original reports abstract

Efficacy and Safety of Vandetanib in Progressive and Symptomatic Medullary Thyroid Cancer: Post Hoc Analysis From the ZETA Trial

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PURPOSE We conducted a post hoc analysis of the vandetanib phase III trial involving patients with advanced medullary thyroid cancer (MTC) to assess the efficacy and safety of vandetanib in patients with progressive and symptomatic MTC. The primary objective of the analysis was to determine progression-free survival (PFS) of these patients.

PATIENTS AND METHODS Eligible patients from the ZETA trial were divided into 4 disease severity subgroups: progression and symptoms, symptoms only, progression only, and no progression and no symptoms assessed at baseline. PFS, determined from objective tumor measurements performed by the local investigator, overall survival (OS), time to worsening of pain (TWP), and objective response rate (ORR) were evaluated.

RESULTS Of the 331 patients in this trial, 184 had symptomatic and progressive disease at baseline. In this subgroup, results were similar in magnitude to those observed in the overall trial for PFS (hazard ratio [HR], 0.43; 95% CI, 0.28 to 0.64; $P < .0001$), OS (HR, 1.08; 95% CI, 0.72 to 1.61; $P = .71$), and TWP (HR, 0.67; 95% CI, 0.43 to 1.04; $P = .07$), and the observed adverse events were consistent with the known safety profile of vandetanib. In this subgroup, the ORR was 37% in the treatment arm versus 2% in the placebo arm.

CONCLUSION Vandetanib demonstrated clinical benefit—specifically, increased PFS—in patients with symptomatic and progressive MTC.

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INTRODUCTION

Medullary thyroid cancer (MTC) is a rare neuroendocrine malignancy that derives from parafollicular cells (C cells) of the thyroid gland that secrete the polypeptide hormone calcitonin.[1,2] It accounts for almost 5% of all thyroid cancers[1,3] and occurs in either a hereditary (25%) or a sporadic (75%) pattern.[4,5] The 10-year overall survival rate in unselected patients with MTC is approximately 75%, but it decreases to ≤ 40% in patients with locally advanced or metastatic disease.[6]

Hereditary MTC is a component of multiple endocrine neoplasia (MEN) types 2A (including familial MTC) and 2B.[1,5] Virtually all patients with MEN2A or MEN2B have germline mutations in the *RET* proto-oncogene, and a high percentage of sporadic MTCs have somatic *RET* mutations at diagnosis.[2,7-10] Therefore, targeting patients with *RET*-positive status and MTC has a therapeutic potential.[7,8] The only other driver point-mutations found in MTC are *RAS* mutations.[11,12] Vascular endothelial growth factor receptor (VEGFR) and epidermal growth factor receptor (EGFR) also contribute to growth and invasiveness of MTC.[13] Cytotoxic chemotherapies have yielded low response rates, so tyrosine kinase inhibitors (TKIs) have emerged as systemic first-line therapy for patients with unresectable, locally advanced, or metastatic thyroid cancer.[1] Vandetanib is a once-daily, oral TKI that acts by targeting several cell receptors in combination, including those involved in RET, VEGFR2, and EGFR signaling. Vandetanib was approved in the United States for the treatment of symptomatic or progressive MTC in patients with unresectable locally advanced or metastatic disease. In Japan, vandetanib was approved for unresectable MTC on the basis of findings of the phase III ZETA (Zactima Efficacy in Thyroid Cancer Assessment) trial.[14,15] In the European Union, approval was granted for treatment of aggressive and symptomatic advanced (unresectable locally advanced or metastatic disease) MTC. Patients with progressive and symptomatic advanced MTC represent a subset of the ZETA trial cohort with a strong medical need, and it is of interest to explore the clinical benefits of vandetanib treatment in patients with differing levels of disease.

ASSOCIATED CONTENT

Appendix

Protocol

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

Is vandetanib also effective and safe in patients with progressive and symptomatic medullary thyroid cancer (MTC; ZETA trial; ClinicalTrials.gov identifier: NCT00410761), as analyzed in accordance with progression-free survival (PFS)?

Knowledge Generated

Of the 331 patients in the original ZETA trial, 184 (55.6%) had symptomatic and progressive disease at baseline. In this subgroup, results were similar in magnitude to those observed in the overall trial for PFS (hazard ratio [HR], 0.43; 95% CI, 0.28 to 0.64; $P < .0001$), overall survival (HR, 1.08; 95% CI, 0.72 to 1.61; $P = .71$), and time to worsening of pain (HR, 0.67; 95% CI, 0.43 to 1.04; $P = .07$), and the observed adverse events were consistent with the known safety profile of vandetanib.

Relevance

In conclusion, this post hoc analysis of the vandetanib pivotal trial in MTC demonstrates clinical benefit in patients with symptomatic and progressive disease.

Here, we report the results of a post hoc analysis of the ZETA trial (ClinicalTrials.gov identifier: NCT00410761) assessing the efficacy and safety of vandetanib in 4 disease severity subgroups of patients with MTC. The primary objective of the analysis was to determine the efficacy of vandetanib for the cohort of patients with aggressive (ie, with documented progression) and symptomatic disease that formed the basis for the patients defined in the vandetanib label in the European Union.

PATIENTS AND METHODS

Study Design

This post hoc analysis assessed subgroups of patients from the ZETA trial, a randomized, placebo-controlled, double-blind, phase III clinical study (ClinicalTrials.gov identifier: NCT00410761), details of which have been reported previously.[16] Patients eligible for the ZETA trial were adults who had measurable, unresectable, locally advanced or metastatic, hereditary or sporadic MTC. Submission of a tumor sample was required except for patients with hereditary MTC who had a documented germline *RET* mutation. Other key inclusion criteria were WHO performance status of 0-2 and serum calcitonin level $\geq$ 500 pg/mL. All patients provided written informed consent. The protocol was approved by all relevant institutional ethical committees or review bodies, and the study was conducted in accordance with the Declaration of Helsinki and good clinical practice.

A total of 331 patients with unresectable locally advanced or metastatic MTC were randomly assigned in a 2:1 ratio to receive oral vandetanib at a starting dose of 300 mg/day (n = 231) or placebo (n = 100) until disease progression occurred. Upon objective disease progression, on the basis of investigator assessment, patients discontinued the study drug and were unblinded. The choice to offer patients open-label vandetanib was based on local site review. Those with post-progression status could elect to enter open-label treatment with vandetanib until a withdrawal criterion was met. In addition, patients determined by central review not to have progressive disease also had the option to be unblinded and receive open-label medication. All patients were observed for survival. The patients signed an informed consent to enter the study.

In this post hoc analysis, the eligible patients from the ZETA trial were divided into 4 disease severity subgroups: those with both progression and symptoms at baseline, those with symptoms only, those with progression only, and those with no progression and no symptoms at baseline. Progression was defined as documented disease progression within 12 months before enrollment according to the recorded recent progression date collected during the screening/baseline visit. Symptoms were defined as at least 1 of the following symptoms at baseline: average Brief Pain Inventory (BPI) questionnaire pain score $>$ 4, opioid use $\geq$ 10 mg/day, diarrhea, flushing, fatigue, pain, nausea, dysphagia, dysphonia, respiratory symptoms, and weight loss.

Outcomes

The primary outcome of interest for this post hoc analysis was progression-free survival (PFS), which was determined from objective tumor measurements performed at screening and then every 12 weeks until progression or withdrawal of consent by the local investigator occurred. PFS was defined from the date of random assignment to the date of objective progression or death (by any cause in the absence of progression). Patients who had not experienced progression or died at the time of statistical analysis were censored at the time of their latest objective tumor assessment. This included patients who were lost to follow-up or had withdrawn consent. For patients lost to follow-up without having experienced progression, death within an additional 12 weeks was considered an event; otherwise the patient was censored for PFS at the time of their last tumor assessment date.

Secondary outcomes included objective response rate (ORR), overall survival (OS), time to worsening of pain (TWP), and assessment of adverse events (AEs) with a frequency of ≥ 10% in any treatment group. ORR was based on site-read RECIST assessments, excluding any assessments of scans performed while on open-label treatment. OS was calculated from the date of random assignment to the date of death, with patients observed every 12 weeks until withdrawal of consent or death. Patients who had not died at the time of analysis were censored at the time they were last known to be alive. TWP was a composite endpoint determined from patient-reported opioid analgesic use and responses to the BPI questionnaire administered at baseline and every week thereafter. Worsening of pain was defined as an adverse change of ≥ 2 points from baseline on the BPI worst pain scale (0-10 points) or an increase from baseline in opioid analgesic use of ≥ 10 mg/day morphine sulfate equivalent. TWP was the interval from the date of random assignment to the date of worsening of pain (with no evidence of improvement within 14 days). If worsening of pain was not observed at the time of analysis, TWP was censored at the last evaluable assessment of pain or opioid usage. Outcomes were assessed in all 4 baseline disease severity subgroups.

Assessments

Tumor assessments were categorized by the local investigators by using RECIST v1.0, as described previously. Upon objective determination of disease progression by the local investigator, all imaging scans were assessed for progression and response by an independent central read. Patients continued to be observed for survival thereafter regardless of whether they continued post-progression treatment, unless they withdrew consent.

For the primary ZETA analysis, data from the central read, which was not conducted in real time, were used in preference to data from the local site review. However, the choice to offer the patients open-label vandetanib was based on local site review. This resulted in patients not progressive by central review receiving open-label medication. To exclude this source of potential bias and to avoid it in the current post hoc analysis, local investigator-assessed progression was used to determine PFS. Additional details can be found in the Discussion.

Statistical Considerations

Kaplan-Meier survival curves for PFS, OS, and TWP were compared for the vandetanib and placebo arms in each of the 4 disease severity subgroups using log-rank tests. No statistical comparisons were made between disease severity subgroups for treatment outcomes. Hazard ratios (HRs) for PFS, OS, and TWP in the subgroups were estimated using Cox proportional hazards regression. The ORR within each disease severity subgroup was summarized as the number and percentage of patients experiencing objective response. For the safety analysis, we reported the proportion of patients in each treatment arm who required dose reductions and summarized common AEs within each of the 4 severity subgroups, defined as events with a frequency of ≥ 10% in any treatment group.

RESULTS

Patients

Overall, 331 patients were randomly assigned in a 2:1 ratio to receive vandetanib (n = 231) or placebo (n = 100; Fig 1). As of the July 31, 2009, cut-off date, 44 patients in the vandetanib arm and 58 patients in the placebo arm

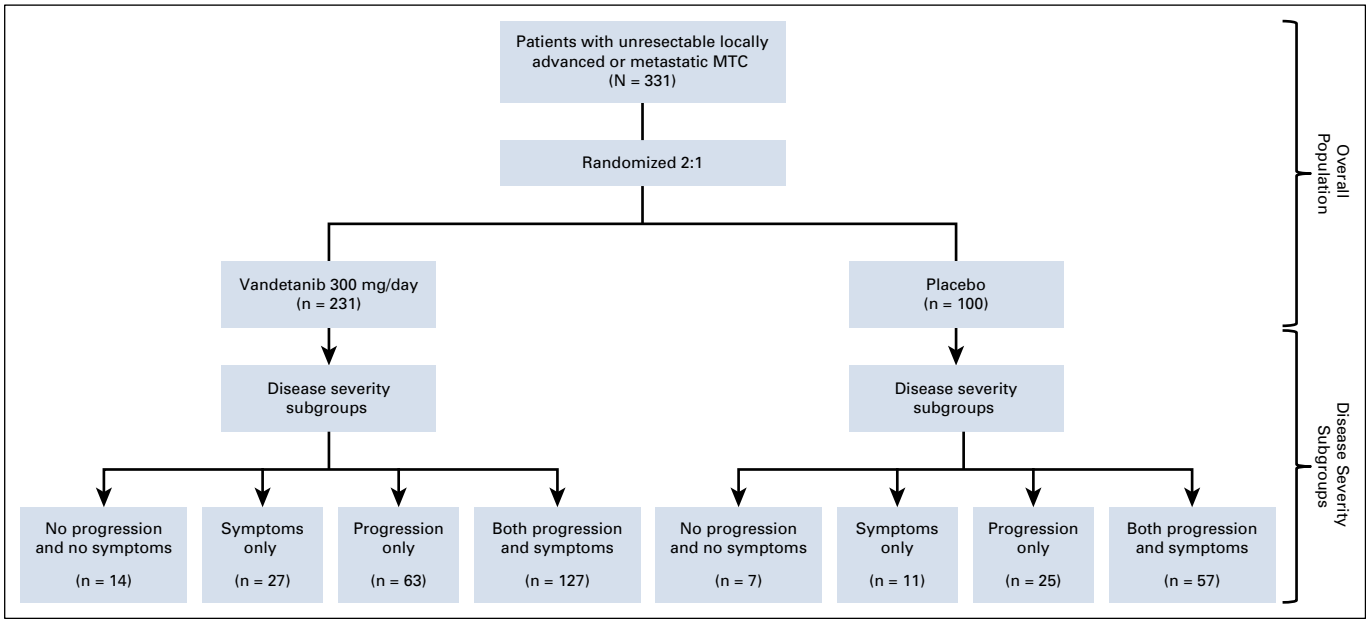

FIG 1. Patient disposition in the 4 disease severity subgroups of patients with medullary thyroid cancer (MTC) from the ZETA trial.

received post-progression, open-label treatment with vandetanib. Baseline demographic characteristics and baseline clinical characteristics of all disease severity subgroups in the vandetanib 300 mg and placebo arms are provided in Table 1 and Appendix Table A1 (online only).

PFS

As of July 31, 2009, 163 patients experienced progression during the primary analysis period according to investigator RECIST assessments: 103 in patients with both progression and symptoms at baseline, 34 in patients with progression only, 20 in patients with symptoms only, and 6 in patients with neither progression nor symptoms at baseline. In patients with both progression and symptoms at baseline, the survival curves for PFS were significantly different comparing vandetanib with placebo (Fig 2A; log-rank $P <$ .0001), with decreased risk of progression in the vandetanib arm when compared with placebo (Table 2; HR, 0.43; 95% CI, 0.28 to 0.64; $P <$ .0001). The median PFS was 21.43 months in the vandetanib group and was 8.40 months in the placebo group. Results for PFS and other outcome measures were not substantially changed with adjustment for age and sex (Appendix Table A2, online only).

Similar trends were observed in the remaining baseline disease severity subgroups, with statistically significant differences in the symptoms-only subgroup (Fig 2C; log-rank $P = .04$; Table 2; HR, 0.41; 95% CI, 0.17 to 1.00, $P = .05$) comparing vandetanib with placebo. The median PFS was 22.43 months in the vandetanib group and was 9.68 months in the placebo group.

At the time of investigator-assessed ORR, 92 events had occurred: 90 in vandetanib and 2 in placebo groups. The ORR was higher in patients treated with vandetanib than with placebo in each disease severity subgroup (Table 2). No significant associations were observed for OS when comparing vandetanib with placebo treatment assignment in the 4 baseline disease severity subgroups (Table 2). The median follow-up times per baseline disease severity subgroup were 53.7 months (range, 0.6-104.9 months) for patients with both progressive and symptomatic disease, 95.1 months (range, 2.7-104.3 months) for patients with progressive disease only, 33.7 months (range, 2.0-104.3 months) for patients with symptomatic disease only, and 75.5 months (range, 3.3-103.8 months) for patients with neither progressive nor symptomatic disease at baseline. Fifty-eight patients on random assignment to placebo entered the open-label period as of July 31, 2009. Their average total duration of exposure to placebo during the primary analysis period was 7.9 months (median, 6.1 months). The median time to progression for these patients during the open-label period was 22.2 months.

TWP

In patients with both progression and symptoms at baseline, there was no statistically significant treatment effect in TWP between the vandetanib- and placebo-treated groups (log-rank $P = .07$; Table 2; HR, 0.67; 95% CI, 0.43 to 1.04;

TABLE 1. Patient Baseline Clinical Characteristics in the 4 Disease Severity Subgroups of Patients With MTC

	Progression and Symptoms		Progression Only		Symptoms Only		No Progression and No Symptoms	
Variable	Vandetanib 300 mg (n = 127)	Placebo (n = 57)	Vandetanib 300 mg (n = 63)	Placebo (n = 25)	Vandetanib 300 mg (n = 27)	Placebo (n = 11)	Vandetanib 300 mg (n = 14)	Placebo (n = 7)
Mean (SD) age, years	53.1 (13.5)	53.6 (12.2)	46.8 (13.3)	52.6 (10.7)	51.9 (14.9)	55.4 (12.8)	44.8 (18.0)	52.0 (15.6)
Sex								
Male	79 (62.2)	38 (66.7)	36 (57.1)	8 (32.0)	14 (51.9)	7 (63.6)	5 (35.7)	3 (42.9)
Female	48 (37.8)	19 (33.3)	27 (42.9)	17 (68.0)	13 (48.1)	4 (36.4)	9 (64.3)	4 (57.1)
Prior systemic therapy for MTC								
0	82 (64.6)	29 (50.9)	40 (63.5)	20 (80.0)	12 (44.4)	4 (36.4)	7 (50.0)	5 (71.4)
≥ 1	45 (35.4)	28 (49.1)	23 (36.5)	5 (20.0)	15 (55.6)	7 (63.6)	7 (50.0)	2 (28.6)
Hereditary disease status								
Hereditary disease	13 (10.2)	2 (3.5)	8 (12.7)	1 (4.0)	4 (14.8)	2 (18.2)	3 (21.4)	0 (0.0)
Sporadic or unknown disease	114 (89.8)	55 (96.5)	55 (87.3)	24 (96.0)	23 (85.2)	9 (81.8)	11 (78.6)	7 (100.0)
RET status								
Positive	77 (60.6)	30 (52.6)	35 (55.6)	11 (44.0)	16 (59.3)	5 (45.5)	9 (64.3)	4 (57.1)
Negative	1 (0.8)	5 (8.8)	0 (0.0)	1 (4.0)	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)
Unknown	49 (38.6)	22 (38.6)	28 (44.4)	13 (52.0)	10 (37.0)	6 (54.5)	5 (35.7)	3 (42.9)

NOTE. Data presented as No. (%) unless otherwise indicated.

Abbreviations: MTC, medullary thyroid cancer; SD, standard deviation.

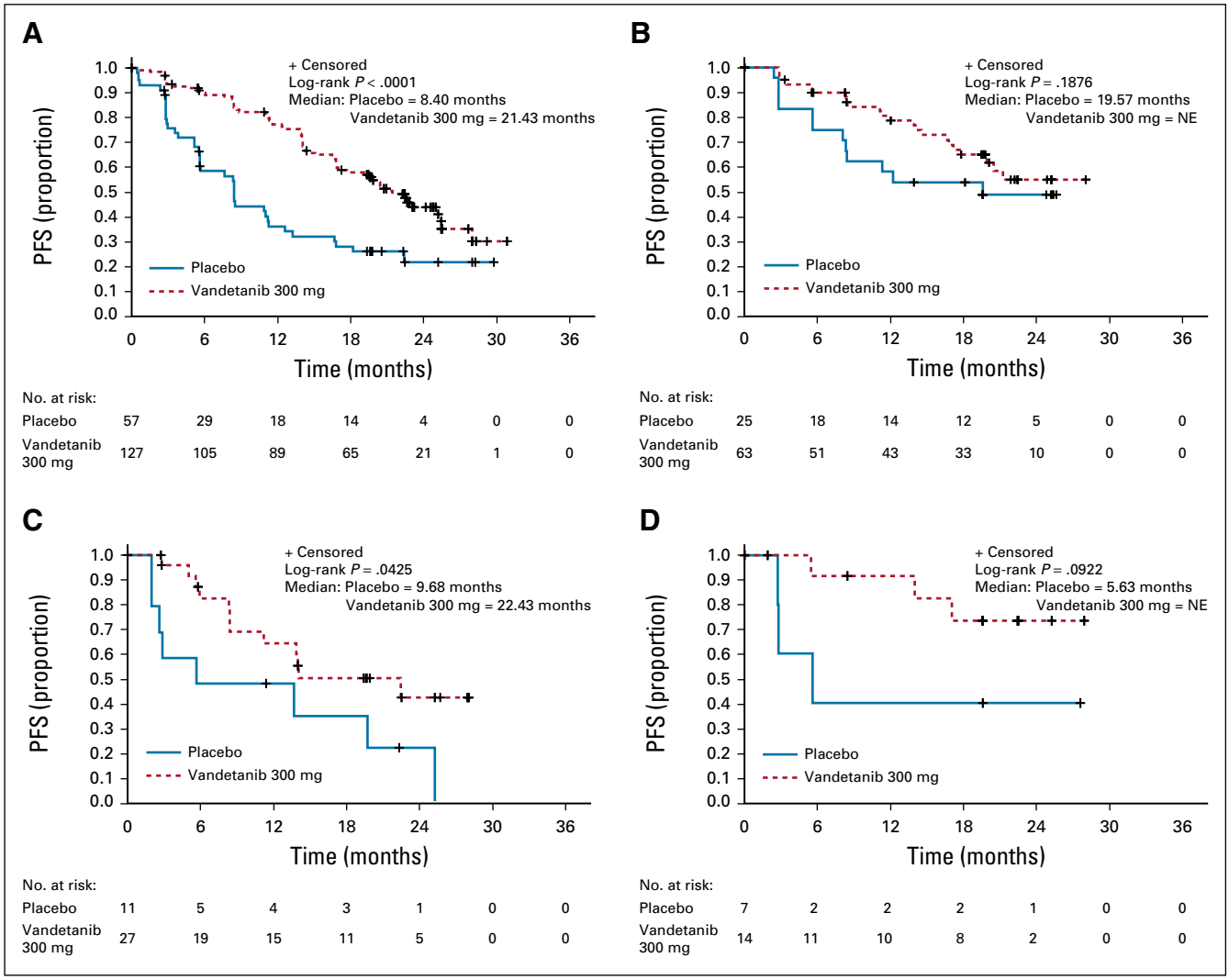

FIG 2. Kaplan-Meier curves for investigator-assessed progression-free survival (PFS) in the 4 disease severity subgroups of patients with medullary thyroid cancer. (A) Patients with both progression and symptoms, (B) progression only, (C) symptoms only, and (D) no progression and no symptoms. NE, not estimable median because of the small number of patients experiencing disease progression of medullary thyroid cancer.

$P = .07$). There was a statistically significant improvement in TWP for vandetanib compared with placebo in the symptoms-only disease severity subgroup (log-rank $P = .01$; Table 2; HR, 0.32; 95% CI, 0.13 to 0.81; $P = .02$). The median TWP was 6.30 months in patients treated with vandetanib compared with 2.57 months in patients receiving placebo in the symptoms-only subgroup. No significant treatment effects were observed in the other patient subgroups.

Safety

The median duration of treatment in the randomized phase was 20.0 months with vandetanib and was 9.2 months with placebo. The number of patients who required dose reductions was greater with vandetanib (n = 83; 35.93%) than with placebo (n = 3; 3.03%). Ninety-eight percent of patients reported at least 1 AE in the vandetanib group compared with 91.9% in the placebo group.

The types of AEs observed with vandetanib were consistent with its known safety profile and the mechanism of action of VEGFR and EGFR inhibition.[14] There were no notable ventricular arrhythmias or sudden cardiac death in patients with corrected QT interval prolongation. The AE profiles were similar among the 4 subgroups. The most frequently reported common AEs across all groups in patients treated with vandetanib were GE disorders and skin and subcutaneous tissue disorders (Table 3), which is consistent with what was reported in the primary ZETA trial.[16]

DISCUSSION

The objective of this post hoc analysis was to investigate the efficacy and safety of vandetanib in the subgroup of patients with symptomatic and progressive MTC from the ZETA trial. This subgroup was considered an appropriate representation for the EU label cohort, "aggressive and

TABLE 2. Summary of Efficacy Results in the 4 Subgroups of Patients With MTC

Cohort	Treatment	No.	No. (%) of Events	HR (95% CI)[a]	*P*
PFS					
Progression and symptoms	Vandetanib 300 mg	127	64 (50.4)	0.43 (0.28 to 0.64)	< .0001
	Placebo	57	39 (68.4)		
Progression only	Vandetanib 300 mg	63	22 (34.9)	0.63 (0.31 to 1.27)	.19
	Placebo	25	12 (48.0)		
Symptoms only	Vandetanib 300 mg	27	12 (44.4)	0.41 (0.17 to 1.00)	.05
	Placebo	11	8 (72.7)		
No progression and no symptoms	Vandetanib 300 mg	14	3 (21.4)	0.27 (0.05 to 1.37)	.12
	Placebo	7	3 (42.9)		
Overall survival[b]					
Progression and symptoms	Vandetanib 300 mg	127	77 (60.6)	1.08 (0.72 to 1.61)	.71
	Placebo	57	35 (61.4)		
Progression only	Vandetanib 300 mg	63	17 (27.0)	0.77 (0.34 to 1.74)	.54
	Placebo	25	9 (36.0)		
Symptoms only	Vandetanib 300 mg	27	17 (63.0)	1.12 (0.44 to 2.84)	.82
	Placebo	11	6 (54.5)		
No progression and no symptoms	Vandetanib 300 mg	14	5 (35.7)	0.81 (0.16 to 4.21)	.80
	Placebo	7	2 (28.6)		
Time to worsening of pain					
Progression and symptoms	Vandetanib 300 mg	127	61 (48.0)	0.67 (0.43 to 1.04)	.07
	Placebo	57	31 (54.4)		
Progression only	Vandetanib 300 mg	63	31 (49.2)	0.66 (0.35 to 1.24)	.19
	Placebo	25	14 (56.0)		
Symptoms only	Vandetanib 300 mg	27	11 (40.7)	0.32 (0.13 to 0.81)	.02
	Placebo	11	8 (72.7)		
No progression and no symptoms	Vandetanib 300 mg	14	11 (78.6)	1.22 (0.37 to 4.07)	.74
	Placebo	7	4 (57.1)		
Objective response rate					
Progression and symptoms	Vandetanib 300 mg	127	47 (37.0)	—	< .0001*
	Placebo	57	1 (1.8)		
Progression only	Vandetanib 300 mg	63	30 (47.6)	—	.0001*
	Placebo	25	1 (4.0)		
Symptoms only	Vandetanib 300 mg	27	8 (29.6)	—	.08**
	Placebo	11	0		
No progression and no symptoms	Vandetanib 300 mg	14	5 (35.7)	—	.12**
	Placebo	7	0		

Abbreviations: HR, hazard ratio; MTC, medullary thyroid cancer; PFS, progression-free survival.

[a]The reference group for HR is the placebo arm within each subgroup.

[b]Overall survival included open-label data.

*P value derived from χ^2 test.

**P value derived from Fisher's exact test.

symptomatic MTC in patients with unresectable locally advanced or metastatic disease."

Vandetanib showed statistically significant prolonged median PFS in both the progression and symptoms subgroup and the symptoms-only subgroup, compared with placebo, but not in the progression-only and no symptoms/no progression subgroups. It should be noted that the number of patients in the symptoms only and the no progression/no

TABLE 3. Common AEs With a Frequency of > 10% Overall in Either Treatment Group

	No. (%)							
	Progression and Symptoms		Progression Only		Symptoms Only[a]		No Progression and No Symptoms[a]	
Adverse Event	Vandetanib 300 mg (n = 127)	Placebo (n = 56)	Vandetanib 300 mg (n = 63)	Placebo (n = 25)	Vandetanib 300 mg (n = 27)	Placebo (n = 11)	Vandetanib 300 mg (n = 14)	Placebo (n = 7)
GI disorders	90 (70.9)	22 (39.3)	47 (74.6)	12 (48.0)	21 (77.8)	5 (45.5)	9 (64.3)	3 (42.9)
Abdominal pain	18 (14.2)	4 (7.1)	7 (11.1)	1 (4.0)	6 (22.2)	0 (0.0)	2 (14.3)	0 (0.0)
Diarrhea	67 (52.8)	11 (19.6)	42 (66.7)	8 (32.0)	13 (48.1)	4 (36.4)	8 (57.1)	3 (42.9)
Dyspepsia	16 (12.6)	2 (3.6)	7 (11.1)	2 (8.0)	2 (7.4)	0 (0.0)	0 (0.0)	0 (0.0)
Nausea	45 (35.4)	8 (14.3)	17 (27.0)	5 (20.0)	11 (40.7)	2 (18.2)	4 (28.6)	1 (14.3)
Vomiting	19 (15.0)	5 (8.9)	9 (14.3)	0 (0.0)	4 (14.8)	2 (18.2)	2 (14.3)	0 (0.0)
General disorders and administration-site conditions	56 (44.1)	19 (33.9)	13 (20.6)	9 (36.0)	9 (33.3)	4 (36.4)	4 (28.6)	0 (0.0)
Asthenia	22 (17.3)	6 (10.7)	6 (9.5)	3 (12.0)	4 (14.8)	2 (18.2)	2 (14.3)	0 (0.0)
Fatigue	37 (29.1)	14 (25.0)	10 (15.9)	7 (28.0)	6 (22.2)	2 (18.2)	2 (14.3)	0 (0.0)
Infections and infestations	12 (9.4)	5 (8.9)	5 (7.9)	2 (8.0)	6 (22.2)	1 (9.1)	3 (21.4)	1 (14.3)
Nasopharyngitis	12 (9.4)	5 (8.9)	5 (7.9)	2 (8.0)	6 (22.2)	1 (9.1)	3 (21.4)	1 (14.3)
Investigations	38 (29.9)	6 (10.7)	9 (14.3)	4 (16.0)	7 (25.9)	3 (27.3)	1 (7.1)	0 (0.0)
Electrocardiogram QT prolonged	20 (15.7)	0 (0.0)	6 (9.5)	0 (0.0)	7 (25.9)	1 (9.1)	0 (0.0)	0 (0.0)
Weight decreased	20 (15.7)	6 (10.7)	3 (4.8)	1 (4.0)	0 (0.0)	2 (18.2)	1 (7.1)	0 (0.0)
Metabolism and nutrition disorders	49 (38.6)	7 (12.5)	9 (14.3)	6 (24.0)	10 (37.0)	1 (9.1)	1 (7.1)	1 (14.3)
Decreased appetite	35 (27.6)	6 (10.7)	9 (14.3)	5 (20.0)	4 (14.8)	1 (9.1)	1 (7.1)	0 (0.0)
Hypocalcemia	18 (14.2)	2 (3.6)	0 (0.0)	1 (4.0)	7 (25.9)	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	33 (26.0)	20 (35.7)	6 (9.5)	9 (36.0)	6 (22.2)	4 (36.4)	2 (14.3)	0 (0.0)
Arthralgia	12 (9.4)	4 (7.1)	4 (6.3)	5 (20.0)	2 (7.4)	1 (9.1)	0 (0.0)	0 (0.0)
Back pain	15 (11.8)	13 (23.2)	2 (3.2)	6 (24.0)	3 (11.1)	1 (9.1)	1 (7.1)	0 (0.0)
Pain in extremity	13 (10.2)	9 (16.1)	1 (1.6)	1 (4.0)	1 (3.7)	3 (27.3)	1 (7.1)	0 (0.0)
Nervous system disorders	35 (27.6)	6 (10.7)	13 (20.6)	2 (8.0)	6 (22.2)	1 (9.1)	5 (35.7)	0 (0.0)
Headache	35 (27.6)	6 (10.7)	13 (20.6)	2 (8.0)	6 (22.2)	1 (9.1)	5 (35.7)	0 (0.0)
Psychiatric disorders	22 (17.3)	8 (14.3)	7 (11.1)	1 (4.0)	1 (3.7)	1 (9.1)	0 (0.0)	0 (0.0)
Insomnia	22 (17.3)	8 (14.3)	7 (11.1)	1 (4.0)	1 (3.7)	1 (9.1)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	17 (13.4)	6 (10.7)	4 (6.3)	2 (8.0)	1 (3.7)	2 (18.2)	3 (21.4)	0 (0.0)
Cough	17 (13.4)	6 (10.7)	4 (6.3)	2 (8.0)	1 (3.7)	2 (18.2)	3 (21.4)	0 (0.0)
Skin and subcutaneous tissue disorders	105 (82.7)	18 (32.1)	48 (76.2)	2 (8.0)	22 (81.5)	1 (9.1)	10 (71.4)	2 (28.6)
Acne	20 (15.7)	4 (7.1)	15 (23.8)	1 (4.0)	9 (33.3)	0 (0.0)	2 (14.3)	0 (0.0)
Dermatitis acneiform	21 (16.5)	2 (3.6)	9 (14.3)	0 (0.0)	3 (11.1)	0 (0.0)	2 (14.3)	0 (0.0)
Dry skin	20 (15.7)	2 (3.6)	7 (11.1)	2 (8.0)	6 (22.2)	0 (0.0)	2 (14.3)	1 (14.3)
Photosensitivity reaction	17 (13.4)	0 (0.0)	8 (12.7)	0 (0.0)	5 (18.5)	0 (0.0)	1 (7.1)	0 (0.0)
Pruritus	16 (12.6)	2 (3.6)	6 (9.5)	2 (8.0)	2 (7.4)	0 (0.0)	1 (7.1)	0 (0.0)
Rash	63 (49.6)	8 (14.3)	27 (42.9)	1 (4.0)	9 (33.3)	1 (9.1)	5 (35.7)	1 (14.3)
Vascular disorders	39 (30.7)	3 (5.4)	23 (36.5)	2 (8.0)	8 (29.6)	0 (0.0)	3 (21.4)	0 (0.0)
Hypertension	39 (30.7)	3 (5.4)	23 (36.5)	2 (8.0)	8 (29.6)	0 (0.0)	3 (21.4)	0 (0.0)

[a]Total number of patients having the same disease severity in safety population.

symptoms subgroups, both in the vandetanib and placebo arms, was low and that these results should be interpreted with caution. The fact that OS was not significantly different between vandetanib- and placebo-treated patients in any of the subgroups may be due to a treatment effect from participation in the open-label arm for this outcome measure.

The ORR was higher in patients treated with vandetanib than placebo in each disease severity subgroups. Although objective responses were observed in all severity subgroups, no comparisons were made between the severity subgroups, because the number of patients in the symptoms-only group and the no progression/no symptoms group was very small. Previous studies of TKIs that included patients with MTC with documented disease progression and symptoms at baseline have reported an overall ORR of 28% while on treatment.[17] In this study, 37.0% percent of the subgroup with progression and symptoms, and 47.6% of patients with progression only, had an objective response during randomly assigned treatment with vandetanib.

One of the important symptoms for patients with MTC is pain. TWP was a predefined endpoint to assess symptomatic benefits in the ZETA trial. This analysis suggests that patients with symptoms only treated with vandetanib would take longer for their pain to worsen, potentially avoiding the need for escalating doses of opiates. Although the analysis did not achieve statistical significance in the symptomatic and progressive subgroup, our results also suggest an increase in TWP in these patients. However, it should be noted that the number of patients in the symptoms-only subgroup, both in the vandetanib and placebo arms, was low, so these results should be interpreted with caution.

The strengths of this study include a well-characterized sample and standardized approaches for evaluating clinically relevant outcomes over a median follow-up time of 23.8 months. This allowed us to evaluate outcomes in patients on the basis of their baseline disease severity status, in particular for the patients with symptomatic and progressive disease at baseline; however, our study should be interpreted in the context of its limitations. As in the original ZETA trial, disease progression was assessed by radiographic evaluation in patients with measurable, unresectable, locally advanced or metastatic MTC; however, this may not have captured slower forms of progression that could have been observed through measurement of calcitonin and/or carcinoembryonic antigen doubling time. The study sample is small, and the primary clinical trial was not designed to evaluate the subgroups defined in this post hoc analysis, so we may be underpowered when investigating outcomes of interest, in particular within the smaller subgroups. Of note, our primary subgroup of interest (symptomatic and progressive at baseline) is the largest of the 4 disease severity subgroups, comprising 55.6% of the overall study sample. Using our available data, we have defined a subgroup with severe disease at baseline that we believe best reflects aggressive and symptomatic disease, as described in the EU label; however, it should be noted that our definition may not be generalizable to all patients who have aggressive and symptomatic disease. Similarly, our results in the remaining smaller disease severity subgroups (progression only, symptom only, and no progression/no symptoms) may not be generalizable to all patients with these disease severity characteristics. In the TWP analysis, death or RECIST progression was not considered a worsening of pain, so there may be misclassification of treatment status during TWP follow-up after disease progression as those who experienced progression could elect to enter open-label treatment with vandetanib.

Finally, it is worth noting that local review of the imaging data was used to determine progression. This approach was chosen to circumvent the problem of the original analysis of the ZETA trial. In the ZETA trial, patients could receive open-label medication if the local investigator found progressive disease.[16] However, the image data were also reviewed centrally, and a substantial number of patients received open-label vandetanib without central read–confirmed progression. This resulted, upon data analysis, in a relative high ORR of 13% in the placebo arm, because patients with no confirmed progression by central read switched to the open-label drug (because of progression found by the local investigator) and experienced a response to it.

When comparing the data from this analysis with the results of the EXAM trial,[18] a phase III trial evaluating the efficacy of cabozantinib in progressive MTC, many differences can be noted. The study population in the EXAM trial was different in many ways compared with the aggressive and symptomatic subgroup in the ZETA trial. This difference also is indicated by the different values of PFS in patients receiving placebo: 4.0 months in the EXAM trial and 8.4 months in the aggressive and symptomatic subgroup in this analysis. Hence, the results obtained cannot be compared with the results of the EXAM trial.

In conclusion, this post hoc analysis of the vandetanib pivotal trial in MTC demonstrates clinical benefit in patients with symptomatic and progressive disease.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Efficacy and Safety of Vandetanib in Progressive and Symptomatic Medullary Thyroid Cancer: Post Hoc Analysis From the ZETA Trial

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APPENDIX

TABLE A1. Baseline Characteristics of the 4 Disease Severity Subgroups

Variable	Progression and Symptoms (n = 184)	Progression Only (n = 88)	Symptoms Only (n = 38)	No Progression and No Symptoms (n = 21)	*P*
Mean (SD) age, years	53.2 (13.1)	48.4 (12.8)	52.9 (14.2)	47.2 (17.2)	.02[a]
Sex					.04[b]
Male	117 (63.6)	44 (50.0)	21(55.3)	8 (38.1)	
Female	67 (36.4)	44 (50.0)	17 (44.7)	13 (61.9)	
Prior systemic therapy for MTC					.06[b]
0	111 (60.3)	60 (68.2)	16 (42.1)	12 (57.1)	
≥ 1	73 (39.7)	28 (31.8)	22 (57.9)	9 (42.9)	
Hereditary disease status					.39[c]
Hereditary disease	15 (8.2)	9 (10.2)	6 (15.8)	3 (14.3)	
Sporadic or unknown disease	169 (91.8)	79 (89.8)	32 (84.2)	18 (85.7)	
RET status					.85[c]
Positive	107 (58.2)	46 (52.3)	21 (55.3)	13 (61.9)	
Negative	6 (3.3)	1 (1.1)	1 (2.6)	0	
Unknown	71 (38.6)	41 (46.6)	16 (42.1)	8 (38.1)	

NOTE. Data presented as No. (%) unless otherwise indicated.
Abbreviations: MTC, medullary thyroid cancer; SD, standard deviation.
[a]*P* value is calculated using analysis of variance.
[b]*P* value is calculated using χ^2 test, if expected frequency is ≥ 5.
[c]*P* value is calculated using Fischer's exact test, if expected frequency is < 5.

TABLE A2. Unadjusted and Age- and Sex-Adjusted HRs for Progression-Free Survival, Overall Survival, and Time to Worsening of Pain

Variable	Unadjusted HR (95% CI)[a]	*P*	Age- and Sex-Adjusted HR (95% CI)[a]	*P*
Progression-free survival				
Progression and symptoms	0.43 (0.28 to 0.64)	< .0001	0.42 (0.28 to 0.63)	< .0001
Progression only	0.63 (0.31 to 1.27)	.19	0.55 (0.26 to 1.17)	.13
Symptoms only	0.41 (0.17 to 1.00)	.05	0.41 (0.16 to 1.03)	.07
No progression, no symptoms	0.27 (0.05 to 1.37)	.12	0.19 (0.03 to 1.12)	.07
Overall survival[b]				
Progression and symptoms	1.08 (0.72 to 1.61)	.71	1.12 (0.75 to 1.67)	.58
Progression only	0.77 (0.34 to 1.74)	.54	0.83 (0.37 to 1.91)	.67
Symptoms only	1.12 (0.44 to 2.84)	.82	1.13 (0.44 to 2.94)	.79
No progression, no symptoms	0.81 (0.16 to 4.21)	.80	0.78 (0.13 to 4.52)	.78
Time to worsening of pain				
Progression and symptoms	0.67 (0.43 to 1.04)	.07	0.66 (0.43 to 1.03)	.08
Progression only	0.66 (0.35 to 1.24)	.19	0.71 (0.36 to 1.41)	.34
Symptoms only	0.32 (0.13 to 0.81)	.02	0.33 (0.13 to 0.85)	.03
No progression, no symptoms	1.22 (0.37 to 4.07)	.74	1.37 (0.41 to 4.63)	.60

Abbreviation: HR, hazard ratio.

[a]The reference group for HR is the placebo arm within each subgroup.

[b]Overall survival included open-label data.