTP, time to progression; UK, United Kingdom.