Projector and public observer slides – no ACiC

Lead team presentation

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

1st 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

19 July 2017

Disease background and management

Kidney cancer

- 7th most common cancer in UK
- More common in men than women
- 5-year survival is 56%, varying with age
- 86% of renal cancers are renal cell carcinoma

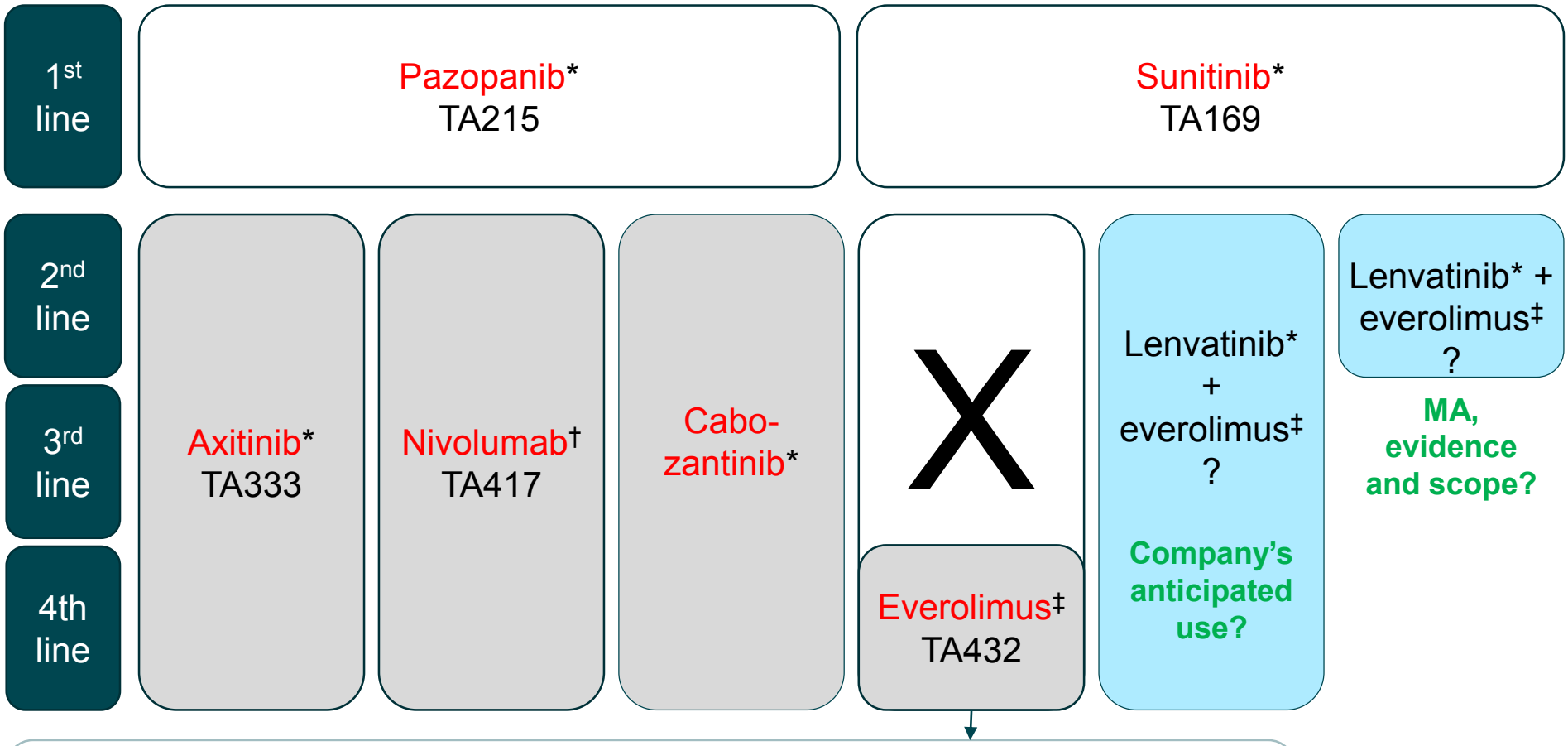
Renal cell carcinoma

- Estimated 9,045 new diagnoses in England per year
- Disease is often locally advanced or metastatic at point of diagnosis
- Early stage disease can be treated surgically – half of patients who have surgical treatment will develop metastatic disease
- Overall survival for people with metastatic disease is 8 months to 3.6 years

Lenvatinib (Kisplyx®)

Marketing authorisation (granted August 2016)	Indicated in combination with everolimus for adults with advanced renal cell carcinoma **following one prior vascular endothelial growth factor (VEGF)-targeted therapy**
Administration	Oral
Recommended dose	18 mg (one 10 mg capsule and two 4 mg capsules) in combination with 5 mg of everolimus
Dosing frequency	Once daily
List price (excluding VAT)	• Lenvatinib: £1,437.00 for 4 mg and 10 mg packs (30 capsules) • Everolimus: £2,250.00 for 5 mg pack (30 tablets) • Company is offering lenvatinib with a simple discount patient access scheme

Potential place of lenvatinib + everolimus (LEN+EVE) in current treatment pathway



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

⊙ *Would LEN+EVE be used 2nd line only, or 2nd line and beyond?*

Decision problem (final scope)

Population in line with marketing authorisation

Population	Adults with advanced renal cell carcinoma who have had 1 prior VEGF-targeted therapy
Intervention	Lenvatinib in combination with everolimus
Comparators	• Axitinib • Nivolumab • Everolimus • Cabozantinib • Best supportive care (BSC)*
Outcomes	• Overall survival • Progression-free survival • Response rate • Adverse effects of treatment • Health-related quality of life
Subgroups	None

*BSC not considered a relevant comparator in company submission; ERG agrees

Patient and professional feedback

- Impact of this disease on physical and mental health of patients as well as friends and family is significant
- Patient organisations note that there is a significant unmet need for second and third line therapies
- Aim of treatment is tumour reduction or stabilisation of disease while maximising quality of life
- Patients place significant value on having a choice of treatments
  - Particularly given the side effect profiles of the available drugs
- Lack of ability to target treatments means that there has to be a ‘trial and error’ approach to find the best option
- Noted that this combination has more side effects than the individual treatments but were considered manageable

Clinical trial evidence

1 key clinical trial: HOPE 205

<table>
<tr><th>Trial</th><th>Population</th><th>Intervention</th><th>Comparator</th><th>Outcomes</th></tr>
<tr><td rowspan="2">HOPE 205

Randomised, phase II, open-label, multicentre study (n=153)

11/35 UK sites</td><td rowspan="2">• ≥18 years
• Unresectable or advanced RCC, predominant clear cell RCC
• Only 1 prior VEGF-targeted therapy
• Disease progression on or within 9 months of stopping prior therapy
• ECOG performance status 0 or 1</td><td>• Lenvatinib 18 mg/day + everolimus 5 mg/day (n=51)
• Lenvatinib 24 mg/day (n=52) – not licensed</td><td>Everolimus 10 mg/day (n=50)</td><td rowspan="2">1°
• Investigator-assessed progression-free survival

2°
• Overall survival
• Disease response (e.g. objective response rate)
• Tolerability and safety</td></tr>
<tr><td colspan="2">Treatment continued until disease progression, unacceptable toxicity or withdrawal of consent</td></tr>
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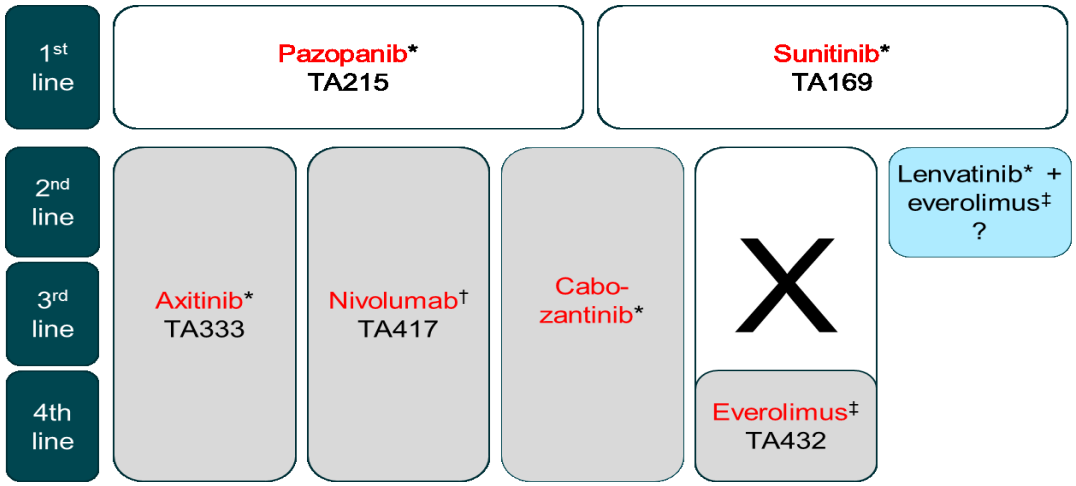
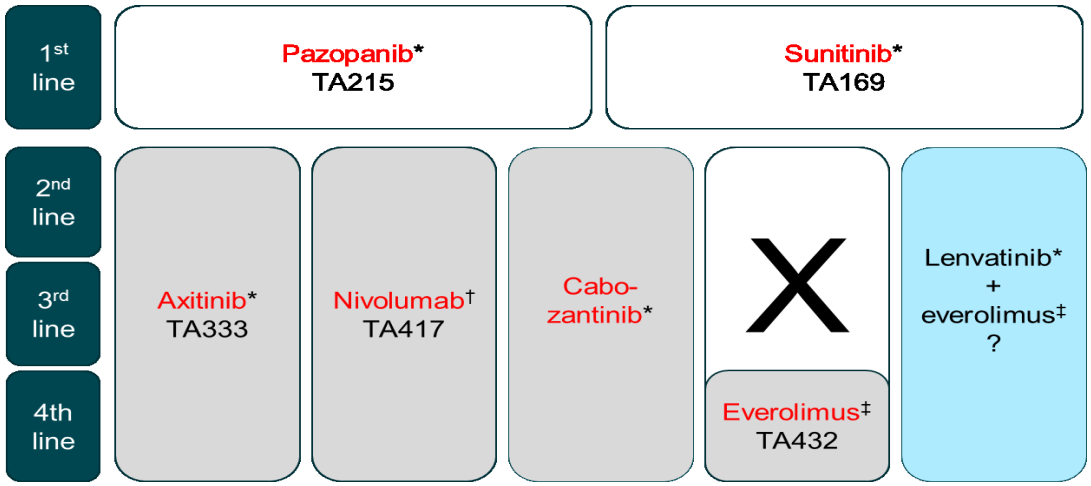
Evidence limited to 2nd-line treatment

Evidence, MA and scope narrower than company positioning

Position supported by clinical evidence, MA and scope



Position suggested by company



⊙ *Which position is supported by evidence? Which is not?*

ERG critique of trial design

- Small sample size means uncertainty around the observed efficacy and safety
- Open-label design introduces bias
  - Progression-free survival assessed by ‘unblinded’ investigator
- Trial did not collect data on health-related quality of life

- *Are the results of HOPE 205 valid given open-label design and small sample size?*
- *Are more data expected?*

HOPE 205: baseline characteristics

Most patients had received either sunitinib (56-71%) or pazopanib (18-26%) 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

⊙ *Does the distribution + duration of prior VEGF therapies reflect NHS patients?*

ERG critique of participant flow and baseline characteristics

- Trial population in line with final scope
- Baseline characteristics generally similar to population in clinical practice
  - However, patients may be healthier in the trial than in clinical practice
    - ECOG performance status 0 or 1 in all patients (0 in > 50% of patients)
- Baseline characteristics generally well balanced between trial arms
- Some differences potentially indicate better prognosis in lenvatinib + everolimus group
  - A smaller proportion of patients had >1 metastases
  - The duration of prior VEGF-targeted therapy was longer
  - More patients had complete or partial response to prior therapy

⊙ *Are the imbalances between treatment arms identified by the ERG likely to introduce bias?*

HOPE 205: analyses presented by company

1 data cut for PFS, 3 data cuts for OS

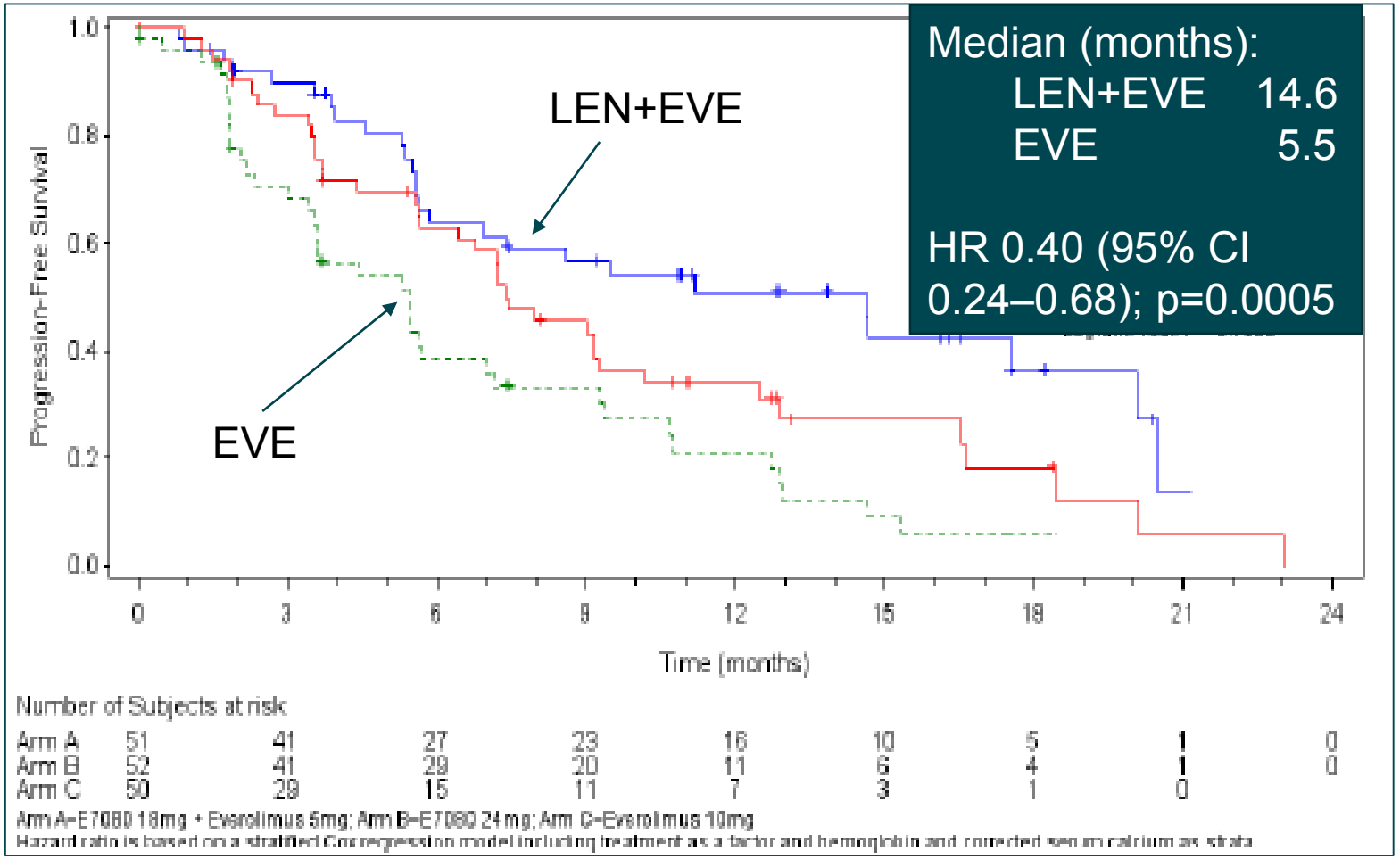
Data cut	Description	Progression-free survival		Overall survival	
		Median follow-up (months)	*Events**	*Median follow-up (months)*	*Events**
Jun 2014	Protocol-specified primary analysis	**LEN+EVE 13.9** **EVE 17.5**	**62%**	LEN+EVE 18.5 EVE 16.5	45%
Dec 2014	Protocol-specified updated analysis	-	-	LEN+EVE 24.2 EVE 25.0	56%
Jul 2015	Analyses requested by regulators: • EMA: increase follow-up for OS • FDA: change calculation of stratification variables 2 analyses but same data-cut	-	-	**LEN+EVE 32.0** **EVE 32.7**	**68%**

Data-cut used for modelling

*Weighted average across the LEN+EVE and EVE groups

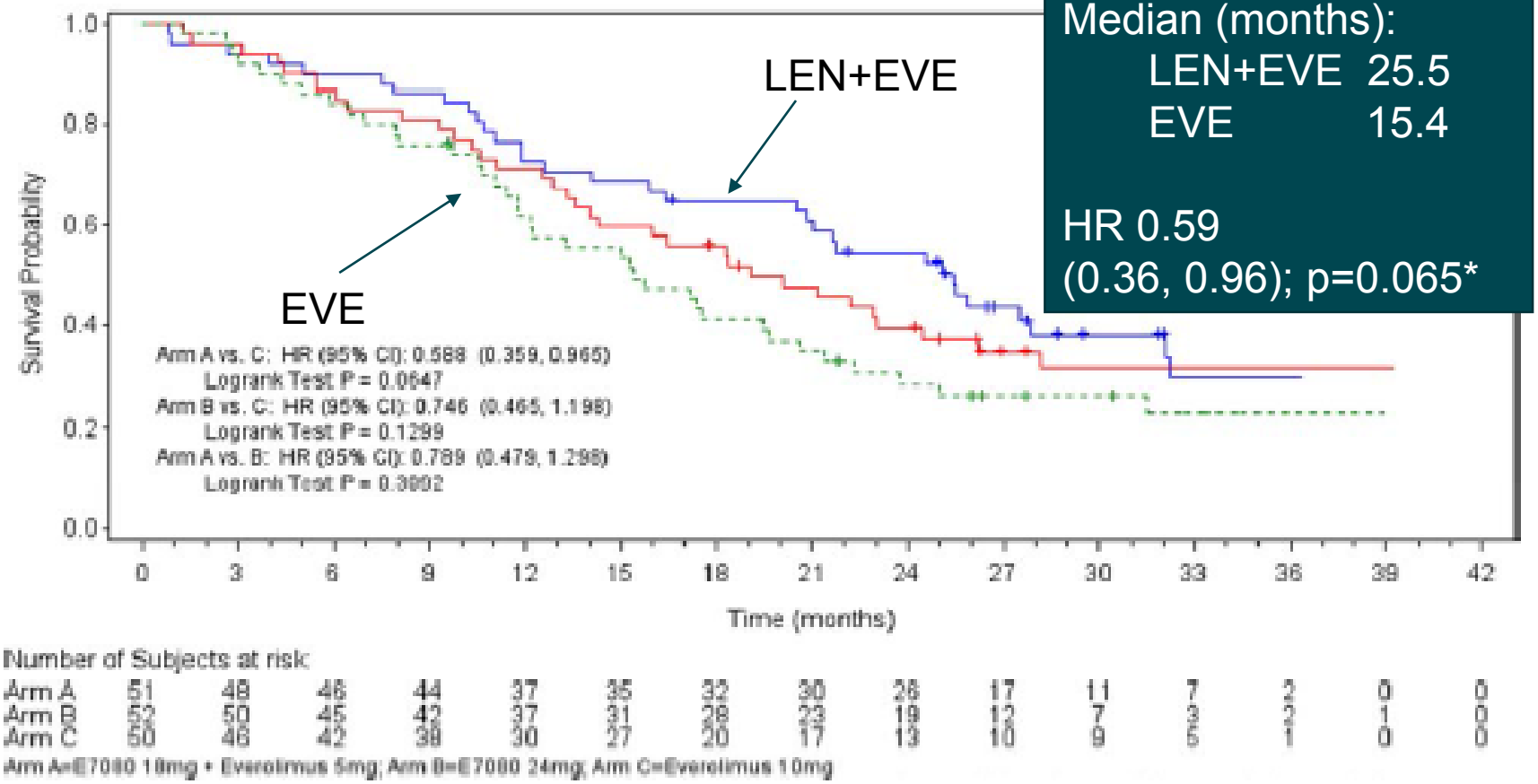
Investigator-assessed PFS (1° outcome)

Lenvatinib plus everolimus significantly increases PFS



Overall survival (July 2015 cut-off)

OS is statistically significantly longer for patients treated with lenvatinib combination therapy (95% CI does not cross 1)



*p-value for the log rank test did not reach statistical significance

⊙ *Is the OS estimate from HOPE 205 robust?*

Safety

Treatment-related adverse events (TRAEs) higher in LEN+EVE group than in EVE group

	LEN+EVE (n=51)	EVE (n=50)
	n (%)	n (%)
Any TRAEs	51 (100.0)	49 (98.0)
TRAEs with CTCAE Grade ≥3	33 (64.7)	21 (42.0)
STRAEs	16 (31.4)	11 (22.0)
Treatment-related deaths	1 (2.0)	0
Other STRAEs	15 (29.4)	11 (22.0)
TRAEs leading to study treatment adjustment	42 (82.4)	22 (44.0)
TRAEs leading to study treatment withdrawal	8 (15.7)	3 (6.0)
TRAEs leading to dose reduction	33 (64.7)	7 (14.0)
TRAEs leading to dose interruption	33 (64.7)	19 (38.0)

Key: CTCAE, Common Terminology Criteria for Adverse Events; SAE, serious adverse event; STRAE, serious treatment-related adverse event; TRAE, treatment-related adverse event

No direct evidence comparing LEN+EVE with comparators available

Company performed 2 indirect comparisons

	Original submission	Company's clarification
Method	Traditional indirect treatment comparison using everolimus as common comparator	Bayesian network meta-analysis using fractional polynomials
Reference	Bucher et al. (1997)	Jansen et al. (2011)
Network	Includes all treatments separately	Simplified, assumes everolimus = axitinib
Included trials	HOPE 205, AXIS, CHECKMATE-025, METEOR, RECORD-1, TARGET	HOPE 205 CHECKMATE-025 METEOR
Assumes proportional hazards?	Yes	No
Use in economic analyses	• Company base case	• ERG alternative base case and scenario analyses • Company scenario analysis

Company's original indirect treatment comparison

- For PFS and OS, company used published HRs and associated 95% CI
- Requires proportional hazards assumption being fulfilled within trial and between trials

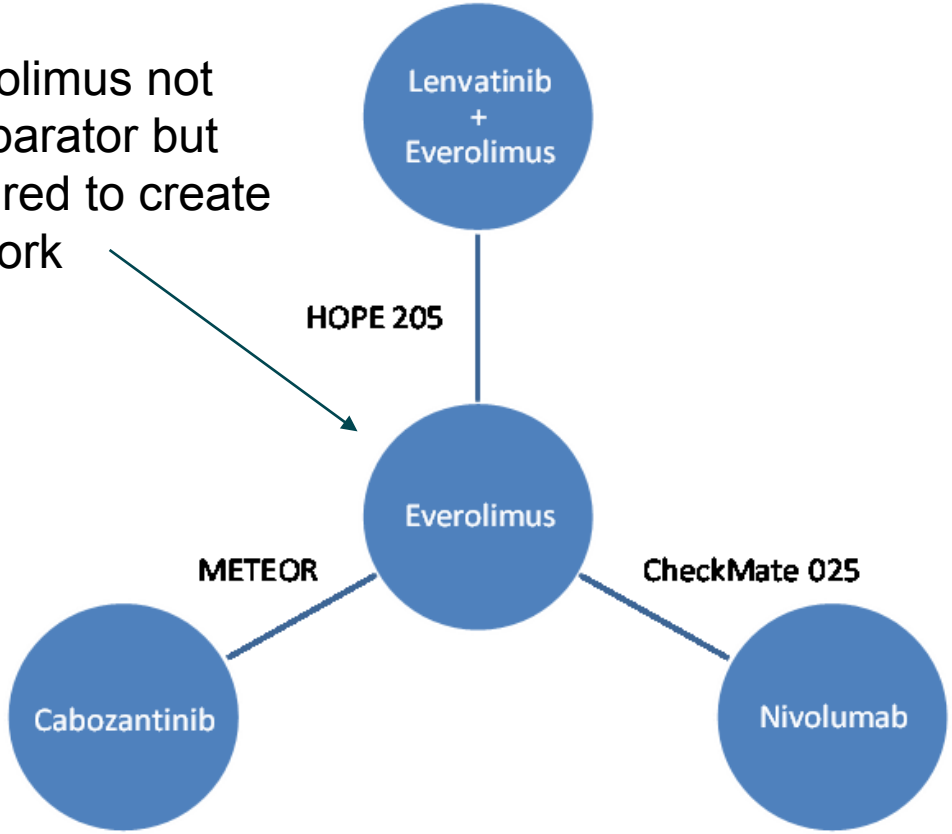
- ERG noted that CheckMate 025 and TARGET (for PFS and OS) and potentially METEOR (for PFS) did not show proportional hazards
- ERG considers it inappropriate for company to use methods for the indirect treatment comparison which rely on proportional hazards
- ERG prefers alternative method using fractional polynomials

- ***Only revised analysis discussed hereafter***

⊙ *Which analysis does the company consider represents its base case?*

Network meta-analysis using fractional polynomials (company's revised analysis)

Everolimus not comparator but required to create network



- Company used individual patient data from HOPE 205, and digitally extracted data from relevant Kaplan-Meier curves in CheckMate 025 (nivolumab) and METEOR (cabozantinib)
- Extracted data included survival time, censored events, total number of events, and numbers at risk
- Only fixed-effect models considered

Summary of trials included in the NMA

Study	Study design	Treatments	N	Prior therapies permitted
CheckMate 025	Phase III open label RCT	Nivolumab	410	1 or 2 prior antiangiogenic; no prior mTORi permitted
		Everolimus	411	
HOPE 205	Phase II open label RCT	Lenvatinib combination therapy	51	1 prior TKI; other prior therapies permitted
		Everolimus	50	
METEOR	Phase III open label RCT	Cabozantinib	330	1 or more prior TKIs; no prior mTORi permitted
		Everolimus	328	

Abbreviations: RCT, randomised control trials; TKI, tyrosine kinase inhibitor; mTORi, mammalian target of rapamaycin inhibitor

NMA results – PFS (investigator)

Hazard ratio over time

NMA results – PFS (investigator)

Company's estimated survival curves

NMA results - OS

Hazard ratio over time

NMA results - OS

Company's estimated survival curves

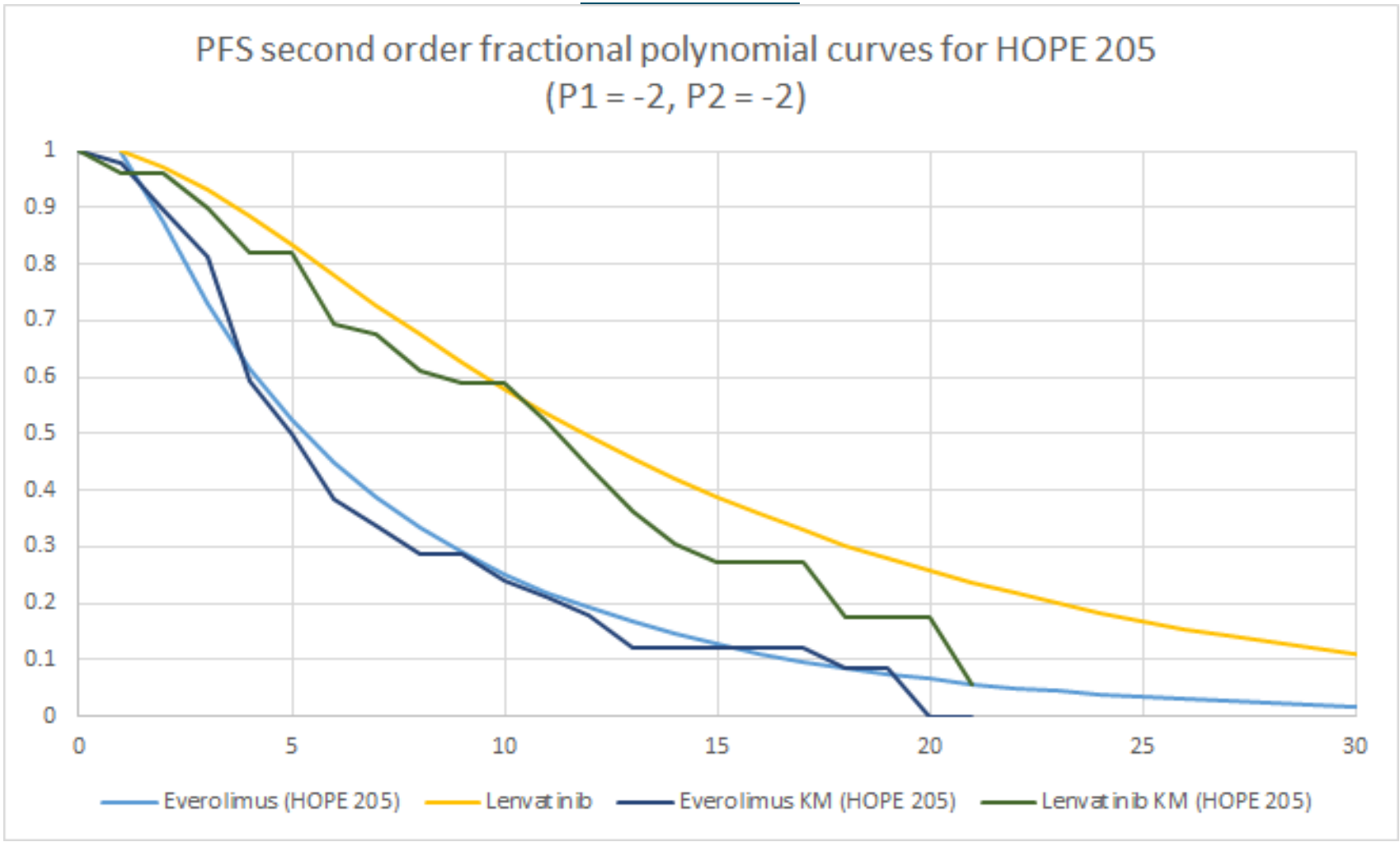
ERG's critique of company's network meta-analysis to estimate PFS/OS between treatments

- Company's 'best' model fit for PFS was a '2nd order fractional polynomial model'; P1=-2 and P2=-2. No other curves provided a plausible fit
- Company's 'best' model fit for OS was a '1st order fractional polynomial model; P1=-1, DIC 640.3
  - 1 other curve provided a plausible fit (1st order fractional polynomial with P = -0.5)
  - ERG explored this curve in a scenario analysis within ERG's preferred base case
- Fractional polynomial method implemented appropriately, however:
  - Company's plots of limited value to validate model fit
- ERG tested how well fractional polynomials fit trial Kaplan-Meier survival curves for PFS and OS for each treatment
- ERG digitised only the Kaplan-Meier curves for CheckMate 025 and used individual patient-level Kaplan-Meier data for HOPE 205 supplied by the company (see next slides)

ERG - Progression-free survival

Curve fits to extracted Kaplan-Meier data from HOPE 205

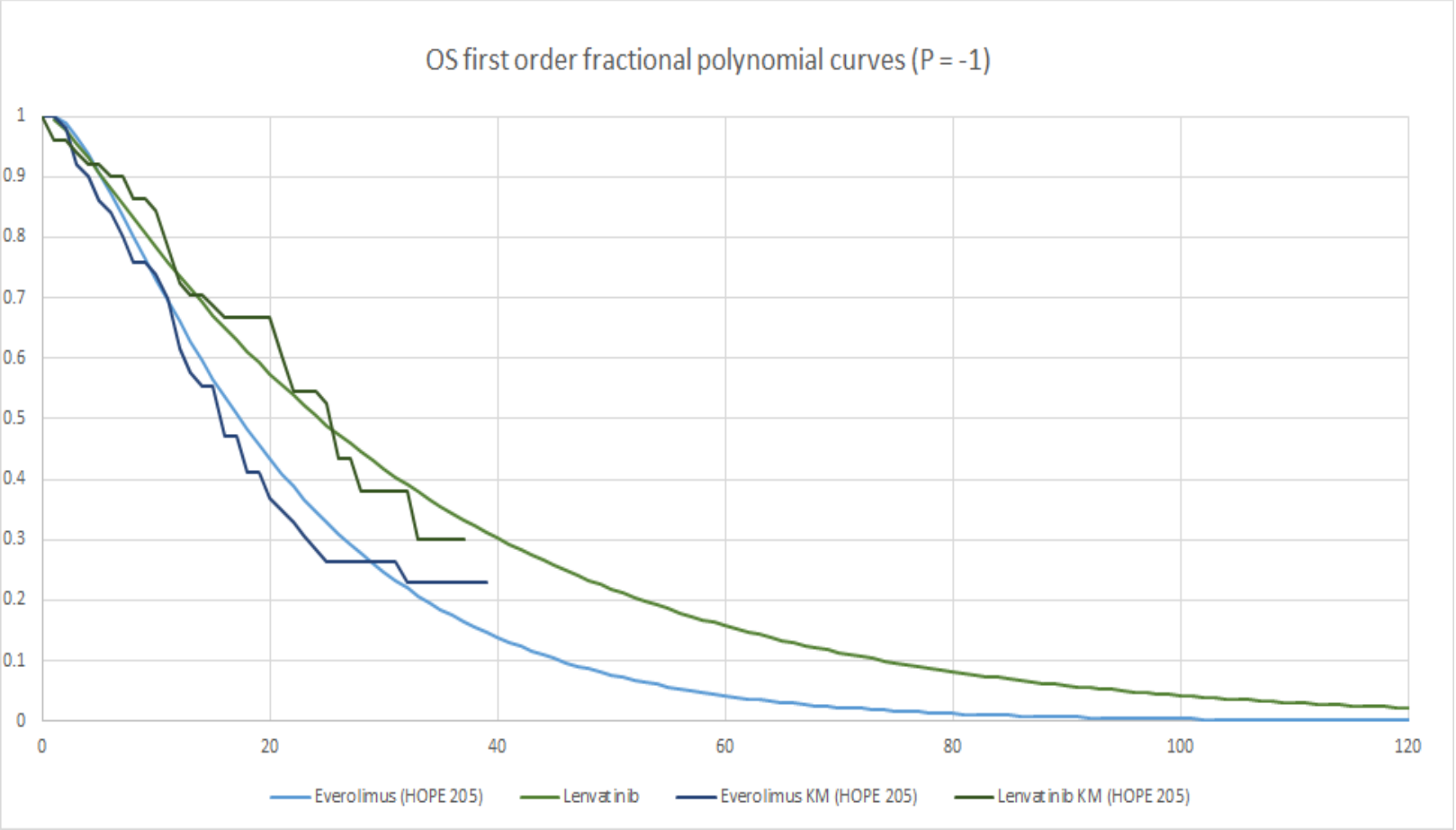
Curves fit data well in HOPE 205 but overestimates PFS for LEN+EVE



⊙ *Is the curve fit for LEN+EVE reasonable?*

ERG - Overall survival

Visual inspection of these curves overlaid on the underlying Kaplan-Meier data shows a good fit for both trial arms in HOPE 205



Key clinical issues for consideration

- Does the committee consider the results of HOPE 205 valid/generalisable given its:
  - Open-label design and PFS assessed by unblinded assessors?
  - Small sample size?
  - Uncertainties around the observed efficacy and safety of lenvatinib combination therapy?
  - Comparator treatment of everolimus alone?
  - Patient population?
  - Better prognosis for the lenvatinib + everolimus group than for the everolimus group?
  - How reliable is the estimate of efficacy? Fractional polynomial curves showed a potential overestimate of PFS in the lenvatinib + everolimus group
- The evidence base is exclusively 2nd-line treatment. Can 3rd-line recommendations be made without evidence?

Cost-effectiveness evidence

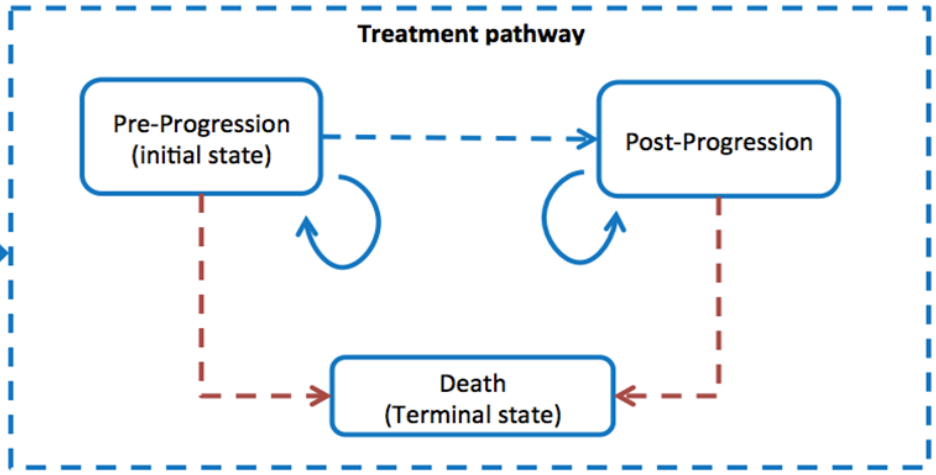
Company's model structure

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

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

Intervention
Lenvatinib + everolimus

Comparators
Axitinib, cabozantinib, everolimus monotherapy, nivolumab



Source: Figure 56 of company submission

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

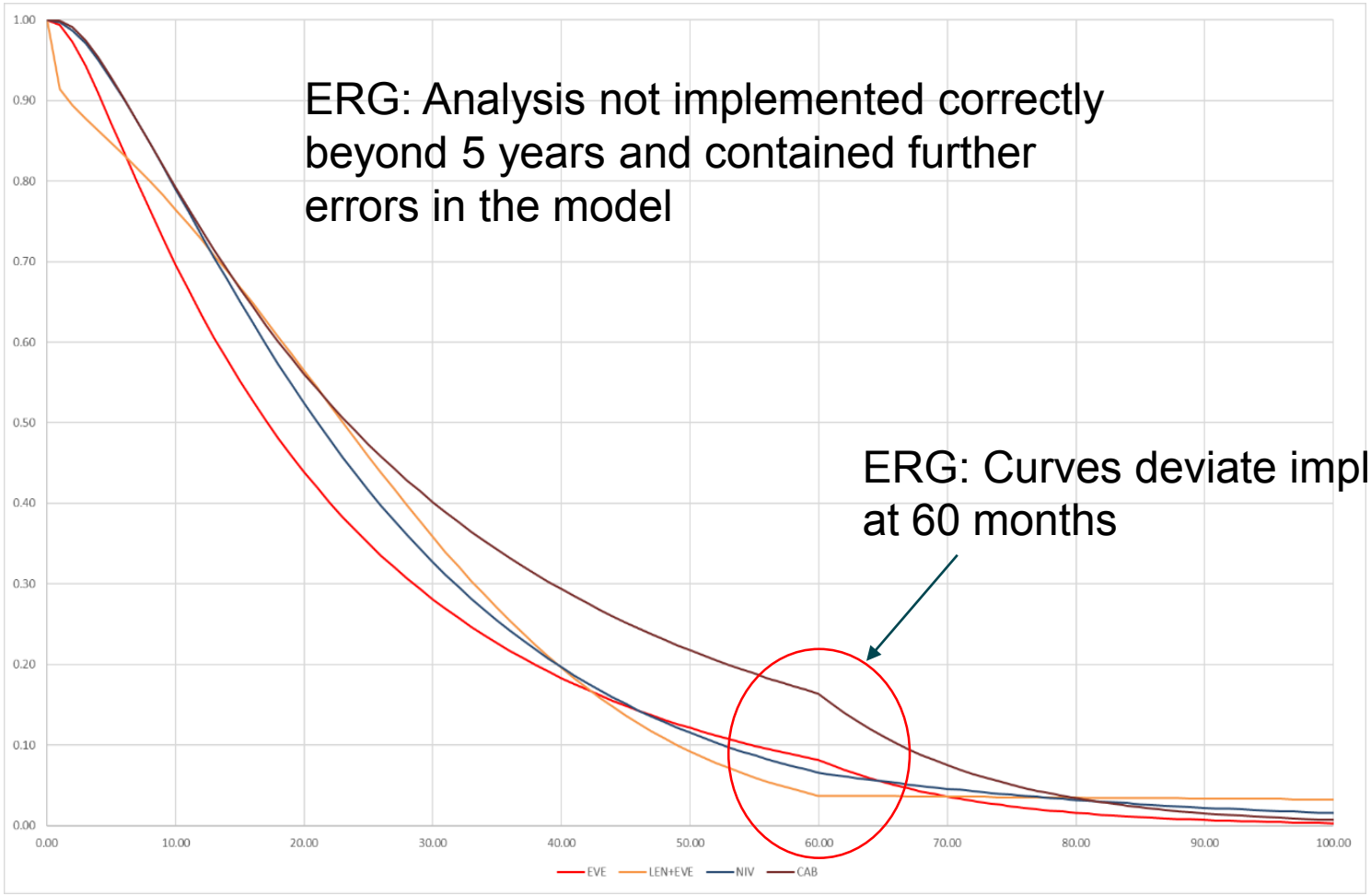
ERG's comment on company's model structure

Company's base case	ERG comment
Population	Company's analysis reflects population outlined in NICE final scope
Comparators	Company's analysis includes all relevant comparators Excluding best supportive care appropriate
Model structure	• Model structure reasonable, and includes all relevant health states • Chosen cycle length and time horizon reasonable

ERG critique of treatment effectiveness (PFS and OS): fractional polynomials

- ERG prefers fractional polynomials to estimate PFS and OS, as proportional hazards not required to hold
- Limitation is that goodness-of-fit measured across all treatment curves
  - May not reflect a good fit to individual treatment curves
- Company used fractional polynomials incorrectly because:
  - Company generated survival curves up to 5 years only, beyond which estimated survival probabilities by multiplying the previous probability by 1 minus the hazard rate
  - Mathematically incorrect
  - Survival curves deviate implausibly at 60 months (see next slide)
- ERG regenerated fractional polynomial curves for entire time horizon based on ERG's network meta-analysis
- ERG's curves to 5-year time point deviate slightly from company's curves, but no much difference
- ERG used own curves in its base case

Company's fractional polynomial curves for OS



⊙*Is the company's modelling of OS plausible?*

Modelling of duration of treatment

Company's approach	ERG's critique	ERG's preferred approach
<u>For LEN+EVE and everolimus:</u> • Directly used Kaplan–Meier data on time-to-treatment discontinuation (TTD) from HOPE 205 <u>For remaining comparators</u>: • Applied ratio of median TTD relative to LEN+EVE, estimated using data from the respective trials used in the ITC, as powers to the LEN+EVE TTD Kaplan–Meier data	• Approach incorrect: assumes ratio of median treatment duration = ratio of hazard rates for TTD • Results in discrepancies between observed and modelled TTD (see next slide)	• Fit parametric curves to digitised Kaplan–Meier data and extrapolate the best-fitting curve beyond follow-up period • Log-normal and '2-knot spline' reasonable, but latter fitted data for LEN+EVE better • ERG's base case used 2-knot spline; log-normal explored in scenario analysis

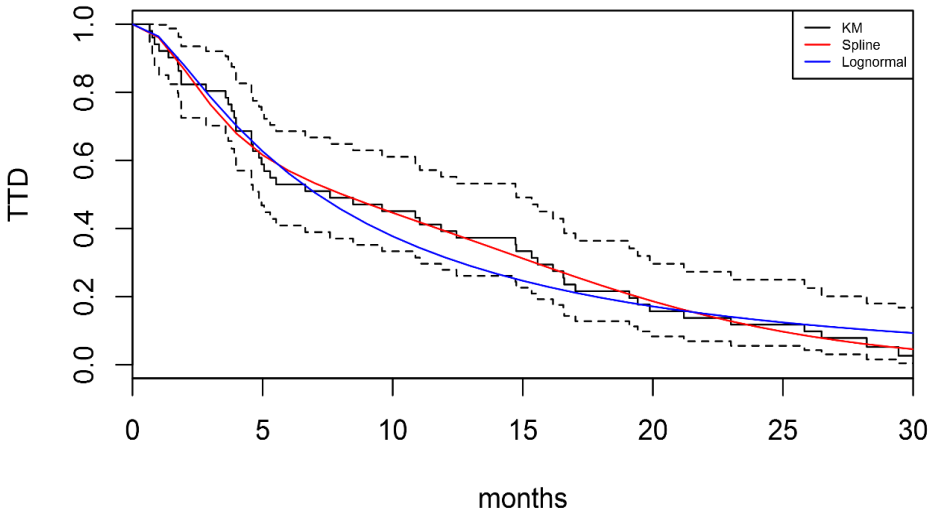
Modelled treatment durations in company's base case

Median treatment durations (month)	LEN+EVE	Everolimus	Axitinib	Cabo-zantinib	Nivolumab
Trial (observed)	**8.0**	**4.1**	**8.2**	**8.3**	**6.2**
Company base case	<7	<4	~7	~7	<5
ERG analysis: 2-knot spline	8.1	4.3	Assumed equal to PFS	8.9	6.7
ERG analysis: log-normal distribution	7.1	4.2		9.3	7.0

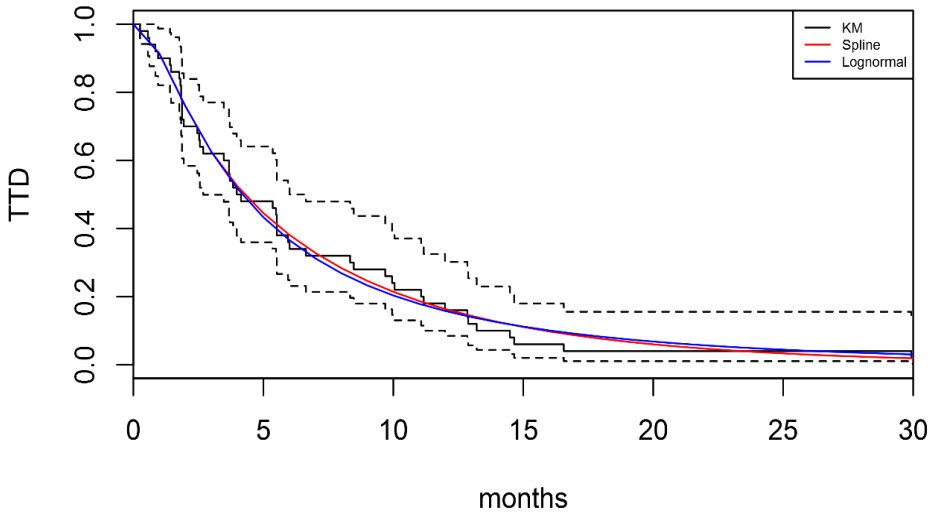
⊙ *Which approach to modelling treatment duration does the committee prefer?*

ERG's curve fits for TTD

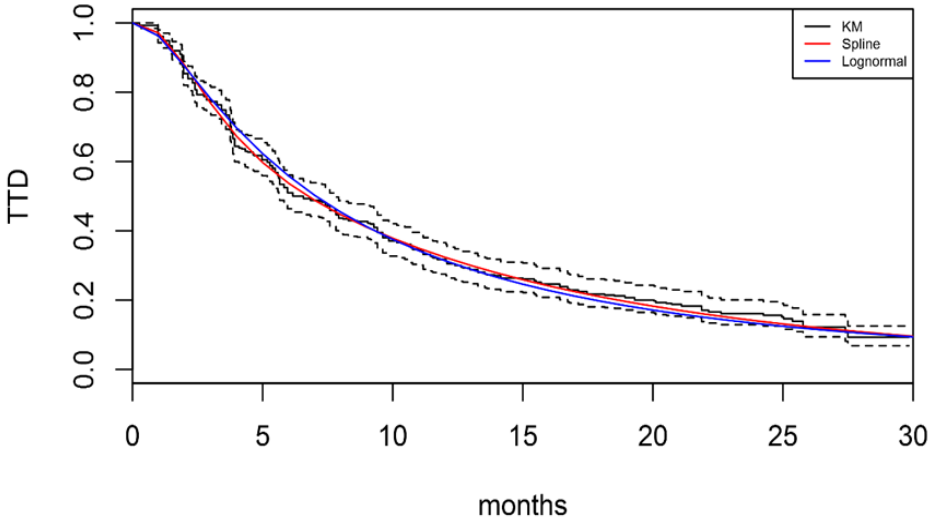
Lenvatinib combination TTD



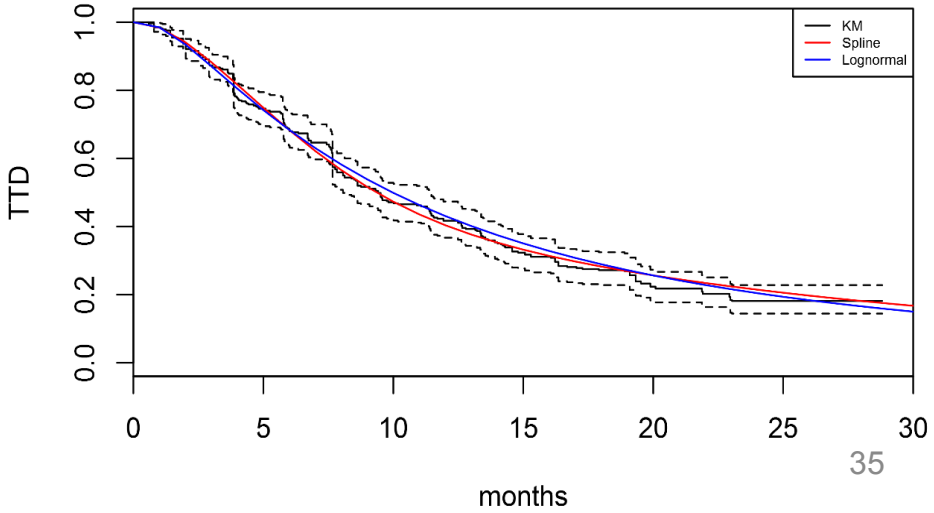
Everolimus TTD



Nivolumab TTD



Cabozantinib TTD

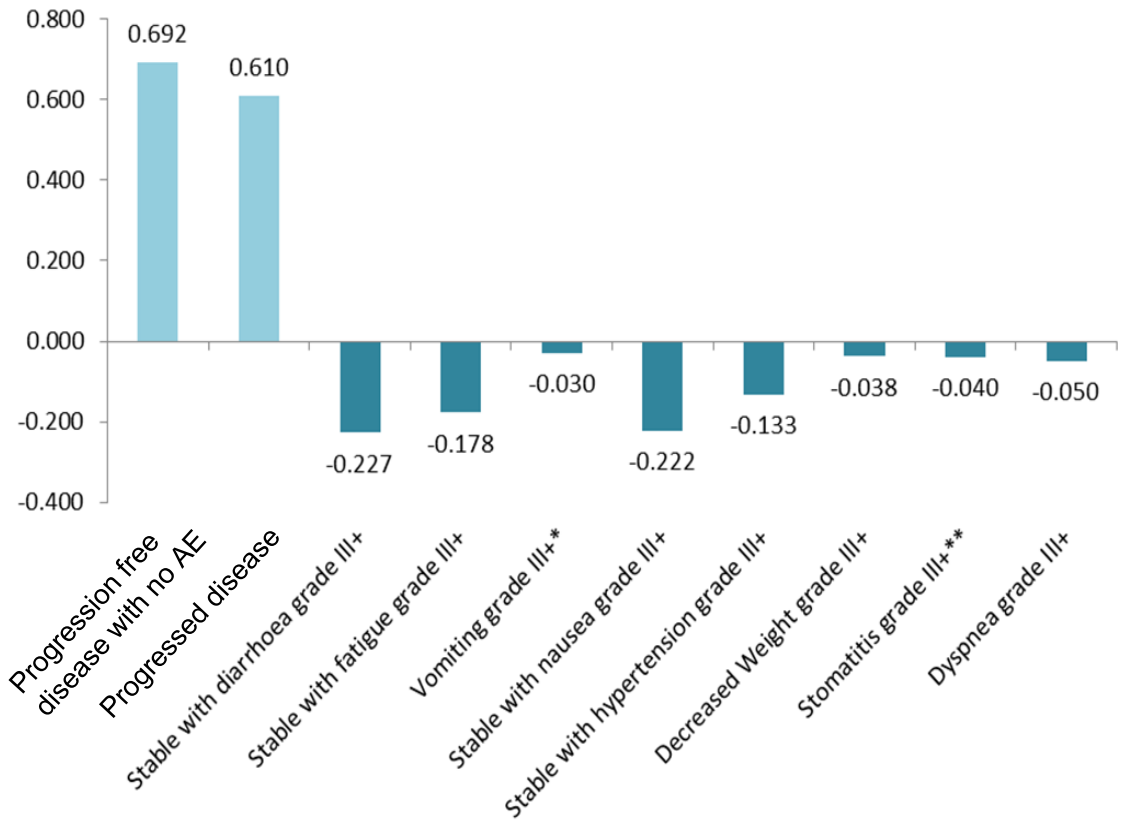


Health-related quality of life in the model

Model used literature-based values

- No utility data available from HOPE 205
- Utility values sourced from AXIS study (base case) and a separate vignette utility study (scenario analysis)
- Additional utility decrements (not included in AXIS) obtained from published literature

Unadjusted utility scores used in the model



⊙ *Is it appropriate to take the utility values from AXIS?*
⊙ *Should the utility values be adjusted for age?*

Health-related quality of life in the model

Adverse event	LEN+EVE	EVE	Axitinib	Cabo-zantinib	Nivo-lumab
Stable disease – on treatment	0.69				
					
Disutility	-0.013	-0.003	-0.010	-0.011	-0.002
					
Stable disease – on treatment	0.68	0.69	0.68	0.68	0.69
Stable disease – off treatment	0.69				
Progressive state	0.61				

⊙*Do the utility values reflect the adverse event profile of the drugs?*

ERG comments on utility values in the model

- Reasonable to use AXIS to source utility values
  - Population in AXIS reflects patients seen in UK clinical practice
- The company assumed adverse events cause a utility decrement
  - Utility value of 0.69 already includes the impact of adverse events on QoL
    - ◊ Double counting the impact of adverse events, for axitinib at least
  - Company's approach assumes all patients start with a value of 0.69
  - Using the proportions of adverse events experienced in the trials is fair and should reflect the difference in safety profiles across treatments
- Utility decrements for adverse events obtained from TA333 and 2 published utility studies (Shabaruddin et al. and Shiroiwa et al.)
  - ERG disagrees with the use of values elicited in Shiroiwa et al.
  - Data collected from members of general population
  - Estimates elicited for patients with colorectal cancer
    - ◊ May not be generalisable to patients with RCC

Resource use and costs

- The company included the following cost categories:
  - Intervention and comparators' costs
  - Drug dosing costs
  - Administration costs
  - Health-state costs
  - Routine care costs
  - Mortality costs
  - Adverse reaction costs
- Based on UK reference costs, literature and expert opinion

Subsequent therapies in HOPE 205

	HOPE 205		CheckMate 025		METEOR	
	LEN+EVE	*EVE*	*Nivo-lumab*	*EVE*	*Cabo-zantinib*	*EVE*
Any	35%	36%	55%	63%	50%	55%
Any VEGF	18%	26%	-	-	24%	47%
Axitinib	12%	24%	24%	36%	17%	27%
Everolimus	10%	4%	26%	-	29%	-
Pazopanib	-	-	9%	16%	-	-
Sorafenib	-	-	-	9%	-	-
Sunitinib	-	-	-	-	-	10%

Cost of subsequent therapies

Company did not originally include cost of subsequent therapies in model, as no treatments approved as 3rd line

ERG preferred including costs based on proportion of subsequent treatments received in respective trials for each treatment arm

Company disagreed because:

(1) Data not available for all drugs

(2) Difference in cost could be related to expensive secondary therapy and would bias the ICER

(3) Secondary therapy biased by availability of drugs at the end of the trial, and not based on clinical practice

Instead,

(1) Company estimated cost of subsequent therapies based on the UK market share of subsequent therapies received in HOPE 205

(2) Applied these to all treatment groups

Modelled cost of subsequent therapies

ERG's preferred approach

- ERG disagreed with justification put forward by the company
- Patients in the HOPE 205, METEOR, CheckMate 025, and AXIS trials received further line of therapy after stopping treatment
- Estimates from these trials included benefits conferred by these subsequent treatments not attributed to initial drugs received in trials

Used actual proportion of treatments received in the trials in a manner reflective of what is available in the UK

⊙ *Should the cost of subsequent therapies be included in the model, and if so, where should the distribution of these therapies come from?*

Additional work undertaken by the ERG

Analyses within the company's base case

- ERG corrected 2 errors in the model
  - **Half cycle correction**: company inconsistently applied half cycle correction for costs and QALYs, which overestimated QALYs for all treatments (favours lenvatinib + everolimus)
  - **Correction of utility values**: company applied pre-progression utility values to all patients on treatment, and therefore, did not account for patients who progressed but remained on treatment

<u>Scenario analyses within the company's base case</u>

- Trial based subsequent treatments
- ITC based HR applied for everolimus PFS and OS
- Utility values based on TA417 (for nivolumab only)
- Apply general population mortality to 50% of patients who are progression-free and still receiving nivolumab after 5 years

Additional work undertaken by ERG

Analyses within the ERG's preferred base case

ERG's preferred base case:

1. ERG's preferred survival curves: Best fitting fractional polynomials for OS and PFS, and 2-knot spline for TTD
2. Subsequent treatment costs based on trials

Scenario analyses within ERG's preferred base case:

- Alternate first order OS fractional polynomial (P = -0.5)
- Alternate TTD curve (lognormal distribution)
- Utility values based on TA417 (for nivolumab only)
- Apply general population mortality to 50% of patients who are progression-free and still receiving nivolumab after 5 years

Innovation

- Lenvatinib plus everolimus is considered to be innovative:
  - A synergistic effect has been shown for the combination
    - higher efficacy levels in terms of PFS and response rate than for each of the individual agents separately
  - Proved clinically significant for the combination compared to everolimus
  - The combination allows the administration of lower doses than those used for each of the individual agents
    - offers an acceptable safety profile at a convenient once daily oral regimen

End of life

- Company comment
  - Eisai does not believe that the lenvatinib in combination with everolimus is suitable for consideration as a 'life extending treatment at the end of life'
- ERG comment
  - In terms of an extension to life, lenvatinib extends (modelled) life by more than 3 months (mean) compared with the next less effective treatment, cabozantinib
  - Increase is greater still when compared with remaining treatments

End of life

Company does not make a case for end of life

Criterion	Comparator	Mean overall survival estimates (discounted, months)	
LEN+EVE is indicated for patients with a short life expectancy, normally < 24 months		**$survival_{comparator}$**	
		Company's base case	*ERG's base case*
	Axitinib	16.08	22.2
	Cabozantinib	24.7	28.3
	Nivolumab	23.3	26.4
LEN+EVE has the prospect of offering an extension to life, **normally** of a mean value of ≥ 3 months, compared with current NHS treatment		**$survival_{LEN+EVE} - survival_{comparator}$**	
		Company's base case	*ERG's base case*
	Axitinib	10.56	10.08
	Cabozantinib	1.92	3.96
	Nivolumab	3.36	5.88

⊙ *Does LEN+EVE extend life by 3 months compared with the comparators?*

Cost-effectiveness results

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.

Key economic issues for consideration

- Did the company correctly implement its scenario analysis based on fractional polynomials beyond 5 years?
- Drug costs: What is the appropriate way to estimate and model treatment duration?
- Utility values
  - The HOPE 205 trial did not measure quality of life. Does the committee consider the data from the AXIS trial appropriate?
  - Is it appropriate to correct utility values to account for patients who remain on treatment after progression?
- The company included the benefits but not the costs of subsequent treatments that patients received in all the trials. What is the appropriate approach?
- Does LEN+EVE meet the end-of-life criteria?

Back-up slides

Utility decrements assumed for adverse events

Health state	Mean utility	Disutility of AEs	Source of disutility
Stable with no AE	0.692	NA	N/A
Progressive	0.610	NA	
Stable with diarrhoea Grade III+	0.465	-0.227	Swinburn 2010[86]
Stable with fatigue Grade III+	0.514	-0.178	
Vomiting Grade III+	NR	-0.030	Shiroiwa 2009[87]
Stable with nausea Grade III+	0.470	-0.222	Swinburn 2010[86]
Stable with hypertension Grade III+	0.559	-0.133	
Decreased Weight Grade III+	NR	-0.038	Hudgens 2014 (Using decreased appetite as a proxy)[88]
Stomatitis Grade III+	NR	-0.040	Shiroiwa 2009[87]

Adverse events prevalence for disutility estimation

Adverse event	LEN+EVE	EVE	Axitinib	Cabo-zantinib	Nivo-lumab
Diarrhoea	19.60%	2.00%	11.00%	13.00%	1.23%
Fatigue/ Asthenia	9.80%	0.00%	10.00%	11.00%	2.46%
Vomiting	7.80%	0.00%	1.00%	2.00%	0.00%
Nausea	5.90%	0.00%	2.00%	5.00%	0.25%
Hypertension	13.70%	2.00%	17.00%	15.00%	0.00%
Decreased Weight	2.00%	0.00%	3.00%	3.00%	0.00%
Stomatitis	0.00%	2.00%	1.00%	2.00%	0.00%
Dyspnoea	2.00%	8.00%	0.00%	3.00%	0.74%
Disutility	-0.013	-0.003	-0.010	-0.011	-0.002