Public observer slides

Lead team presentation

Cabozantinib and vandetanib for treating unresectable locally advanced or metastatic medullary thyroid cancer [ID56] – MTA

1st Appraisal Committee meeting

Cost Effectiveness

Committee D

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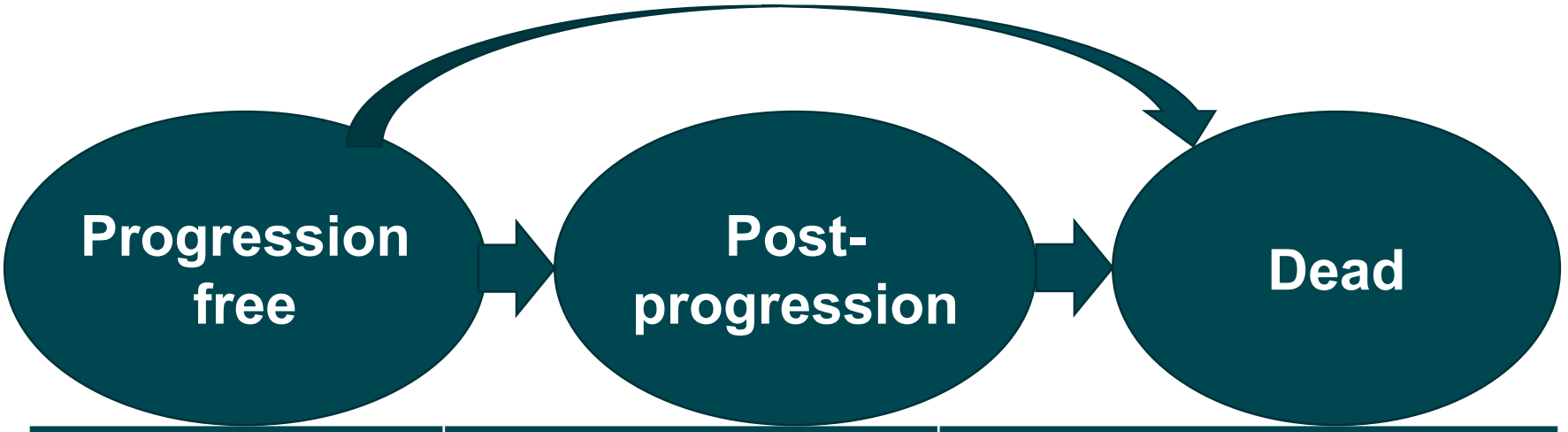
The economic models



	Sanofi's model	Assessment Group's model
Type	Partitioned survival	Partitioned survival
Cycle length	1 month	1 month
Time horizon	20 years (lifetime)	20 years (lifetime)
Population	Restricted EU label	EU label Restricted EU label
Interventions	Vandetanib	Cabozantinib Vandetanib
Comparators	Best supportive care	Best supportive care Cabozantinib Vandetanib

Sanofi's base case
Using list price, with errors corrected by AG

Technical programming errors corrected by Assessment Group related to:

- Proportion of patients discontinuing vandetanib before progression (company later corrected this in their submission)
- Duration over which QALY losses from adverse events applied (company later corrected this in their submission)

	Total		Incremental		ICER
	Costs	QALYs	Costs	QALYs	
Probabilistic					
Best supportive care	£138,915	2.19			
Vandetanib	£181,130	3.53	£42,215	1.34	**£31,546**
Deterministic					
Best supportive care	£132,292	2.13			
Vandetanib	£175,316	3.49	£43,024	1.36	**£31,731**

AG's critique of Sanofi's model (1)

1. Relevance of restricted EU label population
   - In clinical practice vandetanib used in patients with symptomatic and progressive disease irrespective of CEA/CTN biomarker levels
   - Biomarkers used for monitoring, rather than informing treatment decisions
2. Not adjusting for continued vandetanib use/crossover post-progression
   - Survival data confounded because of treatment crossover
   - Use of vandetanib post-progression does not reflect usual clinical practice
   - Attempts made by Sanofi to adjust for crossover reported as unsuccessful
3. Likely overestimation of costs of vandetanib use post-progression
   - Post-progression vandetanib assumed to continue until death
   - Unlikely in reality – overestimates costs in both arms
4. Questionable implementation of vandetanib discontinuation parameter
   - Applied as fixed proportion of patients in pre-progression, resulting in vandetanib costs being less than post-progression in BSC arm
   - Lacks face validity (**significant impact on ICER when corrected**)

AG's critique of Sanofi's model (2)
Survival modelling

5. Robustness of covariate-adjusted survival modelling to reflect restricted EU label population
   - Parametric functions fitted to ZETA ITT population for PFS and safety population for OS with covariate adjustment to reflect restricted EU population (symptomatic, progressive disease with CTN/CEA doubling time ≤24 months). **More appropriate to fit parametric functions directly to population of interest.**
   - **Sanofi's interpretation of predicted and observed survival comparison is incorrect**. 2 different populations are being compared:
     - Observed survival: Kaplan-Meier ZETA ITT/safety population with CTN/CEA doubling time ≤24 months (not symptomatic or progressive)
     - Predicted survival: Parametric function applied with covariate adjustment to reflect restricted EU label population (symptomatic, progressive disease with CTN/CEA doubling time ≤24 months)

Sanofi's survival modelling

Modelled OS compared with observed – ITT & CEA/CTN population

[redacted]

Observed Kaplan Meier data
ZETA *ITT/safety population with CEA/CTN doubling time ≤24 months*

Modelled survival (Weibull)
Parametric function applied with covariate adjustment for restricted EU population (progressive, symptomatic, CEA/CTN doubling time ≤24 months)

Sanofi's survival modelling – AG's critique

Modelled OS compared with observed – restricted EU population

[redacted]

Observed Kaplan Meier data
ZETA *restricted EU label population*

Modelled survival (Weibull)
Parametric function applied with covariate adjustment for restricted EU population (progressive, symptomatic, CEA/CTN doubling time ≤24 months)

Weibull no longer a good fit

AG's critique of Sanofi's model (3)

6. Technical programming errors
   - Model not adjusted for logical inconsistencies
   - Proportion of patients discontinuing vandetanib pre-progression
   - Duration over which QALY losses from adverse events applied
7. Concerns regarding health utility parameters
   - FACT-G mapped to EQ-5D, but trial didn't use a preference-based measure
   - Beusterien study related to melanoma, so relevance to MTC unclear
   - More appropriate to use Fordham study because relates to thyroid cancer and health utilities valued using a preference-based measure
8. Limited exploration of uncertainty around survivor functions in Deterministic Sensitivity Analysis
9. Concerns regarding costings
   - BSC post-progression costs overestimated (**significant impact on ICER when corrected**)
   - Vandetanib monitoring costs underestimated
   - Adverse event costs overestimated

Assessment Group's model
Analyses presented

#	Comparison	Comment
1	Pairwise **Cabozantinib vs BSC**	• Does not include all treatment options
2	Pairwise **Vandetanib (EU label) vs BSC**	• Does not include all treatment options • Confounded by crossover
3	**Incremental** PFS: Vandetanib (EU label) treatment effect applied to EXAM placebo arm OS: Vandetanib (EU label) assumed equivalent to cabozantinb	• Not confounded
4	**Incremental** Vandetanib (EU label) PFS, OS assumed equivalent to cabozantinib	• Not confounded
5	Pairwise **vandetanib (restricted EU label) vs BSC**	• Does not include all treatment options • Confounded by crossover

Comparison between models

	Sanofi's model	Assessment Group's model
Comparisons	Vandetanib vs BSC	Cabozantinib vs BSC Vandetanib vs BSC Full incremental analysis; all options
Trial evidence for OS and PFS outcomes	ZETA ITT/safety population	EXAM ITT ZETA EU label ZETA Restricted EU label
Survival modelling	Covariate-adjusted survivor functions fitted to ITT/safety dataset	Survivor functions fitted directly to data for relevant populations
Vandetanib discontinuation	Applied in full only to pre-progression vandetanib group, as fixed proportion of patients incurring no vandetanib costs	Half of total value applied to all patients receiving vandetanib in progression-free and post-progression states (where applicable)
Modelled costs and outcomes	Includes treatment switching and post-progression vandetanib use observed in ZETA	

Comparison between models
Health related quality of life, resource use and costs

	Sanofi's model	Assessment Group's model
Health state utilities		
Pre-progression	Mapped from ZETA FACT-G results using Dobrez **Value: 0.84**	Obtained from Fordham **Value: 0.80**
Post-progression	Decrement applied based on Beusterien **Value: 0.64**	Obtained from Fordham **Value: 0.50**
Adverse events	Decrement applied based on Beusterien **Value: -0.11**	Decrement applied based on Beusterien **Value: -0.11**
Resource use and costs		
Pre-progression and post-progression	BSC: many outpatient appts. Vandetanib: ECGs, biochemistry Adverse events: inpatient treatment	BSC: less outpatient appts. Vandetanib: add. outpatient appts. Adverse events: outpatient treatment

Assessment Group's model results (list price)
Analysis 1: pairwise cabozantinib vs BSC

	Life years gained	Total		Incremental		Probabilistic ICER
		Costs	QALYs	Costs	QALYs	
Best supportive care	3.91	£15,793	1.79			
Cabozantinib	4.49	£88,527	2.28	£72,734	0.48	**£150,874**
Log logistic models fitted independently to both arms for PFS and OS						

Deterministic sensitivity analysis

- ICER remains >£135k per QALY gained across all scenarios

- Scenarios impacting ICER significantly (all ICERs remain very high):
  - choice of survivor functions
  - excluding dose reductions

- Survival functions chosen by AG represent favourable scenario

Assessment Group's model results (list price)
Analysis 2: pairwise vandetanib (EU label) vs BSC

	Life years gained	Total		Incremental		Probabilistic ICER
		Costs	QALYs	Costs	QALYs	
Best supportive care	7.58	£175,932	3.79			
Vandetanib	7.32	£255,677	4.02	£79,745	0.23	**£352,508**

Log logistic models fitted independently to both arms for PFS and OS

Deterministic sensitivity analysis

- ICER remains >£123k per QALY gained across all scenarios
- Scenarios impacting ICER significantly (all ICERs remain very high):
  - choice of survivor functions
  - choice of utility values
  - assuming no vandetanib discontinuation
  - excluding post-progression vandetanib costs
- Survival functions chosen by AG represent neither most nor least favourable scenario

Assessment Group's model results (list price)

Analysis 3: incremental (vandetanib PFS treatment effect applied to EXAM; OS assumed equivalent)

	Life years gained	Total		Incremental		Probabilistic ICER
		Costs	QALYs	Costs	QALYs	
Best supportive care	3.91	£15,793	1.79			
Vandetanib	4.49	£67,968	2.17	£52,175	0.38	**£138,405**
Cabozantinib	4.49	£88,527	2.28	£20,559	0.11	**£195,593**

Single parametric model with covariate for treatment arm considered for ZETA EU label to obtain vandetanib treatment effect compared with placebo, which was then applied to EXAM placebo arm for PFS; log logistic model for PFS and OS

Deterministic sensitivity analysis

- ICER remains >£85k per QALY gained for vandetanib; >£148k for cabozantinb
- Scenarios impacting ICER significantly (all ICERs remain very high):
  - choice of survivor function
  - choice of utility values
  - assuming no vandetanib discontinuation
- Survival functions chosen by AG represent neither most nor least favourable

Assessment Group's model results (list price)
Analysis 4: incremental (PFS & OS assumed equivalent)

	Life years gained	Total		Incremental		Probabilistic ICER
		Costs	QALYs	Costs	QALYs	
Best supportive care	3.91	£15,793	1.79			
Vandetanib	4.49	£86,276	2.28	£70,482	0.49	**£144,841**
Cabozantinib	4.49	£88,527	2.28	-	-	**Dominated**
Log logistic models fitted independently to both arms for PFS and OS						

Deterministic sensitivity analysis

- Cabozantinb remains dominated across all scenarios except where no vandetanib discontinuation
- Vandetanib ICER remains >£130k across all scenarios
- Scenarios impacting ICER significantly (all ICERs remain very high):
  - choice of survivor function
  - assuming no vandetanib discontinuation
- Survival functions chosen by AG close to most favourable for vandetanib

Assessment Group's model results (list price)
Analysis 5: pairwise vandetanib (restricted EU label) vs BSC

Represents Sanofi's base case analysis but with:

- Survivor models fitted directly to relevant observed data (see critique point 5)
- Different utilities, costs, discontinuation application (see critique points 4, 7, 9)

	Life years gained	Total		Incremental		Probabilistic ICER
		Costs	QALYs	Costs	QALYs	
Best supportive care	3.34	£96,759	1.83			
Vandetanib	6.50	£204,539	3.45	£107,780	1.61	**£66,779**

Individual log normal models for PFS; individual Gompertz models for OS

Deterministic sensitivity analysis

- ICER remains >£51k per QALY gained across all scenarios
- Scenarios impacting ICER significantly (all ICERs remain very high):
  - choice of survivor function
  - choice of utility values
  - excluding post-progression vandetanib costs
  - assuming no vandetanib discontinuation
- Survival curves used by AG represent neither most nor least favourable scenario

End of life

Criterion	Trial populations	Trial results (median)	Assessment Group's model results (mean)
Short life expectancy, normally less than 24 months	EXAM ITT	21.1 months	3.91 years (~47 months)
	ZETA EU label	[redacted]	7.58 years (~91 months)
	ZETA restricted EU label	[redacted]	3.34 years (~40 months)
Extension to life, normally of at least 3 months	EXAM ITT	5.5 months	0.59 years (~7 months)
	ZETA EU label	[redacted]	-0.27 years (~-3 months)
	ZETA restricted EU label	[redacted]	3.16 years (~38 months)
Note: ZETA survival data confounded so true survival duration unknown			

Innovation and equalities

Innovation

- Sanofi (vandetanib):
  - First systemic therapy for medullary thyroid cancer to:
    - Demonstrate significant clinical benefit
    - Gain marketing authorisation
    - Address unmet need
  - Manageable adverse event profile
  - First TKI to receive marketing authorisation for treatment in children

Equalities

- Sanofi: Vandetanib and cabozantinib currently funded via the CDF however the 2 drugs are not interchangeable
  - Removal of vandetanib would create inequity amongst the MTC patient population, (patients unsuitable for cabozantinib would not have a systemic treatment option)

Assessment Group report consultation
Response from companies (1)

Ipsen

- Broadly in agreement with conclusions reached; no further comments

Sanofi

- MTC is ultra-orphan disease; usual cost-effectiveness thresholds not reasonable
- Restricted EU label population represents those currently treated with vandetanib
  - Company accept that CTN/CEA doubling times not used for decision to start treatment, but may be useful in identifying optimal time to start treatment
  - SmPC notes “in view of the associated risks, it is important to limit treatment with vandetanib to patients who are in real need for treatment”
  - Likely that many patients starting treatment in UK will have CTN/CEA doubling times ≤24 months
  - Do not propose CTN/CEA doubling times as additional eligibility criteria
- Data collection via CDF
  - Plausible that true UK patient lies between EU label and restricted EU label
  - If vandetanib remains in CDF, company commit to collecting data on clinical characteristics to reduce uncertainty about relevant population

Assessment Group report consultation
Response from companies (2)

Sanofi (continued)

- Crossover and open label vandetanib use
  - Acknowledge outcomes confounded; suggest patients may remain on treatment post-progression if progression slow/treatment response evident
- Meets end of life criteria
  - True advantage of vandetanib over BSC unknown because data confounded
  - EXAM data showed median OS in placebo arm of 21.1 months; population considered equivalent to ZETA EU label
  - National Cancer Database shows median OS <24 months in MTC patients with distant metastases
- Economic model
  - Application of discontinuation parameter: additional analysis undertaken to linearly increase proportion discontinuing to reach full amount after 1 year (considered more likely than AG approach)
  - Results of analysis not presented
- Some factual inaccuracies identified *(not presented here)*

Key cost effectiveness issues

- The most appropriate population to assess vandetanib; EU label or restricted EU label
- The most appropriate model for decision-making for vandetanib: Sanofi or Assessment Group, main differences are:
  - Modelled population from ZETA (see slide 4)
  - Survival modelling method (see slides 5-7)
  - Health utilities data source (see slides 8, 11)
  - Application of vandetanib discontinuation parameter (see slide 4)
  - Costs (see slide 8)
- The most appropriate AG analyses for decision-making; pair-wise or fully incremental
- Are the end of life criteria met?
- Innovation – any health-related benefits not captured in analyses?
- Any equalities issues?
- CDF consideration? *(to the companies)*