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

Background and Clinical Effectiveness

Committee D

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Medullary thyroid cancer (MTC)

- One of 4 types of thyroid cancer
- Accounts for <1% cancer cases in UK
- Accounts for ~3% of adult thyroid cancer cases
- Rare cancer occurring in parafollicular cells (C-cells)
- Sporadic (~75%), or genetically determined: familial, Multiple Endocrine Neoplasia (MEN) 2 or MEN3 (~25%)
- ~90 cases diagnosed in England in 2014
- Patients typically present with a lump in the neck
- ~50% patients with sporadic MTC present with stage III or IV disease
- Distant metastases present in 7-23% newly diagnosed cases
- 10-year survival for stage III disease (advanced) ~71%
- 10-year survival for stage IV disease (advanced and metastatic) ~21%

Patient perspective

- Common symptoms of MTC include rash, diarrhoea, muscle weakness, fatigue, bone pain and fractures which all impact on quality of life
- Metastatic thyroid cancer is rare and vital support services may not be available
- Preventing disease progression, management of side effects and symptom control are important outcomes for patients
- Non-progressing disease can boost psychological wellbeing and improve symptoms
- Existing treatments offer symptom relief only and clinical trials are rare
- Cabozantinib and vandetanib expected to halt disease progression, offer simpler, non-invasive oral treatment and alleviate symptoms

Clinical expert perspective

- Current treatments can be useful in controlling or improving symptoms but none are disease-modifying
- Cabozantinib and vandetanib are the only disease modifying drugs licensed in this setting
- Consistency amongst professionals that targeted therapy (cabozantinib or vandetanib) is modality of choice in patients with unresectable, advanced or metastatic disease
- Progression-free survival benefit may translate into delay in presentation of, or worsening of, symptoms, and may reduce need for other interventions (painkillers, palliative radiotherapy, surgery)
- Side effects are generally manageable

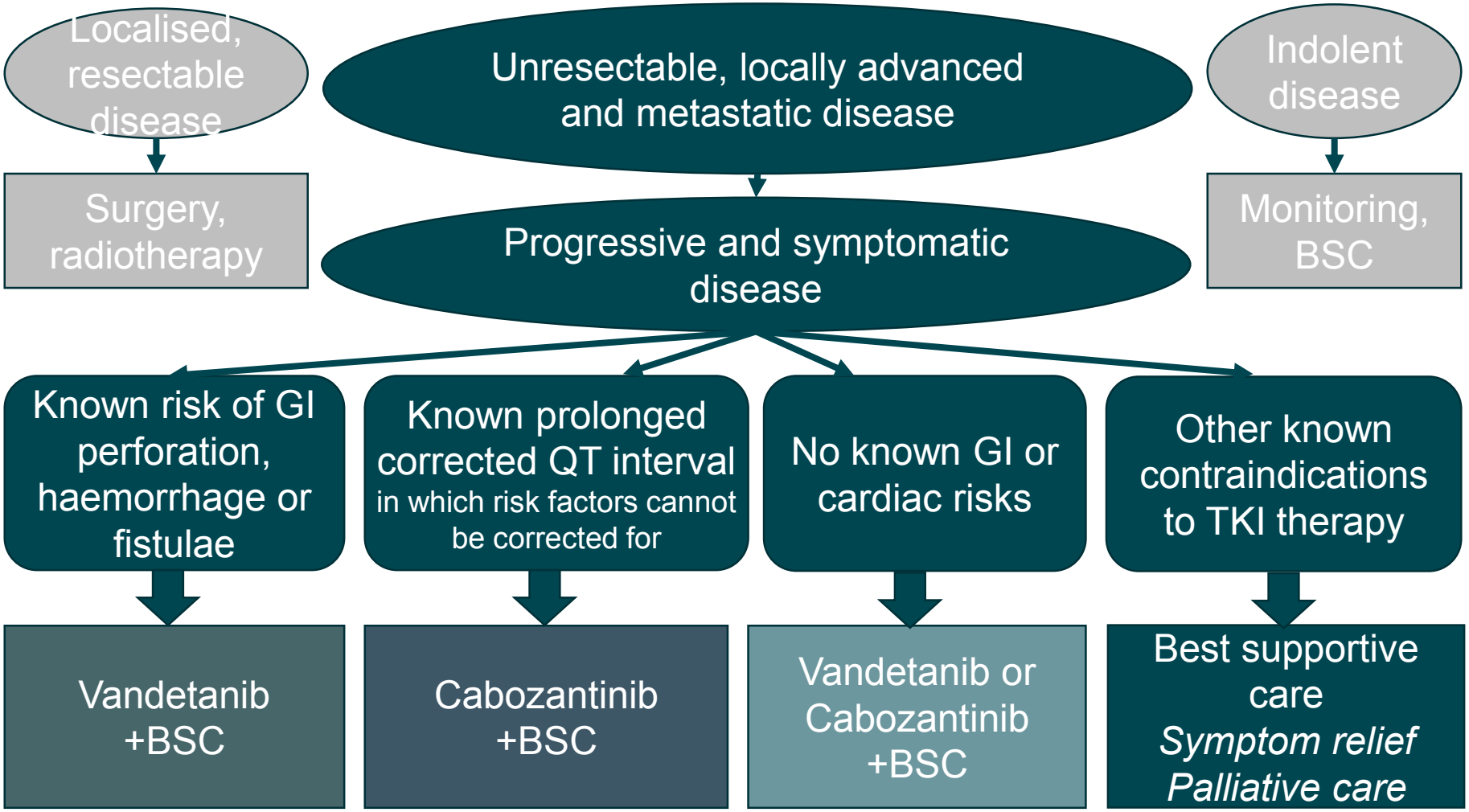
NHS England perspective

- Disease is rare; small numbers of patients starting either drug via CDF
- People generally live for a long time; disease progresses slowly
- Systemic therapy is indicated when disease becomes symptomatic
- Cabozantinib & vandetanib the only effective systemic treatment options
- Pedigree of evidence better for cabozantinib than vandetanib
- Both drugs have significant toxicities; patients require close monitoring
- Ongoing trials for both drugs comparing different doses
- RET status not for treatment decisions; more robust data needed
- Symptomatic disease main consideration when starting systemic therapy; serum marker doubling times of interest but not used routinely
- No treatment beyond progression in practice (treatment not working, quality of life can be improved by stopping side-effects of treatment)
- No data on sequential use of 2 agents; biological plausibility of lesser average benefit with 2nd drug after disease progression on 1st

Current treatment

- No NICE guidance
- Surgery most common treatment; radiation can be given afterwards but often not effective at treating MTC
- Cabozantinib and vandetanib are available on the Cancer Drugs Fund as 1st line treatments for histologically confirmed, unresectable, locally advanced/metastatic MTC:
  - if the disease is progressive and symptomatic, and
  - if no previous tyrosine kinase inhibitor (TKI) unless:
    - intolerant of previous TKI within 3 months of starting therapy, and
    - toxicity that cannot be managed by dose delay/modification, and
    - no disease progression on previous TKI
- Best Supportive Care can be used in conjunction with systemic treatment to provide symptom control

Treatment pathway
(Adapted from AG report; figure 1)



Patient may switch to other TKI if intolerant or severe adverse events experienced within 3 months

Interventions

	Cabozantinib (Cometriq, Ipsen)	Vandetanib (Caprelsa, Sanofi)
Action	Tyrosine kinase inhibitor (TKI)	Tyrosine kinase inhibitor (TKI)
Marketing authoris.	Treatment of adults with **progressive**, unresectable locally advanced or metastatic MTC	Treatment of **aggressive and symptomatic** MTC in patients with unresectable locally advanced or metastatic disease
	For patients in whom RET mutation is not known or is negative, a possible lower benefit should be taken into account before individual treatment decision.	
Admin.	Oral, capsule	Oral, tablet
Dose	140mg once daily (reduced doses: 100mg, 60mg)	300mg once daily (reduced doses: 200mg, 100mg)
Stopping	Until patient is no longer clinically benefitting from therapy or until unacceptable toxicity occurs	Until disease progression or until the benefits of treatment continuation do no longer outweigh its risk
List price	£4,800 per monthly pack Simple discount PAS agreed	£5,000 per monthly pack Simple discount PAS agreed

RET mutation

- Rearranged during Transfection (RET) a genetic mutation in MTC cells
- Associated with development of distant metastases and poor prognosis
- Present in ~95% hereditary cases (germline mutations); ~50% sporadic cases (somatic mutations)
- Germline RET-mutation testing standard practice in NHS to identify hereditary MTC
- Although BTA guidelines recommend RET mutation analysis in all confirmed cases, somatic RET mutation testing not funded in NHS
- RET-mutation testing not undertaken to inform treatment decisions
- Clinical advice suggests inadvisable to base treatment decisions on RET mutation status without full picture of significance of somatic RET status

Decision problem

Population	Adults with unresectable locally advanced or metastatic MTC
Interventions	Cabozantinib Vandetanib
Comparators	Cabozantinib and vandetanib compared with each other, and Best support care, including locally ablative treatments such as radiotherapy
Outcomes	Overall survival Progression-free survival Response rates* Adverse effects of treatment Health-related quality of life
Subgroups	If the evidence allows subgroups according to RET mutation status will be considered**

*not included in NICE scope but considered a clinically relevant outcome

**included in Ipsen submission but not considered in AG's health economic analysis

Key trials

	EXAM (cabozantinib)	ZETA (vandetanib)
Design	Phase III international, multicentre, parallel-group double-blinded RCT	
Population	Patients with unresectable, locally advanced, metastatic **and progressive** MTC **(n=330)**	Patients with unresectable, locally advanced and metastatic MTC **(n=331)**
Intervention	Cabozantinib 140mg	Vandetanib 300mg
	. . . until disease progression or intolerable toxicity	
Comparator	Placebo	Placebo
1° outcome	Progression-free survival	
2° outcomes	Overall survival, objective response rate, duration of response, biomarker changes	
Health-related quality of life	MD Anderson Symptom Inventory for thyroid conditions (MDASI-THY)	Functional Assessment of Cancer Therapy (FACT-G)
Follow-up for 1° analysis	Median 13.9 months	Median 24 months

Baseline characteristics in trials

	EXAM		ZETA	
	Cabozantinib n=219	Placebo n=111	Vandetanib n=231	Placebo n=100
Performance status (EXAM: ECOG; ZETA: WHO)				
0	56%	51%	67%	58%
1-2	43%	50%	33%	42%
RET mutation status				
Positive	46%	52%	59%	50%
Negative	14%	9%	1%	6%
Unknown	40%	39%	40%	44%
Previous TKI therapy				
Yes	20%	22%	NR	NR
No	78%	78%	NR	NR
Unknown	2%	1%	NR	NR

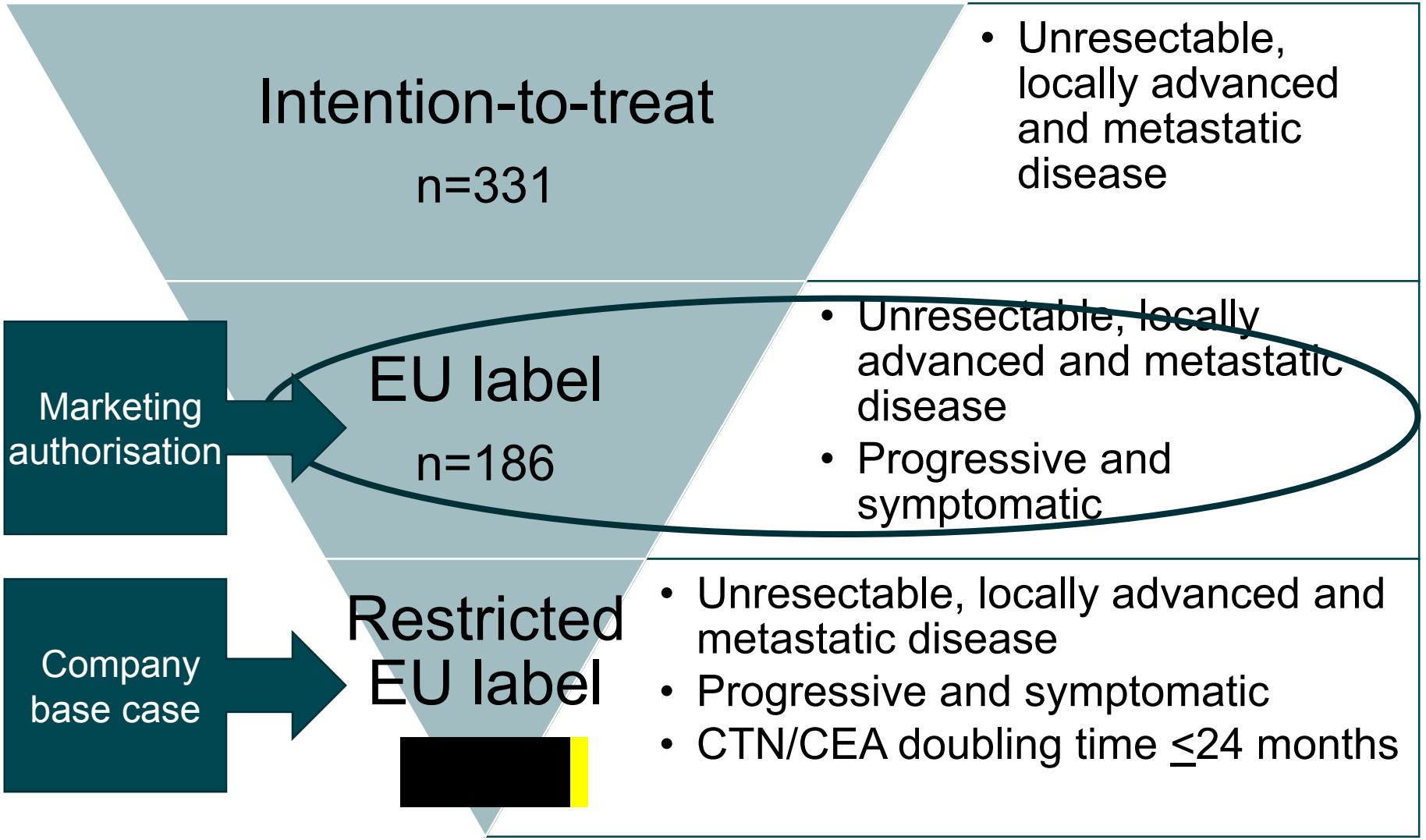
ZETA trial crossover

- Patients received open-label vandetanib at investigator-assessed progression, before confirmation by central review
- Results uncensored ➡ Central review PFS; OS results confounded (overestimate of placebo arm)
- OS data likely to show impact of treatment with immediate vs delayed vandetanib rather than true comparison of vandetanib vs placebo
- Company tried to adjust for crossover but not successful; AG unable to because no access to patient level data

Total proportion of patients receiving open-label vandetanib post-progression in intention-to-treat population and subgroups:

Vandetanib			Placebo		
ITT	EU label	Restricted	ITT	EU label	Restricted
47.2%	43.8%	[redacted]	79.0%	79.7%	[redacted]

ZETA subgroups



Restricted EU label subgroup

Company's rationale:

- 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 symptomatic progression
- 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

Trial results summary
Progression-free survival

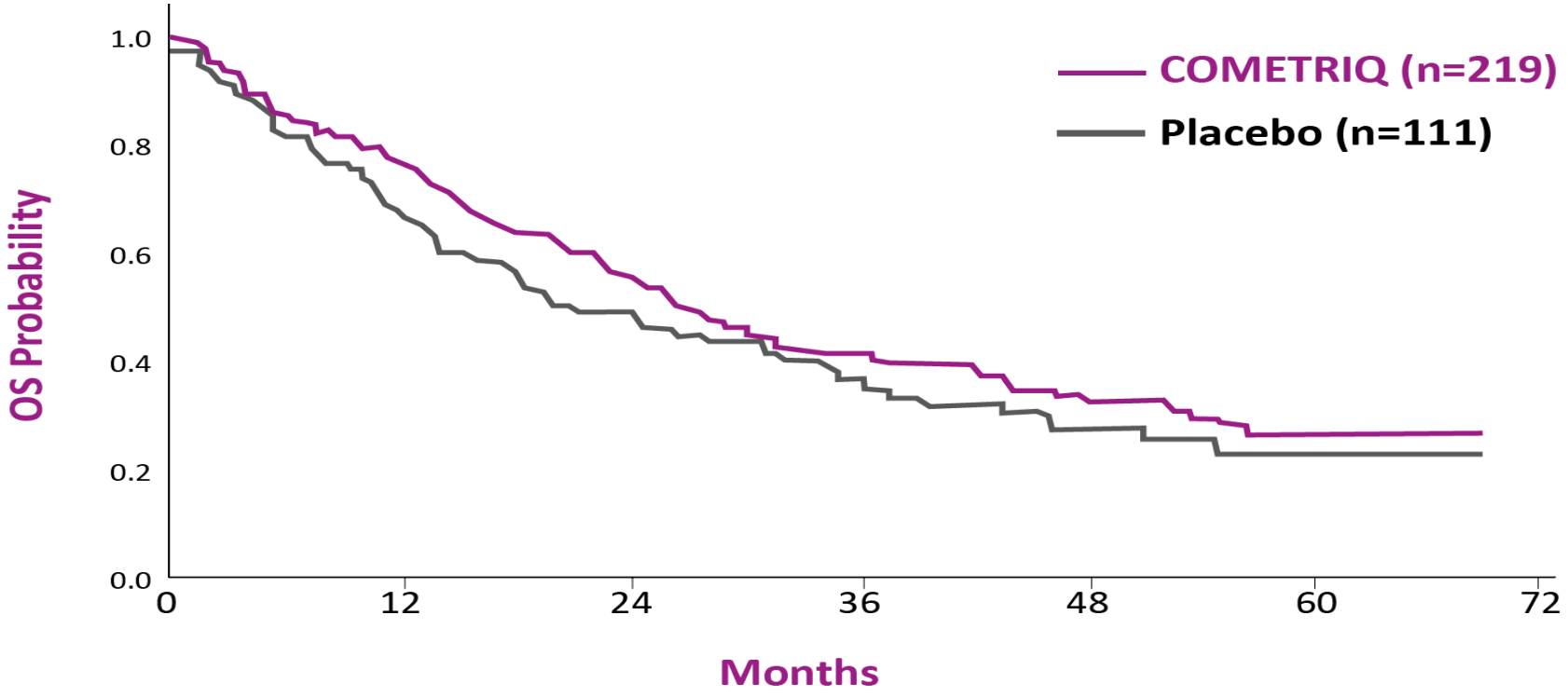
EXAM		ZETA EU label		ZETA restricted EU label	
Median follow-up 14 mths		Median follow-up 24 mths			
Cabozantinib n=219	Placebo n=111	Vandetanib n=126	Placebo n=60	Vandetanib n=[redacted]	Placebo n=[redacted]
Central review					
11.2 mths	4.0 mths	28.0 mths	16.4 mths	[redacted]	[redacted]
HR 0.28 95% 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			

Trial results summary
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					

EXAM overall survival

Kaplan-Meier (Ipsen submission; figure E)



	COMETRIQ	Placebo
Median OS	26.6 months	21.1 months
HR* (95% CI)	0.85 (0.64, 1.12)	
P-value	0.2409	

*Stratified hazard ratios shown

ZETA overall survival

EU label subgroup Kaplan-Meier (Sanofi appendix 6; figure 2)

ZETA overall survival

Restricted EU label subgroup Kaplan-Meier (Sanofi submission; figure 7)

AG's network meta-analysis

- No direct head-to-head evidence for cabozantinib vs. vandetanib
- Indirect comparison published (Rinciog et al, 2014), but inappropriate because of differences between EXAM and ZETA trial populations
- Comparison with EU label subgroup of ZETA trial appropriate
- For progression-free survival outcomes only because OS confounded by treatment-switching in both treatment groups
- Random effects model used because of potential heterogeneity in trial populations, to ensure uncertainty reflected in results
- Cabozantinib and vandetanib shown to be broadly similar
- Magnitude of treatment effect favours cabozantinib (when central-read PFS used) but difference not statistically significant
- NMA limited by sparsity of the network and use of hazard ratios which ignore any treatment by time interaction
- Results not used in economic model

Adverse effects, dose modifications

	EXAM		ZETA (ITT)	
	Cabozantinib n=214	Placebo n=109	Vandetanib n=231	Placebo n=99
Any adverse event	100%	95.4%	99.6%	90.9%
Any grade 3 or 4 adverse event	77.6%	33.9%	55.4%	24.2%
Any serious adverse event	53.3%	23.9%	30.7%	13.1%
Any adverse event leading to drug dose modification	87.4%	22.0%	49.4%	15.2%
Any adverse event leading to treatment discontinuation	23.4%	9.2%	12.1%	3.0%
At least 1 first level dose reduction	82.2%	11.0%	N/A	N/A
Dose reduction or interruption	N/A	N/A	49.4%	15.2%

Assessment Group comment: patients have substantial disease burden, demonstrated by adverse events and comorbidities in placebo arm and baseline data for EXAM and ZETA trial patients

Clinical effectiveness summary
Assessment Group's critique

- EXAM low risk of bias; ZETA moderate to high risk of bias because of crossover design leading to confounding of outcomes data
- Different populations in 2 trials (EXAM progressive; ZETA less severe)
- EXAM trial and ZETA EU label subgroup populations comparable, and reflect patients likely to present in clinical practice in England
- Biomarkers (CTN/CEA) unlikely to be relevant when other criteria indicate progressive disease (e.g. RECIST, symptoms) – not used to inform decisions about starting TKI treatment
- Significant PFS benefit for both drugs, but OS benefit not stat. significant
- Treatment effects of both broadly similar, but uncertainty in NMA results
- RET mutation testing not routinely undertaken to inform treatment choices so subgroup analyses not relevant
- No difference found in quality of life measurements
- Both drugs produced frequent adverse effects; more led to dose modification for cabozantinib than vandetanib

Key clinical effectiveness issues

- What is the most appropriate ZETA population to consider the clinical effectiveness of vandetanib: the EU label or restricted EU label?
  - Is CTN/CEA doubling time an appropriate way to identify people in most need of treatment?
- Is RET mutation status an appropriate subgroup in which to consider clinical effectiveness?
- What is the impact of crossover on the ZETA trial results?
- Are the treatments continued beyond progression in clinical practice?
- Is there evidence to show whether cabozantinib or vandetanib is more clinically effective than the other?
- Could 1 drug be used after the other in practice?
  - Approximately 20% in EXAM had a previous TKI; not reported in ZETA
  - Current CDF recommendations allow switching to the other TKI if toxicity occurs with one TKI.
  - Clinical advisors to AG consider there is value in having access to both TKIs.