Lenvatinib with pembrolizumab for untreated advanced renal cell carcinoma

For public observers – all AIC and CIC information is redacted

Multiple technology appraisal

Technology appraisal committee B

Chair: Baljit Singh

Lead team: James Fotheringham, Nicholas Latimer, Nigel Westwood

Evidence review group: Liverpool Reviews and Implementation Group (LRiG)

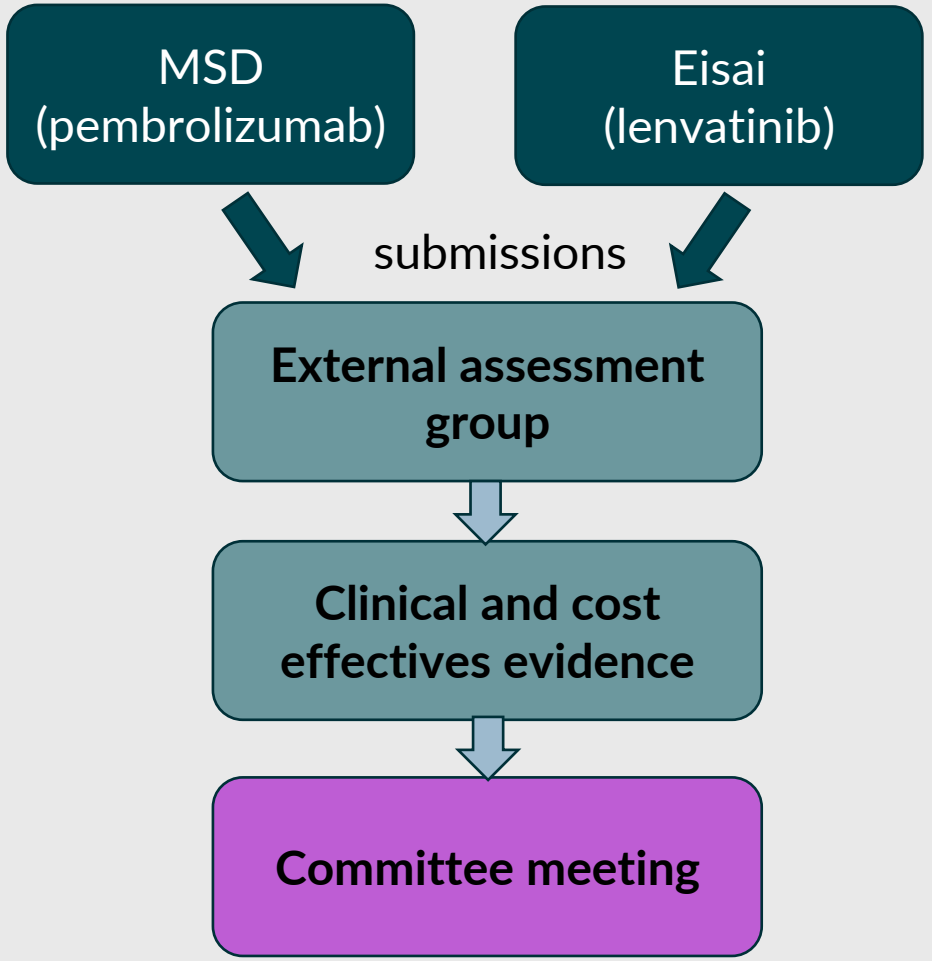
Technical team: Luke Cowie, Henry Edwards

Companies: Eisai and Merck Sharp & Dohme (MSD)

NICE

MTA context

- Combination therapy with 2 companies
- Both companies wishing to prepare and submit to NICE
- Agreed to accept both submissions but it will be considered as an MTA
- External assessment group will develop the clinical and cost effectiveness evidence (including economic model)
- Only the combination is being considered as part of the decision



NICE

Key issues

Key: Large impact  Small/moderate impact  Unknown impact 

No.	Issue	ICER impact
1	Relevant comparators	N/A
2	Generalisability of the trial and consideration of subsequent treatment used	
3	Approach to the indirect comparison	
4	Modelling overall survival, progression frere survival and time to treatment discontinuation	
5	Utilities values used	
6	Modelling of subsequent treatments	

Background and decision problem

Background on renal cell carcinoma

Causes and epidemiology

- Renal cell carcinoma (RCC) originates in the lining of the kidney tubule (smallest tubes in the nephrons)
- RCC is the **most common type of kidney cancer (>80% of cases)** with the highest rate in people over 85 years of age as incidence rate increases with age

Diagnosis and classification

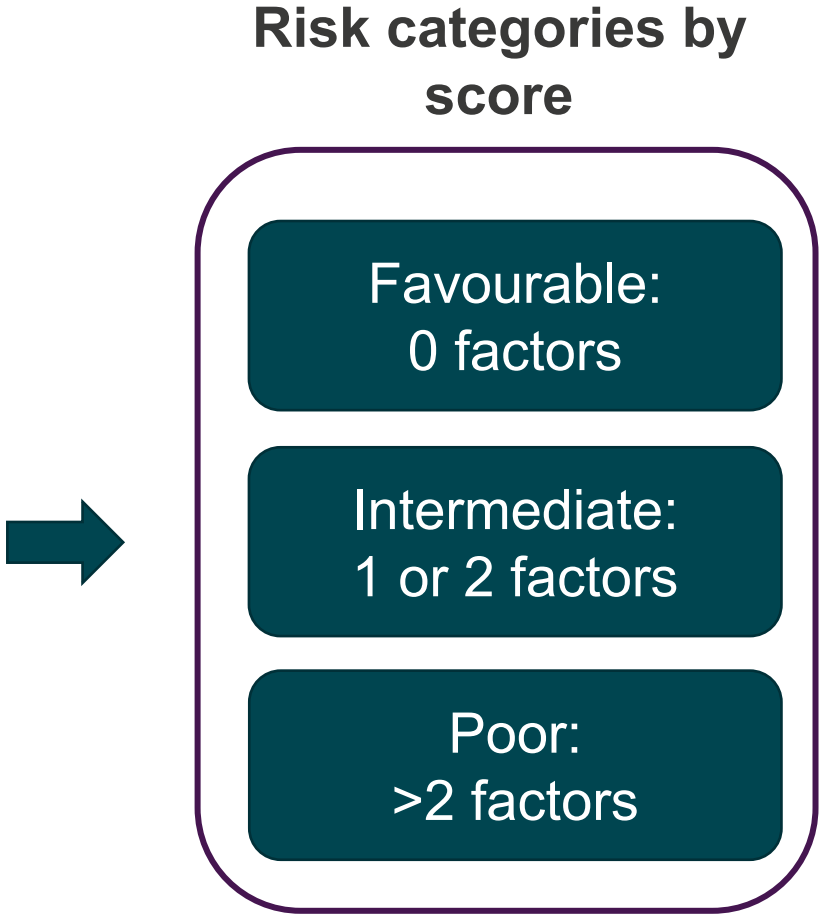
- ~ 11,000 new cases of kidney cancer in England in 2017
- ~ 2/3 diagnosed without evidence of metastatic disease
- RCC cancer stages range from I to IV; stages III and IV indicate that the cancer has locally advanced or that distant metastases are present (beyond the regional lymph nodes)

Symptoms and prognosis

- Symptoms can include blood in urine, persistent pain in lower back or side, extreme tiredness, loss of appetite, persistent hypertension and night sweats
- Prognosis for early-stage disease is favourable, but advanced or metastatic RCC has a poor prognostic outlook, with 5-year net survival rates of approximately 12%

International Metastatic Renal Cell Carcinoma (IMDC) risk score risk categories

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



How are IMDC risk scores used clinically?

Technologies

Technology	Lenvatinib	Pembrolizumab
Manufacturer	Eisai Ltd	Merck Sharp & Dohme (MSD)
Marketing authorisation	Pembrolizumab, in combination with lenvatinib, is indicated for the first-line treatment of advanced renal cell carcinoma in adults	
Class of drug	Multiple receptor tyrosine kinase inhibitor	Monoclonal antibody
Mechanism of action	Inhibits the activity of VEGFR	Blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2
Administration	20mg (oral) once daily until disease progression or unacceptable toxicity	200mg every 3 weeks or 400mg every 6 weeks administered as an intravenous infusion over 30 minutes Maximum duration of 2 years
Price	30 capsules (4mg)=£1,437 30 capsules (10mg)=£1,437	100mg vial=£2,630 200mg = £5,260 400mg = £10,520
Discount	Simple discount PAS	Simple discount PAS

Abbreviations: VEGFR, vascular endothelial growth factor receptor; PAS, patient access scheme

Decision problem (1)

	Final scope	Assessment group
Population	Adults with untreated* aRCC	The EAG considered the following groups of patients: • intermediate/poor risk subgroup • favourable risk subgroup • all-risk population
Intervention	Lenvatinib plus pembrolizumab	As per scope

* Untreated refers to systemic treatment, people may have received prior surgical intervention.

Abbreviations: IMDC, international mRCC database consortium; NMA, network meta-analysis

Decision problem (2)

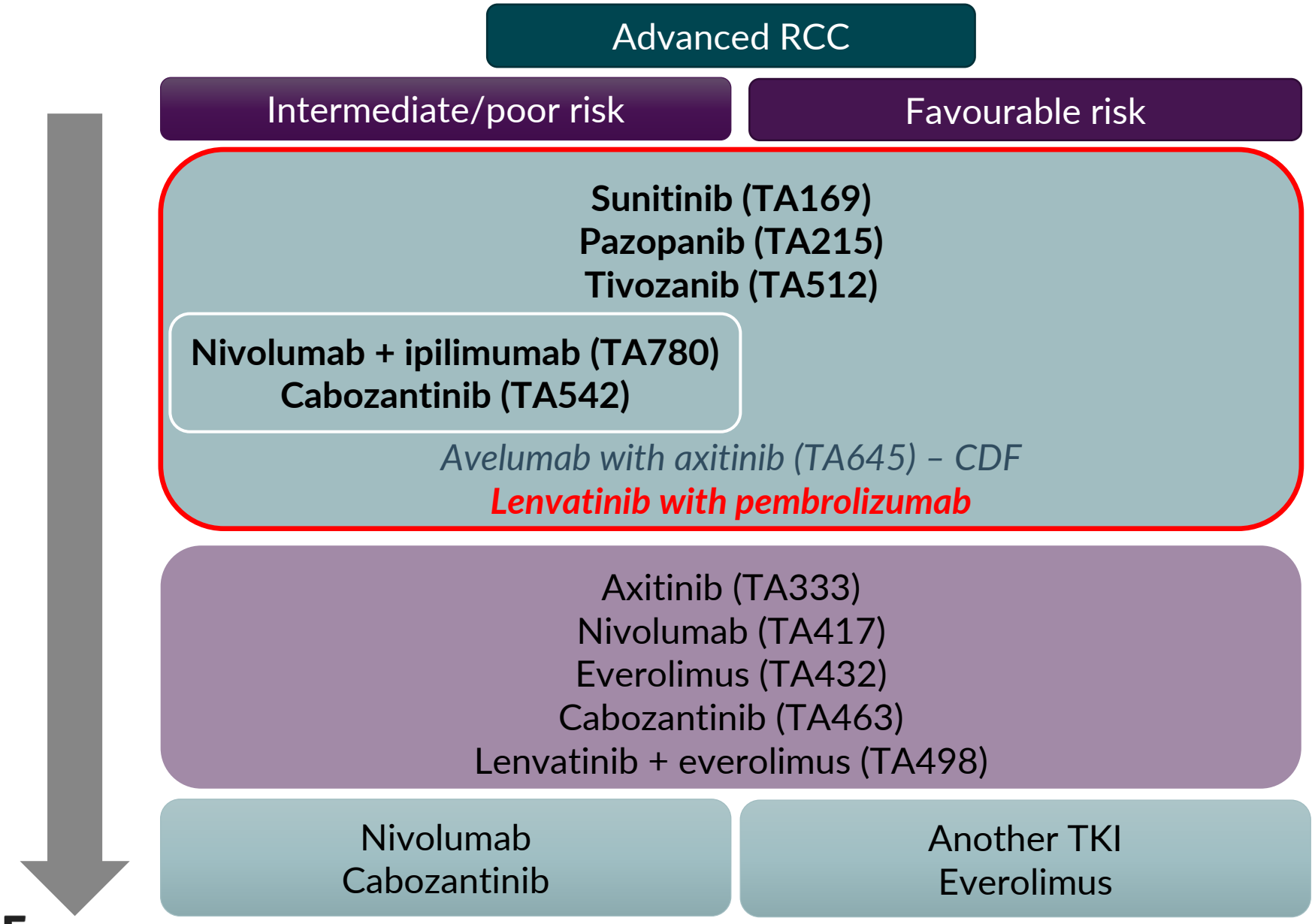
	Final scope	Assessment group
Comparators	• Sunitinib • Pazopanib • Tivozanib • Cabozantinib (intermediate- or poor-risk only) • Nivolumab plus ipilimumab (only for intermediate- or poor-risk disease as defined in IMDC criteria) - subject to ongoing appraisal *	• Direct evidence - only available versus sunitinib (CLEAR trial) • Indirect evidence is available for all relevant comparators from Eisai, MSD and EAG NMAs
Outcomes	• Overall survival • Progression-free survival • Response rates • Adverse effects of treatment • Health-related quality of life	As per scope

Company comment:

- MSD do not consider nivolumab + ipilimumab to be a relevant comparator for the intermediate/poor risk subgroup → not recommended for routine commissioning at the start of appraisal.

*** Niv+ipi was ongoing appraisal at time of scope.**
Available via CDF since April 2019, available in routine commissioning from 3 February 2022.

Treatment pathway



EAG comments:

- Clinical expert advice suggests that 1st line treatment for people with intermediate or poor risk disease is Nivo + Ipi, or cabozantinib for the fitter among this subgroup who have rapidly progressing disease (approx. 20%).
- Sunitinib, pazopanib, and tivozanib are only offered to people with intermediate or poor risk disease who cannot tolerate Nivo + Ipi or cabozantinib.

Abbreviations: RCC, renal cell carcinoma; TKI, tyrosine kinase inhibitor; CDF, Cancer Drugs Fund

Key issue: Relevant comparators

- A person's risk of disease progression is based on number of prognostic risk factors; patients are categorised as having intermediate/poor risk or favourable risk of disease progression.
- Previous NICE technology appraisals have made recommendations based on these risk subgroups, and so the available treatments differ according to risk of disease progression.
- 1/3 of patients in the CLEAR trial were in the favourable risk subgroup.

EAG assessment of relevant comparators

Intermediate/poor risk	Favourable risk
Nivolumab + ipilimumab (TA780) Cabozantinib (TA542)	**Sunitinib (TA169) Pazopanib (TA215) Tivozanib (TA512)**

Company comments:

- MSD/Eisai consider all-risk population to be most relevant - in line with marketing authorisation.
- No NICE recommendations for favourable risk population, and this group was not considered separately in previous appraisals for this condition (TA645 & TA650).
- Eisai consider that CLEAR trial not powered for risk subgroup analysis, especially for favourable risk subgroup.

Should committee consider the favourable risk and intermediate/poor risk groups separately?
Is Nivolumab with ipilimumab a relevant comparator?

Patient perspective

Submissions from Kidney Cancer Support Network & Kidney Cancer UK

Metastatic RCC

- People can be living with constant pain and other adverse effects from metastatic tumours in the brain, bones, lungs, liver, and other sites.
- Find daily living difficult, regularly needing periods of rest during the day.

Current treatment

- Forced to give up work because the disease and current treatments are very debilitating.
    - financial pressures, psychological problems, depression, and loss of confidence and self-worth.
- QoL is an important consideration - preferring treatment that allows them to lead as normal a life as possible

Intervention

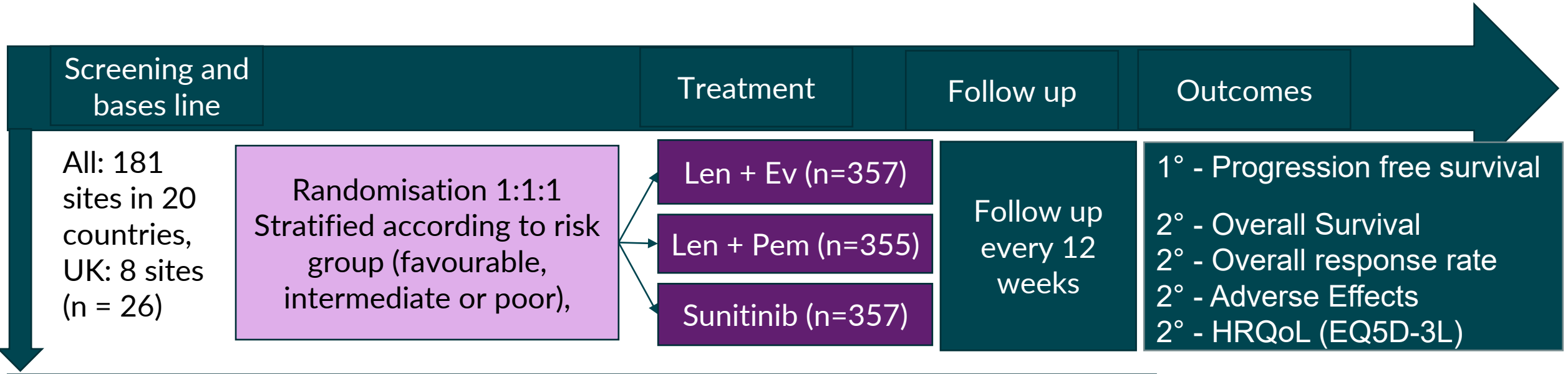
- Requires spending half a day at the hospital every 3 weeks
    - balanced against improved side effect profile and enhanced quality of life, compared with standard first-line treatment with oral VEGFR inhibitors.
- Hopeful that the combination of an immune checkpoint inhibitor with a VEGFR inhibitor will improve response to treatment and subsequent survival, with minimal side effects and little impact on quality of life.

People with advanced RCC would welcome a new treatment option

Abbreviations: RCC, renal cell carcinoma; VEGFR, vascular endothelial growth factor receptor

CLEAR trial design

Phase 3, randomised, open-label, multicentre, active-controlled study



Eligibility criteria

- Aged ≥18 years
- Previously untreated aRCC with a clear-cell component
- ≥1 measurable lesion according to RECIST version 1
- KPS score ≥70 (scores range from 0 to 100, lower scores mean greater disability)
- Adequately controlled blood pressure, with or without medications
- Adequate organ function

Data cuts

- August 2020 Interim OS and final PFS
- March 21 updated OS (median OS follow-up 33 months)
- Final OS due Q3 2022

Abbreviations: aRCC, advanced renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors; KPS, Karnofsky Performance Status; OS, overall survival; PFS, progression-free survival

Clinical effectiveness overview

NICE National Institute for Health and Care Excellence

CLEAR baseline characteristics

Assessment group: Patient characteristics generally well balanced & generalisable

Characteristic	Lenvatinib + pembrolizumab (N=355)	Sunitinib (N=357)
Mean (SD) age, years	[redacted]	[redacted]
Median (range) age, years	64 (34, 88)	61 (29, 82)
<65 years, n (%)	194 (54.6)	225 (63.0)
Male, n (%)	255 (71.8)	275 (77.0)
KPS, n (%)		
90-100	295 (83.1)	294 (82.4)
70-80	60 (16.9)	62 (17.4)
Missing	0	1 (0.3)
IMDC risk subgroup, n (%)		
Favourable	110 (31.0)	124 (34.7)
Intermediate	210 (59.2)	192 (53.8)
Poor	33 (9.3)	37 (10.4)
Could not be evaluated	2 (0.6)	4 (1.1)

Are patients in CLEAR generalisable to those seen in NHS clinical practice?

Abbreviations: SD, standard deviation; KPS, Karnofsky Performance Status; IMDC, international mRCC database consortium

CLEAR trial PFS results

Primary outcome, *All-risk population and IMDC subgroups, August 2020*

Outcomes	All-risk		Intermediate/poor risk		Favourable risk	
	Len + Pem (N=355)	Sunitinib (N=357)	Len + Pem (N=243)	Sunitinib (N=229)	Len + Pem (N=110)	Sunitinib (N=124)
Number of events (%)	160 (45.1)	205 (57.4)	115 (47.3)	136 (59.4)	43 (45.1)	67 (54.0)
Death from PFS (%)	[redacted]	[redacted]	NR	NR	NR	NR
Median PFS in months (95% CI)	23.9 (20.8 to 27.7)	9.2 (6.0 to 11.0)	[redacted]	[redacted]	[redacted]	[redacted]
Stratified HR (95% CI) p-value		0.39 (0.32 to 0.49) p<0.001		[redacted]		0.41 (0.28 to 0.62) p<0.001
PFS rates at 12 months *% (95% CI)*	[redacted]	[redacted]				
18 months	[redacted]	[redacted]				
24 months	[redacted]	[redacted]	NR	NR	NR	NR
36 months	[redacted]	[redacted]				

FAS, full analysis set; PFS, progression-free survival; CI, confidence interval; NE, not estimated; HR, hazard ratio

CLEAR trial PFS Kaplan–Meier

Progression-free Survival – ALL risk population, August 2020

PFS – Favourable risk population

PFS – Intermediate/poor risk population

CLEAR trial OS results

All-risk population and IMDC subgroups, March 2021

Characteristic/outcome	All-risk		Intermediate/poor risk		Favourable risk	
	Len + Pem (n=355)	Sunitinib (n=357)	Len + Pem (n=243)	Sunitinib (n=229)	Len + Pem (n=110)	Sunitinib (n=124)
OS – updated OS analysis						
Number of deaths (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median OS in months (95% CI)	[redacted]	[redacted]	NR	NR	[redacted]	[redacted]
Stratified HR (95% CI)		[redacted]		[redacted]		[redacted]
p value		NR		NR		NR
OS rate at 12 months % (95% CI)	[redacted]	[redacted]	NR	NR	NR	NR
18 months	[redacted]	[redacted]				
24 months	[redacted]	[redacted]				
36 months	[redacted]	[redacted]				

EAG comments:

- Significant improvement for the intermediate/poor risk subgroup and the all-risk population
- Too few events in the favourable risk subgroup for robust OS conclusions to be drawn

CLEAR trial OS Kaplan–Meier

Overall Survival – All risk population, updated OS analysis, 31 March 2021

OS – Favourable risk population, final PFS analysis, 28 August 2020

OS – Intermediate/poor risk population, final PFS analysis, 28 August 2020

Key Issue: Subsequent treatments (1)

- [redacted] of patients in the CLEAR trial received subsequent treatment following progression
- More patients in the sunitinib arm received subsequent treatment.

	All-risk		Intermediate/poor		Favourable / unknown	
Subsequent treatments	Len + Pem	Sunitinib	Len + Pem	Sunitinib	Len + Pem	Sunitinib
Any, n (%)	[redacted]					
Treatment received:						
Anti-VEGF therapy, %	[redacted]					
PD-1/PD-L1 checkpoint inhibitor, %	[redacted]					
- nivolumab, %	[redacted]					
- other checkpoint inhibitor, %	[redacted]					
mTOR inhibitor, %[c]	[redacted]					
- everolimus, %	[redacted]					
- temsirolimus, %	[redacted]					
CTLA-4 inhibitor, %	[redacted]					
Other, %	[redacted]					

Are subsequent treatments received in CLEAR trial generalisable to NHS practice?

CLEAR trial – Adverse events

Generally well tolerated; the AEs experienced consistent with the known safety profile

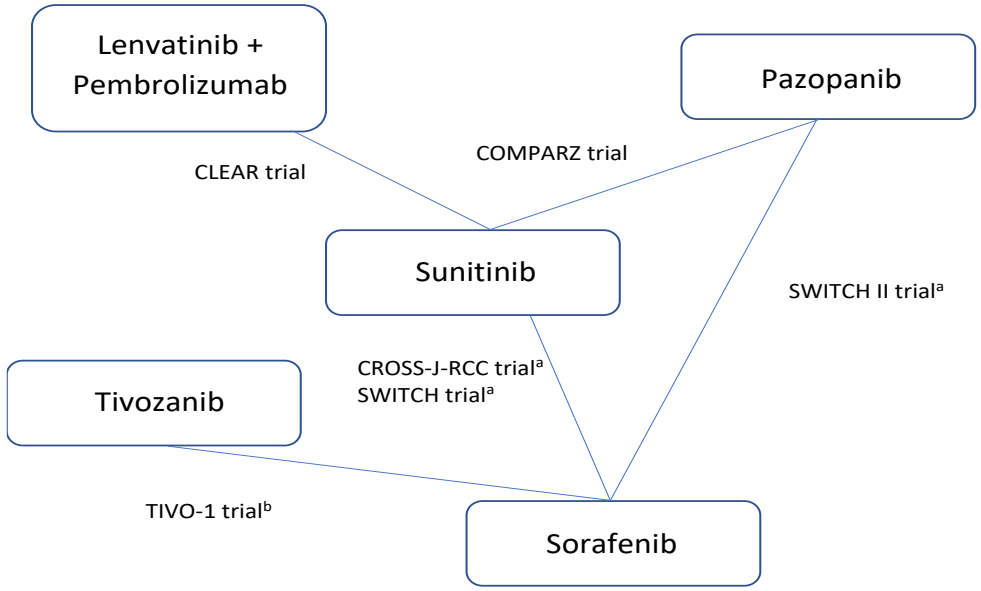
Type of AE, n (%)	Lenvatinib + pembrolizumab (N=352)	Sunitinib (N=340)
Any TEAE	351 (99.7)	335 (98.5)
TRAE	341 (96.9)	313 (92.1)
Any Grade ≥3 TEAE	290 (82.4)	244 (71.8)
Non-fatal serious TEAE	178 (50.6)	113 (33.2)
Non-fatal serious treatment-related TEAE	119 (33.8)	51 (15.0)
TEAE leading to treatment interruption	276 (78.4)	183 (53.8)
Interruption of lenvatinib	257 (73.0)	NA
Interruption of pembrolizumab	194 (55.1)	NA
Interruption of both lenvatinib and pembrolizumab	138 (39.2)	NA
TEAE leading to dose reduction	242 (68.8)	171 (50.3)

- 37.2% discontinued lenvatinib **or** pembrolizumab due to treatment-emergent adverse events (TEAEs)
- 13.4% discontinued both lenvatinib **and** pembrolizumab due to TEAEs
- 14.4% discontinued sunitinib due to TEAEs
- The rates of TEAEs were generally similar across risk subgroups in both treatment arms

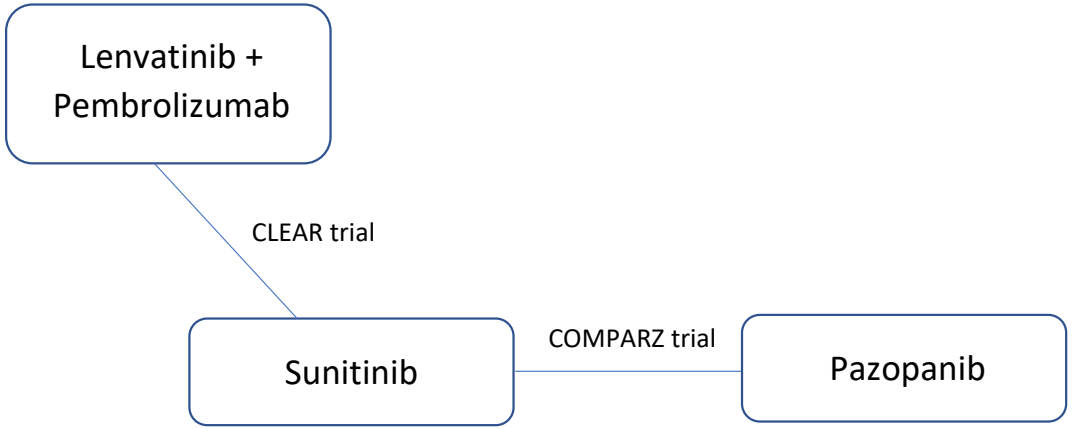
Indirect comparison

Not direct evidence with all comparators → Network meta analysis

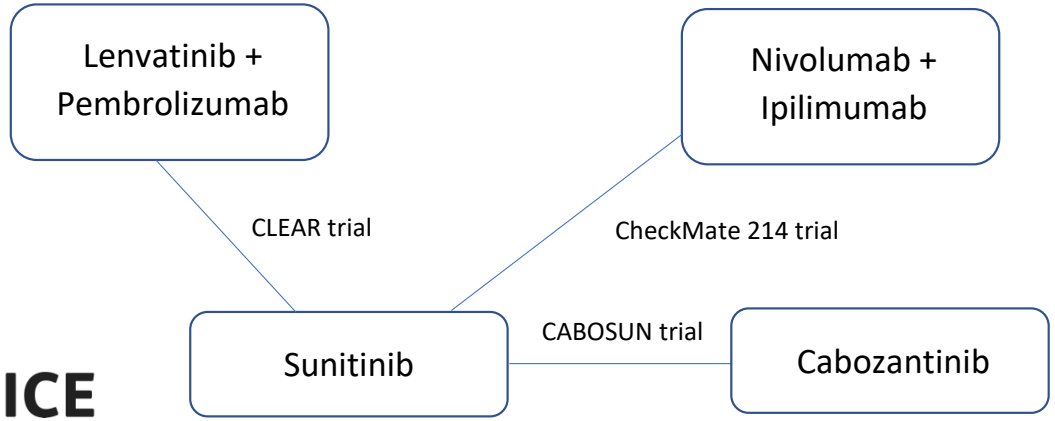
All-risk population - PFS



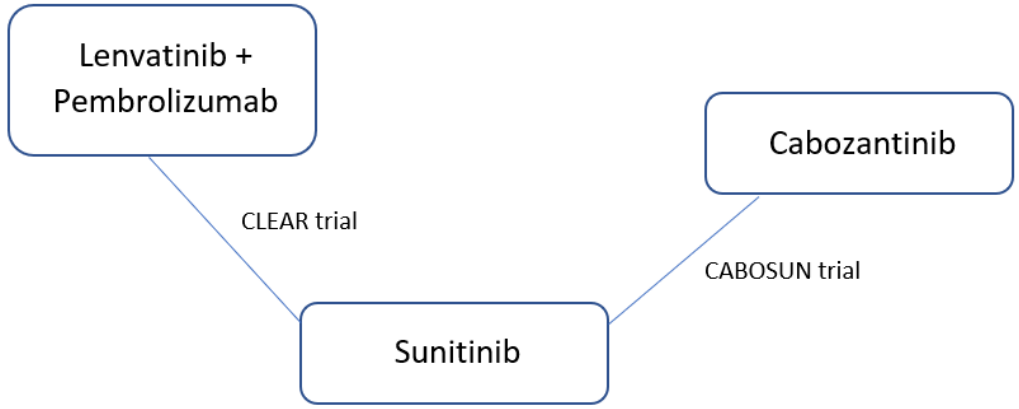
All-risk population – OS and ORR
Favourable risk – PFS, OS, Grade ≥3 AEs



Intermediate/poor risk subgroup – PFS, OS and ORR



Intermediate/poor risk subgroup – Grade ≥3 AEs



Network meta-analysis

Approach

- EAG considered the trials in the NMAs were of good methodological quality
- Uncertainty regarding the validity of the proportional hazards assumption for PFS and OS
- EAG chose a Bayesian hazard ratio network meta-analyses – preferred over more flexible approaches, such as fractional polynomial
- Due to limited data, not possible to carry out NMAs for all outcomes and for all risk groups
- As networks were sparse, only possible to generate results using fixed effect NMAs

Consultation comments:

- MSD's fractional polynomial approach predicts a more appropriate median PFS for cabozantinib, and results of more flexible models should not be discounted for decision making.
- A time-varying HR may be more appropriate than fixed HR, given that assumption of proportional hazards was deemed to be violated.

Is the NMA approach reasonable?

NMA results

Progression free survival, fixed effects NMAs

PFS	Comparator	Fixed effects HR (95% CrI)
Intermediate/poor risk subgroup		
Lenvatinib + pembrolizumab	Sunitinib	0.36 (0.28 to 0.46)
	Cabozantinib	0.75 (0.45 to 1.25)
	Nivolumab plus ipilimumab	0.48 (0.35 to 0.66)
IMDC/MSKCC favourable risk subgroup		
Lenvatinib + pembrolizumab	Sunitinib	0.41 (0.28 to 0.60)
	Pazopanib	0.40 (0.21 to 0.75)
All-risk population		
Lenvatinib + pembrolizumab	Sunitinib	0.39 (0.32 to 0.48)
	Pazopanib	0.34 (0.26 to 0.43)
	Tivozanib	0.50 (0.34 to 0.73)
	Sorafenib	0.38 (0.29 to 0.50)

Overall survival, fixed effects NMAs

OS	Comparator	Fixed effects HR (95% CrI)
Intermediate/poor risk subgroup		
Lenvatinib + pembrolizumab	Sunitinib	0.62 (0.46 to 0.83)
	Cabozantinib	0.78 (0.47 to 1.28)
	Nivolumab + ipilimumab	0.94 (0.66 to 1.32)
IMDC/MSKCC favourable risk subgroup		
Lenvatinib + pembrolizumab	Sunitinib	1.22 (0.66 to 2.25)
	Pazopanib	1.38 (0.69 to 2.80)
All-risk population		
Lenvatinib + pembrolizumab	Sunitinib	0.72 (0.55 to 0.94)
	Pazopanib	0.79 (0.58 to 1.06)

EAG comments:

- Due to PH violations or uncertainty, NMA HRs and 95% CrIs cannot be used to infer statistically significant difference for:
  - Any treatment comparisons in PFS NMAs
  - Any treatment comparison in favourable risk subgroup and all-risk population in OS NMAs

Key Issue: Network meta-analysis

Limitations

- EAG noted that there were a number of differences between the trials that could introduced heterogeneity:
  - populations characteristics - disease stage, disease risk (definitions and proportions)
  - PFS and ORR assessment methods – BIRC, investigator, or not reported
  - baseline characteristics
  - differences in median PFS, OS, ORR and Grade ≥3 follow-up times
- Unable to consider/adjust for the impact of observed heterogeneity between the trials

Interpretation

- Results should be interpreted with caution (limited data, PH violations or uncertainty)
- Results demonstrated a numerical advantage for Len + Pem vs cabozantinib and vs Nivo + Ipi (not statistically significant)

- Comparisons with sunitinib, pazopanib and tivozanib: previous NICE appraisals (TA512, TA542, TA581, TA645) concluded that:
  - sunitinib and pazopanib are of equivalent clinical effectiveness in the all-risk population
  - tivozanib may have a similar effect to sunitinib or pazopanib

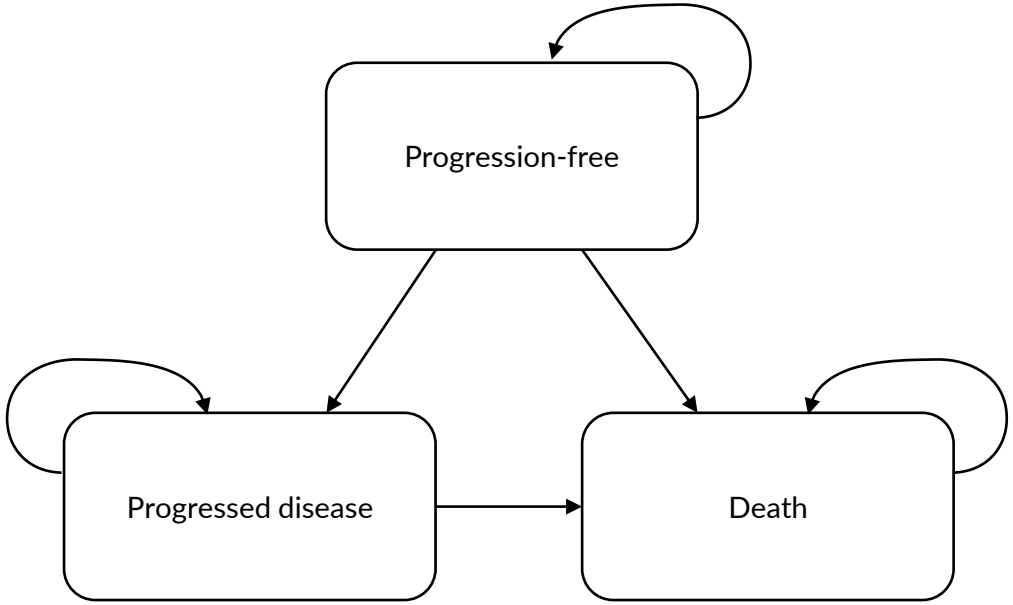
Abbreviations: NMA, network meta-analysis; HR, hazard ratio; CrI, credible interval; OS, overall survival; PFS, progression-free survival; PH, proportional hazards

Cost effectiveness overview

NICE National Institute for Health and Care Excellence

Company & EAG model structure

Structure
- Partitioned survival model with 3 health states: pre-progression, post-progression and death.
- Same structure as models accepted by NICE for untreated aRCC
- Cycle length = 1 week
- No half cycle correction
- 40 year time horizon
- Transitions informed by CLEAR trial and NMA



EAG comments:
- Both company submitted similar models
- EAG adapted 1 company model – made different assumptions and parameter choices
  - How PFS, OS and time to treatment discontinuation (TTD) for the intervention and comparator treatments are estimated
  - Modelling 2 lines of subsequent treatment, rather than 1

NB. 2 errors were corrected by the EAG following consultation
- tivozanib engine for AE costs
- application of oral administration costs

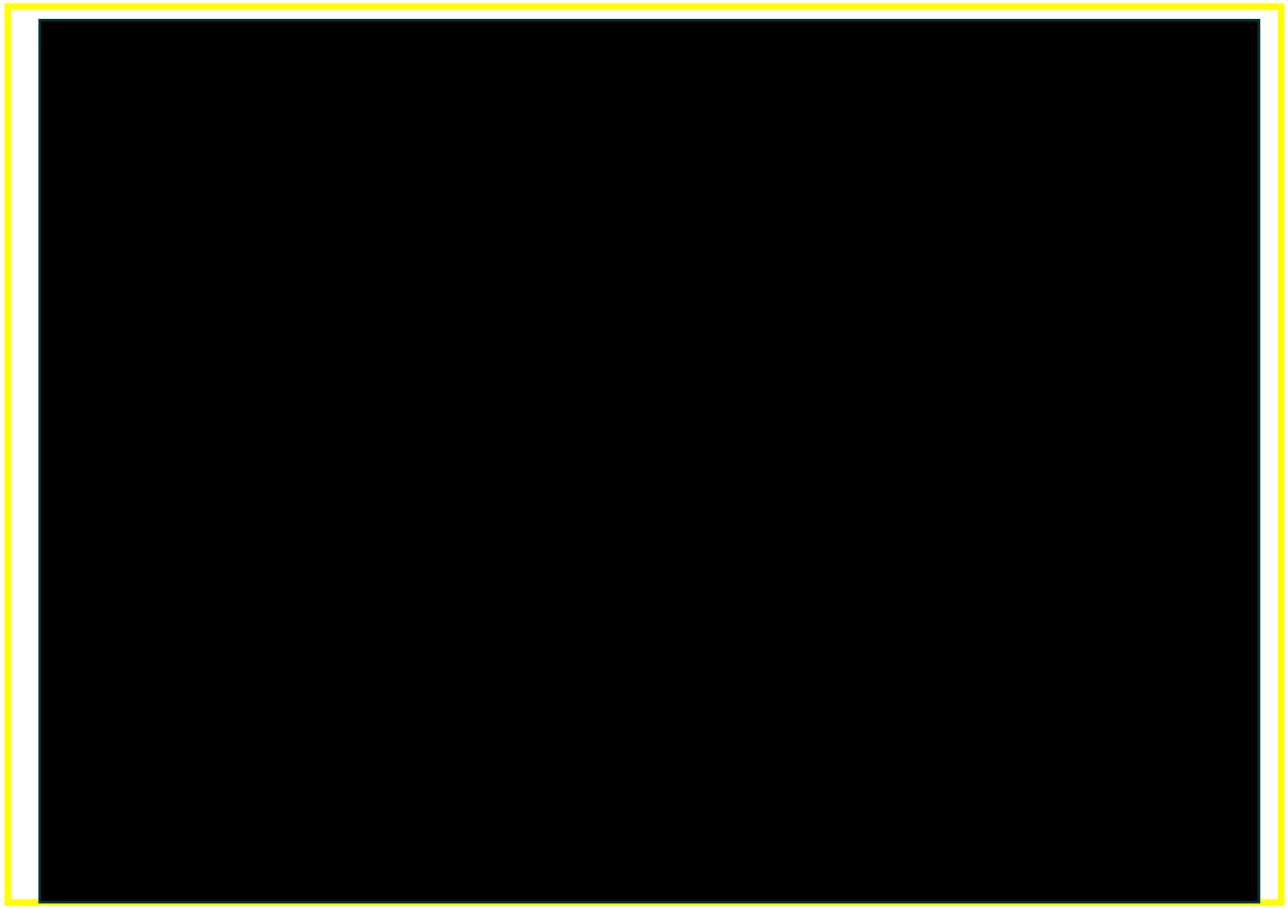
Modelled progression-free survival (1)

Treatment	EAG	Company comments
Intermediate/poor risk subgroup		
Len + Pem	Exponential	Consider exponential appropriate
Cabozantinib	EAG NMA result: HR=[redacted]	Proportional hazards assumption is violated, therefore unreasonable to assume a constant HR Median modelled PFS of [redacted] significantly higher than cabozantinib trial (CABOSUN, [redacted]) - overly optimistic. Time-varying HR approach s more appropriate e.g. fractional polynomial used by company [redacted]
Nivo + Ipi	EAG NMA result: HR=[redacted]	-
Favourable risk subgroup		
Len + Pem	Generalised gamma	-
Sunitinib	Log-normal	-
Pazop/tivo	Equal to sunitinib	-

Model inputs: Progression-free survival (2)

Model inputs: Progression-free survival (3)

PFS distributions for sunitinib, pazopanib and tivozanib, **favourable risk** subgroup



Model inputs: Progression-free survival (4)

EAG base case PFS distributions, **intermediate/poor risk** subgroup

EAG base case PFS distributions, **favourable risk** subgroup

[redacted]

Model inputs: Overall survival (1)

Treatment	EAG	Company comments
Intermediate/poor risk		
Len + Pem	K-M + exponential	Uses a subset of trial follow-up to extrapolate (average hazard between Weeks 80–120, applied weeks 120+ → not clinically validated, not made use of all available data Erroneous application of a greater risk of death [redacted] instead of [redacted] beyond week 120 - leads to more pessimistic survival estimates Both companies suggest alterative approach independently extrapolating using the exponential distribution
Cabozantinib	EAG NMA: HR=[redacted]	Proportional hazards assumption violated → unreasonable to assume a constant HR Median modelled OS of [redacted] significantly higher than cabozantinib trial (CABOSUN, [redacted]) - overly optimistic. Time-varying HR approach s more appropriate e.g. fractional polynomial used by company (predicts [redacted])
Nivo + Ipi	EAG NMA: HR=[redacted]	-
Favourable risk		
Len + Pem	Log-logistic	-
Sunitinib	Gamma	Lacks clinical plausibility- benefit of TKI monotherapy typically early in treatment → survival advantage with sunitinib, expected to be in the short term. 2-year survival rate in Len+Pem (~[redacted]) > sunitinib (~[redacted]). Wide confidence intervals around the OS HR (1.22; 95% CI [0.66 – 2.26], undermines assumption that sunitinib has a sustained survival benefit
Pazo/Tiv	Equal to sunitinib	-

Model inputs: Overall survival (2)

OS distributions for lenvatinib plus pembrolizumab, **intermediate/poor risk** subgroup

OS distributions for lenvatanib plus pembrolizumab, **favourable risk** subgroup

Model inputs: Overall survival (3)

OS distributions for sunitinib, pazopanib or tivozanib, **favourable risk** subgroup

Model inputs: Overall survival (4)

EAG base case OS distributions, **intermediate/poor risk** subgroup

EAG base case OS distributions, **favourable risk** subgroup

Model inputs: Time to treatment discontinuation (1)

Treatment	EAG
Intermediate/poor risk subgroup	
Lenvatinib	Generalised gamma (Eisai modelling)
Pembrolizumab	K-M data (CLEAR trial data are complete)
Cabozantinib	Log-logistic (Eisai modelling)
Nivolumab plus ipilimumab	Set equal to lenvatinib
Favourable risk subgroup	
Lenvatinib	Exponential
Pembrolizumab	K-M data (CLEAR trial data are complete)
Sunitinib	Exponential
Pazopanib	Equal to sunitinib
Tivozanib	Equal to sunitinib

Company (Eisai) comments:

- Model includes the KM curves for PEM time-to-discontinuation (TTD) from CLEAR and use this to calculate the drug costs for pembrolizumab.
- CLEAR trial – maximum of 24 months of treatment with pembrolizumab
  - 23% remain on treatment at Year 2
- TA650, the committee concluded that capping pembrolizumab at 2 years was appropriate for RCC, and was in line with the clinical- and cost-effectiveness evidence.

EAG comments:

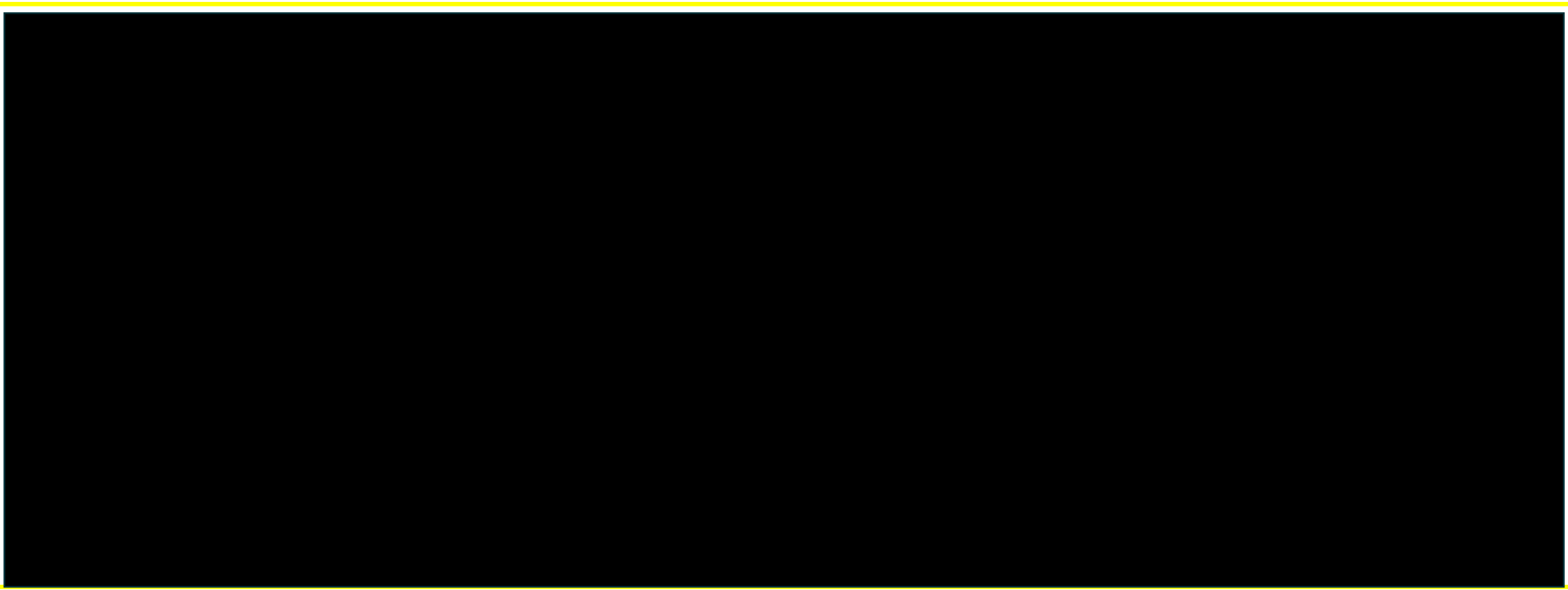
- Nivo + Ipi assumption uncertain
- Considered more robust to use TTD for lenvatinib for Nivo + Ipi due to uncertainty of effect of 2 year stopping rule for pembrolizumab

Would the 2-year stopping rule for pembrolizumab be implemented in clinical practice for RCC? Is assumption equal TTD between Lenvatinib and Nivo+ipi appropriate?

Model inputs: Time to treatment discontinuation (2)

TTD distributions for lenvatanib, **intermediate/poor risk** subgroup

TTD distributions for lenvatinib, **favourable risk** subgroup



Model inputs: Time to treatment discontinuation (3)

EAG base case TTD distributions, **intermediate/poor risk** subgroup

EAG base case TTD distributions, **favourable risk** subgroup

[redacted]

Model inputs: Utilities (1)

Background

- EAG used the a time-to-death approach to predict health-related quality of life (HRQoL).
  - Proximity to death is the driver of HRQoL,
  - Same approach used in MSD submission
  - Considered the approach provided best reflection of utilities of long-term survivors

Utility values

Risk subgroup	Time to death (days)					
	360+	270-359	180-269	90-179	30-89	0-29
Intermediate/poor	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Favourable	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
All-risk	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Do time to death utility values reflect patients HRQoL in RCC?
Is using modelled utilities by health state a preferred approach?

Model inputs: Utilities (2)

Company comments (Eisai):

- Preference to use health state utility value approach, with treatment specific utilities in the progression-free health state
- Previous NICE RCC appraisals have used modelled utilities by health state (exception was PEM+AXI, TA650)
  - In TA650 pre-progression utilities were considered 'important and acceptable for decision making'
- Statistically significant difference in pre- and post-progression utility scores between the Len + Pem and sunitinib trial

Utility values from CLEAR, treatment-specific		
Health state	Treatment	Mean
	Overall population	
Progression-free	Len + Pem	[redacted]
	Sunitinib	[redacted]
Post progression	All	[redacted]
	Intermediate and poor risk population	
Progression-free	Len + Pem	[redacted]
	Sunitinib	[redacted]
Post progression	All	[redacted]

Utility values from CLEAR, non-treatment specific	
Health state	Mean
Progression-free	[redacted]
Post progression	[redacted]

CLEAR, EQ-5D UK tariff values

Key Issue: Modelling of subsequent treatments

EAG subsequent treatment following cabozantinib

- 60% would receive nivolumab
- 40% would receive a tyrosine kinase inhibitor (TKI), i.e., sunitinib, pazopanib or tivozanib.

Company comments

- MSD: Clinical advice is more likely to be 80% receive nivolumab and 20% receive a TKI
  - treatment costs allocated to the cabozantinib arm likely to be an underestimate
- Also, EAG's assumption that all progression-free patients will receive a subsequent treatment is not likely to be the case in clinical practice.
- Assumption that 100% of patients in the progression-free (PF) health state progress and receive a subsequent treatment.
  - Patients may progress without receiving a subsequent treatment, e.g. electing not to receive any subsequent therapies.

How many people will go on to receive a TKI second line following cabozantinib?

EAG scenario analyses: Summary

ICERs per QALY gained did not change significantly for most of the scenarios considered

- All ICERs are reported in PART 2 slides because they include confidential comparator PAS discounts
- Results presented for All risk, intermediate/poor risk and favourable risk

Scenario explored by AEG
Choice of PFS distribution – multiple explored
Choice of OS distribution – multiple explored
Time to treatment discontinuation
Using health state utilities
+/- subsequent treatment costs

Other considerations

Equality considerations

- Use of lenvatinib and pembrolizumab is not expected to raise any equalities issues

Innovation as described by the companies

- Until very recently, current treatments for advanced renal cell carcinoma comprised TKI monotherapies only. Pembrolizumab plus lenvatinib is a transformative combination treatment for patients with advanced RCC.
- The combined pembrolizumab plus lenvatinib treatment regimen offers convenient dosing and administration, with the option for less frequent infusion visits vs many comparator therapies.
- Treatment schedules for the IV-administered components of other key combination therapies may be less convenient for the patient compared with pembrolizumab

Cost-effectiveness results

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

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Thank you.

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Backup slides (if required)

CLEAR trial design

Parameter	CLEAR trial
Key eligibility criteria	Inclusion: • Aged ≥18 years • Previously untreated aRCC with a clear-cell component • ≥1 measurable lesion according to RECIST version 1 • KPS score ≥70 (scores range from 0 to 100, lower scores mean greater disability) • Adequately controlled blood pressure, with or without medications • Adequate organ function
Recruitment period	13 October 2016 to 24 July 2019
Number of centres (patients)	All: 181 sites in 20 countries, including 93 sites in Europe (407 patients) UK: 8 sites (26 patients)
Drug doses and schedule	• Lenvatinib administered at 20mg orally once daily for each 21-day treatment cycle. Pembrolizumab administered at 200mg intravenously on day 1 of each 21-day cycle • Sunitinib administered at 50mg orally once daily for 4 weeks of treatment followed by 2 weeks with no treatment (4/2 schedule)
Dose modifications	Dose interruptions were permitted for all study drugs Dose reductions were not permitted for pembrolizumab If one drug in the combination treatment arm was discontinued (e.g., due to toxicity), the other drug could be continued

Abbreviations: aRCC, advanced renal cell carcinoma; RECIST, Response Evaluation Criteria in Solid Tumors; KPS, Karnofsky Performance Status

Objective response rate

Characteristic / outcome	All-risk (FAS)	
	Lenvatinib + pembrolizumab (N=355)	Sunitinib (N=357)
ORR (CR + PR) by BIRC, % (95% CI)	71.0 (66.3 to 75.7)	36.1 (31.2 to 41.1)
Difference, % (95% CI)	[redacted]	
Odds ratio (95% CI)		
p value		
Best objective response:		
Complete response (CR), n (%)	57 (16.1)	15 (4.2)
Partial response (PR), n (%)	195 (54.9)	114 (31.9)
Stable disease, n (%)	68 (19.2)	136 (38.1)
Progressive disease, n (%)	19 (5.4)	50 (14.0)
Unevaluable for response / not known, n (%)	16 (4.5)	42 (11.8)
No postbaseline tumour assessment	12 (3.4)	38 (10.6)
≥1 Lesion NE	1 (0.3)	2 (0.6)
Early stable disease (<7 Weeks)	3 (0.8)	1 (0.3)
Median time to response, months (range)	1.94 (1.41 to 18.50)	1.94 (1.61 to 16.62)
Median duration of response, months (95% CI)	25.8 (22.1 to 27.9)	14.6 (9.4 to 16.7)

	Lenvatinib + pembrolizumab (N=243)	Sunitinib (N=229)
ORR (CR + PR) by BIRC, % (95% CI)	[redacted] (Not reported)	[redacted] (Not reported)
Difference, % (95% CI)	[redacted]	
Odds ratio (95% CI)		
p value		

	Lenvatinib + pembrolizumab (N=110)	Sunitinib (N=124)
ORR (CR + PR) by BIRC, % (95% CI)	[redacted] (Not reported)	[redacted] (Not reported)
Difference, % (95% CI)	[redacted]	
Odds ratio (95% CI)		
p value		

NICE

RCTs included in EAG NMAs

RCT	Randomised treatments	Notes
RCTs included:		
CABOSUN	• Cabozantinib • Sunitinib	Included in PFS, OS, ORR and safety NMAs for intermediate/poor risk subgroup only
CheckMate 214	• Nivolumab + ipilimumab • Sunitinib	Included in PFS, OS and ORR NMAs for intermediate/poor risk subgroup only
CLEAR trial	• Lenvatinib + pembrolizumab • Sunitinib	Included in PFS, OS, ORR and safety NMAs for favourable risk and intermediate/poor risk subgroup and all-risk population
COMPARZ	• Pazopanib • Sunitinib	Included in PFS, OS, ORR and safety NMAs for favourable risk subgroup and all-risk population OS data taken from final OS analysis
CROSS-J-RCC	• Sunitinib • Sorafenib	Included in PFS NMAs for all-risk population only
SWITCH	• Sunitinib • Sorafenib	Included in PFS NMAs for all-risk population only
SWITCH II	• Pazopanib • Sorafenib	Included in PFS NMAs for all-risk population only
TIVO-1	• Tivozanib • Sorafenib	Included in PFS NMAs for all-risk population only

RCTs excluded from EAG NMAs

RCT	Randomised treatments	Notes
RCTs excluded:		
Escudier 2009[98]	• Interferon-alpha • Sorafenib	OS data not reported so cannot be included in OS NMAs Excluded from PFS, ORR and safety NMAs as neither treatment is a relevant comparator and this trial data cannot be used to connect relevant comparators to the network
Motzer 2007[23]	• Interferon-alpha • Sunitinib	Excluded from PFS, OS, ORR and safety NMAs as interferon-alpha is not a relevant comparator and this trial data cannot be used to connect relevant comparators to the network

Model inputs: Progression-free survival

PFS distributions for sunitinib, pazopanib and tivozanib, **favourable risk** subgroup

Model inputs: Overall survival

OS distributions for sunitinib, pazopanib or tivozanib, **favourable risk** subgroup

Model inputs: Time to Treatment Discontinuation

TTD distributions for cabozantinib, **intermediate/poor risk** subgroup

TTD distributions for sunitinib, pazopanib and tivozanib, **favourable risk** subgroup

EAG scenarios: Progression-free survival

Intermediate/poor risk subgroup:

- Explored parametric distributions with AIC statistics within five points of distribution used to model PFS for people treated with lenvatinib plus pembrolizumab
- Explored MSD FP NMA results to model PFS for patients treated with cabozantinib

Favourable risk subgroup:

- Explored parametric distributions with AIC statistics within five points of distribution used to model PFS for people treated with lenvatinib plus pembrolizumab
- Explored parametric distributions with AIC statistics within five points of distribution used to model PFS for people treated with sunitinib (pazopanib and tivozanib

EAG scenarios: Overall survival

Intermediate/poor risk subgroup:

- Explored Eisai and MSD base case approaches to modelling OS:
  - exponential distribution to model OS for lenvatinib plus pembrolizumab
  - Eisai and MSD OS NMA HRs applied to EAG lenvatinib plus pembrolizumab distribution to generate cabozantinib OS estimates
  - MSD FP NMA HR to the EAG lenvatinib plus pembrolizumab distribution to generate cabozantinib OS estimates
- HR=1 for the comparison of lenvatinib plus pembrolizumab versus nivolumab plus ipilimumab and for comparison of lenvatinib plus pembrolizumab versus cabozantinib

Favourable risk subgroup:

- EAG OS NMA HR for comparison of lenvatinib plus pembrolizumab versus sunitinib applied to log-logistic distribution used to represent OS for people treated with lenvatinib plus pembrolizumab in EAG base case
- OS HR=1 for the comparison of lenvatinib plus pembrolizumab versus sunitinib, versus pazopanib and versus tivozanib.

EAG scenarios: Time to treatment discontinuation

Intermediate/poor risk subgroup:

- Explored parametric distributions with AIC statistics within five points of distribution used to model TTD for people receiving lenvatinib
- Explored alternative parametric distributions (i.e. five distributions not used in EAG base case analysis) to model TTD for people treated with cabozantinib
- MSD TTD FP NMA results applied to EAG TTD lenvatinib distribution to model TTD for people treated with cabozantinib.
- Distribution used in the base case to model TTD for patients treated with pembrolizumab (Weibull) to model TTD for people treated with nivolumab plus ipilimumab.

Favourable risk subgroup:

- Explored parametric distributions with AIC statistics within five points of distribution used to model TTD for patients treated with lenvatinib
- Explored parametric distributions with AIC statistics within five points of distribution used to model TTD for people treated with sunitinib and pazopanib and tivozanib

Key Issue: Subsequent treatments (2)

- Noted difference in OS from those that did/did not have a subsequent treatment

Received any subsequent systemic anti-cancer treatment, All-risk			
	Lenv + pem	Sunitinib	Total
Updated OS analysis, n (%)	[redacted]	[redacted]	[redacted]

OS results for patients who did and did not receive subsequent treatment, All-risk population				
	Received subsequent treatment		Did not receive subsequent treatment	
	Len + pem	Sunitinib	Len + pem	Sunitinib
Median OS, months (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
HR (95% CI)	[redacted]		[redacted]	

Is this difference in subsequent treatments expected to lead to a difference in overall survival?

Key Issue: Subsequent treatments (3)

- For overall survival the proportional hazards assumption was violated for patients who received subsequent treatment → the OS HR should not be used to infer magnitude of treatment effect or statistical significance.
  - [redacted]
  - [redacted]
- Company (Eisai) tested whether adjusting for the effect of subsequent treatments affected OS → [redacted]

[redacted]