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Safety and efficacy of two starting doses of vandetanib in advanced medullary thyroid cancer

Mimi I Hu[1], Rossella Elisei[2], Marek Dedecjus[3], Aron Popovtzer[4], Maralyn Druce[5], Ellen Kapiteijn[6], Furio Pacini[7], Laura Locati[8], Jolanta Krajewska[9], Richard Weiss[10] and **Robert F Gagel[1]**

[1]Department of Endocrine Neoplasia and Hormonal Disorders, University of Texas MD Anderson Cancer Center, Houston, Texas, USA
[2]Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy
[3]M. Sklodowska-Curie Memorial Cancer Center and Institute of Oncology, Warsaw, Poland
[4]Davidoff Cancer Center, Tel-Aviv University, Petah Tikva, Israel
[5]William Harvey Research Institute, Barts and the London School of Medicine and Dentistry, London, UK
[6]Leiden University Medical Center, Leiden, The Netherlands
[7]Thyroid Unit, University of Siena, Siena, Italy
[8]Head and Neck Medical Oncology Department, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy
[9]M. Sklodowska-Curie Memorial Institute Cancer Center, Gliwice Branch, Gliwice, Poland
[10]Sanofi Genzyme, Cambridge, Massachusetts, USA

Correspondence should be addressed to M I Hu: mhu@mdanderson.org

Abstract

Vandetanib is an oral tyrosine kinase inhibitor approved for treatment of advanced symptomatic or progressive medullary thyroid cancer (MTC). The current study (NCT01496313) evaluated the benefit–risk of two starting doses of vandetanib in patients with symptomatic or progressive MTC. Patients were randomized 1:1 to receive vandetanib 150 or 300 mg daily and followed for a maximum of 14 months (Part A), with the option to then enter an open-label phase (Part B) investigating vandetanib 100, 150, 200 and 300 mg daily doses. Efficacy was assessed in Part A, and safety and tolerability during Parts A and B up to 2 years post randomization. Eighty-one patients were randomized in Part A and 61 patients entered Part B, of whom 37 (60.7%) received 2 years of treatment. Overall, 25% of patients experienced an objective response (OR) at 14 months (OR rate, 0.29 (95% CI, 0.176–0.445) for 300 mg, and 0.20 (95% CI, 0.105–0.348) for 150 mg; one-sided *P* value approximately 0.43). The most common adverse events (AEs) included diarrhea, hypocalcemia, asthenia, QTc prolongation, hypokalemia and keratopathy, all at generally higher incidence with 300 vs 150 mg (Part A). Part B safety and tolerability was consistent with Part A. OR was observed with both vandetanib doses; the 300 mg dose showed a more favorable trend vs 150 mg as initial dose. Thus, for most patients, 300 mg vandetanib is the most appropriate starting dose; dose reductions to manage AEs and lower initial doses for patients with particular comorbidities can be considered.

Key Words

- vandetanib
- medullary thyroid cancer
- safety
- efficacy

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Introduction

Medullary thyroid cancer (MTC) is a malignancy of the parafollicular C cells of the thyroid gland, accounts for an estimated 1–2% of all thyroid cancers, and is either hereditary (in 25% of patients) or sporadic (Wells Jr *et al.* 2015). If treated early, 10-year survival is 70–80%, but this decreases to 40% or lower for patients with locally advanced or metastatic disease, with a median overall survival of 2–3 years in these patients (Modigliani *et al.* 1998, Roman *et al.* 2006, Kloos *et al.* 2009). Progress in identifying the key genetic alterations and dysregulated signaling pathways involved in MTC have led to the development of targeted therapies for this disease (Martins *et al.* 2006, Wells Jr *et al.* 2015).

Vandetanib (Caprelsa) is a once-daily, oral tyrosine kinase inhibitor that selectively targets rearranged during transformation (RET) receptor, vascular endothelial growth factor receptor and epidermal growth factor receptor signaling (Carlomagno *et al.* 2002, Wedge *et al.* 2002, Wells *et al.* 2010). In the Phase III ZETA clinical trial in patients with locally advanced or metastatic hereditary MTC (Wells *et al.* 2012), median progression-free survival was significantly prolonged from 19.3 months with placebo to a predicted 30.5 months (median not yet reached at data cut-off) with vandetanib (hazard ratio, 0.46; $P<0.0001$) (Wells *et al.* 2012). Based on these results, the US Food and Drug Administration (FDA) approved vandetanib for the treatment of symptomatic or progressive MTC in patients with unresectable locally advanced or metastatic disease in 2011.

A key issue relating to the use of vandetanib is whether the Phase III study identified the correct dose of vandetanib given several unexplained deaths in the vandetanib treatment group. To address this concern and to help inform decision-making on vandetanib starting doses, this study was designed to identify the objective response rates (ORR) and evaluate the safety and tolerability of two starting doses of vandetanib (150 and 300 mg) in patients with symptomatic or progressive MTC.

Materials and methods

Patients

Eligible patients were adults aged ≥18 years with histologically confirmed, unresectable, locally advanced or metastatic, hereditary or sporadic MTC. Patients were required to have objective disease progression (within 14 months of randomization) and/or one or more symptoms related to the patient's MTC (investigator assessed). Other key inclusion and exclusion criteria are detailed in the Supplementary data (see section on supplementary data given at the end of this article).

Study design and treatment

This study was an international, randomized, double-blind study (NCT01496313) in two parts: double-blind and randomized Part A and open-label Part B. In Part A, patients were randomized 1:1 to receive once-daily oral vandetanib at either 150 or 300 mg and followed for a maximum of 14 months. The 150 mg dose was produced for clinical trial purposes only. Patients who received blinded treatment for 14 months after randomization were eligible to enter Part B. A more detailed description of the study design can be found in the Supplementary data.

All patients provided written informed consent. The protocol was approved by all relevant institutional ethical committees or review bodies (full details provided in the Supplementary data), and the study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

Objectives

The primary objective was to assess the ORR for the two vandetanib starting doses (150 and 300 mg) in patients with unresectable locally advanced or metastatic MTC with progressive or symptomatic disease. Secondary objectives included best percentage change in target lesion size during Part A, pharmacokinetics (PK) in Part A and safety and tolerability during Parts A and B.

Assessments

Efficacy: Part A

OR (defined as complete response (CR) and partial response (PR)) was based on objective tumor measurements performed at screening, and then every 12 weeks until progression, or up to 14 months on randomized treatment, whichever came first. Patients who discontinued vandetanib prior to objective progression or 14 months on randomized treatment continued to have tumor assessments performed until objective progression. Tumor assessments were categorized based on Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, with additional confirmatory scans performed ≥4 weeks and ≤12 weeks following the date of first response.

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Safety: Parts A and B

Safety was assessed throughout the study (Parts A and B) by monitoring and recording adverse events (AEs) by Common Terminology Criteria for Adverse Events v4.0, vital signs, laboratory data, electrocardiogram (ECG) parameters and echocardiograms, ophthalmological evaluation and physical examination. A QTcF prolongation was defined as QTc interval >450 ms. Prolongations with QTcF >480 and >500 ms were also summarized. QTcF was summarized both as a continuous variable, using the observed values, and as a categorical variable, using the categories ≤500 and >500 ms. If a patient's dose was reduced for an AE or QT prolongation, the investigator had the option to continue the patient on the reduced dose (vandetanib 100 mg for patients randomized to 150 mg, or 200 mg for patients randomized to 300 mg) in Part B if the patient was assessed as receiving benefit from vandetanib.

Statistical methods

A sample size of 40 patients per arm (80 in total) would allow the ORR in each treatment arm to be estimated with adequate precision. For example, if 8/40 patients respond, the ORR would be 20%. The corresponding 95% CI using the Wilson score method would be (10.5–34.8%), which lies entirely to the right of zero, thus providing evidence that the ORR for this treatment group was likely to be greater than zero. The proposed sample size for this study was therefore 80 patients in total, with 40 patients to be randomized in each treatment group. As the aim of the study was to provide additional information on the likely range of response rates with a starting dose of either 150 mg or 300 mg, there was no formal hypothesis testing to compare the ORR between the two treatment groups.

Relative dose intensity (RDI) was calculated as the ratio of the total vandetanib dose received over the total exposure period, in mg, divided by the total number of days from the beginning of treatment to the day of discontinuation or data cut-off date multiplied by 100% (this analysis was only conducted for Part A).

The efficacy population (Part A) included all randomized patients regardless of the treatment received. The per protocol (PP) population included all patients who received at least one dose of randomized treatment and who had at least two follow-up RECIST assessments while on treatment. The safety population included all patients who received at least one dose of treatment. Additional information is provided in the Supplementary data.

Results

Patients

A total of 81 patients were randomized in Part A. Of these, 61 (87.5% of patients in the 150 mg group, 63.4% of patients in the 300 mg group) completed Part A, entered Part B and received open-label vandetanib (Fig. 1). Twenty patients discontinued treatment in Part A (12.5% in the 150 mg group and 36.6% in the 300 mg group); the main reason for discontinuation was AEs (Fig. 1). Of the 61 patients who entered Part B, 37 (60.7%) received a total of 2 years of treatment and 24 (39.3%) discontinued treatment in Part B prior to 2 years, most commonly as a result of worsening of the condition under investigation (14 (23.0%) patients; Fig. 1). All 81 randomized patients received treatment and were included in the efficacy and safety populations; 65 patients were included in the PP population.

Patient characteristics and baseline demographics were similar in both arms (Table 1). The mean age of patients was 52.5 years, with over half (51.9%) aged ≥40 to <65 years. Most patients presented with sporadic disease (71.6%) and had metastatic disease (61.7%).

Efficacy: Part A

Of the 81 patients analyzed for efficacy, 24.7% experienced an OR at 14 months: 19 patients had an objective PR and 1 patient had a CR (Table 2). There were more responders in the 300 mg group (ORR, 29.3%; 95% CI, 17.6–44.5%) than in the 150 mg group (ORR, 20.0%; 95% CI, 10.5–34.8%; *P*-value approximately 0.43 for one-sided comparison); duration of response and time to onset were similar between groups (Table 2). Primary analysis of ORR was also determined for the PP population and showed greater improvements than for the efficacy population: 30.8% of patients experienced an objective response by 14 months (23.5% receiving 150 mg and 38.7% receiving 300 mg (Table 2)). Of the patients who did not respond, a smaller proportion in the 300 mg group (4.9%) had disease progression than in the 150 mg group (22.5%) (Table 2).

At baseline, the mean target lesion size was bigger in the 300 mg group (76.6 mm) compared with the 150 mg group (60.1 mm). Most patients had a reduction in target lesion size, with more reductions observed with 300 mg compared with 150 mg (Supplementary Fig. 1).

Safety: Parts A and B

Median duration of treatment in randomized Part A was 11.8 months with 150 mg and 13.7 months with 300 mg.

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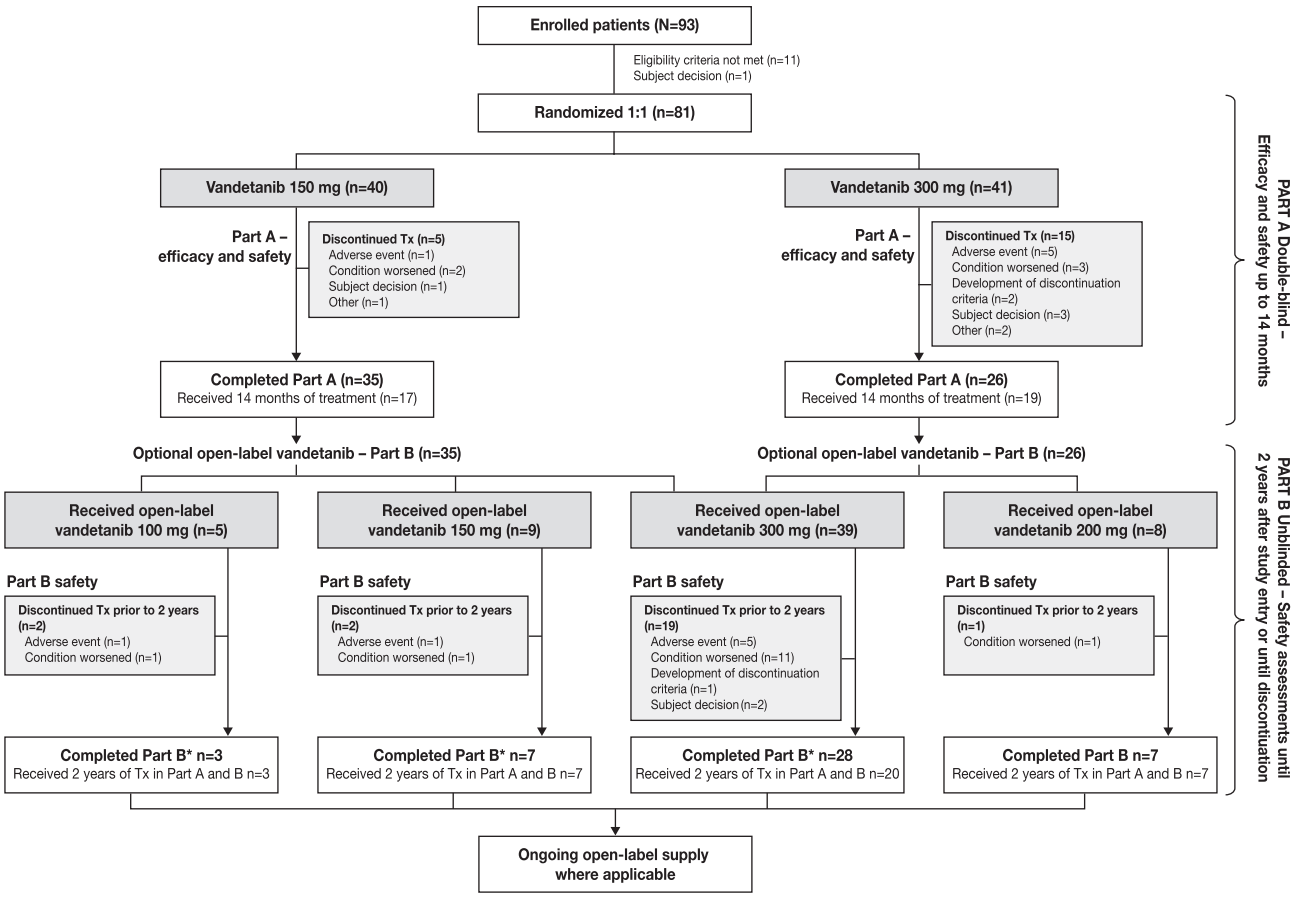

Figure 1
Patient disposition.

In Part A in the 150 and 300 mg groups, dose reductions were required by 6 (15%) and 12 (29%) patients, respectively (all because of AEs), and dose interruptions were required by 18 (45%) and 15 (37%) patients, respectively (the primary reason was AEs (16.0%)).

RDI was calculated for each dose cohort in Part A as the percentage of the actual dose intensity delivered relative to the intended dose intensity through treatment discontinuation. The mean RDI for the 150 mg and 300 mg dose groups were 93.1 and 91.4%, respectively, indicating that the majority of patients in each group received close to the full expected dose intensity over the course of their treatment in Part A.

Seven patients in Part A (two in the 150 mg group, five in the 300 mg group) and seven patients in Part B (one each in the 100 and 150 mg groups, five in the 300 mg group (four of whom were initially randomized to 150 mg)) reported an AE leading to discontinuation of vandetanib (Table 3). Three of the AEs leading to discontinuation were considered to be causally related to vandetanib in Part A: one event each of angina pectoris (150 mg group), peripheral motor neuropathy and cholecystitis (both in the 300 mg group). In Part B, one AE of QT prolongation on ECG leading to discontinuation was considered to be causally related to vandetanib; this patient was initially randomized to 150 mg but received 100 mg in Part B.

In Part A, the most frequently reported AEs in the vandetanib 150 mg group were diarrhea (37.5%), increased blood thyroid-stimulating hormone (27.5%), rash (20.0%), hypocalcemia (20.0%), hypertension (20.0%) and fatigue (20.0%); the most frequently reported AEs in the 300 mg group were diarrhea (43.9%), QT prolongation on ECG (34.1%), rash (31.7%), keratopathy (31.7%), hypocalcemia (29.3%), hypertension (26.8%) and increased blood thyroid-stimulating hormone (22.0%; Table 4). Generally, the incidence of AEs was similar between treatment groups in Part A, although prolonged QT on ECG was reported in a higher proportion of patients receiving 300 mg than in the 150 mg group (14 vs 5 patients (34.1 vs 12.5%)). Grade ≥3 AEs occurred in 21 (51.2%) and 17 (42.5%) patients receiving 300 mg and 150 mg, respectively in Part A. The most common AEs of grade ≥3 were hypertension

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Table 1 Patient demographics and baseline clinical characteristics (full population).

	Vandetanib		**Total** (*n* = 81)
	150 mg (*n* = 40)	300 mg (*n* = 41)	
Sex, *n* (%)			
Male	25 (62.5)	29 (70.7)	54 (66.7)
Female	15 (37.5)	12 (29.3)	27 (33.3)
Mean age (years)	52.2	52.7	52.5
Age group, *n* (%)			
≥18 to <40 years	9 (22.5)	9 (22.0)	18 (22.2)
≥40 to <65 years	22 (55.0)	20 (48.8)	42 (51.9)
≥65 to <75 years	7 (17.5)	10 (24.4)	17 (21.0)
≥75 years	2 (5.0)	2 (4.9)	4 (4.9)
Race, *n* (%)			
White	39 (97.5)	37 (90.2)	76 (93.8)
Black or African American	0	1 (2.4)	1 (1.2)
Asian	1 (2.5)	2 (4.9)	3 (3.7)
Other	0	1 (2.4)	1 (1.2)
Ethnic group, *n* (%)			
Non-Hispanic or Latino	39 (97.5)	41 (100)	80 (98.8)
Hispanic or Latino	1 (2.5)	0	1 (1.2)
WHO performance status			
0	28 (70.0)	23 (56.1)	51 (63.0)
1	12 (30.0)	17 (41.5)	29 (35.8)
2	0 (0.0)	1 (2.4)	1 (1.2)
Disease type, *n* (%)			
Hereditary	3 (7.5)	4 (9.8)	7 (8.6)
Sporadic	32 (80.0)	26 (63.4)	58 (71.6)
Unknown	5 (12.5)	11 (26.8)	16 (19.8)
Prior disease-related treatment, *n* (%)			
Chemotherapy	6 (15.0)	7 (17.1)	13 (16.0)
Other systemic anticancer therapy	7 (17.5)	10 (24.4)	17 (21.0)
Other tyrosine kinase inhibitors	7 (17.5)	3 (7.3)	10 (12.3)
Hormonal therapy	1 (2.5)	0	1 (1.2)
Immunotherapy	1 (2.5)	0	1 (1.2)
Prior systemic therapy for MTC, *n* (%)			
None	34 (85.0)	34 (82.9)	68 (84.0)
≥1	6 (15.0)	7 (17.1)	13 (16.3)
Progression at trial entry, *n* (%)	37 (92.5)	40 (97.6)	77 (95.1)
Median (range) time from most recent disease progression to randomization (days)	65.0 (7–445)	58.5 (3–420)	65.0 (3–445)

MTC, medullary thyroid cancer; WHO, World Health Organization.

(8 (9.9%) patients; 5 receiving 300 mg, 3 receiving 150 mg) and dermatitis acneiform (3 (3.7%) patients; all received 150 mg).

In open-label Part B, 10 AEs were reported in >10% of patients in total (Table 4). The most common AE was diarrhea, which was reported in 13 (21.3%) patients (Table 4). A total of 20 (32.8%) patients reported a grade ≥3 AE. In most cases, grade ≥3 AEs were reported in no more than one patient in total, except for hypocalcemia and asthenia (both *n* = 3, 4.9%), hypertension, hyponatremia, diarrhea and QT prolongation on ECG (all *n* = 2, 3.3%).

No serious AEs (SAEs) occurred in more than one patient during Part A or B, with the exception of hypocalcemia, which was reported by two patients (one patient receiving 200 mg, one patient receiving 300 mg). In Part A, 10 SAEs in seven patients were considered treatment related (four events in three patients receiving 150 mg, six events in four patients receiving 300 mg). In Part B, four SAEs in three patients were considered treatment related (general physical health deterioration in a patient receiving 200 mg, hypocalcemia and colitis in a patient receiving 300 mg and post-procedural fistula in a patient receiving 300 mg).

During Parts A and B, five and eight patients, respectively, died. None of these deaths were considered related to vandetanib. Further details are described in the Supplementary data.

In Part A, ophthalmology results showed a slow increase in eye conditions over time, with slightly higher prevalence

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Table 2 Summary of efficacy results.

	Vandetanib		
	150 mg (*n* = 40)	300 mg (*n* = 41)	**Total** (*n* = 81)
Primary efficacy analysis			
Efficacy population, *n*	40	41	81
ORR (CI)	20.0% (10.5–34.8%)	29.3% (17.6–44.5%)	24.7% (16.6–35.1%)
PP population, *n*	34	31	65
ORR (CI)	23.5% (12.4–40.0%)	38.7% (23.7–56.2%)	30.8% (20.9–42.8%)
Best objective response, *n* (%)			
Response			
Total	8 (20.0)	12 (29.3)	20 (24.7)
CR	0	1 (2.4)	1 (1.2)
PR	8 (20.0)	11 (26.8)	19 (23.5)
Non-response			
Total	32 (80.0)	29 (70.7)	61 (75.3)
Stable disease	21 (52.5)	23 (56.1)	44 (54.3)
Progressive disease	9 (22.5)	2 (4.9)	11 (13.6)
Non-evaluable	2 (5.0)	4 (9.8)	6 (7.4)
	Vandetanib		
	150 mg (*n* = 8)	300 mg (*n* = 12)	**Total** (*n* = 20)
Median duration of response (months) (95% CI)	9.8 (2.8, 11.2)	8.4 (3.0, 11.2)	8.4 (3.0, 11.2)
Median onset of response (months) (95% CI)	4.2 (2.8, 11.2)	4.4 (2.8, 11.1)	4.3 (2.8, 11.1)

Results are for the efficacy population unless otherwise stated. The confirmed ORR was defined as the percentage of patients with a best response of CR or PR according to RECIST version 1.1 at the end of the 14-month blinded phase (Part A) or before progression, whichever came first. The best objective response was derived from the post-baseline assessments of objective tumor response within 14 months after randomization using the hierarchy CR > PR > stable disease > progressive disease > non-evaluable.
CI, confidence interval; CR, complete response; ORR, objective response rate; PP, per protocol; PR, partial response.

of vortex keratopathy and cornea epithelium in the 300 mg group compared with the 150 mg group, although there was no visual compromise. In Part B, the incidence of vortex keratopathy increased slightly from baseline; however, the incidence of cornea epithelium and cornea stroma abnormalities remained stable throughout the dosing groups.

In Part A, four (4.9%) patients had QTcF >500 ms (three patients receiving 300 mg, one patient receiving 150 mg; Table 5). In Part B, no patients had QTcF >500 ms

Table 3 Summary of adverse events in any category for Part A (randomized, double-blind phase) and Part B (open-label phase): safety population.

	Part A (randomized, double blind)			**Part B** (open label)				
	Vandetanib			Vandetanib				
Patients, *n* (%)*	150 mg (*n* = 40)	300 mg (*n* = 41)	Total (*n* = 81)	100 mg (*n* = 5)	150 mg (*n* = 9)	200 mg (*n* = 8)	300 mg (*n* = 39)	Total (*n* = 61)
Any AE	39 (97.5)	40 (97.6)	79 (97.5)	5 (100)	7 (77.8)	8 (100)	34 (87.2)	54 (88.5)
AE of grade ≥3	17 (42.5)	21 (51.2)	38 (46.9)	1 (20.0)	1 (11.1)	2 (25.0)	16 (41.0)	20 (32.8)
AE of grade ≥3 causally related to vandetanib	11 (27.5)	12 (29.3)	23 (28.4)	1 (20.0)	0	2 (25.0)	3 (7.7)	6 (9.8)
Any AE with outcome of death	0	2 (4.9)	2 (2.5)	0	0	0	2 (5.1)	2 (3.3)
Any AE with outcome of death causally related to vandetanib	0	0	0	0	0	0	0	0
Any SAE†	8 (20.0)	9 (22.0)	17 (21.0)	0	1 (11.1)	1 (12.5)	10 (25.6)	12 (19.7)
Any SAE causally related to vandetanib†	3 (7.5)	4 (9.8)	7 (8.6)	0	0	1 (12.5)	2 (5.1)	3 (4.9)
AE leading to treatment discontinuation	2 (5.0)	5 (12.2)	7 (8.6)	1 (20.0)	1 (11.1)	0	5 (12.8)	7 (11.5)
AE leading to treatment discontinuation causally related to vandetanib	1 (2.5)	2 (4.9)	3 (3.7)	1 (20.0)	0	0	0	1 (1.6)

*Patients with multiple events in the same category were counted only in that category; †including events with outcome of death.
AE, adverse event; SAE, serious adverse event.

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across any vandetanib dose groups; five (12.8%) patients (all receiving 300 mg) had QTcF prolongations >480 ms. In Parts A and B, QTcF prolongations (>450 ms) occurred sooner and more frequently in the 300 mg group, but there were no reports of torsades de pointes (Table 5).

Pharmacokinetic data for Part A are provided in the Supplementary data.

Discussion

Patients with advanced or metastatic MTC have a poor prognosis, with chemotherapy and radiation therapy being largely ineffective (Hundahl *et al*. 1998, Modigliani *et al*. 1998, Roman *et al*. 2006). Increased understanding of the molecular pathogenesis of MTC has resulted in the development of targeted therapies and represents an important advance for clinical management of this disease. In 2011, the US FDA approved vandetanib for the treatment of symptomatic or progressive MTC in patients with unresectable locally advanced or metastatic disease. In the EU, vandetanib was approved by the EMA in 2012, for the treatment of aggressive and symptomatic MTC in patients with unresectable locally advanced or metastatic disease. Assessment of the benefit–risk relationship of different vandetanib starting doses has not previously been performed. This may be especially important for populations that are less able to tolerate treatment-related side effects, particularly given the potential for long-term vandetanib treatment. We therefore set out to investigate the safety and efficacy of two vandetanib starting doses, 150 and 300 mg, in patients with unresectable locally advanced or metastatic MTC with progressive or symptomatic disease.

Overall, 25% of patients experienced an objective response in the first 14 months of treatment, with more responders in the vandetanib 300 mg group compared with the 150 mg group (ORR, 29 vs 20%). Duration of response and time to onset of response were similar between treatment groups, although it should be noted that the duration results were heavily censored at the last RECIST visit. Progressive disease was observed in 22.5% of patients in the vandetanib 150 mg group and in 4.9% of patients in the 300 mg group. Although the confidence intervals overlapped, our findings suggest a trend toward a better response for 300 mg vs the 150 mg dose. PK data showed that clearance was similar after dosing at 150 and 300 mg, with steady-state exposure approximately two-fold higher with the 300 mg dose than with the 150 mg dose.

Safety and tolerability assessments were conducted in Parts A and B. Overall, vandetanib was well tolerated; the rate of discontinuation due to toxicity was low and,

Table 4 Common adverse events (frequency ≥15% in any treatment group for Part A or >10% for total treatment group in Part B) for Part A (randomized, double-blind phase) and Part B (open-label phase): safety population.

	Part A (randomized, double blind)			**Part B** (open label)				
	Vandetanib			Vandetanib				
Patients, *n* (%)	150 mg (*n* = 40)	300 mg (*n* = 41)	Total (*n* = 81)	100 mg (*n* = 5)	150 mg (*n* = 9)	200 mg (*n* = 8)	300 mg (*n* = 39)	Total (*n* = 61)
Any AE	39 (97.5)	40 (97.6)	79 (97.5)	5 (100)	7 (77.8)	8 (100)	34 (87.2)	54 (88.5)
Diarrhea	15 (37.5)	18 (43.9)	33 (40.7)	1 (20.0)	2 (22.2)	3 (37.5)	7 (17.9)	13 (21.3)
Rash	8 (20.0)	13 (31.7)	21 (25.9)	0	0	1 (12.5)	5 (12.8)	6 (9.8)
Blood thyroid-stimulating hormone increased	11 (27.5)	9 (22.0)	20 (24.7)	0	0	1 (12.5)	5 (12.8)	6 (9.8)
Hypocalcemia	8 (20.0)	12 (29.3)	20 (24.7)	2 (40.0)	0	1 (12.5)	9 (23.1)	12 (19.7)
ECG QT prolonged	5 (12.5)	14 (34.1)	19 (23.5)	1 (20.0)	0	2 (25.0)	7 (17.9)	10 (16.4)
Hypertension	8 (20.0)	11 (26.8)	19 (23.5)	1 (20.0)	1 (11.1)	0	6 (15.4)	8 (13.1)
Keratopathy	5 (12.5)	13 (31.7)	18 (22.2)	2 (40.0)	2 (22.2)	0	6 (15.4)	10 (16.4)
Fatigue	8 (20.0)	7 (17.1)	15 (18.5)					
Alanine aminotransferase increased	5 (12.5)	7 (17.1)	12 (14.8)	0	1 (11.1)	0	6 (15.4)	7 (11.5)
Dermatitis acneiform	6 (15.0)	6 (14.6)	12 (14.8)	1 (20.0)	0	0	2 (5.1)	3 (4.9)
Asthenia	5 (12.5)	6 (14.6)	11 (13.6)	1 (20.0)	1 (11.1)	0	9 (23.1)	11 (18.0)
Hypomagnesemia	4 (10.0)	7 (17.1)	11 (13.6)	2 (40.0)	0	1 (12.5)	5 (12.8)	8 (13.1)
Aspartate aminotransferase increased	3 (7.5)	6 (14.6)	9 (11.1)	1 (20.0)	0	0	6 (15.4)	7 (11.5)
Decreased appetite	2 (5.0)	7 (17.1)	9 (11.1)	1 (20.0)	1 (11.1)	1 (12.5)	1 (2.6)	4 (6.6)
Hypokalemia	2 (5.0)	7 (17.1)	9 (11.1)	2 (40.0)	1 (11.1)	1 (12.5)	6 (15.4)	10 (16.4)

AE, adverse event; ECG, electrocardiogram.

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Table 5 Summary of QT/QTcF intervals for Part A (randomized, double-blind phase) and Part B (open-label phase): safety population.

	Part A* (randomized, double blind)			**Part B†** (open label)				
	Vandetanib			Vandetanib				
Patients, *n* (%)	150 mg (*n* = 40)	300 mg (*n* = 41)	Total (*n* = 81)	100 mg (*n* = 5)	150 mg (*n* = 9)	200 mg (*n* = 8)	300 mg (*n* = 39)	Total (*n* = 61)
QTcF value at any time during treatment (ms)								
>500	1 (2.5)	3 (7.3)	4 (4.9)	0	0	0	0	0
≤500	40 (100)	39 (95.1)	79 (97.5)	5 (100)	9 (100)	8 (100)	39 (100)	61 (100)
Incidence of QTcF prolongation (ms)								
>450	16 (40.0)	20 (48.8)	36 (44.4)	1 (20.0)	4 (44.4)	2 (25.0)	18 (46.2)	25 (41.0)
>480	3 (7.5)	7 (17.1)	10 (12.3)	0	0	0	5 (12.8)	5 (8.2)
>500	1 (2.5)	3 (7.3)	4 (4.9)	0	0	0	0	0
Mean time to first QTcF prolongation (days)	105.2	82.6	92.6	244.0	149.5	210.5	104.4	125.7
Mean duration of QTcF prolongation (days)	106.8	125.5	118.3	91.0	68.6	58.0	67.1	67.2
Number of QTcF prolongations, *n* (%)								
1	12 (30.0)	9 (22.0)	21 (25.9)	1 (20.0)	3 (33.3)	1 (12.5)	12 (30.8)	17 (27.9)
2	2 (5.0)	8 (19.5)	10 (12.3)	0	1 (11.1)	1 (12.5)	5 (12.8)	7 (11.5)
3	2 (5.0)	2 (4.9)	4 (4.9)	0	0	0	1 (2.6)	1 (1.6)
4	0	1 (2.4)	1 (1.2)	0	0	0	0	0

*Includes QTcF prolongations (>450 ms) with an onset date on or after the date of first dose and up to and including 60 days following the date of last dose of vandetanib, excluding any prolongation events that started after the first dose in Part B; †includes QTcF prolongations (>450 ms) with an onset date on or after the date of first dose of open-label vandetanib up to and including 60 days after the last dose of open-label vandetanib. Prolongations that started in Part A and continued in Part B are not reported here.

of the patients entering the open-label phase of the study, 61% received 2 years of treatment with vandetanib and 74% completed the study (including deaths). The most common cause of discontinuation of treatment prior to completing 2 years of treatment was worsening of the patient's condition. The overall safety and tolerability of vandetanib in Part B was consistent with that observed in Part A. The most common AEs included diarrhea, hypocalcemia, asthenia, QTc prolongation, hypokalemia and keratopathy. The number and type of AEs reported during the study were consistent with what would be expected in this patient population and the current safety profile for vandetanib (Robinson *et al.* 2010, Wells *et al.* 2010, 2012). Although there were no clinically relevant differences between the safety profiles of vandetanib 150 and 300 mg, the incidence of the most common AEs was higher in general in the 300 mg group and there were fewer patients in the 150 mg dose cohort requiring dose reductions than the 300 mg group. There were fewer study discontinuations due to AEs in the group treated with 150 mg than the 300 mg dose group. However, only 4 out of the 14 withdrawals secondary to AEs in Parts A and B were attributed to vandetanib at varying doses (300 mg (*n* = 2), 150 mg (*n* = 1) and 100 mg (*n* = 1)). The small number of withdrawals makes it difficult to make definitive conclusions.

Abnormalities in clinical laboratory parameters, vital signs, ECG and left ventricular ejection fraction data were consistent with the known safety profile for vandetanib. QTcF prolongations occurred sooner and more frequently in the 300 mg group than in the 150 mg group, and recovery time was also longer for the former. In Part B, QTcF prolongations (>480 ms) occurred in five patients in the 300 mg group; however, there were no QTc prolongations >500 ms across any vandetanib dose groups, and no reports of torsades de pointes during the study. Ophthalmology results also showed a more favorable safety profile for the lower dose group, although abnormalities appeared to stabilize across different dose groups during Part B.

Our study showed clinical benefits at both vandetanib doses of 150 and 300 mg. The study was not powered to identify a statistically significant difference between doses, but there was an overall trend toward greater efficacy with 300 mg vs 150 mg as the initial dose. Physicians experienced in treating patients with advanced MTC can individualize therapy based on approved dosing strategies. The vandetanib prescribing information states that the

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recommended dose is 300 mg once daily; this dose can be reduced to 200 mg and then to 100 mg if needed due to AEs (Sanofi Genzyme 2016). This strategy aims to improve tolerability, while delivering similar efficacy based on the data from the present study, and allow treatment to continue for a longer duration.

Patient tolerability and safety are important considerations in the use of this agent as therapy may be continued long term in patients who show continued response to therapy. In such patients, it is necessary to balance the therapeutic benefit (response or lack of progression of the malignancy) with annoying (diarrhea or skin rash) or unsafe (QTcF prolongation, renal dysfunction, profound hypocalcemia, or hypothyroidism unresponsive to replacement) AEs. It seems reasonable to initiate therapy at the approved dose and then to adjust the dose over time to optimize the therapeutic and AE profile. The prolonged half-life of vandetanib makes it possible to titrate the dose downward, if needed, using the available 100 and 300 mg vandetanib tablets. For example, patients initially treated with vandetanib 300 mg/day who develop unsafe or intolerable AEs and have an initial tumor response should be considered for dose reduction. Given that both vandetanib doses in this study showed clinical benefit, patients with renal dysfunction, severe hypertension, or a significantly low body mass index have the option to start with a low initial dose. Previous publications have also described AE management strategies with vandetanib (Cabanillas *et al*. 2011, Grande *et al*. 2013).

Patients in our study whose disease had progressed on the 150 mg dose were able to enter the open-label part of the study at the increased dose of 300 mg. However, efficacy was not assessed in these patients, and further assessments will be required to determine the efficacy benefits of increasing the vandetanib dose and overcoming potential drug resistance.

To conclude, in the absence of a curative treatment for locally advanced or metastatic MTC, the availability of treatments with the ability to substantially prolong time to disease progression with limited side effects is an important clinical advance for this disease. Although the results of our study showed clinical response with both vandetanib doses, the 300 mg dose showed a more favorable trend compared with the 150 mg group in ORR. This indicates that, for most patients, 300 mg vandetanib is the most appropriate starting dose; however, dose reductions to manage AEs and lower initial doses for patients with particular comorbidities can be considered.

Supplementary data

This is linked to the online version of the paper at https://doi.org/10.1530/ERC-18-0258.

Declaration of interest

Mimi I Hu: Research support: Sanofi Genzyme; Consulting or advisory role: Blueprint Medicines, Eisai Medical Research; Speakers' bureau: Eisai Medical Research. Rossella Elisei: Consulting or advisory role: Eisai, Sanofi Genzyme, Exelixis, Loco; Speakers' bureau: Eisai, Sanofi Genzyme; Travel: Sanofi Genzyme. Marek Dedecjus: No relationship to disclose. Aron Popovtzer: No relationship to disclose. Maralyn Druce: Consulting or advisory role: Ipsen; Travel: Ipsen, Novartis. Ellen Kapiteijn: No relationship to disclose. Furio Pacini: Speakers' bureau: Sanofi Genzyme. Laura Locati: Consulting or advisory role: Eisai, BMS, Ipsen; Research funding: Eisai. Jolanta Krajewska: No relationship to disclose. Richard Weiss: Employment: Employee of Genzyme at the time of the study, now employed by Radius Health. Robert F Gagel: Stock or other ownership interest: Varian Medical Systems (VAR), Varex Imaging Corporation (VREX); Patents: holder of patent formulations of the sulfonylurea receptor in persistent hypoglycemic hyperinsulinemia of infancy (currently no commercial value).

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