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Medullary thyroid cancer treated with vandetanib: predictors of a longer and durable response

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Abstract

Vandetanib is an important treatment option for advanced metastatic medullary thyroid cancer. The aims of this study were to evaluate the predictors of both a longer response to vandetanib and the outcome. Medical records of 79 medullary thyroid cancer patients treated with vandetanib at our center were analysed. Twenty-five patients were treated for <12 months, 54 were treated for ≥12 months and 24 of these latter were treated for ≥48 months (short-, long- and very long-term). The median progression free survival of the long and very long-term treated patients was significantly longer than in the ZETA trial. When comparing the groups of short- and long-term treated patients the only significant difference was that these latter were less frequently previously treated with a tyrosine kinase inhibitor. However, the long-term treated patients had a younger age, both at diagnosis and enrolment, which was statistically significant in the very long-term treated patients. In the long-term treated group, younger age, enrolment for symptoms and development of adverse events were significantly correlated with a better outcome. The enrolment for symptoms remained the only statistically significant predictor of a good outcome in the very long-term treated patients. In conclusion, early treatment with vandetanib, when patients are younger, with a good ECOG performance status and symptomatic disease, not necessarily progressing for RECIST, seem to be the best predictors of a longer and durable response. Further studies are needed to confirm these results.

Key Words

- ▶ medullary thyroid cancer
- ▶ RET
- ▶ vandetanib
- ▶ calcitonin
- ▶ tyrosine kinase inhibitors

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Introduction

Medullary thyroid carcinoma (MTC) is a rare malignancy originating from the parafollicular C cells of the thyroid gland. MTC represents 5–10% of all thyroid cancers, and it can be sporadic (75%) or inherited (25%). The pathogenesis of MTC is related to activating mutations of the rearranged during transfection (*RET*) gene, which are somatic (45% of cases) in sporadic tumors and germline (98% of cases) in hereditary tumors (Romei *et al.* 2015).

The 10-year overall survival rate in unselected patients with MTC is approximately 75%, but it decreases to approximately 40% in patients with locally advanced or metastatic MTC (Hundahl *et al.* 1998, Lakhani *et al.* 2007, Wells *et al.* 2012). Any type of cytotoxic chemotherapy has been demonstrated to have limited and transient antitumor activity in patients with unresectable or metastatic disease (Droz *et al.* 1984, Schlumberger *et al.*

1995, Orlandi *et al.* 2001). Postoperative radiotherapy of the neck can determine locoregional disease control with limited morbidity (Schwartz *et al.* 2008). In contrast, 'target therapy' with tyrosine kinase inhibitors (TKIs) represents an important therapeutic option in advanced MTC cases. As demonstrated in preclinical studies, the RET kinase receptor, the vascular endothelial growth factor receptor (VEGFR) and the EGF receptors (EGFR), whose signaling pathways contribute to the growth and invasiveness of MTC, are therapeutic targets for several TKIs (Poon *et al.* 2001, Carlomagno *et al.* 2002, Wedge *et al.* 2002, Santoro & Carlomagno 2006).

Vandetanib is an oral agent that selectively targets RET, VEGFR and EGFR signaling pathways, as demonstrated in phase II and phase III clinical trials, and it has been approved by the Food and Drug Administration (FDA) in 2011 and the European Medicines Agency (EMA) in 2013 for the treatment of patients with locally advanced or metastatic MTC (Wedge *et al.* 2002, Wells *et al.* 2010, 2012).

Over the years, starting from the time of the phase III trial (ZETA study) (Wells *et al.* 2012), we had the opportunity to treat a large number of MTC patients with vandetanib, and we observed that there was a great variability in the length and duration of the response to the drug. The aim of this study was to find those factors that could predict a relatively long and durable response of the disease to vandetanib. To this purpose, we analyzed the epidemiological, pathological, clinical and genetic features of patients with locally advanced or metastatic MTC treated with vandetanib in our center. In particular, we focused on the subgroup of those patients who were treated for at least 12 months and longer, who have been considered as long-term treated patients. A comparison between the short-term (treated for <12 months) and the long-term treated patients (≥ 12 months) was also performed to verify if we could better predict the longer responsiveness to the drug. The analysis of a subgroup of very long-term treated patients (≥ 48 months) was also carried out.

Patients and methods

Patients

We included all MTC patients who were treated with vandetanib and were followed up at our center both within AstraZeneca clinical trials and with the commercial drug after its approval. The AstraZeneca clinical trials that we could participate by enrolling patients were:

AZ58 – An International, Phase III, Randomized, Double-Blinded, Placebo-Controlled, Multi-Center Study to Assess the Efficacy of ZD6474 (ZACTIMA™) versus Placebo in Subjects with Unresectable Locally Advanced or Metastatic Medullary Thyroid Cancer (D4200C00058) (Wells *et al.* 2012); AZ68 – A Phase II, Open-Label Study to Assess the Efficacy of ZD6474 (ZACTIMA™) 100 mg Monotherapy in Subjects with Locally Advanced or Metastatic Hereditary Medullary Thyroid Cancer (D4200C00068) (Robinson *et al.* 2010); AZ88 – A Randomized, International, Open-Label, Multi-Centre, Phase III Study to Assess the Effect of a Patient Outreach Program on the Percentage of Time Patients with Locally Advanced or Metastatic Medullary Thyroid Cancer Experience Grade 2 or Higher Adverse Events during the First 12 Months of Treatment with Vandetanib (D4200C00088) (Bastholt *et al.* 2016); AZ97 – An International, Randomized, Double-Blind, Two-Arm Study to Evaluate the Safety and Efficacy of Vandetanib 150 And 300 mg/day in patients with Unresectable Locally Advanced or Metastatic Medullary Thyroid Carcinoma with Progressive or Symptomatic Disease (D4200C00097) (Hu *et al.* 2019); and AZ104 – European, Observational, Prospective Study to Evaluate the Benefit/Risk of Vandetanib (CAPRELSA™) 300 mg in *RET* Mutation Negative and *RET* Mutation Positive Patients with Symptomatic, Aggressive, Sporadic, Unresectable, Locally Advanced/Metastatic Medullary Thyroid Cancer (MTC) (D4200C00104).

Patients were all adults with histologically confirmed, unresectable, locally advanced or metastatic MTC. Patients enrolled in clinical trials were requested to satisfy the enrolling criteria of the specific clinical trial. In some trials (i.e. AZ58, AZ68, AZ88, AZ97 and AZ104) enrollment criteria included patients with radiographic disease progression per the modified Response Evaluation Criteria in Solid Tumors (RECIST) guidelines (Eisenhauer *et al.* 2009) at screening. In other trials (i.e. AZ58, AZ88, AZ97 and AZ104) patients were enrolled both for progression and if a symptomatic metastatic disease was present. In the majority of trials prior systemic anticancer therapy within 4 weeks or significant cardiac, hematopoietic, hepatic or renal failure were considered exclusion criteria. Similar inclusion criteria were used to start vandetanib after its approval, although in real life clinical judgment became fundamental. For patients treated after the approval of the drug, there was no limit on prior therapy, including exposure to other TKIs. The main exclusion criterion was the presence of cardiac disorders (i.e. QTc longer than 480 ms) or important alterations in blood

samples before starting the drug. All patients provided written informed consent to participate in the clinical trials. For patients who were treated after the approval of the drug, vandetanib treatment was started either for the evidence of progression or for symptoms according to clinical judgment. Treatment was withdrawn in case of severe adverse events or progression of disease according to RECIST. The present observational study was approved by the local ethics committee (CEAVNO – Comitato Etico Area Vasta Nord Ovest). As per the policy of our university hospital, at the time of first entering into the hospital, all patients gave their signed approval to the use of their clinical and biochemical data for research and scientific purposes.

RET genetic analysis

In 72/79 patients, tumor tissues were available for *RET* genetic analysis which was performed according to our standard protocols (Elisei *et al.* 2019). The analysis was performed in 49 primary tissues, 14 lymphnode metastases and 9 distant metastases. In all cases, blood DNA extraction and the search of germline *RET* mutations were also performed to distinguish the somatic from the germline *RET* mutations.

Data analysis

We collected all epidemiological, clinical, biochemical, electrocardiographic, radiological and pathological data of each patient both at the time of starting therapy and during follow-up. In particular, patients were investigated after 1, 3, 6 and 12 weeks in the first 3 months of therapy and then every 12 weeks. Radiographic tumor assessment with a CT scan was performed every 12 weeks using RECIST until progression or withdrawal of consent. Progressive disease (PD), stable disease (SD) and partial response (PR) were established according to RECIST. This strategy was followed both in the clinical trials and for patients treated after the approval of the drug.

For the purpose of this study, we arbitrarily distinguished two groups of patients according to the duration of treatment: short-term treated patients (duration of treatment <12 months) and long-term treated patients (duration of treatment ≥12 months). The choice to consider a cutoff of 12 months to distinguish the two groups is arbitrary but conceivable with a real effectiveness of the drug in clinical practice. We also analysed a subgroup of very long-term treated patients (duration of treatment ≥48 months).

As mentioned previously, the main objective of the present study was to identify the epidemiological, clinical, pathological and/or genetic factors of MTC patients that could predict a long and durable response to vandetanib for at least 12 months or more. In this analysis we included the objective response rate (ORR), progression free-survival (PFS), morphological (RECIST) and biochemical responses (i.e. decreases in serum levels of calcitonin [Ct] (ELSA-hCt; Cis-Bio-International, Gif sur Yvette, France, until September 2013 and with Immulite® 2000 Calcitonin, Siemens Health Care Diagnostics Products LTD, Llanberis, UK, thereafter September 2013) and carcinoembryonic antigen [CEA] (Elecsys CEA, Roche Diagnostics).

Safety and tolerability

The safety and tolerability of the treatment were evaluated by monitoring adverse events (AEs) as indicated by the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) (NIH 2009). Vandetanib dose reductions were made for grade 3 or 4 toxicities.

Statistical analysis

Pearson's chi-squared test and Fisher's exact test were used to evaluate differences in counts and frequency between groups, as appropriate. Student's *t*-test and Mann–Whitney *U* test were used to assess differences between groups for continuous variables with Gaussian and skewed distributions, respectively. The Kaplan–Meier 'time-to-event' method was used to calculate curves of progression-free survival (PFS). Progression was defined according to RECIST criteria. Patients who did not show progressive disease (PD) were included in the analysis until they stopped treatment. Statistical analyses were performed using SPSS (version 21; IBM). Alpha was set at 0.05. Data are presented as mean ± s.d. or frequency (percentage).

Results

Clinical, pathological, epidemiological and genetic features of MTC patients treated with vandetanib

Between February 2007 (when we enrolled the first patient in the ZETA study) and December 2018 a total of 79 locally advanced or metastatic MTC patients, referred to our center, started vandetanib therapy: 62 within the frame of a clinical trial and 17 after the approval of the commercial drug. Overall, 56/79 (71%) were males and 23/79 (29%) were females. The median age at the time of

Figure 1

(Panel A) Kaplan-Meier curves of progression-free survival of all our patients overlying those of the ZETA study; (panel B) Kaplan-Meier curves of progression-free survival of the group of long-term treated patients overlying those of the ZETA study. Progression was defined according to RECIST criteria. Patients who did not show disease progression were included in the analysis until they stopped the treatment.

starting therapy was 56 years (range 20–79 years) and the median age at the time of MTC diagnosis was 50 years (range 13–79). The mean time elapsing from diagnosis to start of therapy was 5.4 years. The median PFS of all enrolled patients was 47 months (95% CI: 25–91 months) which was longer than that estimated in patients treated with vandetanib in the ZETA trial (Fig. 1, panel A).

Fifty four of 79 patients (68.3%) were able to continue the vandetanib treatment for at least 12 months and represent our group of long-term treated patients. The median follow-up was 41 months (mean: 54.8 months and range: 12–140 months). As shown in Table 1, 40/54

(74.1%) were males and 14/54 (25.9%) were females. The median age at the time of starting therapy was 51.5 years (range 20–76 years) and the median age at the time of the MTC diagnosis was 45 years (range 13–73). The mean time elapsing from diagnosis to start of therapy was 5.4 years. The majority of patients (88.9%) had metastatic disease (stage IVC) when vandetanib was started. Among them, 32/54 patients (59.3%) started the therapy for progressive disease according to RECIST, while 22/54 (40.7%) started vandetanib for symptomatic metastatic disease. The median PFS of this subgroup was 87 months (95% CI: 38–91 months) (Fig. 1, panel B), which is significantly longer than that of the entire group.

The estimated ORR of this subgroup at the first morphological evaluation after 3 months of treatment was 26.0%. The best response was observed after 3 months of treatment in 50/54 (92.6%) patients. For the remaining four patients, the best response was after 6 months in three patients and after 9 months in one patient (Fig. 2).

Twenty-five of 79 patients were treated with vandetanib for less than 12 months. All these patients discontinued vandetanib before 12 months of treatment due to PD ($n=9$), an important adverse event ($n=7$), patient death ($n=6$) or consent withdrawal ($n=3$) for the deterioration of their quality of life, and these 25 patients represent our group of short-term treated patients. As shown in Table 1, 16/25 (64.0%) were males and 9/25 (36.0%) were females. The median age at the time of starting therapy was 61 years (range 24–79 years) and the median age at the time of the MTC diagnosis was 55 years (range 22–79). The mean time elapsing from diagnosis to the start of therapy was 6 years. Among them, 17/25 patients (68.0%) were enrolled for progressive disease according to RECIST, while only 8/25 (32.0%) were enrolled for symptomatic metastatic disease (Table 1).

The *RET* genetic screening of the 54 long-term treated patients showed that 8/54 (14.8%) and 46/54 (85.2%) cases were hereditary and sporadic, respectively. The study of *RET* somatic mutations was performed in a total of 43/46 (93.5%) sporadic cases, and it was found that 41/43 (95.3%) patients were carrying a *RET* somatic mutation (Table 1). Among the 25 short-term treated patients, *RET* screening showed that 4/25 (16.0%) and 21/25 (84.0%) cases were hereditary and sporadic, respectively. The study of *RET* somatic mutations was performed in a total of 17/21 (80.9%) sporadic cases, and it was observed that 14/17 (82.3%) patients were positive for a *RET* somatic mutation (Table 1). Moreover, it was observed that 3/4 (75%) patients with *RET* Val804Met mutation,

Table 1 Epidemiological, pathological, clinical and genetic features of patients, either long or short term, treated with vandetanib.

Characteristics	Long-term treated patients (n = 54)		Short-term treated patients (n = 25)		P-value ^a
	No.	% ^c	No.	% ^c	
Sex					
Male	40	74.1	16	64.0	0.43
Female	14	25.9	9	36.0	
Age at diagnosis, years					
Mean	46.3		52.2		0.08
Median	45		55		
Range	13–73		22–79		
Age at screening, years					
Mean	51.9		58.3		0.054
Median	51.5		61.0		
Range	20–76		24–79		
Extent of disease at screening					
Locally advanced	6	11.1	3	12.0	1
Distant metastases	48	88.9	22	88.0	
Stage at screening					
III	1	1.8	1	4.0	0.84
IVA	5	9.3	2	8.0	
IVC	48	88.9	22	88.0	
Progressive disease at screening	32	59.3	17	68.0	0.62
Sites of metastases					
Lymph nodes	53	98.1	22	88.0	0.09
Liver	36	66.7	18	72.0	0.8
Lung	28	51.9	15	60.0	0.63
Bone	10	18.5	8	32.0	0.25
Prior therapy for thyroid cancer					
Surgery (thyroidectomy)	54	100	25	100	1
Re-surgery	25	46.3	17	68.0	0.09
Radiotherapy	11	20.4	5	20.0	1
Chemotherapy	4	7.4	6	24.0	0.06
Tyrosine kinase inhibitors	5	9.3	7	28.0	0.04
Other	3	5.6	4	16.0	0.2
Sporadic medullary thyroid cancer	46	85.2	21	84.0	1
RET codon mutation in sporadic medullary thyroid cancer ^b					
620	1	2.4	0	0	1
634	0	0	1	5.9	1
804	2	4.6	0	0	1
883	1	2.4	0	0	1
891	1	2.4	0	0	1
918	32	74.4	12	70.6	0.47
Del ex 11	2	4.6	0	0	1
Del ex 15	2	4.6	1	5.9	1
Negative	2	4.6	3	17.6	1
RET codon mutation in hereditary medullary thyroid cancer ^b					
618	0	0	1	25.0	1
634	3	37.5	2	50.0	1
709	1	12.5	0	0	1
768	1	12.5	0	0	1
871	1	12.5	0	0	1
918	1	12.5	0	0	1
804	1	12.5	1	25.0	1
ECOG at screening					
0	43	79.6	9	36.0	0.40
1	8	14.8	10	40.0	
2	3	5.6	6	24.0	

(Continued)

Table 1 Continued.

Characteristics	Long-term treated patients (n = 54)		Short-term treated patients (n = 25)		P-value ^a
	No.	% ^c	No.	% ^c	
The largest tumor metastasis size (cm) at screening					
0–5	49	90.7	20	80.0	0.15
5–10	4	7.4	4	16.0	
>10	1	1.9	1	4.0	

^aStatistical significance was calculated via chi-squared test, Fisher's exact test, Student's *t*-test or Mann–Whitney *U* test as appropriate. ^bData are not available for three cases in the long-term treated group and for four cases in the short-term treated group. ^cFrequency was rounded to the nearest decimal digit.

which is known to be associated with *in vitro* resistance to vandetanib (Carlomagno *et al.* 2004), belonged to the long-term treated patient group and, in particular, two of them showed PR and one had SD. Their specific median follow-up was 22 months (range 12–66 months).

Efficacy of vandetanib in the long-term treated patients

At the first CT scan evaluation, performed after 3 months of treatment, 14/54 (26.0%) patients exhibited partial response (PR), 39/54 (72.2%) patients had stable disease (SD) and 1/54 (1.8%) had progressive disease (PD). In the longest term outcome, considering the last CT scan performed at data cut-off, during the treatment, 29/54 (53.7%) had SD and 25/54 (46.3%) patients had PD while no patient showed PR (Fig. 3). The duration and the type of long-term response in each patient of this group of long-term treated patients are shown in Fig. 4: after an initial response to treatment, either PR or SD, 24/54 (44.4%) patients started to progress (i.e. escape's

phenomenon) after a median follow-up of 25.5 months (range 12–91 months). So far 22/54 (40.7%) patients are still under therapy after a median follow-up of 88 months (range 17–140 months), and the disease is still stable in 20/22 (90.9%) of these patients. Among those still under therapy, 2/22 (9.1%) patients are still treated with vandetanib and had PD at the last CT scan. In one patient, progression was limited to liver metastases and was treated with transarterial chemoembolisation (TACE), while the other patient showed the appearance of a brain micrometastasis that did not require treatment but only radiological follow-up. 18/54 (33.3%) patients of this group of long-term treated patients died during follow-up after a median time survival of 25 months (mean 46.6 months and range 12–136 months).

During the follow-up of this group, we also observed a reduction in the Ct levels (median Ct at screening: 1820.5 pg/ml vs median Ct at data cut-off: 1112.5 pg/ml). At variance, CEA levels showed a tendency to a slight increase (median CEA at screening: 74 ng/ml vs median CEA at data cut-off: 98 ng/ml).

Figure 2

Morphological response (RECIST) at first CT scan after 3 months of vandetanib treatment: these responses corresponded to the best objective response (ORR) in all cases, but four cases (indicated with dots) reached the best ORR after 6 or 9 months.

Figure 3

Vandetanib treatment efficacy per RECIST: comparison of results after 3 months and at data cut-off.

Figure 4

Morphological response to vandetanib in the long-term follow-up: each bar represents one patient with his/her own specific response to treatment (PR and/or SD) and progression of the disease (PD), if occurred, during the entire period of treatment and the indication if they are still under therapy.

Safety and tolerability in the long and short-term treated patients

The common AEs observed during the treatment are summarized in Table 2. As far as the group of long-term treated patients was concerned, with the exception of hypothyroidism that was present in 100% of patients, any symptom was present in more than 48% of cases, the most prevalent being cutaneous rash. In this group, seven patients required to discontinue the treatment because of a very severe AE (i.e. heart attack, stroke, orbital edema,

hypertension, weight loss, asthenia and creatinine increase). One patient developed a QTc-prolongation but there were no reports of torsades de pointes. Other common AEs that were present in $\geq 20\%$ of patients were diarrhea (39%), asthenia (35%), hypertension (28%) and nausea/anorexia (20%) (Table 2).

As far as the group of short-term treated patients was concerned, with the exception of hypothyroidism that was present in 92%, the most prevalent AE was the cutaneous rash, but its prevalence was 28%. Also in this group, seven patients were required to discontinue

Table 2 Common adverse events related to vandetanib treatment in long and short-term treated patients.

	Long-term treated patients by Event Grade						Short-term treated patients by Event Grade					
	Total		Grades 1 or 2 ^a		Grades 3 or 4 ^a		Total		Grades 1 or 2 ^b		Grades 3 or 4 ^b	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Hypothyroidism ^c	54/54	100	54	100	0	0	23/25	92.0	23	100	0	0
Rash	26/54	48.1	22	84.6	4	15.4	7/25	28.0	5	71.4	2	28.6
Diarrhea ^c	21/54	38.9	20	95.2	1	4.8	3/25	12.0	2	66.7	1	33.3
Asthenia	19/54	35.2	17	89.5	2	10.5	5/25	20.0	4	80.0	1	20.0
Hypertension	15/54	27.8	11	73.3	4	26.7	6/25	24.0	6	100	0	0
Biochemical alteration ^a	12/54	22.2	12	100	0	0	3/25	12.0	3	100	0	0
Dysgeusia	7/54	12.9	7	100	0	0	2/25	8.0	2	100	0	0
Corneal alterations	3/54	5.5	3	100	0	0	2/25	8.0	2	100	0	0
Oral mycosis	2/54	3.7	2	100	0	0	0/25	0	0	0	0	0
Neuropathy	2/54	3.7	2	100	0	0	2/25	8.0	0	0	2	100
Headache	2/54	3.7	1	50.0	1	50.0	1/25	4.0	1	100	0	0
Weight loss	3/54	5.5	2	66.7	1	33.3	4/25	16.0	4	100	0	0
Nausea/anorexia	11/54	20.3	7	63.6	4	36.4	5/25	20.0	2	40	3	60
Pancreatitis	1/54	1.8	0	0	1	100	1/25	4.0	0	0	1	100
Orbital edema	1/54	1.8	0	0	1	100	0/25	0	0	0	0	0
QTc prolongation	1/54	1.8	1	100	0	0	2/25	8.0	2	100	0	0
Heart attack	1/54	1.8	0	0	1	100	0/25	0	0	0	0	0
Embolism	1/54	1.8	0	0	1	100	0/25	0	0	0	0	0
TIA	1/54	1.8	0	0	1	100	0/25	0	0	0	0	0

^aIn long-term treated patients, in four cases creatinine increased; in two cases proteinuria increased; four cases had AST, ALT or γ GT alterations; three cases had electrolytes alterations and one case had thrombocytopenia. ^bIn short-term treated patients, in two cases creatinine increased and in one case CPK increased. ^c $P < 0.05$ between long- and short-term treated patients by chi-squared test or Fisher's exact test as appropriate.

treatment because of a very severe AE (i.e. creatinine increased, anorexia, neuropathy, weight loss, asthenia or diarrhea). Two patients developed a QTc-prolongation but there were no reports of torsades de pointes. Other common AEs that were present in $\geq 20\%$ of patients were hypertension (24%), asthenia (20%) and nausea/anorexia (20%) (Table 2).

By comparing the AEs in the two groups of patients, we could observe that they were, in general, much more prevalent in the group of long-term treated patients with hypothyroidism and diarrhea that were significantly more prevalent ($P < 0.05$) in the long-term treated group while, at variance, weight loss and neuropathy were present only in 5.5% and 3.7% of them, while they reached the prevalence of 16% and 8.0% in the short-term treated patients ($P = \text{ns}$).

Predictors of longer responses to vandetanib

As shown in Table 1, the comparison of different clinical, epidemiological and pathological features between the two groups of short- and long-term treated patients did not show any statistically significant difference with the exception that the short-term treated patients have been more frequently previously treated with other TKIs ($P = 0.04$). However, looking carefully at the results, we could observe that the median age at diagnosis (55 vs 45 years, $P = 0.08$) and at screening (61 vs 51.5 years, $P = 0.054$) was greater in short-term treated patients than in long-term treated patients (Table 1) with a mean of 10 years of difference. A greater frequency of liver (72% vs 66.7%, $P = 0.8$), lung (60% vs 51.9%, $P = 0.63$) and in particular bone metastases (32% vs 18.5%, $P = 0.25$) was found in short-term treated patients compared with long-term treated patients. Otherwise, the long-term treated patients showed a greater frequency of lymph node metastases than short-term treated patients (98.1% vs 88.0%, $P = 0.09$) (Table 1).

Other comparisons showed that a greater number of short-term treated patients were previously treated with re-surgery (68% vs 46.3%, $P = 0.09$), chemotherapy (24% vs 7.4%, $P = 0.06$), radiotherapy (20% vs 20.4%, $P = 1$), TKIs (28% vs 9.3%, $p = 0.04$) or other treatments (16% vs 5.6%, $P = 0.2$) compared with long-term treated patients (Table 1).

A higher percentage of short-term treated patients (68.0%) compared with long-term treated patients (59.3%) were enrolled for the progression of disease, according to RECIST (Table 1), although this difference did not reach statistical significance ($P = 0.62$).

RET somatic mutations were highly frequent in both groups and their distribution was similar in the short- and long-term treated patients, and the *RET* Met918Thr mutation was the most, but equally, represented in both groups (Table 1).

No differences were observed between these two groups either when the ECOG performance status or when the tumor burden were compared.

Predictors of better outcome in the long-term treated patients group

We analyzed the predictors of the outcome of patients looking at both radiological response (PR, SD and PD) and clinical response (disappearance of the initial symptoms associated to SD) using univariate analysis.

Sex and tumor stage did not correlate with the outcome of the long-term treated MTC patients to vandetanib, while patients with age ≤ 45 years at screening showed a better outcome than patients with age > 45 years at screening ($P = 0.01$) (Table 3). A positive correlation was also observed between the absence of RECIST progressive disease at screening (i.e. patients enrolled for symptoms) and response to treatment ($P < 0.0001$) (Table 3), as well as between the presence of AEs, any type, and a better response to treatment ($P = 0.02$) (Table 3). Unfortunately, the relatively low number of cases did not allow to perform a multivariate analysis.

At variance, all the other examined features, including the presence of *RET* mutations, did not show any predictive value of the outcome of the disease in this subgroup of long-term treated patients (Table 3).

The subgroup of very long-term treated patients

Twenty-four patients belonging to the long-term treated patients were able to continue vandetanib treatment for ≥ 48 months and represent our group of 'very long' term treated patients. The median follow-up was 89.5 months (mean: 93.1 months and range 52–140 months). As shown in Table 4, 19/24 (79.2%) were males and 5/24 (20.8%) were females. The median age at the time of starting therapy was 47.5 years (range 20–75 years) and the median age at the time of the MTC diagnosis was 43 years (range 13–71). The mean time elapsing from diagnosis to the start of therapy was 5.7 years. Only 11/24 (45.8%) very long-term treated patients started the therapy for progressive disease, according to RECIST. *RET* M918T mutation was the most prevalent as in the other groups. The majority of patients (87.5%) had a metastatic

disease (stage IVC) when vandetanib was started, but the largest metastases were not bigger than 5 cm in 23/24 patients, and the ECOG performance status was 0 in 22/24 patients. The mean PFS of this subgroup was 120 months (95% CI: 105–135 months).

When we compared this subgroup of very long-term treated patients (≥ 48 months) with the short-term treated patients, we found that the very long-term treated patients were significantly younger than short-term treated patients both at diagnosis of MTC and at screening for

Table 3 Correlation between epidemiological, pathological, clinical and genetic features with the outcome of the long-term treated patients at the data cut-off of this study.

No. of patients (<i>n</i> = 54)	PD	SD	P-value ^a
Sex			
Male	19	21	0.7
Female	6	8	
Age at diagnosis			
≤ 45	10	18	0.1
> 45	15	11	
Age at screening			
≤ 45	4	14	0.01
> 45	21	15	
Stage at diagnosis ^b			
II	0	1	0.4
III	7	6	
IVA	8	14	
IVB	0	1	
IVC	8	4	
Stage at screening			
III	0	1	0.6
IVA	2	3	
IVC	23	25	
Progressive disease at screening			
Yes	22	10	<0.0001
No	3	19	
<i>RET</i> gene mutation ^c	24/51	25/51	0.1
Liver metastases	18	18	0.4
Lung metastases	12	16	0.6
Lymph node metastases	25	28	0.3
Bone metastases	6	4	0.3
Adverse events	19	28	0.02
ECOG at screening			
0	17	26	0.08
1	5	3	
2	3	0	
The largest tumor metastasis size (cm) at screening			
0–5	20	29	0.05
5–10	4	0	
> 10	1	0	

^aStatistical significance was calculated via chi-squared test or Fisher's exact test as appropriate. ^bFor five cases data were not available.

^cFor three cases data were not available.

Table 4 Epidemiological, pathological, clinical and genetic features of very long-term treated patients.

Characteristics of patients (<i>n</i> = 24)	No.	% ^b
Sex		
Male	19	79.2
Female	5	20.8
Age at diagnosis, years		
Mean	43.3	
Median	43	
Range	13–71	
Age at screening, years		
Mean	48.9	
Median	47.5	
Range	20–75	
Extent of disease at screening		
Locally advanced	3	12.5
Distant metastases	21	87.5
Stage at screening		
III	1	4.2
IVA	2	8.3
IVC	21	87.5
Progressive disease at screening	11	45.8
Sites of metastases		
Lymph nodes	23	95.8
Liver	15	62.5
Lung	12	50.0
Bone	2	8.3
Prior therapy for thyroid cancer		
Surgery (thyroidectomy)	24	100
Re-surgery	10	41.7
Radiotherapy	2	8.3
Chemotherapy	1	4.2
Tyrosine kinase inhibitors	0	0
Other	1	4.2
Sporadic medullary thyroid cancer	16	66.7
<i>RET</i> codon mutation in sporadic medullary thyroid cancer ^a		
883	1	4.3
918	12	52.2
Del ex 15	1	4.3
Negative	1	4.3
<i>RET</i> codon mutation in hereditary medullary thyroid cancer ^a		
634	3	13
709	1	4.3
768	1	4.3
871	1	4.3
918	1	4.3
804	1	4.3
ECOG at screening		
0	22	91.7
1	2	8.3
2	0	0
The largest metastasis size (cm) at screening		
0–5	23	95.8
5–10	1	4.2
> 10	0	0

^aFor one case data were not available. ^bFrequency was rounded to the nearest decimal digit.

Table 5 Correlation between the epidemiological, pathological, clinical and genetic features with the outcome of the very long-term treated patients at the data cut-off of this study.

No. of patients (<i>n</i> = 24)	PD	SD	<i>P</i> -value ^a
Sex			
Male	4	15	0.9
Female	1	4	
Age at diagnosis			
≤45	2	12	0.3
>45	3	7	
Age at screening			
≤45	1	10	0.2
>45	4	9	
Stage at diagnosis ^b			
II	0	1	0.9
III	1	3	
IVA	2	10	
IVB	0	1	
IVC	1	3	
Stage at screening			
III	0	1	0.5
IVA	1	1	
IVC	4	17	
Progressive disease at screening			
Yes	5	6	0.006
No	0	13	
<i>RET</i> gene mutation ^c	5/23	17/23	0.6
Liver metastases	3	12	0.9
Lung metastases	3	9	0.6
Lymph node metastases	5	18	0.6
Bone metastases	0	2	0.4
Adverse events	5	18	0.6
ECOG at screening			
0	3	19	0.004
1	2	0	
2	0	0	
The largest tumor metastasis size (cm) at screening			
0–5	4	19	0.05
5–10	1	0	
>10	0	0	

^aStatistical significance was calculated via chi-squared test or Fisher's exact test as appropriate. ^bFor two cases data were not available. ^cFor one case data were not available.

vandetanib treatment ($P=0.03$) and ($P=0.02$), respectively. Moreover, they had a statistically significant better ECOG performance status at screening than short-term treated patients ($P<0.001$).

Also in this subgroup we then analyzed the predictors of the outcome of patients looking at both the radiological response (PR, SD and PD) and clinical response (disappearance of initial symptoms associated to SD) using univariate analysis (Table 5). Sex, tumor stage

and age at screening did not correlate with the outcome of the very long-term treated MTC patients to vandetanib. Moreover, the presence of AEs, any type, did not correlate with a better outcome ($P=0.6$), as well as the presence of liver metastases ($P=0.9$), lung metastases ($P=0.6$), lymph nodes metastases ($P=0.6$), bone metastases ($P=0.4$) and the presence of *RET* mutations ($P=0.6$). Conversely, at the data cut-off of the present study, we found a statistically significant correlation of a better outcome (SD vs PD) with both the enrollment for symptoms ($P=0.006$) and the ECOG performance status ($P=0.004$).

Discussion

Medullary thyroid cancer is a relatively indolent tumor, and the use of systemic therapies is limited to patients with progressive or symptomatic locally advanced or metastatic disease (Elisei & Matrone 2018). Cytotoxic chemotherapy, external beam radiation, hormone therapy, cytokines and radioiodine are associated with high toxicity and low efficacy (Droz *et al.* 1984, De Besi *et al.* 1991, Brierley 2011). A new treatment is now available using TKIs (Viola *et al.* 2016, Valerio *et al.* 2017). Vandetanib is a TKI with antitumor activity against RET, VEGFR and EGFR signaling pathways which has been demonstrated to be able to prolong the PFS in patients with locally advanced or metastatic MTC in a phase III clinical trial (i.e. ZETA trial) (Wells *et al.* 2012).

In this study, we have analyzed the presence of epidemiological, clinical, pathological and genetic factors that could predict either the duration of the response to vandetanib and a better outcome in patients with locally advanced or metastatic MTC referred to our center and treated with vandetanib, within the AstraZeneca clinical trials or with vandetanib after its approval by the FDA and EMA.

When we compared the short- and the long-term treated patient groups, we did not find any epidemiological factors that could predict a longer response to vandetanib. However, a mean of 10 years younger age was observed in the group of longer term with respect to shorter term treated patients, both at the time of diagnosis and at the time of starting therapy, and when we analyzed the subgroup of very long-term treated patients, younger age, both at the time of MTC diagnosis and at the time of starting therapy, became statistically significant ($P=0.03$ and $P=0.02$, respectively). This finding suggests that, independent of the type of metastatic localization that

was not predictive of the response to therapy in any group, the youngest patients have a greater probability to continue the therapy for more than 12 months and even for more than 48 months. Although in the ZETA trial, several subgroup analyses have been performed (Wells *et al.* 2012), age was not taken into consideration; therefore we cannot confirm our observation. However, it is plausible that younger patients, despite the same tumor burden than the older patients, can better adapt to the therapy and its AEs thus allowing to continue the therapy for a longer period of time. The question of whether an earlier treatment, when patients are still young, could improve the outcome of the disease needs to be clarified.

Another interesting finding was that a larger number of cases treated for symptoms were present in the subgroup of long-term treated patients. Although in the ZETA trial many patients were enrolled for symptoms and randomized either in the drug or in the placebo arm, so far, it has not been revealed if there was a difference in their PFS (Wells *et al.* 2012). As a matter of fact, the real benefit of starting therapy only at the time the disease is progressing according to RECIST, as requested in clinical trials (Wells *et al.* 2012, Elisei *et al.* 2013), is not proven. The major reason for this indication was derived from the evidence that in many cases, even if advanced and multimetastatic, MTC growth is very slow and patients have a good quality of life that could be affected by the use of the drug (Bergholm *et al.* 1997, Hadoux *et al.* 2016, Elisei & Matrone 2018), and for this reason there is a tendency to delay the start of the drug as much as possible. Moreover, vandetanib and TKI in general have a cytostatic action, more than a cytotoxic, and thus they should be used to block the tumoral growth and if there is no growth there is no rationale to use the drug (Viola *et al.* 2016). However, vandetanib action is more than a cytostatic action as demonstrated by the cases with hypercortisolism due to ectopic ACTH that were successfully treated with the drug (Baudry *et al.* 2013, Pitoia *et al.* 2015). The advantage of using vandetanib in patients with symptomatic disease, even if the disease is not progressing, seems to be evident especially when considering that the better outcome of the very long responders significantly ($P=0.006$) correlated with the enrolment for symptoms.

A positive correlation was found in our series between the presence of AEs and response to treatment in the long-term treated patients ($P<0.0001$). This finding is new for vandetanib but is not new for other TKIs. There are reports about sorafenib treatment in hepatocellular carcinoma

that show that the development of AEs could be a marker for treatment efficacy (Granito *et al.* 2016, Lee *et al.* 2019). This observation should induce to strive to continue the therapy despite the AEs, perhaps by reducing the daily dose and finding a compromise between the continuation of the therapy and the tolerability of the AEs.

As far as the PFS of our patients was concerned, we found that when we considered all patients together, this parameter was slightly longer than that of patients treated with the drug in the ZETA trial (47 vs 30.5 months), but, if we considered only the subgroup of those who were able to maintain the therapy for at least 12 months, the PFS almost doubled from 47 to 87 months and became 120 months in the very long-term treated patients. Moreover, the best response ORR in the majority of patients of the long-term treated patients was at 3 months. These two findings suggest that the disease of long-term treated patients, after a good response in terms of maximum shrinkage within the first 3 months of therapy, thereafter become stable for a long time, even up to more than 7 years. According to these results, the escape phenomenon can arrive much later than expected or even never, and patients can find a good balance between the daily dose and the blocking of disease progression. These hypotheses also agrees well with the evidence that serum Ct values, which is mainly related to cancer activity, declined during the follow-up while CEA, which is more related to tumor burden, remained stable over the years. Moreover, there are few studies that show an increased value of tumor markers in patients who have shown a morphologic response of the disease. These results suggest that the mechanisms that control tumor growth and markers secretion, sometimes can present fluctuations during follow-up and can be dissociated in patients treated with TKIs (Schlumberger *et al.* 2009, Hajje *et al.* 2013).

In our patients, the *RET* mutation gene was present in 100% of patients with the hereditary form and in almost 90% of sporadic cases. Among all *RET* mutations, the somatic *RET* Met918Thr mutation was the most represented, and it is known that this mutation is associated with a more aggressive phenotype of MTC (Elisei *et al.* 2008, Mian *et al.* 2011). In our series, the presence of *RET* mutations was not a predictor of longer and/or better response to vandetanib, as already demonstrated in other studies performed with either vandetanib (Wells *et al.* 2010, 2012) or cabozantinib (Elisei *et al.* 2013). However, the very high prevalence of *RET* mutated cases, as expected in advanced cases (Romei *et al.* 2016) and the correspondent low prevalence of

non-mutated cases probably would require a much larger number of samples to reach statistical power. It was also demonstrated in *in vitro* studies that the presence of *RET* Val804Met mutation determines a selective resistance to various TKIs including vandetanib (Carlomagno *et al.* 2004). This mutation requires an increase of vandetanib concentration necessary to obtain 50% of activity receptor reduction (IC₅₀=5 µM). In our study, full resistance to vandetanib was observed in only one patient who presented the *RET* V804M mutation. This patient did not respond to vandetanib and discontinued the treatment after four months. The other three patients, who were carrying this *RET* mutation, showed an initial SD in one case and a PR in two cases. The possible explanation of this significant response, despite the partial resistance induced by V804M mutation, is that the drug is a multikinase inhibitor and it can likely act also through mechanisms of action independent of *RET* inhibition such as VEGFR inhibition (Ciardiello *et al.* 2004). Thus, even when this *RET* mutation is present, it is appropriate to start treatment with vandetanib, especially if no other therapeutic options are available.

It is worth noting that in our study almost 100% of patients showed an increase in TSH which requires an increase of LT4 daily dose. This evidence suggests that TSH must be monitored very frequently especially in the beginning of the treatment to allow for prompt correction of hypothyroidism that can be part of the very common symptoms of asthenia and fatigue. The majority of patients experienced at least one of the other AEs, but AEs were generally manageable with dose interruption or reduction associated with symptomatic therapies. In our series, the permanent discontinuation of vandetanib was needed only in 7/54 (13%) of patients, and these data are in agreement with the data shown in the ZETA study (Wells *et al.* 2012). In this regard, it is important to say that over the years the ability of doctors and nurses in managing AEs improved a lot, and they are now able to better manage AEs with the complicity of the patient who is invited to refer all the AEs as soon as possible.

In conclusion, with this study we found that: (a) the median PFS of our group was significantly longer than that of the ZETA trial; (b) the younger age of patients both at the time of diagnosis and at the starting time of therapy can predict a longer and more durable response to vandetanib; (c) the same observation was for patients with metastatic MTC but treated with vandetanib for symptoms; and (d) the ECOG performance status at the time of starting therapy was significantly lower in the very long-term treated patients; (e) the development of

at least one AE is also correlated with a better outcome of long-term treated patients. No other clinical or pathological features, including the distribution of *RET* mutations, were different among the groups. Larger and possibly multicentric studies are needed to verify whether early treatment with vandetanib will benefit patients who are younger, with a good ECOG performance status and with symptomatic disease, not necessarily progressing for RECIST, and to clarify the right time to start the drug and obtain a better outcome and, hopefully, a long life PFS.

Declaration of interest

E R has been a consultant for Astrazeneca and Sanofi-Genzyme for vandetanib development. However, these commitments did not have any influence on this study which has been developed independently and there was no conflict of interest in writing the paper. The other authors have nothing to disclose.

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References

- Bastholt L, Kreissl MC, Fuhrer D, Maia AL, Locati LD, Maciel L, Wu Y, Heller KN, Webster A & Elisei R 2016 Effect of an outreach programme on vandetanib safety in medullary thyroid cancer. *European Thyroid Journal* **5** 187–194. (<https://doi.org/10.1159/000448919>)
- Baudry C, Paepegaey AC & Groussin L 2013 Reversal of Cushing's syndrome by vandetanib in medullary thyroid carcinoma. *New England Journal of Medicine* **369** 584–586. (<https://doi.org/10.1056/NEJMc1301428>)
- Bergtholm U, Bergstrom R & Ekblom A 1997 Long-term follow-up of patients with medullary carcinoma of the thyroid. *Cancer* **79** 132–138. ([https://doi.org/10.1002/\(sici\)1097-0142\(19970101\)79:1<132::aid-cnrc19>3.0.co;2-5](https://doi.org/10.1002/(sici)1097-0142(19970101)79:1<132::aid-cnrc19>3.0.co;2-5))
- Brierley JD 2011 Update on external beam radiation therapy in thyroid cancer. *Journal of Clinical Endocrinology and Metabolism* **96** 2289–2295. (<https://doi.org/10.1210/jc.2011-1109>)
- Carlomagno F, Vitagliano D, Guida T, Ciardiello F, Tortora G, Vecchio G, Ryan AJ, Fontanini G, Fusco A & Santoro M 2002 ZD6474, an orally available inhibitor of KDR tyrosine kinase activity, efficiently blocks oncogenic *RET* kinases. *Cancer Research* **62** 7284–7290.
- Carlomagno F, Guida T, Anaganti S, Vecchio G, Fusco A, Ryan AJ, Billaud M & Santoro M 2004 Disease associated mutations at valine 804 in the *RET* receptor tyrosine kinase confer resistance to selective

- kinase inhibitors. *Oncogene* **23** 6056–6063. (<https://doi.org/10.1038/sj.onc.1207810>)
- Ciardiello F, Bianco R, Caputo R, Caputo R, Damiano V, Troiani T, Melisi D, De Vita F, De Placido S, Bianco AR, *et al.* 2004 Antitumor activity of ZD6474, a vascular endothelial growth factor receptor tyrosine kinase inhibitor, in human cancer cells with acquired resistance to antiepidermal growth factor receptor therapy. *Clinical Cancer Research* **10** 784–793. (<https://doi.org/10.1158/1078-0432.ccr-1100-03>)
- De Besi P, Busnardo B, Toso S, Girelli ME, Nacamulli D, Simioni N, Casara D, Zorat P & Fiorentino MV 1991 Combined chemotherapy with bleomycin, adriamycin, and platinum in advanced thyroid cancer. *Journal of Endocrinological Investigation* **14** 475–480. (<https://doi.org/10.1007/BF03346846>)
- Droz JP, Rougier P, Goddefroy V, Schlumberger M, Gardet P & Parmentier C 1984 Chemotherapy for medullary cancer of the thyroid. Phase II trials with adriamycin and cis-platinum administered as monochemotherapy. *Bulletin du Cancer* **71** 195–199.
- Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, Dancey J, Arbuck S, Gwyther S, Mooney M, *et al.* 2009 New response evaluation criteria in solid tumours: revised RECIST Guideline, 1.1 version. *European Journal of Cancer* **45** 228–247.
- Elisei R & Matrone A 2018 Medullary thyroid cancer: diagnosis and non surgical management. In *Practical Management of Thyroid Cancer, A Multidisciplinary Approach*, 2nd ed., pp 223–239. Basel, Switzerland: Springer Nature.
- Elisei R, Cosci B, Romei C, Bottici V, Renzini G, Molinaro E, Agate L, Vivaldi A, Faviana P, Basolo F, *et al.* 2008 Prognostic significance of somatic RET oncogene mutations in sporadic medullary thyroid cancer: a 10-year follow-up study. *Journal of Clinical Endocrinology and Metabolism* **93** 682–687. (<https://doi.org/10.1210/jc.2007-1714>)
- Elisei R, Schlumberger MJ, Muller SP, Schoffski P, Brose MS, Shah MH, Licitra L, Jarzab B, Medvedev V, Kreissl MC, *et al.* 2013 Cabozantinib in progressive medullary thyroid cancer. *Journal of Clinical Oncology* **31** 3639–3646.
- Elisei R, Tacito A, Ramone T, Ciampi R, Bottici V, Cappagli V, Viola D, Matrone A, Lorusso L, Valerio L, *et al.* 2019 Twenty-five years experience on RET genetic screening on hereditary MTC: an update on the prevalence of germline RET mutations. *Genes* **10** 698. (<https://doi.org/10.3390/genes10090698>)
- Granito A, Marinelli S, Negrini G, Menetti S, Benevento F & Bolondi L 2016 Prognostic significance of adverse events in patients with hepatocellular carcinoma treated with sorafenib. *Therapeutic Advances in Gastroenterology* **9** 240–249. (<https://doi.org/10.1177/1756283X15618129>)
- Hadoux J, Pacini F, Tuttle RM & Schlumberger M 2016 Management of advanced medullary thyroid cancer. *Lancet: Diabetes and Endocrinology* **4** 64–71. ([https://doi.org/10.1016/S2213-8587\(15\)00337-X](https://doi.org/10.1016/S2213-8587(15)00337-X))
- Hajje G, Borget I, Leboulleux S, Chougnet C, Al Ghuzlan A, Mirghani H, Caramella C, Hartl D, Schlumberger M & Baudin E 2013 Early changes in carcinoembryonic antigen but not in calcitonin levels are correlated with the progression-free survival in medullary thyroid carcinoma patients treated with cytotoxic chemotherapy. *European Journal of Endocrinology* **168** 113–118. (<https://doi.org/10.1530/EJE-12-0771>)
- Hu MI, Elisei R, Dedecjus M, Popovtzer A, Druce M, Kapiteijn E, Pacini F, Locati L, Krajewska J, Weiss R, *et al.* 2019 Safety and efficacy of two starting doses of vandetanib in advanced medullary thyroid cancer. *Endocrine-Related Cancer* **26** 241–250. (<https://doi.org/10.1530/ERC-18-0258>)
- Hundahl SA, Fleming ID, Fremgen AM & Menck HR 1998 A National Cancer Data Base report on 53,856 cases of thyroid carcinoma treated in the U.S., 1985–1995 [see comments]. *Cancer* **83** 2638–2648. ([https://doi.org/10.1002/\(sici\)1097-0142\(19981215\)83:12<2638::aid-cnrc31>3.0.co;2-1](https://doi.org/10.1002/(sici)1097-0142(19981215)83:12<2638::aid-cnrc31>3.0.co;2-1))
- Lakhani VT, You YN & Wells SA 2007 The multiple endocrine neoplasia syndromes. *Annual Review of Medicine* **58** 253–265. (<https://doi.org/10.1146/annurev.med.58.100305.115303>)
- Lee SW, Lee TY, Yang SS, Tong CF, Yeh HZ & Chang CS 2019 Sorafenib-related adverse events in predicting the early radiologic responses of hepatocellular carcinoma. *Gastroenterology Research* **12** 16–20. (<https://doi.org/10.14740/gr1109>)
- Mian C, Pennelli G, Barollo S, Cavedon E, Nacamulli D, Vianello F, Negro I, Pozza G, Boschin IM, Pelizzo MR, *et al.* 2011 Combined RET and Ki-67 assessment in sporadic medullary thyroid carcinoma: a useful tool for patient risk stratification. *European Journal of Endocrinology* **164** 971–976. (<https://doi.org/10.1530/EJE-11-0079>)
- NIH 2009 *Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0*. Bethesda, MD, USA: U.S. Department of Health and Human Services. (available at: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/Archive/CTCAE_4.0_2009-05-29_QuickReference_8.5x11.pdf)
- Orlandi F, Caraci P, Mussa A, Saggiorato E, Pancani G & Angeli A 2001 Treatment of medullary thyroid carcinoma: an update. *Endocrine-Related Cancer* **8** 135–147. (<https://doi.org/10.1677/erc.0.0080135>)
- Pitoia F, Bueno F, Schmidt A, Lucas S & Cross G 2015 Rapid response of hypercortisolism to vandetanib treatment in a patient with advanced medullary thyroid cancer and ectopic Cushing syndrome. *Archives of Endocrinology and Metabolism* **59** 343–346. (<https://doi.org/10.1590/2359-3997000000057>)
- Poon RT, Fan ST & Wong J 2001 Clinical implications of circulating angiogenic factors in cancer patients. *Journal of Clinical Oncology* **19** 1207–1225. (<https://doi.org/10.1200/JCO.2001.19.4.1207>)
- Robinson BG, Paz-Ares L, Krebs A, Vasselli J & Haddad R 2010 Vandetanib (100 mg) in patients with locally advanced or metastatic hereditary medullary thyroid cancer. *Journal of Clinical Endocrinology and Metabolism* **95** 2664–2671. (<https://doi.org/10.1210/jc.2009-2461>)
- Romei C, Tacito A, Molinaro E, Agate L, Bottici V, Viola D, Matrone A, Biagini A, Casella F, Ciampi R, *et al.* 2015 Twenty years of lesson learning: how does the RET genetic screening test impact the clinical management of medullary thyroid cancer? *Clinical Endocrinology* **82** 892–899. (<https://doi.org/10.1111/cen.12686>)
- Romei C, Casella F, Tacito A, Bottici V, Valerio L, Viola D, Cappagli V, Matrone A, Ciampi R, Piaggi P, *et al.* 2016 New insights in the molecular signature of advanced medullary thyroid cancer: evidence of a bad outcome of cases with double RET mutations. *Journal of Medical Genetics* **53** 729–734. (<https://doi.org/10.1136/jmedgenet-2016-103833>)
- Santoro M & Carlomagno F 2006 Drug insight: small-molecule inhibitors of protein kinases in the treatment of thyroid cancer. *Nature Clinical Practice: Endocrinology and Metabolism* **2** 42–52. (<https://doi.org/10.1038/ncpendmet0073>)
- Schlumberger M, Abdelmoumene N, Delisle MJ & Couette JE 1995 Treatment of advanced medullary thyroid cancer with an alternating combination of 5 FU-streptozocin and 5 FU-dacarbazine. The Groupe d'Etude des Tumeurs a Calcitonine (GETC). *British Journal of Cancer* **71** 363–365. (<https://doi.org/10.1038/bjc.1995.73>)
- Schlumberger MJ, Elisei R, Bastholt L, Wirth LJ, Martins RG, Locati LD, Jarzab B, Pacini F, Daumerie C, Droz JP, *et al.* 2009 Phase II study of safety and efficacy of motesanib in patients with progressive or symptomatic, advanced or metastatic medullary thyroid cancer. *Journal of Clinical Oncology* **27** 3794–3801.
- Schwartz DL, Rana V, Shaw S, Yazbeck C, Ang KK, Morrison WH, Rosenthal DI, Hoff A, Evans DB, Clayman GL, *et al.* 2008 Postoperative radiotherapy for advanced medullary thyroid cancer – local disease control in the modern era. *Head and Neck* **30** 883–888. (<https://doi.org/10.1002/hed.20791>)
- Valerio L, Pieruzzi L, Giani C, Agate L, Bottici V, Lorusso L, Cappagli V, Puleo L, Matrone A, Viola D, *et al.* 2017 Targeted therapy in thyroid cancer: state of the art. *Clinical Oncology* **29** 316–324. (<https://doi.org/10.1016/j.clon.2017.02.009>)

- Viola D, Valerio L, Molinaro E, Agate L, Bottici V, Biagini A, Lorusso L, Cappagli V, Pieruzzi L, Giani C, *et al.* 2016 Treatment of advanced thyroid cancer with targeted therapies: ten years of experience. *Endocrine-Related Cancer* **23** R185–R205. (<https://doi.org/10.1530/ERC-15-0555>)
- Wedge SR, Ogilvie DJ, Dukes M, Kendrew J, Chester R, Jackson JA, Boffey SJ, Valentine PJ, Curwen JO, Musgrove HL, *et al.* 2002 ZD6474 inhibits vascular endothelial growth factor signaling, angiogenesis, and tumor growth following oral administration. *Cancer Research* **62** 4645–4655.
- Wells Jr SA, Gosnell JE, Gagel RF, Moley J, Pfister D, Sosa JA, Skinner M, Krebs A, Vasselli J & Schlumberger M 2010 Vandetanib for the treatment of patients with locally advanced or metastatic hereditary medullary thyroid cancer. *Journal of Clinical Oncology* **28** 767–772. (<https://doi.org/10.1200/JCO.2009.23.6604>)
- Wells Jr SA, Robinson BG, Gagel RF, Dralle H, Fagin JA, Santoro M, Baudin E, Elisei R, Jarzab B, Vasselli JR, *et al.* 2012 Vandetanib in patients with locally advanced or metastatic medullary thyroid cancer: a randomized, double-blind phase III trial. *Journal of Clinical Oncology* **30** 134–141. (<https://doi.org/10.1200/JCO.2011.35.5040>)

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