Public observer slides – ACIC redacted

NICE National Institute for Health and Care Excellence

Vandetanib for treating medullary thyroid cancer [ID1415]

Chair's presentation

3rd appraisal committee meeting

Committee D

Lead team: Ian Davidson, Rebecca Harmston, David Bowen

Assessment Group: ScHARR

NICE technical team: Anna Brett, Nwamaka Umeweni

Company: Sanofi

11 September 2018

Key issues

- Does the ‘restricted population’ subgroup reflect the marketing authorisation?
- Does the ‘restricted population’ subgroup reflect the way vandetanib will be used in clinical practice?
- Is the RPSFTM crossover adjustment appropriate?
- Which assumptions are most appropriate regarding:
  - choice of parametric curves for extrapolation?
  - post-progression vandetanib costs and benefits?
  - pre-progression vandetanib discontinuation costs?
- Are the end-of-life criteria met?
- What is the most plausible ICER?

[redacted]

Vandetanib (Caprelsa), Sanofi

Marketing authorisation	For the treatment of aggressive and symptomatic medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease
Mechanism of action	Tyrosine kinase inhibitor
Administration	Oral, tablet
Dose	300mg once daily (reduced doses in case of toxicity: 200mg, 100mg)
Stopping	Until disease progression or until the benefits of treatment continuation no longer outweigh its risk
List price	£5,000 per monthly pack Simple discount PAS agreed

[redacted]

History of appraisal

- Vandetanib available on CDF (since 2012) for progressive and symptomatic disease (final CDF transition topic)
- **2017**: Considered in Multiple Technology Appraisal that included cabozantinib
  - Committee concluded that:
    - the company's base case subgroup population does not reflect NHS practice because the decision to start treatment was not based on the presence of CTN/CEA biomarkers
    - the evidence from the ZETA trial was not suitable for decision-making
- **2018**: Guidance not released for vandetanib (cabozantinib recommended [TA516])
  - Company maintained that base case subgroup was relevant; further analyses and clarifications requested from the company
- **Today**: Committee to discuss the cost-effectiveness of vandetanib based on:
  - Supporting information for relevance of 'restricted population'
  - New crossover-adjusted analyses and Assessment Group's critique
  - Increased PAS discount

CDF, Cancer Drugs Fund; CTN, calcitonin; CEA, carcinoembryonic antigen

[redacted]

Summary of clinical evidence from 2017

Company's rationale for restricted EU label subgroup:

- Better reflects clinical practice: vandetanib prescribed for those in whom disease is sufficiently aggressive and who are most likely to benefit
- CTN and CEA biomarkers shown to be important indicators of tumour burden and prognosis (studies have shown patients with doubling times ≤24 months have progressive disease and reduced survival compared with doubling times >24 months)
- Doubling times routinely used in clinical practice to determine postoperative disease burden, progression, survival (therefore identifying aggressive disease)
- Biomarkers are routinely monitored every 6 months or annually
- Clinicians likely to take into account as part of treatment decision-making

Assessment Group's critique:

- Decision to start TKI therapy principally determined by radiographic evidence
- CEA and CTN doubling times would not usually inform treatment decisions
- Vandetanib used in patients with symptomatic and progressive disease irrespective of CEA/CTN biomarker levels
- Appropriate subgroup is EU label population

[redacted]

CTN, calcitonin; CEA, carcinoembryonic antigen; TKI, tyrosine kinase inhibitor

Summary of clinical evidence from 2017

Progression-free survival results

EXAM		ZETA EU label		ZETA restricted EU label	
Median follow-up 14 mths		Median follow-up 24 mths			
Cabozantinib n=219	Placebo n=111	Vandetanib n=126	Placebo n=60	Vandetanib n=[redacted]	Placebo n=[redacted]
Central review					
11.2 mths	4.0 mths	28.0 mths	16.4 mths	[redacted]	[redacted]
HR 0.28 95% CI 0.19, 0.40 p<0.001		HR 0.47 95% CI 0.29, 0.77 p=0.0024		[redacted]	
Investigator-assessed					
13.8 mths	3.1 mths	22.1 mths	8.3 mths	NR	NR
HR 0.29 95% CI 0.21, 0.42 p<0.001		HR 0.33 95% CI 0.20, 0.53 p<0.001		NR	
		Central read excluding open label vandetanib			
		30.1 mths	11.1 mths		
		HR 0.32 95% CI 0.19, 0.54 p<0.001			

[redacted]

Summary of clinical evidence from 2017

Overall survival, response rates, quality of life

EXAM		ZETA EU label		ZETA restricted EU label	
Median follow-up 52 mths		Median follow-up 105 mths			
Cabozantinib n=219	Placebo n=111	Vandetanib n=126	Placebo n=60	Vandetanib n=	Placebo n=
Overall survival					
26.6 months	21.1 months				
HR 0.85 95% CI 0.64, 1.12 p=0.2409					
Objective response rates					
28%	0%	43.7%	1.7%		
p<0.001		p<0.0001			
Quality of life					
EXAM: MDASI-THY found no difference between treatment arms		ZETA: FACT-G found no difference between treatment arms			
AG note that these tools do not necessarily capture symptomatic benefit					

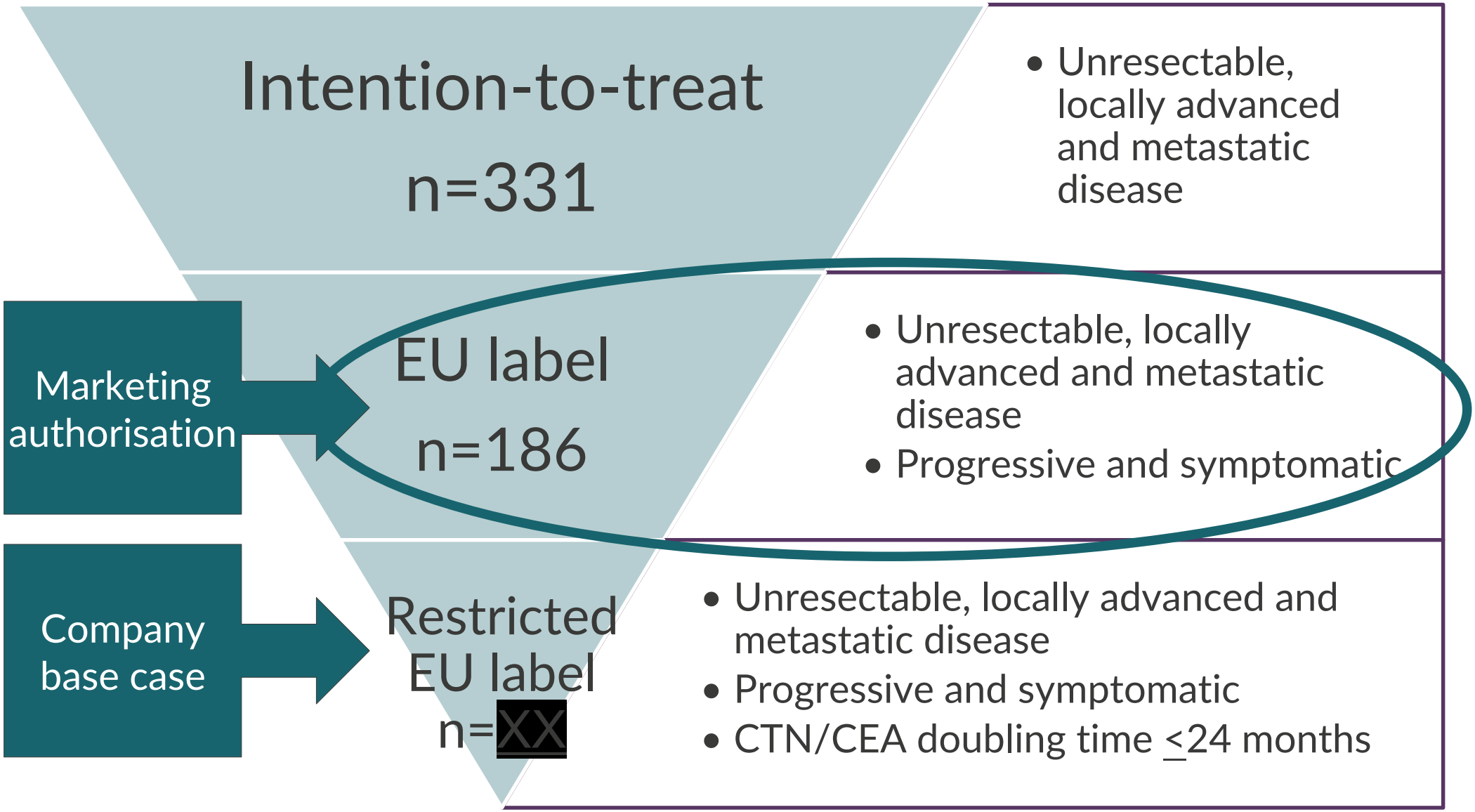
Committee's previous considerations: population

- ZETA trial (vandetanib vs. placebo) inclusion criteria did not specify progressive disease so 2 subgroup analyses presented:
  - 'EU label' = defined by company as people with progressive and symptomatic disease
  - 'restricted EU label' = people with progressive and symptomatic disease and CTN and CEA doubling time ≤24 months
- Committee considered the 'EU label' to best reflect:
  - the marketing authorisation (aggressive and symptomatic disease considered to be the same as progressive and symptomatic)
  - the CDF criteria (progressive and symptomatic disease), and
  - patients in clinical practice (treatment initiation based on when disease progresses and becomes symptomatic)
- Clinical advice that CTN/CEA doubling time is likely to be ≤24 months in patients with progressive and symptomatic disease, but biomarkers are not a selection criterion for starting treatment
- 'Restricted EU label' subgroup not considered to reflect NHS clinical practice

CTN, calcitonin; CEA, carcinoembryonic antigen

[redacted]

Reminder: ZETA trial subgroups



CTN, calcitonin; CEA, carcinoembryonic antigen

[redacted]

Committee's previous considerations: evidence

- ZETA trial allowed open-label vandetanib use after disease progression, so overall survival results in both subgroups confounded by crossover:
  - 'EU label': 80% crossover in placebo arm; 44% open-label continuation in vandetanib arm
  - 'Restricted EU label': XX% crossover in placebo arm; XX% continuation in vandetanib arm
- Unadjusted trial results therefore compare early vs. late vandetanib which is not how vandetanib would be used in NHS practice
- Company's adjustment for crossover ('restricted EU label' only) not considered robust for decision-making because:
  - Common treatment effect may not be plausible
  - Covariates other than those chosen by the company may be imbalanced between groups
  - No adjustment for patients in the vandetanib group continuing to have vandetanib post-progression, which is not NHS practice
- Restricted EU label subgroup:
  - Small patient numbers and difficulties relating to crossover and baseline covariate adjustment results in uncertain survival estimates
  - PFS higher than in the EXAM ITT population (counter-intuitive)

[redacted]

Committee's previous considerations: cost-effectiveness

- Cost-effectiveness decision (for 'EU label') based on cabozantinib trial data because:
  - Cabozantinib and vandetanib considered likely to be similarly effective
  - EXAM trial population considered to reflect patients seen in clinical practice
  - Significant uncertainty in ZETA trial
- Most plausible ICERs substantially above £20-£30k per QALY gained (~£XXk)
- End of life criteria not met in 'EU label' population
- Committee recognised ultra-orphan status of medullary thyroid cancer, the small patient population covered by the marketing authorisation and the severity of the disease
- But given significant uncertainty around clinical effectiveness, the ICERs were too high to justify considerable deviation from NICE principles.

[redacted]

Company's supporting info and new analyses

- Rationale for relevance of 'restricted population'
- New crossover-adjusted analyses of trial data using Rank Preserving Structural Failure Time Modelling (RPSFTM) method
- Revised cost-effectiveness analyses
  - Based on RPSFTM-adjusted trial data and baseline covariate adjustment (base case)
  - Scenario analyses to show impact of:
    - crossover-adjustment
    - covariate adjustment approach
    - different combinations of OS and PFS extrapolations
    - including post-progression vandetanib costs
    - adjusting for post-progression vandetanib (assuming lower survival benefit)
  - Revised PAS discount

[redacted]

Company's rationale for 'restricted population'

- Reflects patients identified by European Medicines Agency as suitable for treatment
  - EMA intended limiting treatment to those in urgent need: **(Section 4.4 of SmPC**)
    "In view of the associated risks, it is important to limit treatment with vandetanib to patients who are in real need for treatment, i.e. with a symptomatic-aggressive course of the disease. Either symptomatic disease or progressive disease alone is not enough to prompt the need of treatment with vandetanib. Rate of change in biomarker levels such as of calcitonin (CTN) and/or carcinoembryonic antigen (CEA) as well as the rate of change of tumour volume during watchful waiting might help to identify not only patients in need for treatment but also the optimal moment to commence treatment with vandetanib"
- Aligns with UK treated population
  - Clinical expert input that patients with tumour marker doubling times ≤24 months likely to reflect the population treated
  - Clinicians weigh up risk vs. benefit, selecting only those in urgent need of treatment
- Represents optimal benefit/risk balance and most potential to benefit
- The company offers to work with treatment centres to support use of vandetanib in this restricted population

SmPC, Summary of Product Characteristics

[redacted]

Company's new crossover-adjusted analysis

[redacted]

RPSFT with covariates for disease duration and prior therapy

AG's critique: crossover-adjustment methods

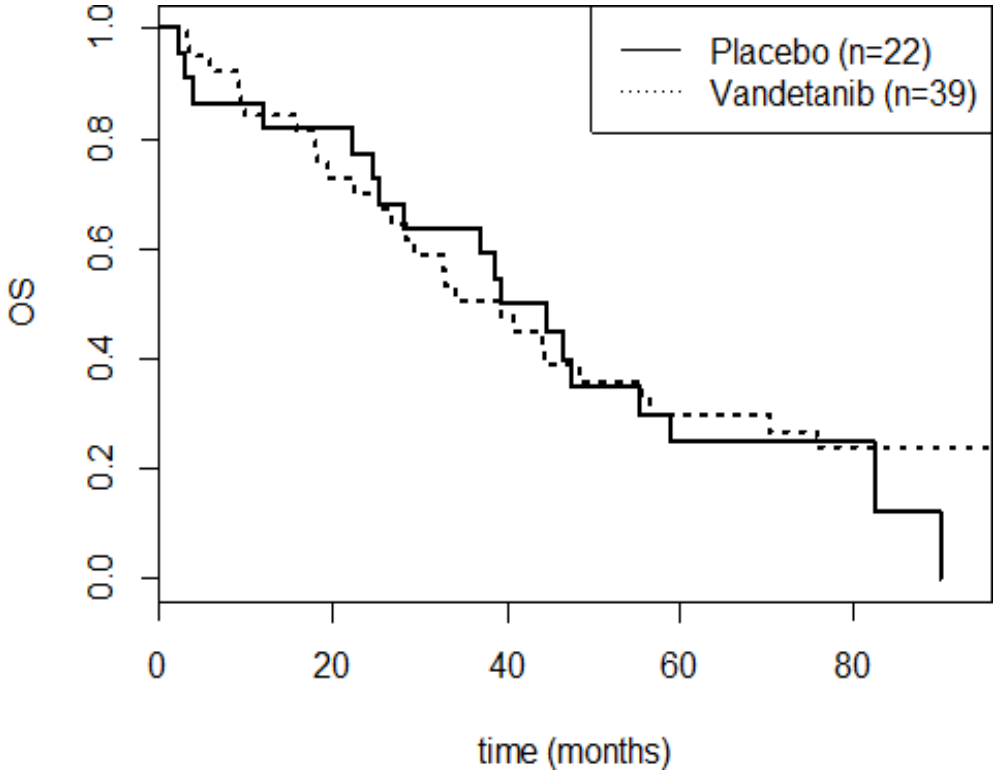
- Treatment effect not statistically significant in any analyses; wide confidence intervals of XXXX to XXXX reflects considerable uncertainty
- Company addressed imbalance in treatment arms by adjusting for baseline covariates (disease duration and prior systemic treatment):
  - covariate adjustment reasonable → but small sample size is limiting factor
  - justification for choice of covariates (and exclusion of others) still not provided
  - covariates other than those chosen may be imbalanced
- RPSFT method corrects crossover for placebo arm only, but not vandetanib arm
- Confidence intervals now more plausible but more thorough description of methods needed to verify approach
- Re-censoring (generally recommended with RPSFTM) not addressed
- Choice of software increases chance of incorrect implementation

[redacted]

AG's critique: impact of missing data

- 'Restricted population' required **both** CTN and CEA doubling times ≤24 months
- XX patients with missing CEA data were excluded from analysis
- Including these patients increases the population by XX%
- Clinical advice that an increase in 1 biomarker indicates an increase in the other; treatment likely to be given with information from just 1 biomarker
- Hazard ratios not used in model but including the missing patients in the unadjusted analysis suggests a less pronounced treatment effect

Kaplan-Meier: 'restricted population' including patients with missing CEA data



Impact of including patients with missing CEA data in unadjusted analysis	Hazard ratio (CI)
Patients with CTN and CEA doubling ≤24 months	XXXXXXXXX
Patients with CTN doubling ≤24 months including those missing CEA data	XXXXXXXXX

[redacted]

Company's overall survival extrapolation

[redacted]

	AIC	BIC
Vandetanib		
Weibull	86.989	92.852
Log-normal	84.122	89.985
Log-logistic	84.414	90.276
Exponential	85.970	90.367
Placebo		
Weibull	44.977	48.309
Log-normal	48.254	51.587
Log-logistic	47.645	50.977
Exponential	48.145	50.645
Gompertz	240.269	243.602

[redacted]

AG's critique: overall survival extrapolation

- Not all parametric curves included
  - according to the company some functions 'did not converge' but AG has previously fitted these models to reconstructed IPD
- Unclear how uncertainty due to RPSFT and covariate adjustments has been represented
  - company may have treated data as if observed trial data rather than model-based estimate
- Unclear why company has chosen different curves to those presented previously
- Company's preferred curves based on statistical goodness-of-fit (AIC/BIC criteria); however Technical Support Document 14 advocates that the plausibility of the extrapolation should also be taken into account
- Clinical expert comments that other parametric functions (including the company's preferred curves) either over- or under-estimate overall survival
  - therefore company's curve selections may not be appropriate
- Clinical expert emphasised difficulty associated with selecting plausible curves from the small dataset

[redacted]

Company's new base case (with PAS)

	Total			Incremental			ICER
	Costs	QALYs	LYs	Costs	QALYs	LYs	
BSC	£[redacted]	[redacted]	[redacted]				
Vandetanib	£[redacted]	[redacted]	[redacted]	£[redacted]	[redacted]	[redacted]	£[redacted]
						Probabilistic (Assessment Group):	£[redacted]

Assumptions

- Survival estimates: RPSFTM with covariate adjustment
- Extrapolation – based on AIC/BIC:
  - Vandetanib (lognormal for OS and PFS)
  - BSC (Weibull for OS and exponential for PFS)
- Post-progression vandetanib: benefit included, cost excluded

[redacted]

NB: results generated from company's model

Company's scenarios: survival estimates

Analysis	Extrapolation	ICER per QALY
Company's base case		£XXXXX
RPSFTM with covariate adjustment	Clinician's	£XXXXX
Confounded data (no adjustment for crossover)	AIC/BIC	£XXXXX
Confounded data (no adjustment for crossover)	Clinician's	£XXXXX
Confounded data with covariate adjustment	AIC/BIC	£XXXXX
Confounded data with covariate adjustment	Clinician's	£XXXXX
RPSFTM-adjusted (no covariate adjustment)	AIC/BIC	£XXXXX
RPSFTM-adjusted (no covariate adjustment)	Clinician's	£XXXXX
Range of curve fittings for base case		£XXXXX - £XXXXX

Note: end of life criteria	**Range (all analyses and extrapolations)**
Life expectancy (normally <24 months)	XXXXXXX months
Extension to life (normally ≥3 months)	XXXXXXX months

XXXX

NB: results generated from company's model

Post-progression vandetanib

- Excluding post-progression vandetanib costs underestimates the ICER but including costs until death overestimates it
- AG prefer including costs because the overestimate may be offset by including benefits of post-progression vandetanib
- In exploratory analysis company adjusted for post-progression benefit by applying BSC mortality risk to proportion of patients who had post-progression vandetanib
- AG do not consider the approach robust because:
    - OS curve applied to progression-free patients still confounded because of continued vandetanib use, and
    - Unclear whether patients who have discontinued vandetanib will have the same mortality risk as those who never had it

Company's scenario analyses: post-progression vandetanib	ICER per QALY
Company's base case	£XXXXX
Including costs (AIC/BIC extrapolation)	£XXXXX
Including costs (Clinician's extrapolation)	£XXXXX
Including costs (range of curve fittings for base case)	£XXXXX - £XXXXX
Reducing benefit (excluding costs)	£XXXXX

NB: results generated from company's model

Comparison of base case assumptions

	Company	Assessment Group
Survival estimates	Crossover-adjusted with covariate adjustment	Crossover-adjusted with covariate adjustment
Extrapolation	AIC/BIC criteria	AIC/BIC criteria and clinical plausibility
Pre-progression vandetanib discontinuation costs	Cost incurred at linearly increasing rate in 1st year; no costs incurred thereafter	Half of pre-progression cost incurred, because the amount of drug taken by patients is unknown
Post-progression vandetanib costs	Excluded	Included, because post-progression benefits included; although ICER may be overestimated
Post-progression vandetanib benefits	Included	Included
Other features	Committee's preferred assumptions	

[redacted]

AG's base case and exploratory analyses

	Total		Incremental		ICER per QALY
	Costs	QALYs	Costs	QALYs	
Base case: assumptions in previous slide					
BSC	£XXXXX	XXXX			
Vandetanib	£XXXXX	XXXX	£XXXXX	XXXX	£XXXXX
Exploratory analysis 1: post-progression vandetanib costs halved					
BSC	£XXXXX	XXXX			
Vandetanib	£XXXXX	XXXX	£XXXXX	XXXX	£XXXXX
Exploratory analysis 2: pre-progression discontinuation costs excluded					
BSC	£XXXXX	XXXX			
Vandetanib	£XXXXX	XXXX	£XXXXX	XXXX	£XXXXX

[redacted]

NB: results generated from Assessment Group's model

End of Life considerations

Criterion	Trial population	Model results (mean)	Source
Short life expectancy, normally less than 24 months	ZETA restricted	[redacted]	Company's new analysis
	EXAM ITT	3.91 years (~47 months)	AG analysis (2017)
Extension to life, normally of at least 3 months	ZETA restricted	[redacted]	Company's new analysis
	EXAM ITT	0.59 years (~7 months)	AG analysis (2017)

In addition, the Appraisal Committee will need to be satisfied that:

- the estimates of the extension to life are sufficiently robust and can be shown or reasonably inferred from either progression-free survival or overall survival (taking account of trials in which crossover has occurred and been accounted for in the effectiveness review) and

- the assumptions used in the reference case economic modelling are plausible, objective and robust.

[redacted]

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[redacted]