Slides for committee, projector and public – no ACIC

Lead team presentation

Lenvatinib with everolimus for previously treated advanced renal cell carcinoma [ID1029]

2nd Appraisal Committee meeting

Committee B

Lead team: Ray Armstrong, John Cairns and Danielle Preedy

Chair: Amanda Adler

ERG: BMJ-TAG

NICE team: Orsolya Balogh, Ahmed Elsada, Elisabeth George

Company: Eisai

20 September 2017

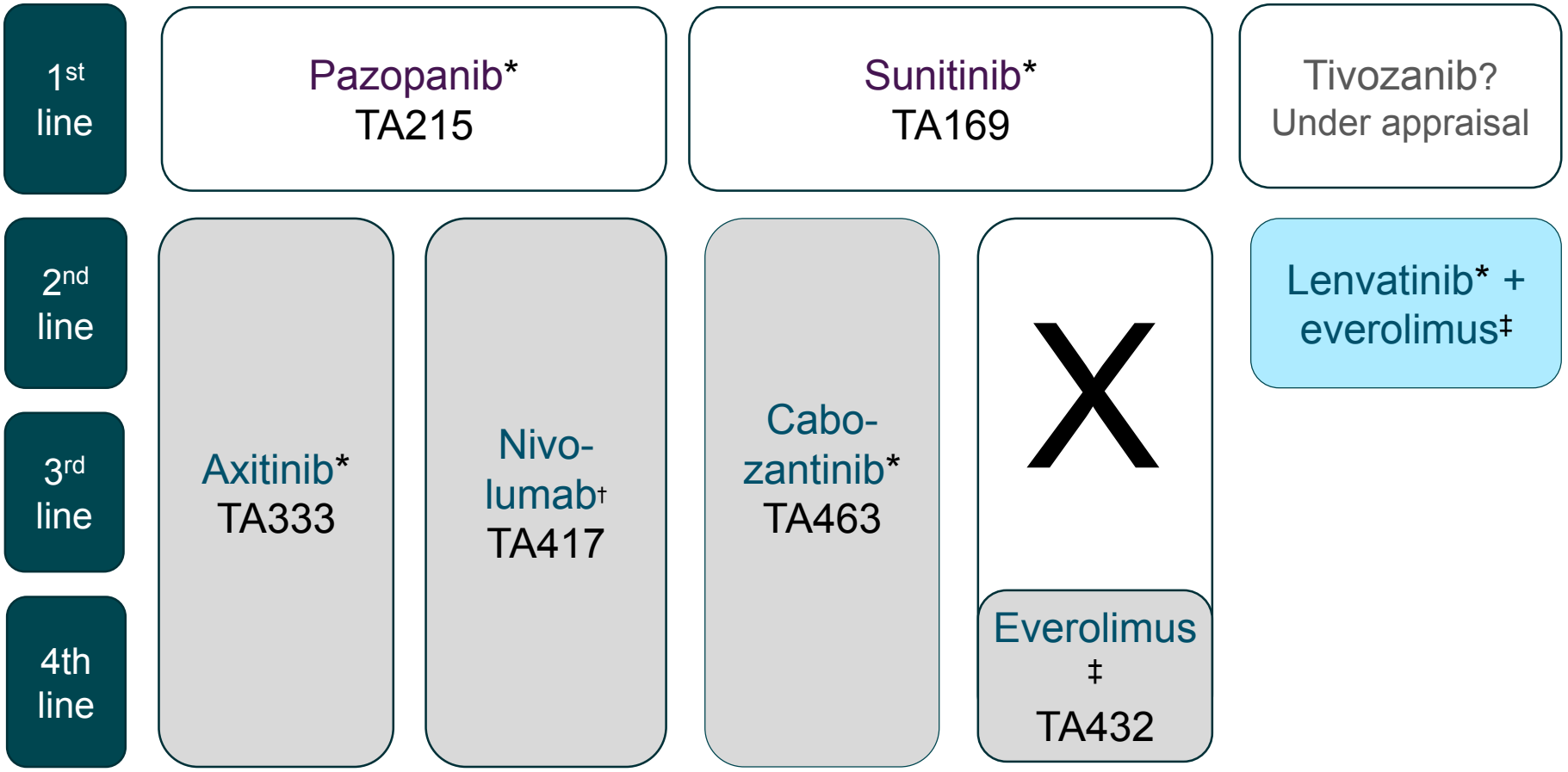
Issues for discussion

- The company revised its modelling of utility decrements. Which is more appropriate: using utility decrements with or without adjusting for duration of each adverse event?
- If committee's recommendation should not change, is LEN+EVE as a potential candidate for the Cancer Drug Fund?

Decision problem

Marketing authorisation	'… in combination with everolimus for adults with advanced renal cell carcinoma following one prior vascular endothelial growth factor (VEGF)-targeted therapy'
Population	Same as marketing authorisation
Intervention	Lenvatinib combined with everolimus
Administration	Oral, once daily
Comparators	1. Axitinib 2. Nivolumab 3. Cabozantinib
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life
Price	Confidential patient access scheme (PAS) simple discount for both lenvatinib and everolimus

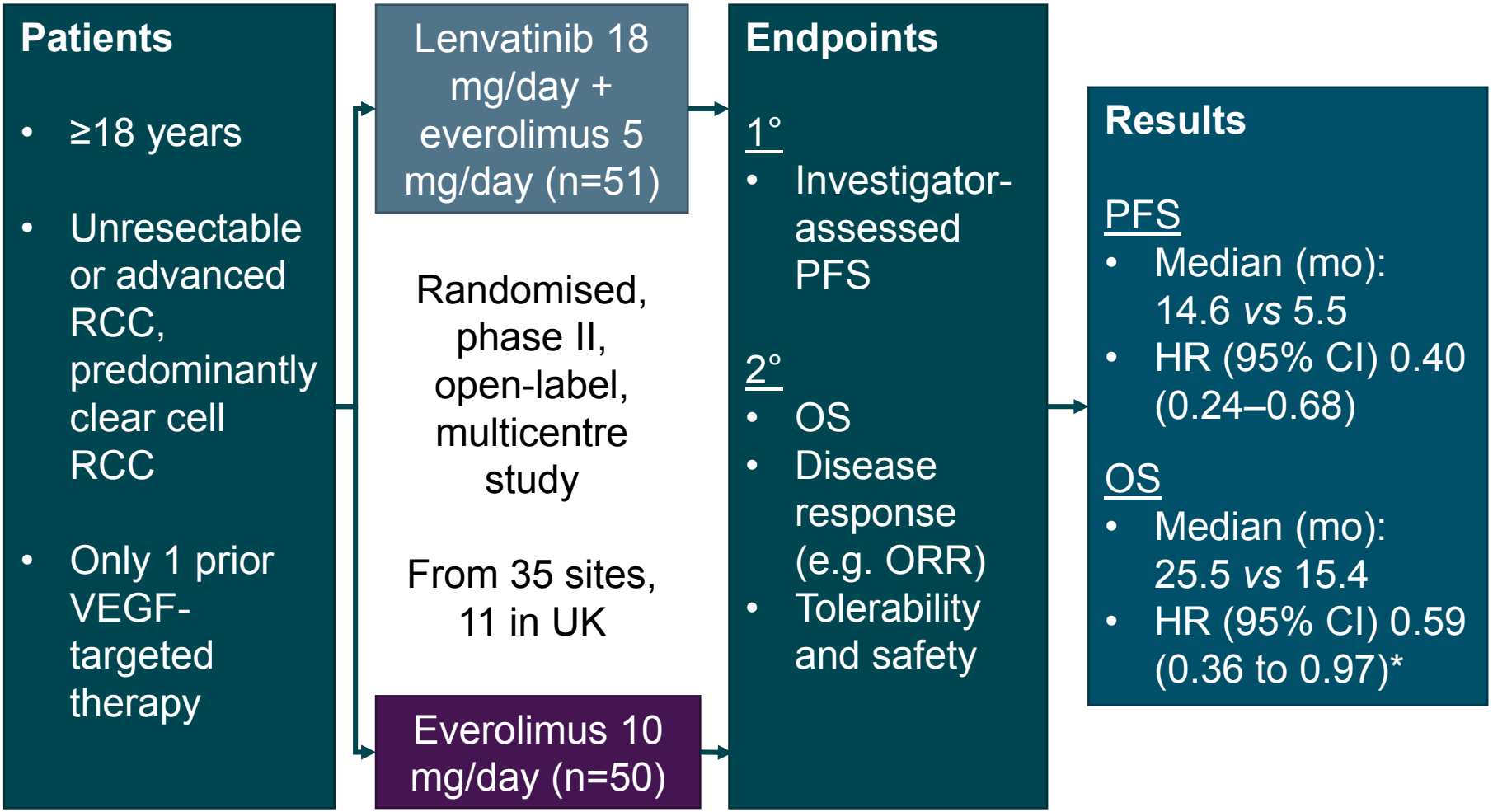
Place of lenvatinib + everolimus (LEN+EVE) in treatment pathway



*Oral tyrosine kinase (TKI) inhibitor
†Programmed cell death protein 1 (PD-1) inhibitor
‡Oral Mammalian target of rapamycin (mTOR) inhibitor

Company's clinical evidence

LEN+EVE vs everolimus: HOPE 205 phase II trial (n=101)

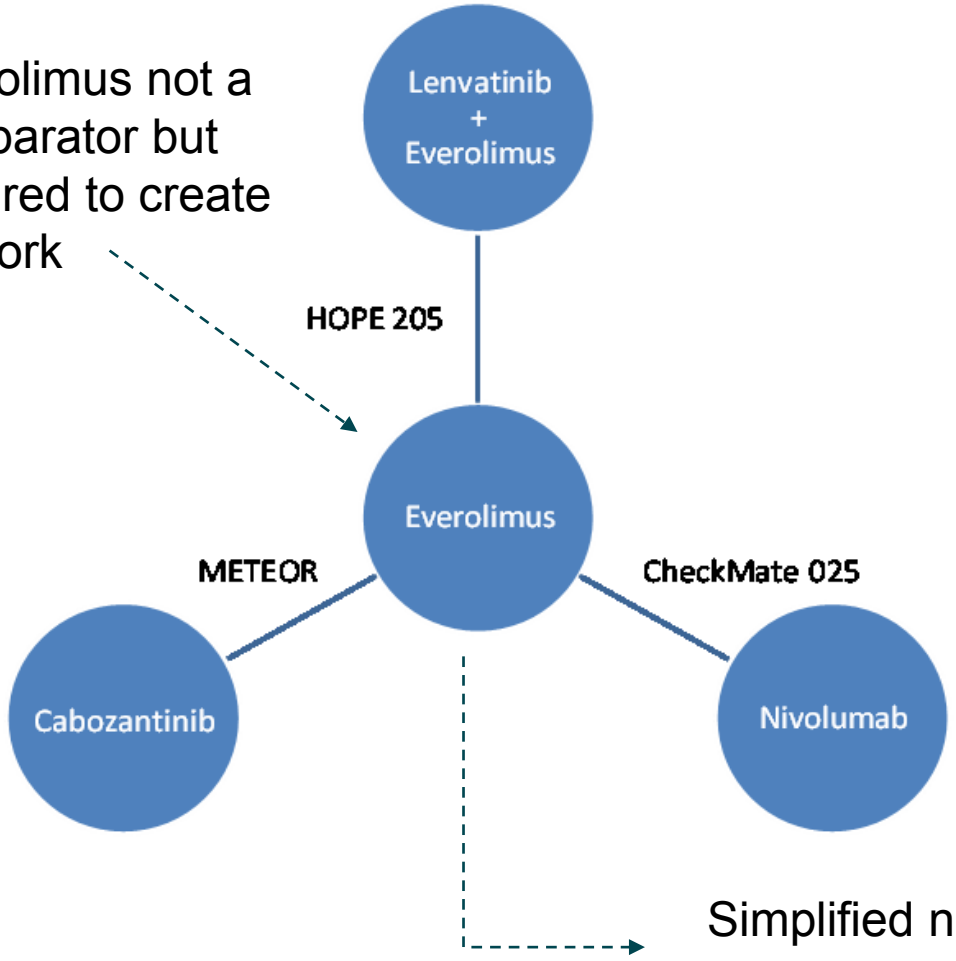


****p value 0.065 for stratified log-rank test not considered statistically significant***

Key: HR, hazard ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RCC, renal cell carcinoma; VEGF, vascular endothelial growth factor

Network meta-analysis (NMA) using fractional polynomials

Everolimus not a comparator but required to create network



Company's sources of survival data:

- **LEN+EVE and EVE**: individual patient data from HOPE 205
- **Comparators**: digitally extracted data from Kaplan-Meier curves reported in CheckMate 025 (nivolumab) and METEOR (cabozantinib)

Simplified network assuming everolimus equally effective as axitinib

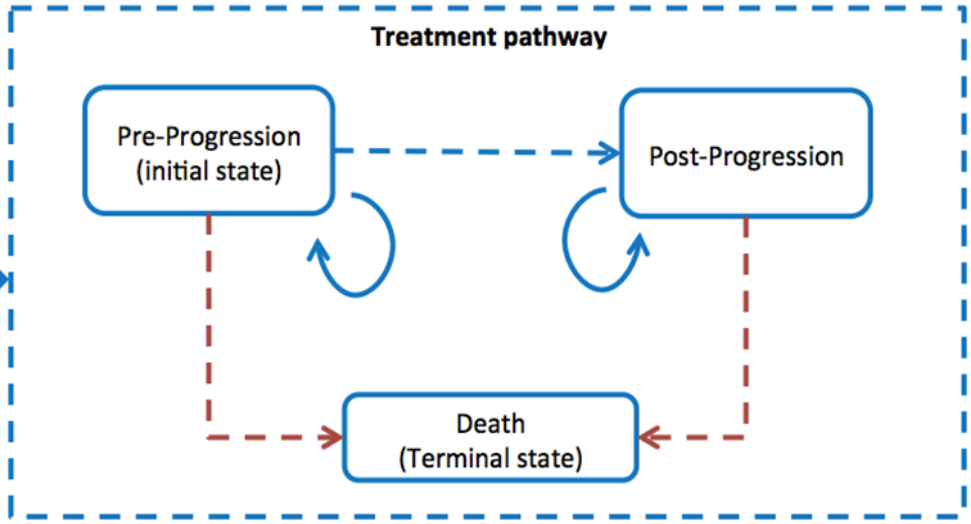
Company's model structure

Partitioned-survival (area-under-the-curve) model

Population
Same as HOPE 205 trial, whole population, adults with 1 prior VEGF-targeted therapy

Intervention
Lenvatinib + everolimus

Comparators
Axitinib, cabozantinib, everolimus monotherapy, nivolumab



- 4-week cycle length (reflecting frequency of consultant oncologist visits)
- 20-year time horizon, 3.5% discount rate for costs and effects

Key: ITT, intention-to-treat; VEGF, vascular endothelial growth factor

Comparison between company and ERG analyses

Parameter	Company base case	ERG base case/scenarios
OS and PFS curves	Fractional polynomial	Fractional polynomial (re-generated by ERG using ERG's output of NMA)
Time to treatment discontinuation (TTD) curve	Kaplan–Meier for LEN+EVE, assumes ratio of median TTD = ratio of hazard rates of TTD for comparators	Parametric curve fitting: 2-knot spline distribution
Subsequent treatment costs	Proportion reflect UK market share of subsequent therapies received in HOPE 205	Proportion of subsequent therapies received in respective trials
Utility values	AXIS study + vignette study	*Scenario*: TA417 (for nivolumab only)
Long-term effect of nivolumab	No predictions of better survival	*Scenario*: general population mortality in 50% of progression-free and on-treatment patients after 5 years

Committee's considerations at 1st committee meeting – clinical

Issue	Committee consideration
Place	• 2nd line only despite broader license – reflects evidence
Comparators	• Axitinib, nivolumab and cabozantinib, not everolimus
Clinical evidence	• HOPE 205's limitations: small sample (n=101), higher risk of false-positives, unblinded investigators for primary outcome PFS • 'Unlikely to form a robust basis for decision-making'
Progression-free survival	• LEN+EVE improves median PFS by 10.1 months. However, experts sceptical about size of benefit given that it is more than is seen for 1st line treatment
Overall survival	• HOPE 205 not powered to detect significant effects between the treatments
Safety	• LEV+EVE has more side effects than LEV or EVE alone
Network meta-analysis	• Fractional polynomials appropriate for decision-making • Analysis overestimated PFS benefit of LEN+EVE compared with trial

Committee's consideration at 1st committee meeting – cost

Issue	Committee consideration
Clinical effectiveness	• Fractional polynomial curves generated by ERG more plausible than company's curves • Assuming effect of LEN+EVE continues beyond trial for up to 20 years is highly uncertain
Treatment duration	• ERG's 2-knot spline distribution suitable
Quality of life	• Utility decrement for LEN+EVE small, did not reflect rate of serious adverse events/stopping treatment
Cost and effect of subsequent treatments	• Could be based either on UK market share, or distribution of treatments in trials
End-of-life criteria	• Company did not make a case • Not met – life expectancy now likely >24 months

Results – incremental analysis	• ERG's base case more appropriate for decision-making
	  • Axitinib and LEN + EVE extendedly dominated cabozantinib
	  • LEN + EVE dominated nivolumab
	  • Leaving only comparator as axitinib: ICER for LEN+EVE vs. axitinib >> £30,000/QALY

Preliminary recommendation

Lenvatinib plus everolimus is not recommended, within its marketing authorisation, for treating advanced renal cell carcinoma in adults who have had 1 previous vascular endothelial growth factor (VEGF)-targeted therapy.

ACD consultation responses

- Consultees
  - Eisai (company)
    - New modelling of utility decrements
    - New confidential Patient Access Scheme (PAS)
  - Ipsen (manufacturer of cabozantinib)
  - Patient/professional organisations
    - Kidney Cancer Support Network

ACD consultation comments

General comments from Kidney Cancer Support Network

- Only multiple kinase inhibitor to gain marketing authorisation
- ‘A breakthrough therapy’
- ‘Well tolerated’ unlike previous drug combinations
- ‘If the government and the pharmaceutical industry cannot agree a price… we question whether patients will continue to support future research... and whether patients and the public will continue to donate to charities’
- ‘There are no biomarkers of response to treatment with current NHS treatments’ so choice is good ‘trial-and-error’ to select most effective treatment for an individual

ACD consultation comments

Comments on individual sections of the ACD from Ipsen – manufacturer of cabozantinib

- 'The Committee is noted as having "concerns" over the ERG's base-case and we echo these. In the appraisals for everolimus (TA432), nivolumab (TA417) and cabozantinib (TA463), each of these drugs was more cost-effective than axitinib. We accept that the network meta-analysis for this appraisal incorporates the studies used in previous appraisals. However, the results are contradictory: axitinib now extendedly dominates cabozantinib. This supports the concern that the evidence base underpinning this appraisal is not robust'.

ACD consultation responses

Design and size of HOPE 205 trial

Committee's discussion at 1st committee meeting:

- HOPE 205 is a small open-label trial
- Design of HOPE 205 a potential source of bias
- Differences between treatment groups uncertain

Company

- HOPE 205 'not pre-planned as a pivotal trial'
- But, results 'so compelling' that Eisai met with regulators to discuss marketing authorisation
  - LEN+EVE improves progression-free survival
  - 'Trend towards improved overall survival'
- Results by investigator assessment were 'corroborated by retrospective blinded independent assessment'
- New large prospective study planned, results due 2020

⊙ *Has the committee seen anything to change its conclusions on the trial design?*

ACD consultation responses

Optimal dose of lenvatinib

Committee's discussion at 1st committee meeting:

- Clinical expert: ongoing trial compares recommended dose (18 mg) with lower dose (14 mg), suggests uncertainty around optimal dose
- Modelled dose should reflect HOPE 205 from which estimates on effectiveness and safety of LEN+EVE were obtained

Company

- Dose modifications: 'disagree' that there is uncertainty
  - Acknowledge that dose modification occurred in HOPE 205
  - But, marketing authorisation of other tyrosine kinase inhibitors for RCC allow dose modification/interruption
- Clinical trial is 'in progress'
  - Comparing the effects of a lower starting dose (14 mg) of lenvatinib with current recommended dose (18 mg)
  - Aims to explore whether it is possible to achieve same efficacy with a better tolerability

Key: RCC, renal cell carcinoma

Recap of baseline characteristics in HOPE 205

Most patients had received either sunitinib or pazopanib as their 1st VEGF-targeted therapy – All patients had received only 1 prior therapy

Previous therapies at baseline	Lenvatinib + everolimus (n=51)	Everolimus only (n=50)
Nephrectomy†	44 (86%)	48 (96%)
VEGF therapy‡		
Pazopanib	9 (18%)	13 (26%)
Sunitinib	36 (71%)	28 (56%)
Axitinib	1 (2%)	0
Bevacizumab	0	4 (8%)
Sorafenib	1 (2%)	2 (4%)
Tivozanib	3 (6%)	2 (4%)
Duration of VEGF therapy (months)	9.8 (2.0–66.2)	8.9 (1.6–57.8)
Checkpoint inhibitor therapy	1 (2%)	2 (4%)
Interferon therapy	4 (8%)	7 (14%)
Radiotherapy	6 (12%)	11 (22%)

1st line in NHS

ACD consultation responses
Baseline characteristics

Committee's discussion at 1st committee meeting:
- The committee could not assess the impact of the differences between the trial groups because they were based on small numbers of patients
- HOPE 205 reflected people who would be offered 2nd-line treatment in NHS

Company
- Tumour burden has no meaningful impact on the PFS and OS results
- LEN+EVE demonstrates 'superior efficacy' compared with everolimus in HOPE 205 regardless of duration of prior anti-VEGF therapy received
- Results for subgroups based on number of baseline metastases or duration of previous treatment consistent with overall population
  - Imbalances do not impact the interpretation of the primary results

ERG: Agree with company, however other imbalances (type of metastases & proportion of patients with complete or partial response to prior therapy) indicate worse prognosis for comparator → potentially overestimate effectiveness of EVE+LEN → results should be interpreted with caution

Key: OS, overall survival; PFS, progression-free survival, VEGF, vascular endothelial growth factor

ACD consultation responses

Safety and utility decrements (1)

Committee's discussion at 1st committee meeting:

- LEN+EVE has a high burden of adverse events, and it is important that the model adequately captures this
- Utility decrements applied by the company contradicted the available evidence on the safety of lenvatinib plus everolimus. The committee concluded that the utility values used in the model did not reflect quality of life appropriately

Company

- LEV+EVE 'have more side effects than the individual treatments, but that these were considered manageable'
- LEN+EVE has a 'predictable and manageable safety profile'
  - With adequate monitoring, dose reduction and interruption, and prompt medical treatment
- 'ACD does not fully reflect the methodology used' for utility values used in the model
  - Incorporate the average duration of each adverse event, taken directly from the HOPE 205 study for LEN+EVE and estimated from the respective phase III clinical trials for the comparators

ACD consultation responses

Safety and utility decrements (2)

Comparator company

- 'Agree that utility decrements applied by the manufacturer seem implausible'
- 'Magnitude of decrement applied to axitinib and cabozantinib
  - more than three times that for everolimus → resulting in utility values which are not supported by the existing guidance documents for these medicines' (TA333, TA463 and TA432)

Company's scenario analysis

Revised calculation of utility decrements

	Original calculation of decrements	Changes to the calculation of decrements
Method used	**LEN+EVE**: • Average duration of each adverse event, taken directly from the HOPE 205 study; also accounting for the proportion of patients who experienced the events **Comparators**: • Estimated from the respective Phase III clinical trials	**LEN+EVE**: • Duration adjustment removed • Duration of adverse events = duration of treatment
Decrements applied	LEN+EVE: -0.013	LEN+EVE: -0.097
	Axitinib: -0.010	Axitinib: -0.072
	Cabozantinib: -0.011	Cabozantinib: -0.084
	Nivolumab: -0.002	Nivolumab: -0.008

+ 0.084
+ 0.062
+ 0.073
+ 0.006

Increased utility decrements for all treatment

ERG comments on company's revised calculation of utility decrements

- Considers the company's original approach reasonable
  - Although prefer to have the decrements **without** adjusting for duration of the event
- Adverse events in the model correlate with those observed in the HOPE 205
  - Prevalence and duration data taken directly from HOPE 205
- Treatment withdrawal relating to severe adverse events allows patients to recover from adverse events
  - Experiencing the reduced quality of life for a shorter duration
  - Captured in the duration adjustment, and supports the company's approach for applying the adjustment
- The treatment duration and treatment effects also capture the impact of treatment withdrawal relating to toxicity
- Approach has a minimal affect on cost-effectiveness results

⊙ *Does the revised calculation of utility decrements address the committee's previous concerns?*

ACD consultation responses
Cancer Drugs Fund

- **Company**
  - Addresses unmet need
    - Against symptomatic, aggressive tumours
  - Large prospective study could capture further information around safety and quality of life with the aim to have results by 2020
  - 'Lenvatinib should be given "conditional approval" for entry into the Cancer Drugs Fund to allow for the opportunity for additional data to be collected to confirm the efficacy demonstrated in the HOPE 205 study'

Cancer Drugs Fund

Decision points

Starting point: drug not recommended for routine use

Proceed down if answer to each question is yes

1. Why is drug not recommended? Is it due to clinical uncertainty?

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

3. Could data collection reduce uncertainty

4. Will ongoing studies provide useful data? **and** 5. Is CDF data collection feasible?

Recommend enter CDF

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

- *Does the committee consider LEN+EVE as a candidate for Cancer Drugs Fund?*

Cost-effectiveness analyses

- **Committee preferred ERG's base case**
  - Survival curves: best fitting fractional polynomials for OS and PFS
  - Time to treatment discontinuation: 2-knot spline
- **Changes submitted by company in response to ACD**
  - Amending its confidential discount for lenvatinib
    - *Note*: everolimus also has a confidential PAS discount, so company not aware of price of combination treatment
  - Providing a scenario analysis with revised utility decrements – using ERG's base case
- **Remaining committee concern in new analyses**
  - Clinical uncertainty (limitations of HOPE 205)
  - Assumption that effect of LEN+EVE continues beyond the trial follow-up for up to 20 years

All the ICERs are reported in PART 2 because they include the PAS discount for LEN+EVE as well as the comparators; axitinib, cabozantinib and nivolumab.