Treatments for renal cell carcinoma – cabozantinib with nivolumab

AIC and cPAS information redacted

Technology appraisal committee B [1 February 2024]

Chair: Charles Crawley

Lead team: Gabriel Rogers, David McAllister, Nigel Westwood

External assessment group: Peninsula Technology Assessment Group (PenTAG)

Technical team: Lewis Ralph, Christian Griffiths, Elizabeth Bell, Jasdeep Hayre

Company: Ipsen

Treatments for renal cell carcinoma – cabozantinib with nivolumab

ACM1 recap

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From pathways to reference models

Following feedback on the pathway approach the team has re-adjusted focus to align with ongoing strategic ambitions.

Therefore, we will no longer:

- Focus on NICE-built, owned and maintained pathways models

Instead, we will:

Develop proposals that enables the use of Reference Models in NICE, that can be implemented within the current STA framework

This is still expected to improve the consistency of decision-making, create efficiencies for TA, and to improve alignment across NICE's Centres

Key outputs from ACM2:

- A decision & guidance about **cabozantinib and nivolumab**, using the model developed by the EAG
- Publish all available documents, including model report from ACM1 if decisions changed
- Working towards publicly available model

Abbreviations: ACM, appraisal committee meeting; EAG, external assessment group; STA, single technology appraisal; TA, technology appraisals.

Recap from ACM1

RECAP

Cabozantinib plus nivolumab is not recommended for untreated advanced RCC:

- Limitations with the clinical evidence mean cost-effectiveness estimates are uncertain
- For all-risk and favourable-risk cancer, cost-effectiveness estimates are above what NICE normally considers cost effective
- For intermediate- and poor-risk cancer it was not possible to determine a reliable estimate

Key committee decisions	• Investigating subgroups by risk status was appropriate • Most appropriate comparators in intermediate-/poor-risk group are pembrolizumab plus lenvatinib and nivolumab plus ipilimumab • Model was appropriate for decision making but no analysis presented all of committee's preferred assumptions
Outstanding uncertainties	• Updated NMA including intermediate-/poor-risk PFS data for pembrolizumab plus lenvatinib • Explore and validate the results for nivolumab plus ipilimumab • Investigate 2 pill RDI scenario for pembrolizumab plus lenvatinib
Managed access	• Not suitable

NICE **Abbreviations:** ACM, appraisal committee meeting; NMA, network meta-analysis; PFS, progression-free survival; RCC, renal cell carcinoma; RDI, relative dose intensity.

Key questions for committee

Category	Question
NMA	Is the fractional polynomial NMA with time-varying hazards still preferred?
	Do updates with intermediate-/poor-risk pem+len PFS data resolve uncertainty?
Surrogacy	Is it still acceptable that PFS is an appropriate surrogate for OS?
	When considering nivo+ipi, is it appropriate to assume that TTNT is an appropriate surrogate for OS, given issues with nivo+ipi PFS data? Do outcomes generated when using TTNT better reflect expectations for nivo+ipi?
Utility	Does the published evidence from previous NICE appraisals, or CheckMate 9ER, better represent expectations for quality of life in advanced RCC?
Relative dose intensity	Are the proportions used in the model to capture lenvatinib titration reflective of NHS practice?
Severity	Does a severity modifier apply?
Equalities	Have any equalities issues been identified? None identified at ACM1

NICE **Abbreviations:** ACM, appraisal committee meeting; NHS, National Health Service; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; TTNT time to next treatment.

RECAP

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 cases of 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.

RECAP

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 tyrosine kinase inhibitor • Nivolumab: PD-1 inhibitor
Administration	• Cabozantinib tablet taken orally at a dose of 40 mg once daily • Nivolumab intravenously at either 240 mg every 2 weeks or 480 mg every 4 weeks
Price	• Cabozantinib: £5,143 per 30 x 40 mg tablet 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)

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

Decision problem

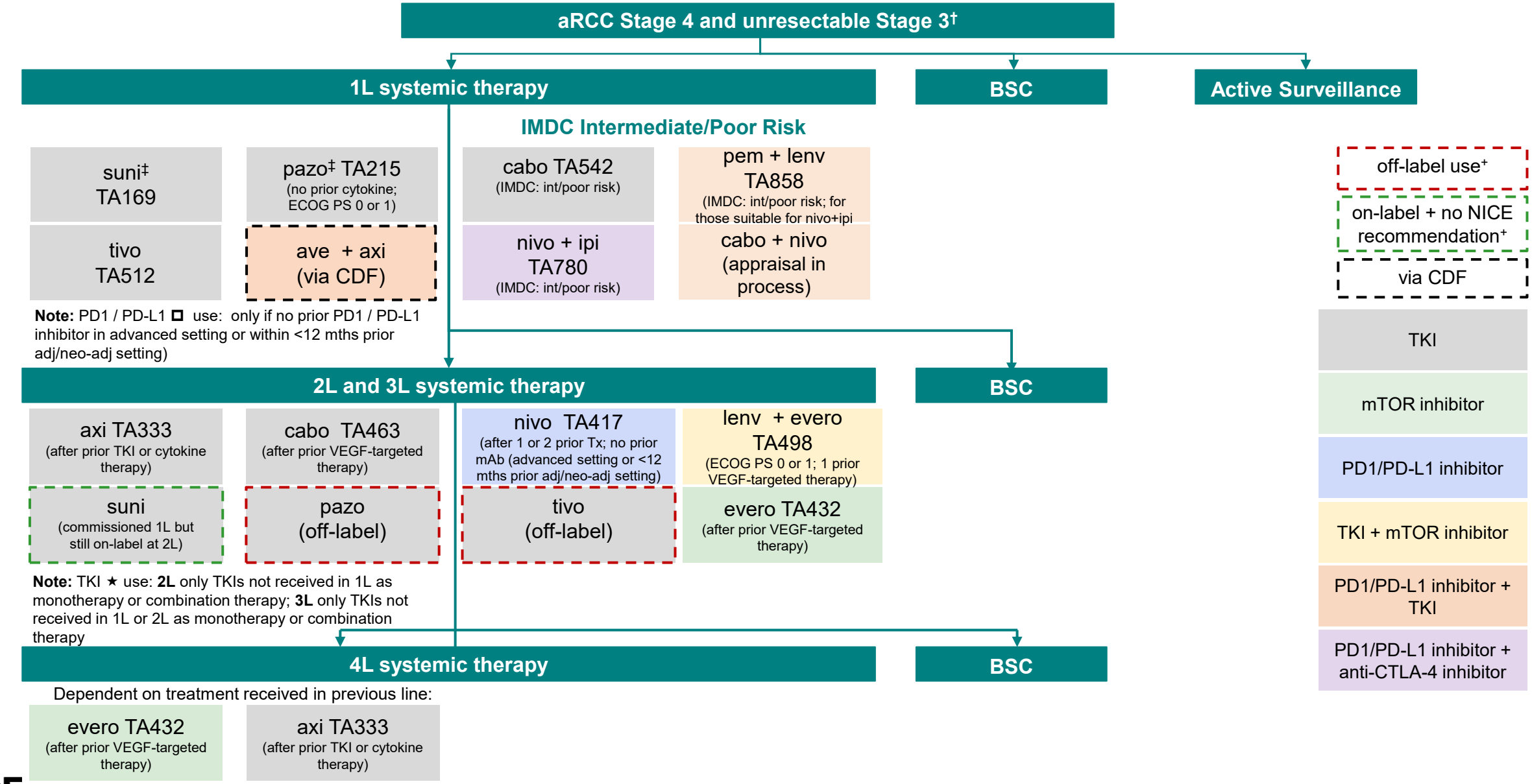
RECAP

	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 but limited data are available for time on treatment and time to next treatment within published literature
Subgroups	If evidence allows: • Intermediate-/poor-risk advanced metastatic RCC as defined in the IMDC criteria • Prior adjuvant treatment	• Intermediate-/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; RCC, renal cell carcinoma.

Treatment pathway: overview

RECAP



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

Consultation responses to draft guidance

Comments received from:

- Ipsen
- Merck Serono
- Action Kidney Cancer
- Kidney Cancer UK
- Merck Sharp and Dohme – *minor wording comments not covered here*

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Consultation responses to draft guidance (1)

Recommendation

Ipsen:

- Disappointed with the decision of NICE not to recommend cabozantinib with nivolumab
- Disagrees that results "*showed cabozantinib plus nivolumab was not cost-effective, or did not reflect the committee's preferred assumptions, when compared with the most appropriate comparators in each risk group*"
- Analyses showing cabo+nivo was cost-effective versus pem+len and nivo+ipi not discussed in depth

Action Kidney Cancer:

- Choice in first line, and access to new innovative treatments remains paramount
- Undue restrictions accessing cabozantinib with nivolumab adds unnecessary additional burden to patients

Kidney Cancer UK:

- Concerned recommendation will affect many patients who urgently need more treatment options

Draft guidance and model report

- As stated in the draft guidance, these analyses *"did not include the committee's preferred assumptions*"
- As stated in the model report, "*The committee… would have still preferred to see a consistent fractional polynomial approach applied to all treatments*"

Abbreviations: cabo+nivo, cabozantinib plus nivolumab; nivo+ipi, nivolumab plus ipilimumab; pem+len, pembrolizumab plus lenvatinib; UK, United Kingdom.

Consultation responses to draft guidance (2)

Efficacy

Action Kidney Cancer

- English cancer survival rates trail behind some other European countries; To improve outcomes and patient experience, vital that innovative treatments made available, or people in England will be disadvantaged

Ipsen

- Incorrect to say PH assumption was violated for **all** treatments for each of the risk groups
- Disagrees with inclusion of CABOSUN in the overall network, as trial includes only int-/poor-risk patients – leads to overestimation of the treatment effect versus sunitinib in the overall population
- Inconsistent methodologies applied in the ITC, and PH methods should be preferred throughout

EAG

- Agree PH not violated for **all** treatments, but was for some including nivo+ipi and pem+len, and a violation in one comparison risks carrying through the network
- Disagree that model "*mixed and matched sources… creating inconsistent assumptions and uncertainties*"
- Inclusion of cabozantinib monotherapy has minimal impact; assumption updated to equal sunitinib for ACM2
- Pilot highlighted uncertainties present in appraisals for RCC and oncology generally that are often unaddressed

Draft guidance and model report

- Model report: "*would have preferred to see a consistent FP approach applied to all treatments (at first line)"*
- Model report: "*while would have preferred a consistent approach across all lines, without an available alternative, the proportional hazards network meta-analyses were acceptable to use for subsequent lines.*"

Abbreviations: EAG, external assessment group; FP, fractional polynomial; ITC, indirect treatment comparison; nivo+ipi, nivolumab plus ipilimumab; pem+len, pembrolizumab plus lenvatinib; PH, proportional hazards; RCC, renal cell carcinoma; UK, United Kingdom

Consultation responses to draft guidance (3)

Real-world evidence

Ipsen

- Has no visibility or access to … efficacy or… treatment sequences from this real-world dataset and thus cannot replicate… or validate… EAG results…, which raises concerns
- Unreasonable and unfair that company with intervention being assessed does not have access to these data
- If Ipsen were submitting RWE as part of an STA and did not allow the EAG or NICE to have sight of these data, Ipsen would be charged with obstruction of process
- Limitations should have been described, including impact on cost-effectiveness outcomes, given the pre-existing lack of transparency surrounding the RWE

Merck Serono

- The lack of stakeholder access to key data raises concerns around transparency.
- Submitting company should have access to RWE to validate and the opportunity to re-create EAG analysis

EAG

- Full access would be ideal, EAG made every effort to allow company to see data; requested access from data holders multiple times but ultimately this was beyond their control as the EAG weren't the data holder
- In place, ensured that all stakeholders had access to curves fitted to UK RWE in survival analysis, provided results using dummy sequencing data and redacted/dummy data for an executable model
- Notes that greater access to the UK RWE data will be possible once the data are published

Abbreviations: EAG, external assessment group; RWE, real-world evidence; STA, single technology appraisal; UK, United Kingdom.

Consultation responses to draft guidance (4)

Surrogacy

Ipsen

- Statements below from Model report Section 1.21 are contradictory:
  1. *Unlike PFS and OS outcomes, there was insufficient published trial data on TTP, TTNT and TTD to inform standalone networks*
  2. *The committee considered the evidence and observed there was moderate to high correlation between PFS and both TTNT and TTD for most comparators*
- 3 out of 24 trials included in the NMA reported TTNT and 4 out of 24 reported TTP. So, for the committee to state "*there was moderate to high correlation… for most comparators*" is incorrect and misleading

Cross-reference: RCC Assessment Report – Post FAC2, Section 4.3.1.2, Figure 37-39.

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

Consultation responses to draft guidance (5)

Utility

Ipsen

- All utility values from previous NICE RCC TAs including TA858, TA650, TA581 should be taken into consideration, not just TA645 (0.753 for pre progression and 0.683 for post progression)
  - TA645 utilities using EQ-5D-5L to EQ-5D-3L crosswalk increases uncertainty compared to trial-derived
- It is unreasonable that some utilities from other appraisals are not considered, despite them being redacted
- CheckMate-9ER values may be high (pre progression [redacted], post progression [redacted]), but should not be dismissed as trial-derived
  - Committee should consider if other utility values (TA858, TA650, TA581) are plausible and have face validity
- ***Proposed a scenario where the percentage drop in utility (from the PFS to PD health state) derived from the base case utilities, is applied to the baseline utility derived from the CheckMate-9ER***

EAG

- Many additional sources provided have limited validity when considering this decision problem, EAG base case uses an alternative source considered to have greater face validity
- EAG have presented the requested scenario (Scenario 89) – minimal impact on ICER

Draft guidance and model report

- Model report: "*committee thought CheckMate 9ER values implausibly high... and small drop from PF to PD did not reflect expected impact on quality of life… and utility from studies with non-trivial decrements were appropriate*"

Cross-reference: RCC Assessment Report – Post FAC2, Section 4.3.7.2, Table 78. Also included as back-up slide.

Abbreviations: EAG, external assessment group; EQ-5D-3L, EuroQol 5-dimension 3-level; EQ-5D-5L, EuroQol 5-dimension 5-level; ICER, incremental cost-effectiveness ratio; PD, progressed disease; PF, progression free; RCC, renal cell carcinoma; TA, technology appraisal.

Consultation responses to draft guidance (6)

Decision uncertainty and probabilistic sensitivity analysis

Ipsen

- Complex model structure - uncertainty couldn't be fully characterised – specifically, results of PSA to demonstrate parameter uncertainty for the base case and scenario analyses not presented
  - Cost-effectiveness planes and cost-effectiveness acceptability curves not presented by EAG
- Despite point estimates of the probabilistic and deterministic analyses being similar, lack of PSA results did not allow full quantification and visualisation of decision uncertainty
- Decision to present deterministic results justified by the EAG on the grounds of computational burden due to the complexity of the cost-effectiveness model structure
  - Given a PSA of 1000 iterations, 4L hybrid STM required approximately 37.5 hours, only for one population
  - Wholly unrealistic situation to enable examination of scenarios and assumptions to address uncertainties

EAG

- PSA was presented in Appendix Q and results were consistent with deterministic analysis
- Benefits of modelling the full pathway and impact of treatment sequences on effectiveness outweighs benefits of characterising uncertainty with PSA

Abbreviations: EAG, external assessment group; L, line; PSA, probabilistic sensitivity analysis; STM, state transition model.

Key updated analyses

- Inclusion of additional pembrolizumab with lenvatinib data in fractional polynomials network meta-analysis
- Explore results vs nivolumab with ipilimumab
    - Time to next treatment as a proxy for progression-free survival
- Explore assumptions around titration of lenvatinib

Other updates

- New prices for sunitinib and everolimus
- Scenario to investigate uncertainty in the relative effect of the subgroup estimates

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Pembrolizumab with lenvatinib int-/poor-risk PFS (1)

RECAP

- At ACM1, the committee concluded that using time-varying hazards with a FP NMA to calculate the effectiveness of all treatments at first line was appropriate
- However, the FP analysis was incomplete in the intermediate-/poor-risk subgroup
  - Pem+len intermediate-/poor-risk PFS data from CLEAR was not publicly available
- So, the EAG used proportional hazards for pem+len in the absence of data
- The committee would have preferred to see consistent FP analysis using time-varying hazards for all treatments

Consultation comments

Ipsen

- Reiterated concerns relating to the use of FP NMA as a base case for 1st line with PH NMA in 2nd line+
- Company preferred the use of a consistent PH NMA instead, assuming constant hazards

EAG

- EAG notes this 'mismatch' but continue to believe that the approach used was most appropriate to manage plausibility of estimates and quantity of evidence
- NICE requested missing CLEAR int/poor PFS data from Eisai which was presented at ASCO 2023
- EAG updated FP NMA to include data

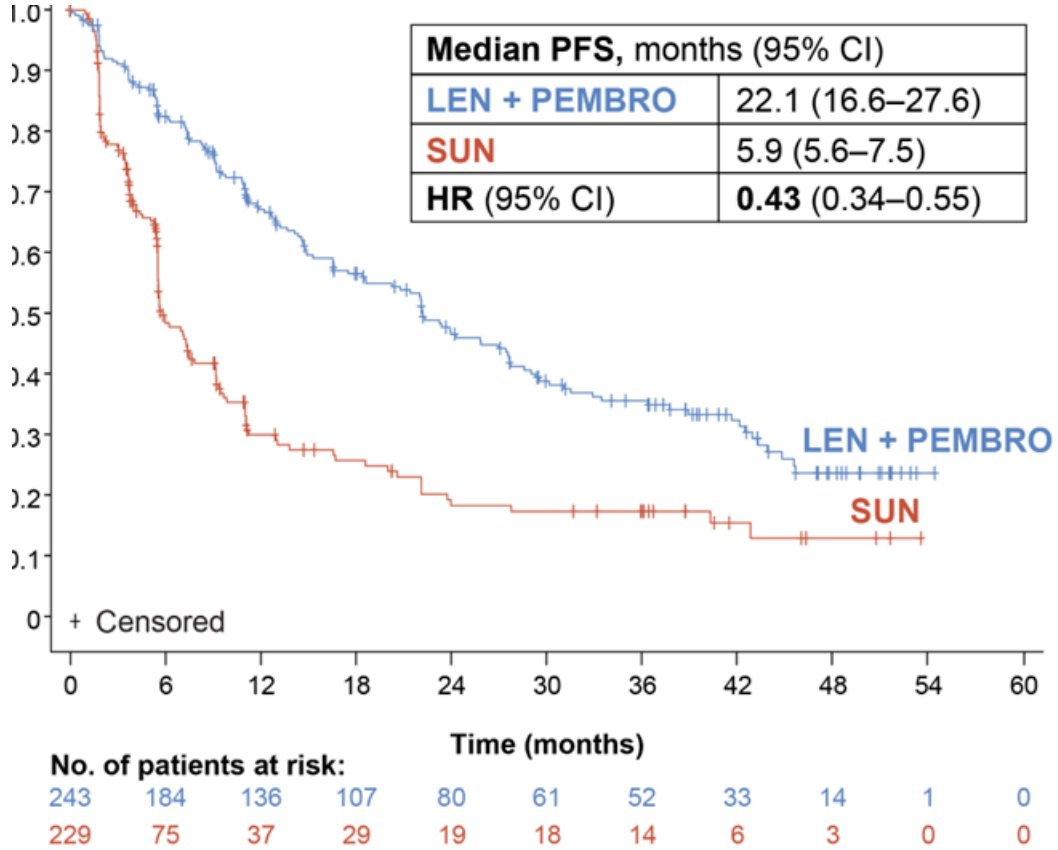
Abbreviations: ACM, appraisal committee meeting; ASCO, American Society of Clinical Oncology; EAG, external assessment group; FP, fractional polynomial; NMA, network meta-analysis; pem+lenv, pembrolizumab plus lenvatinib; PFS, progression-free survival; PH, proportional hazards.

Pembrolizumab with lenvatinib int-/poor-risk PFS (2)

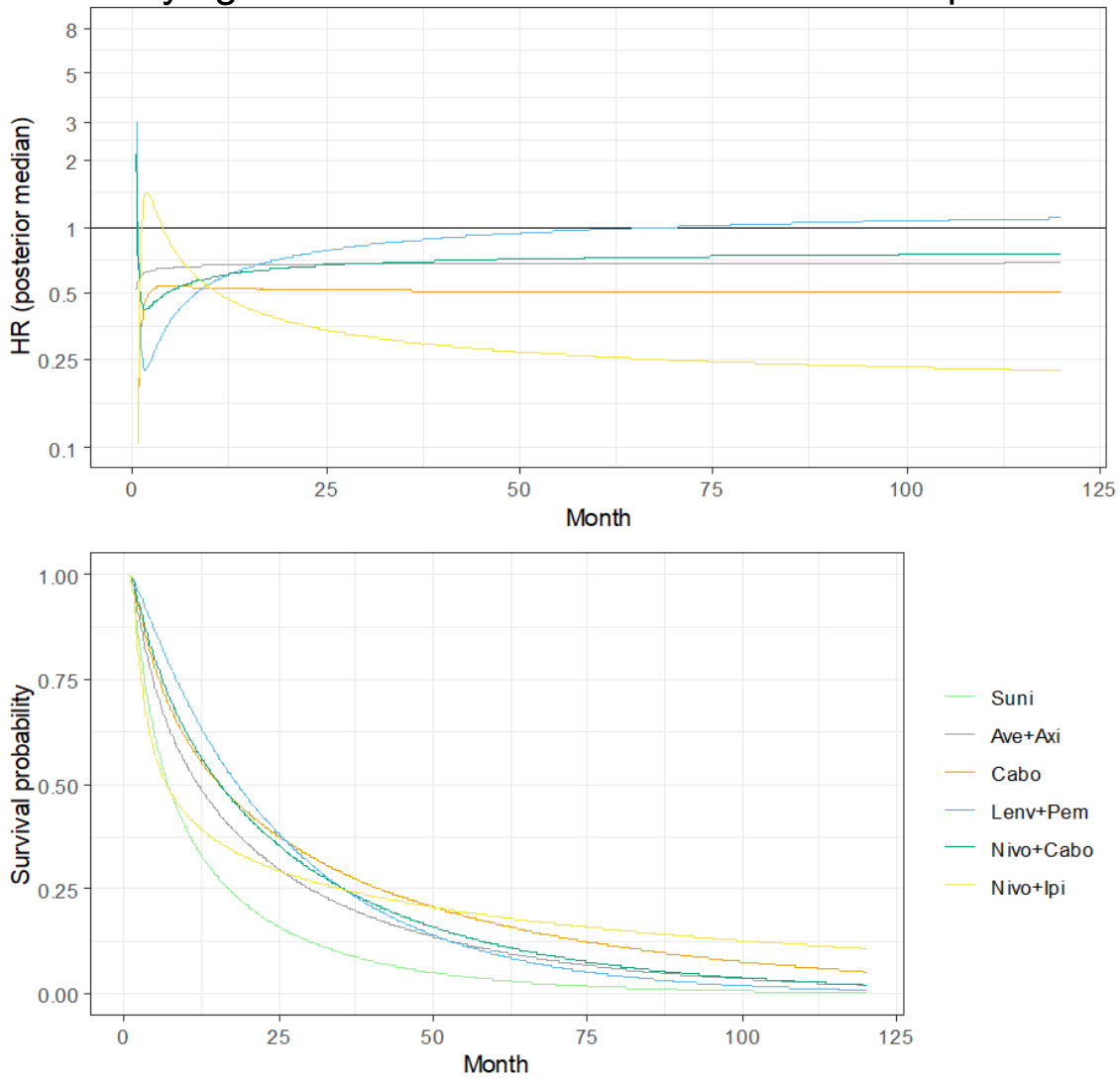
Updates

- Updated CLEAR int/poor PFS data presented at ASCO 2023 included in FP NMA

CLEAR intermediate-/poor-risk PFS



Time-varying PFS hazards from FP NMA and extrapolations



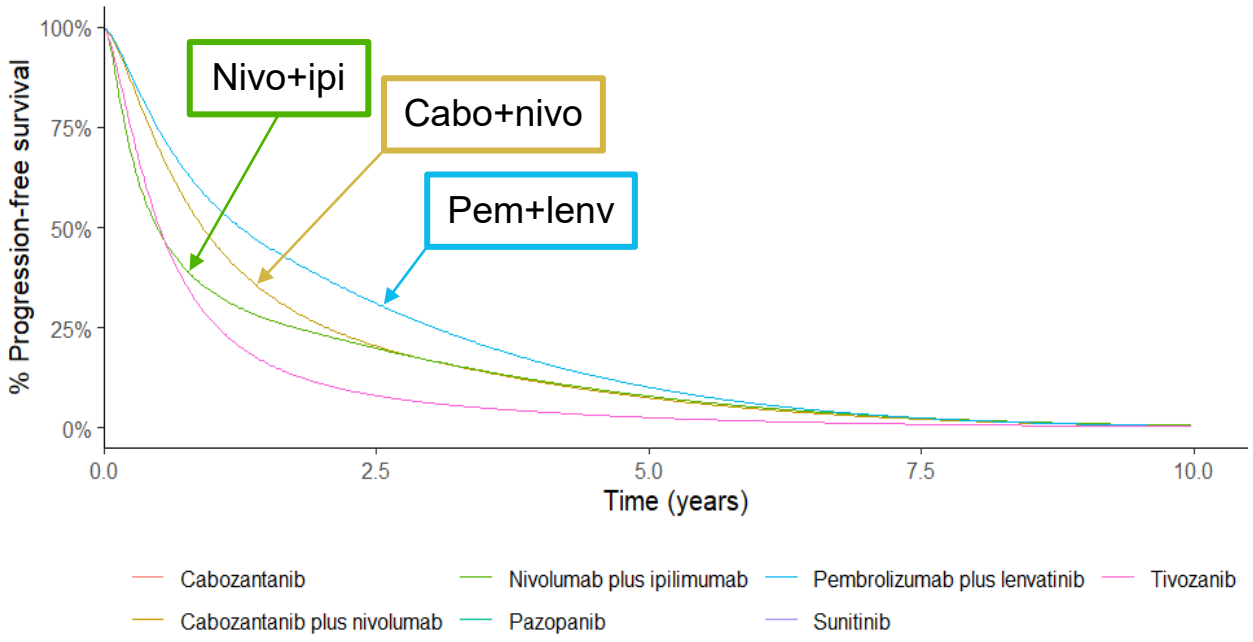
Cross-reference: RCC ACD response – 190124, Section 2.2, Figure 1 and Figure 4.

Abbreviations: ASCO, American Society of Clinical Oncology; CI, confidence interval; EAG, external assessment group; FP, fractional polynomials; HR, hazard ratio; NMA, network meta-analysis; No., number; PFS, progression-free survival

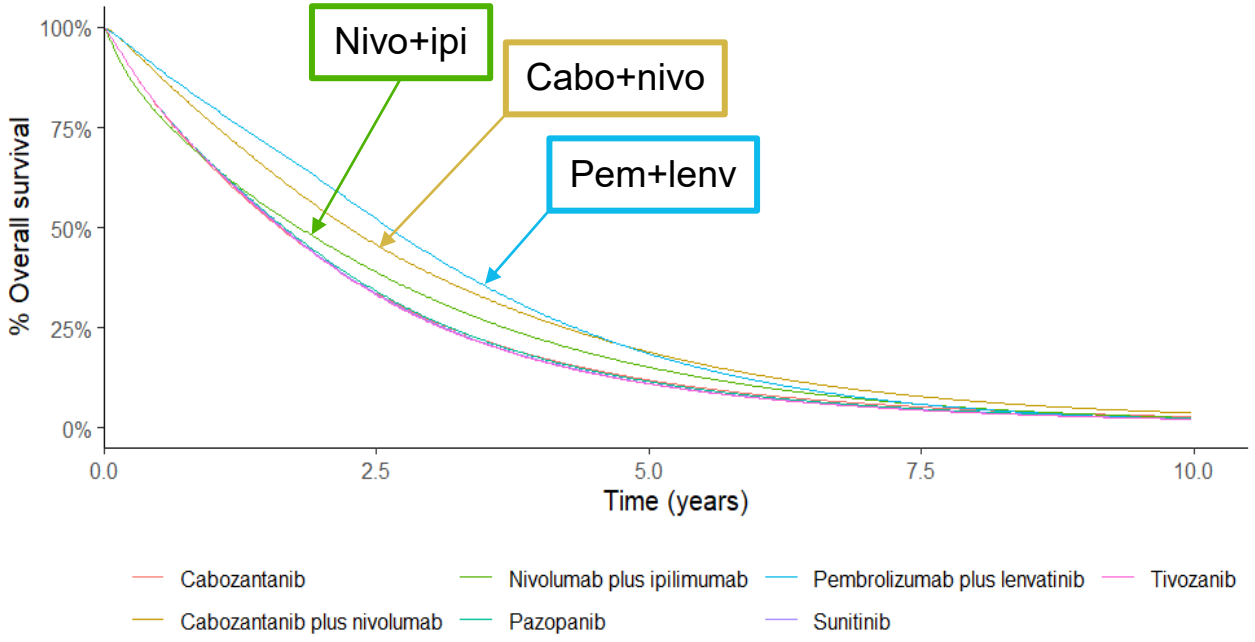
Final modelled first-line efficacy – intermediate/poor risk

Figures show final modelled OS and PFS with the updated FP NMA after all adjustments have been applied within the model accounting for the base case sequence of subsequent treatments

Final adjusted PFS – intermediate/poor risk



Final adjusted OS – intermediate/poor risk



Cross-reference: RCC ACD response – 190124, Section 2.3, Figure 5 and Figure 6.

Abbreviations: FP, fractional polynomials; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival.

Nivolumab with ipilimumab PFS (1)

RECAP

- ACM1: committee asked for further scenarios and additional data to explore and validate the results for nivo+ipi
- → considered the correlation between PFS, TTNT and TTD was less clear for nivo+ipi than other treatments

- Key assumption of STM: PFS an appropriate surrogate for OS
  - Mechanism of action of nivo+ipi meant that the assumption was limited
  - Nivo+ipi was seen to have worse PFS in than other combination treatments but still has sustained OS
  - EAG explained this could be caused by pseudo-progression or tumour flare
  - EAG provided a scenario where TTNT was used as a proxy for PFS to estimate effectiveness of nivo+ipi

Consultation comments

Ipsen

- The scenario previously presented in which TTNT was used as a proxy for PFS for nivo+ipi demonstrated that cabo+nivo was cost-effective, but this scenario was not properly discussed at the 1st committee meeting
- If the TTNT analysis had been properly discussed, it may have avoided the need for a second meeting
- No evidence presented by EAG for the impact of tumour flare on outcomes for nivo+ipi

NICE **Abbreviations:** ACM, appraisal committee meeting; EAG, external assessment group; nivo+ipi, nivolumab plus ipilimumab; OS, overall survival; PFS, progression-free survival; STM, state transition model; TTD, time to discontinuation; TTNT, time to next treatment.

Nivolumab with ipilimumab PFS (2)

EAG

- Pseudo-progression or tumour flare first identified as a potential issue for IO treatments during the ipilimumab trials in melanoma
- Atkins et al (2017) provides a reasonable summary of the issue of pseudo-progression, and some of evidence available for this in advanced RCC
- *as an initial flare of tumor size (suggestive of tumor progression) followed by a reduction in tumor mass,* Society for Immunotherapy of Cancer consensus statement on immunotherapy for advanced RCC notes, "*pseudo-progression, defined is considered an uncommon, but possible, event in solid tumors*"
- While no evidence of pseudo-progression was identified following nivo+ipi, given evidence for this in melanoma populations and the large difference between the KMs for TTNT and PFS observed in CheckMate 214
    - EAG consider it plausible that pseudo-progression could be a reason for the discrepancy between PFS, TTNT and OS outcomes
    - However, the EAG also note that there are other reasons which may explain the difference. For example, investigator assessed PFS in CheckMate-214 versus independent assessment in other trials
- Using TTNT as a proxy for PFS is an imperfect way to estimate the effectiveness of nivo+ipi, but given the poor surrogacy between PFS and OS for nivo+ipi, it provides an additional point of evidence for consideration

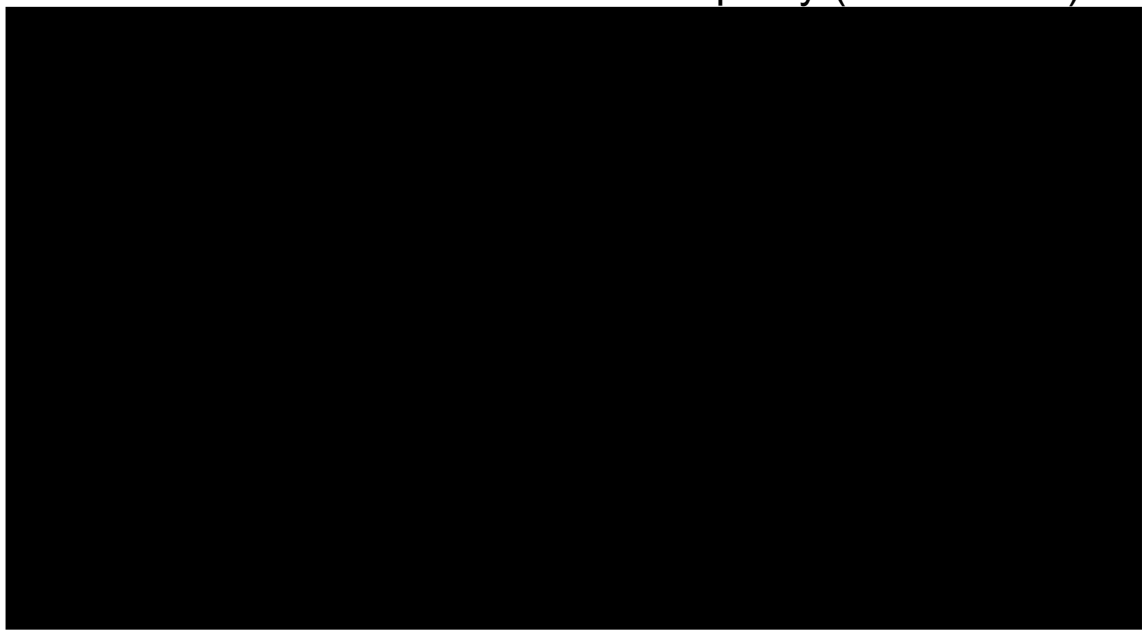
NICE **Abbreviations:** EAG, external assessment group; IO, immune-oncology; nivo+ipi, nivolumab plus ipilimumab; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; TTNT, time to next treatment.

Nivolumab with ipilimumab PFS (3)

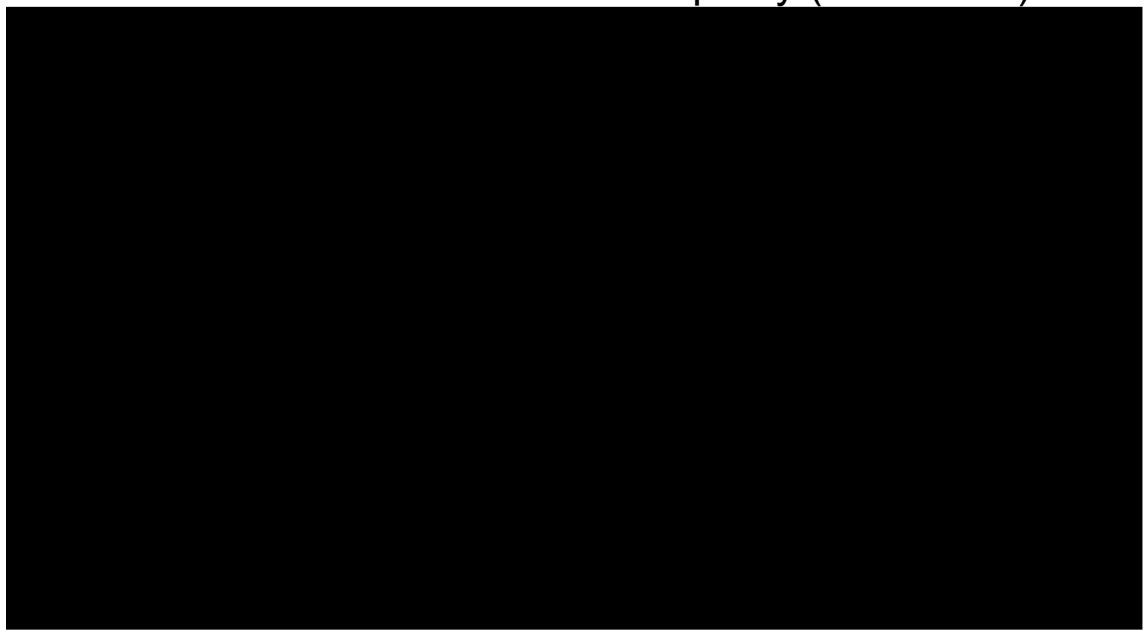
EAG

- When TTNT is used as a proxy for PFS, the model extrapolation fits well to the observed survival for the UK RWE for nivo+ipi
- Use of PFS data in updated NMA now also provides a reasonable prediction during the observed period albeit more pessimistic in the long term
  - Although underlying data for nivo+ipi unchanged, update with pem+len data has resulted in a less pessimistic fit

Model fit to nivo+ipi RWE OS when using suni reference curve from UK RWE and TTNT as a proxy (scenario 73)



Model fit to nivo+ipi RWE OS when using suni reference curve from UK RWE and PFS as a proxy (base case)



Abbreviations: EAG, external assessment group; nivo+ipi, nivolumab plus ipilimumab; NMA, network meta-analysis; OS, overall survival; PFS, progression-free survival; RWE, real-world evidence; TTNT, time to next treatment; UK, United Kingdom.

Relative dose intensity

RECAP

- Lower dose intensities of IOs impacted by toxicity of high dose of TKI (len given at max 20 mg dose CLEAR)
- Len methodology updated at consultation to account for different pill sizes and titration regimen used in UK
  - As len pills flat priced, important to accurately capture number of pills received
  - Clinical advice to the EAG was that patients start at 10mg for 2 weeks, then 75% get 14 mg for next 2 weeks, before 18% get 18 mg then 20 mg
  - EAG use this to approximate the mean number of tablets required (to a reasonable degree of accuracy)
    - Len (len+pem): 25% at 10 (1 pill), 57% at 14 (2 pills), 18% at 20 (2 pills)

Consultation comments

Ipsen

- Identified that the model may not be able to differentiate between up and down titration meaning that the analysis does not fully account for the practical use of the comparators

EAG

- Ipsen correctly identify that the economic model only looks at the proportion of patients on each dose level per time-period, not whether patients are specifically titrated up or down. EAG base case remains the same
- Scenarios investigate: all RDIs set to 100% given the inconsistency in RDI methods; and an average of two tablets in response to Committee requests for additional analyses

Abbreviations: EAG, external assessment group; IO, immune-oncology; mg, milligram; RDI, relative dose intensity; TKI, tyrosine kinase inhibitor; UK, United Kingdom.

Key cost-effectiveness results

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Updated EAG base case

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

Updates to EAG base case from ACM1

- New sunitinib and everolimus prices
- Updated FP NMA for 1st line PFS for intermediate / poor risk
  - Updated NMA related in some changes to model fits
- Equal effectiveness for cabozantinib and sunitinib for 1st line PFS for intermediate / poor risk patients

Impact of changes

- All risk and favourable risk:
  - Updated base case provides the same conclusions, cabo+nivo not cost effective versus TKIs
- Intermediate/poor risk:
  - Cabo+nivo is cost-effective vs pem+lenv (SW quadrant)
    - Reduction in effectiveness (from 2.23 QALYs to 2.02 QALYs) using new data in updated NMA
  - Cabo+nivo remained more effective and more expensive than nivo+ipi, but not cost-effective (>£30,000)
    - Updated model fits altered QALY gains for nivo+ipi (1.46 to 1.66) and cabo+nivo (2.00 to 1.97)

Key results/scenarios

- Updated FP NMA sees a reduction in pem+len effectiveness (closer to the other IO combinations)
- Increased effectiveness predicted for nivo+ipi with TTNT as a proxy outweighed by increased cost
- Results remain sensitive to RDI assumptions
- Probabilistic analysis increases costs and benefits for all, but treatment order remains the same (back-up slide)

NICE **Abbreviations:** ICER, incremental cost-effectiveness ratio; FP, fractional polynomial; IO, immuno-oncology; NMA, network meta-analysis; PFS, progression-free survival; QALY, quality-adjusted life-year; RDI, relative dose intensity; SW, south-west; TTNT, time to next treatment.

Company base case

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

Company base case from ACM1

- Both STM and PartSA base cases provided
- **Key assumptions:** PH NMA used throughout; 2 lines of treatment modelled then BSC; TTD assumed equal to PFS; AEs informed by individual trials; EAG RDI analysis (following ACM1)

Base case results

- All risk and favourable risk:
  - Updated base case provides the same conclusions, cabo+nivo not cost effective versus TKIs
- Intermediate/poor risk:
  - STM
    - Cabo+nivo is cost-effective vs pem+lenv (SW quadrant) and nivo+ipi (<£30,000)
  - PartSA
    - Cabo+nivo dominant vs pem+lenv and cost-effective vs nivo+ipi (<£30,000)

Interpretation

- Key driver is use of the PH NMA, which benefits the more effective therapies by increasing long-term benefit prior to treatment effect waning being implemented

Abbreviations: ACM, appraisal committee meeting; AE, adverse event; BSC, best supportive care; ICER, incremental cost-effectiveness ratio; NMA, network meta-analysis; PartSA, partitioned survival analysis; PFS, progression-free survival; PH, proportional hazards; QALY, quality-adjusted life-year; RDI, relative dose intensity; STM, state transition model; SW, south-west; TKI, tyrosine kinase inhibitor; TTD, time to discontinuation.

EAG scenarios intermediate/poor risk

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

	Scenario	ICER vs nivo+ipi	ICER vs pem+lenv
	Revised EAG base case	>£30,000	SW >£30,000
80	Company base case	<£30,000	SW >£30,000
85	Company base case PartSA	<£30,000	Dominant
Model structure			
1	PartSA	>£30,000	Dominant
3	State transition 2 lines	>£30,000	Dominant
Effectiveness			
11	Preferred 1L NMA, PH	<£30,000	SW >£30,000
21	PH NMA throughout, PartSA	>£30,000	Dominant
73	TTNT data as a proxy for PFS for nivo+ipi	<£30,000	Dominant
74	TTNT data as a proxy for PFS for nivo+ipi, PH NMA	<£30,000	SW >£30,000
Costs/RDI			
41	All RDI set to 100%	>£30,000	SW >£30,000
87	Lenv (pem+lenv) dosing, 2 pills	>£30,000	SW >£30,000
Utility			
89	Utility, CheckMate 9ER for 1L PFS, remainder using same utility decrements (%) as EAG base case	>£30,000	SW >£30,000

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Thank you.

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Back up slides

Utility values in published NICE TAs

Back

TA	Year	Recommendation Population	Intervention	Source of utilities	Utilities
TA858	2023	1L	Pem+lenv	CLEAR trial (EQ-5D-3L)	Redacted
TA830	2022	Adjuvant: increased risk of recurrence after nephrectomy	Pem	KEYNOTE 564 (EQ-5D-5L mapped to EQ-5D-3L)	Disease free: 0.868 PFS (distant metastases): 0.803 PD (distant metastases): 0.772
TA780 (CDF review of TA581)	2022	1L int/poor risk	Nivo+ipi	CheckMate 214 (EQ-5D-3L)	PFS on/off nivo+ipi: 0.793 on and 0.749 off PFS on/off suni: 0.754 on and 0.707 off PPS on/off nivo+ipi: 0.794 on and 0.702 off PPS on/off suni: 0.763 on and 0.707
TA650	2020	1L	Pem+axi	Time-to-death utility values from KEYNOTE 426 (EQ-5D-3L) used in company base case	Redacted Use of utilities from KEYNOTE 426 and published literature were acceptable for decision making.
TA645	2020	1L	Ave+axi	JAVELIN Renal 101 (EQ-5D-5L mapped to EQ-5D-3L)	PFS: 0.753 PD: 0.683
TA542	2018	1L int/poor risk	Cabo	TIVO-1(EQ-5D-3L)	PFS: 0.726 PD: 0.649
TA512	2018	1L	Tivo	TIVO-1 (EQ-5D-3L)	PFS: 0.726 PD: 0.649
TA498	2018	2L (1 prior VEGF, ECOG PS 0-1)	Lenv+evero	AXIS (EQ-5D, version unclear)	PFS: 0.69 PD: 0.61
TA463	2017	2L/3L (Prior VEGF)	Cabo	METEOR (EQ-5D-5L)	PFS: 0.817 PD: 0.777
TA432	2017	2L	Evero	Swinburn et al (2010)[245]	SD: 0.795 PD: 0.36

Updated drug costs

Updates to sunitinib and everolimus costs has little impact on conclusions

- Updated EAG base case includes the new sunitinib and everolimus prices
- Led to a decrease in price of treatment starting with sunitinib, and an increase in price for other sequences, due to the increase in the minimum price per mg for everolimus between eMIT versions
- Price changes, however, had little impact on the conclusions

Drug	Updated price eMIT Version Jul22 to Jun23	Previous eMIT price Version Jul22 to Dec22
Sunitinib 12.5mg x 28	£116.51	£215.86
Sunitinib 25mg x 28	£262.42	£537.62
Sunitinib 50mg x 28	£812.32	£1,388.77
Everolimus 2.5mg x 30	£403.03	£223.91
Everolimus 5mg x 30	£471.99	£747.55
Everolimus 10mg x 30	£536.65	£373.48

Abbreviations: EAG, external assessment group; eMIT, electronic market information tool; mg, milligram.

Base-case results, list price (ordered in increasing cost)

	Costs (£)	LYG	QALYs	Inc. Costs	Inc. LYG	Inc. QALYs	ICER incremental	ICER cabo+nivo pairwise	Severity modifier
Risk population: All risk									
Suni	£76,166	2.78	1.67	£0	0.00	0.00	£0	£268,351	1.0
Pazo	£80,399	2.84	1.70	£4,233	0.06	0.03	£154,645	£274,247	1.0
Tivo	£100,005	2.77	1.66				(dominated)	£223,361	1.0
Cabo+nivo	£225,144	3.71	2.22	£144,745	0.88	0.53	£274,247		-
Risk population: Favourable risk									
Suni	£80,328	3.67	2.20	£0	0.00	0.00	£0	£368,014	1.0
Pazo	£86,100	3.73	2.23	£5,772	0.06	0.03	£208,150	£378,083	1.0
Tivo	£116,790	3.66	2.19				(dominated)	£286,887	1.0
Cabo+nivo	£252,553	4.52	2.67	£166,454	0.78	0.44	£378,083		-
Risk population: Intermediate / poor risk									
Suni	£74,181	2.45	1.46	£0	0.00	0.00	£0	£251,374	1.2
Pazo	£77,793	2.50	1.49	£3,612	0.06	0.03	£133,449	£258,007	1.2
Tivo	£92,997	2.43	1.45				(dominated)	£212,280	1.2
Cabo	£121,724	2.57	1.49				(ext dominated)	£168,478	1.2
Nivo+ipi	£158,987	2.72	1.66				(ext dominated)	£139,508	1.0
Cabo+nivo	£201,953	3.30	1.97	£124,160	0.80	0.48	£258,007		-
Pem+lenv	£221,891	3.23	2.02	£19,938	-0.08	0.05	£396,657	SW £396,657	1.0

Abbreviations: ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALY, quality-adjusted life-year.

EAG base case results – intermediate/poor risk

Base-case results, list price, fully incremental analysis excluding TKIs – intermediate/poor risk

	Costs (£)	LYG	QALYs	Inc. Costs	Inc. LYG	Inc. QALYs	ICER incremental
Nivo+ipi	£158,987	2.72	1.66		-	-	-
Cabo+nivo	£201,953	3.30	1.97	£42,966	0.59	0.31	£139,508
Pem+lenv	£221,891	3.23	2.02	£19,938	-0.08	0.05	£396,657

Base-case probabilistic results, list price, fully incremental analysis excluding TKIs – intermediate/poor risk (mean +/-95%CrI)

Technologies	Costs (£)	LYG	QALYs	Inc. Costs	Inc. LYG	Inc. QALYs	ICER incremental
Nivo+ipi	£154,537 (£117,209, £182,758)	2.849 (2.290, 3.537)	1.788 (1.429, 2.219)				
Cabo+nivo	£198,891 (£157,371, £238,439)	3.381 (2.639, 4.436)	2.086 (1.590, 2.671)	£44,354	0.532	0.298	£148,909
Pem+lenv	£218,520 (£186,447, £252,014)	3.411 (2.702, 4.343)	2.159 (1.643, 2.718)	£19,629	0.030	0.073	£270,489

Abbreviations: CrI, credible intervals; ICER, incremental cost-effectiveness ratio; Inc., incremental; LYG, life-years gained; QALY, quality-adjusted life-year; TKI, tyrosine kinase inhibitor.