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REVIEW

# Evaluating vandetanib in the treatment of medullary thyroid cancer: patient-reported outcomes

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**Abstract:** Medullary thyroid cancers (MTCs) are neuroendocrine tumors, which secrete calcitonin and carcinoembryonic antigen, both of which can serve as tumor markers. Extensive and accurate surgical resection is the primary treatment for MTC, whereas the use of external beam radiotherapy is limited. Moreover, since MTC is derived from thyroid parafollicular cells or C cells, it is not responsive to either radioiodine or thyroid-stimulating hormone suppression, and therefore, they cannot be considered as treatment strategies. Traditional therapies for advanced or metastatic progressive medullary thyroid cancer (pMTC) are poorly effective. Among the new approaches tested in clinical trials, targeted chemotherapies with tyrosine kinase inhibitors (TKIs) are now available and they represent effective interventions for progressive disease, with additional investigational options emerging. This paper reviews the efficacy and safety of vandetanib in patients with a pMTC, as it has been shown to improve progression-free survival (30.5 vs 19.3 months in controls). Vandetanib is approved by the FDA and EMA for symptomatic or progressive MTC in patients with unresectable locally advanced or metastatic disease in adults, adolescents, and children older than 5 years. The most common adverse events in vandetanib-treated patients are diarrhea, rash, folliculitis, nausea, QTc prolongation, hypertension, and fatigue. More data are required to deepen our knowledge on molecular biology of tumor and host defense, with the aim to achieve better prognosis and higher quality of life for affected patients.

**Keywords:** MTC, pediatric MTC, vandetanib, RET, VEGFR, AEs

## Introduction

Thyroid cancer (TC) has the highest incidence among endocrine tumors. The main histologic types of TC are: (a) differentiated TC of follicular origin (DTC): papillary (PTC, 80%), follicular (FTC, 11%), and Hürthle cells TC; (b) medullary TC (MTC) (developed from C cells); and (c) anaplastic TC (ATC) (2% of all TCs).

MTC is a neuroendocrine tumor of parafollicular or C cells of the thyroid gland and the production of calcitonin (CT) is a key feature of this cancer. Most MTC are sporadic, but 25% of the cases are familial as a part of multiple endocrine neoplasia type 2 syndrome (MEN2).[1]

MEN2 is subclassified into two distinct syndromes: MEN2A and MEN2B, each of which results from different mutations of the RET proto-oncogene and it is transmitted in an autosomal dominant fashion. MEN2A represents about 50% of the cases of hereditary MTC, characterized by multicentric, bilateral MTC in more than 90% of the patients, pheochromocytomas in 50% and primary hyperparathyroidism in approximately 15%. MEN2A has 3 variants: the first associated with Hirschsprung disease;[2] the second associated with cutaneous lichen amyloidosis;[3] and the latter is familial MTC (FMTC) with no other manifestations.

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In MEN2B, MTC is found in 100% of the patients, mucosal ganglioneuromas in about 90%, pheochromocytomas in 50%, and a marphanoid habitus almost in all. Because of its rapid spread, early diagnosis of MTC in MEN2B during the first year of life is crucial to achieve a successful clinical outcome.

Almost half of the patients affected with MTC have already locally advanced or metastatic disease at the time of the diagnosis and the prognosis is poor with a 10-year survival rate of 40%. Two of the most important prognostic factors are the RET status and the size of the primary lesion.[4]

The measurement of serum CT is a fundamental tool in the early diagnosis of MTC and during the follow-up, being an unavoidable sensitive and specific tumor marker.[5]

This paper reviews the efficacy and safety of vandetanib in patients with advanced or metastatic progressive MTC, reporting patient outcomes and discussing the most common adverse events reported in literature. We have searched in PubMed, the following keywords: medullary thyroid cancer, and vandetanib. All papers searched were reviewed, and clinical studies were included, after discarding those that presented duplicated published results.

## Genetic alterations in MTC

Among almost all familial MTC cases and in around 40% of the sporadic ones, gain of function mutations of the tyrosine kinase receptor (TKR) RET gene have been found.[6]

The proto-oncogene RET, allocated on chromosome 10q11.2, encodes for a transmembrane TKR, expressed on thyroid C cells.[7]

The fusion of the 3′ end of the RET gene to the 5′ of different genes gives rise to RET/PTC rearrangements, leading to uncontrolled proliferation by the activation of the transcription of RET TK domain.[7,8] RET/PTC rearrangements have been demonstrated in approximately 20–40% of the sporadic PTC,[9] in thyroid adenomas and benign lesions.[10] There are at least 13 subtypes of RET/PTC rearrangements, and the most two common are RET/PTC1, originated from the fusion with the CCDC6, and RET/PTC3, derived from the fusion with the NCOA4.[11]

Activating mutations of RET are present in 98% of the familial MTC and approximately 40% of the sporadic MTC. Germline gain of function RET mutations have been reported in 98% MEN2A families, 85% FMTC, and more than 98% MEN2B.[12]

Cys-634 mutations are more frequent in MEN2A, while M918T and A883F in MEN2B.[6] Among sporadic forms of MTC, the most common mutation is M918T, which is considered a negative prognostic factor since these cases seem to show more aggressiveness and worse clinical outcomes.[13]

Sporadic MTC can be featured with mutations other than RET ones, such as somatic H-RAS mutations (in about 56% of the cases), but also KRAS, or rarely NRAS.[14]

Another proto-oncogenes thought to play a relevant role in the carcinogenesis of many tumors, including MTC, is mesenchymal–epithelial transition (MET) whose genetic product, hepatocyte growth factor (HGF) receptor (HGFR or c-MET), has TK activity.[15] The growth rate and the risk of distant metastasis are enhanced in c-MET mutated cell lines, where an increased level of proliferation, neoangiogenesis, and invasiveness is reported.[16] Furthermore, patients with MET activated cancers showed worse prognosis and higher rates of therapeutic failure.[17] Since high level HGF has been found in a subset of MTCs,[18] MET is considered as a promising new drug target of TC, with first encouraging therapeutic results.[17]

Moreover, a higher expression of VEGF-A, VEGF-C, VEGFR-1, -2, -3 is reported in MTC,[19] and in particular VEGFR-2 results to be overexpressed and this correlates with metastasis.[13] Many antiangiogenic factors able to bind and block VEGF have been tested, but the majority of patients did not show persistent remission with antiangiogenic therapy alone.[20]

Upregulation of EGFR and mammalian target of rapamycin (mTOR) intracellular signaling pathway may represent additional key molecular actors in familial MTC.[21]

The EGFR contributed to the activation of RET kinase, growth stimulation, and signaling,[22] evidencing the leading role of RET-related signaling in MTC carcinogenesis along with other molecular pathways, which are not completely elucidated yet.[23]

Furthermore, the genetic mutations analysis of two MTCs has detected oncogenic BRAF fusion in one of them.[24]

## MTC therapy

Current guidelines on management of MTC from ATA recommend total thyroidectomy and bilateral central compartment lymph nodes dissection for cancer confined to the thyroid, deciding on prophylactic lateral neck dissection based on serum CT levels.[25] Patients with MTC involving

the thyroid, and known cervical lymph nodal involvement preoperatively, should undergo to total thyroidectomy with bilateral central compartment and involved lateral neck compartment(s) dissection.[25] Adjuvant therapy with radioiodine is contraindicated in MTC since C cells do not concentrate iodine.

In patient with locally advanced or metastatic disease, other therapeutic options are needed to improve locoregional control beyond surgery, as external beam radiotherapy (EBRT) and systemic chemotherapy (doxorubicin alone or combined with other agents, as 5FU and dacarbazine). Since these interventions have shown not to be very effective, new approaches were necessary.

Nowadays new targeted agents are available for the treatment of progressive or recurrent locally advanced or metastatic MTC, as the FDA and EMA approved tyrosine kinase inhibitors (TKIs) vandetanib (2010) and cabozantinib (2012), based on phase I, II, and III clinical trials.[25–28]

During the last 10 years, several potential TKIs (as lenvatinib, axitinib, motesanib, pazopanib, cabozantinib, sorafenib, vandetanib, and sunitinib) have been tested alone or in association, in aggressive DTC or MTC, but only a few have been approved.[29–31]

## Vandetanib

Vandetanib (trade name CAPRELSA®) is an oral inhibitor that targets RET, VEGFR-2, VEGFR-3, and EGFR and slightly VEGFR-1 involved in tumor proliferation, angiogenesis, invasion, and metastasis of MTC.[29]

As vandetanib interferes with EGFR-induced production of angiogenic growth factors, it has an "indirect" effect on angiogenesis *in vivo*.[32]

A paper evaluated the vandetanib pharmacokinetics (after a single oral dose) to healthy subjects.[33] Its $t_{½}$ is of about 10 days after a single oral dose. Food does not significantly interfere with the entity of absorption. Upon 21 days about two-thirds of the dose were recovered in feces (44%) and in urine (25%). N-desmethyl and N-oxide metabolites or unchanged vandetanib were observed in plasma, urine, and feces.[33]

## Clinical trials with vandetanib in MTC

### Adult patients with MTC

In 2010, 2 studies evaluated the effect of vandetanib in MTC. In the first study, 30 patients with unresectable, locally advanced, or metastatic hereditary MTC (70% of whom with MEN2A) were administered with vandetanib (300 mg/day).[34] The mutated codons were: 634 (in 33% of the cases), 618 (27%), 620 (13%), 918 (13%), 791 (7%), 768 (3%), and 891 (3%). Confirmed partial response (PR) was detected in 20% (6) of participants and a stable disease (SD) in 53% (16) lasting 24 weeks with a practical common adverse event (AE).[34] In the other study, vandetanib was also tested at a lower dose of 100 mg/day in 19 patients affected by advanced hereditary MTC with similar results (16% PR, 53% SD, for 24 weeks). However, during the trial, 4 patients with disease progression were switched to the higher dose of 300 mg.[35]

The ZETA trial (randomized, double-blind, placebo-controlled multicentre phase III trial) was carried out in patients with advanced (5%) or metastatic (95%) MTC, treated with vandetanib [300 mg daily administered until progressive disease (PD)] in an open-label phase.[36] Inclusion criteria were confirmed diagnosis of unresectable, locally advanced or metastatic hereditary or sporadic MTC; presence of a measurable tumor; capability of swallowing medication.

As high as 10% of recruited patients had hereditary MTC, 90% sporadic or unknown origin MTC; 56% had RET mutations; 2% were RET mutation negative; and 41% unknown. After a median follow-up of 24 months, the progression-free survival (PFS) was superior in patients treated with vandetanib versus placebo (30.5 vs 19.3 months; $P<0.001$), whereas no difference was observed in overall survival (OS) between the two groups. CT (69% vs 3%) and carcinoembryonic antigen (CEA) (52% vs 2%) response rate resulted higher ($P<0.001$). No difference was found between patients with sporadic RET-positive-MTC, M918T-negative tumors or RET unknown status.[36]

After these indisputable results, in 2011 vandetanib gained first the FDA and, then, the EMA approval for treating unresectable, locally advanced or metastatic MTC in patients with symptomatic or PD.[37]

Additionally, more data from a retrospective study supported the positive clinical impact of vandetanib on 11 patients with progressive metastatic MTC and 36% PR.[38]

Another study evaluated the efficacy of vandetanib, outside any trial, in 68 patients treated from August 2010 to February 2012.[39] The obtained data were analyzed in 60 MTC patients, as 8 patients were excluded; 6 had hereditary MTC. Median PFS was 16.1 months. As high as 93% had metastatic disease, in the liver (53%), mediastinum

(82%), lung (53%), or bones (65%), and 4 had only locally advanced disease. There was a complete response in 1 patient, PR in 12 (20%), SD in 33 (55%), and progression in 7 (12%). The main AEs were skin toxicity, diarrhea, and asthenia. Twenty-five patients discontinued treatment for disease progression (range 0.3–29 months), 16 patients (27%) discontinued treatment for toxicity, and 1 patient died from vandetanib-induced cardiac toxicity.[39]

A phase I/II, open-label, nonrandomized study investigated the safety and tolerability of vandetanib (300 mg daily) in Japanese patients with unresectable locally advanced or metastatic MTC.[40] Fourteen patients received vandetanib. All of them experienced at least one AE (79% diarrhea, 64% hypertension, and 43% rash), of ≥3 grade in half of cases. Eleven patients (79%) interrupted the treatment, and the dose was reduced in 8 patients (57%). One patient discontinued treatment because of a serious AE (interstitial lung disease). No patients met the prespecified criterion for QTc prolongation. The ORR was 38% and PFS at 12 months was 85%.[40]

Another paper assessed the role of metabolic imaging using $^{18}$F-FDG PET/CT shortly before and 3 months after initiation of TKI treatment in 18 patients with advanced and progressive MTC.[41] The $^{18}$F-FDG $SUV_{mean/max}$ of the metabolically most active lesion and clinical parameters [as RET mutational status, tumor marker doubling times (calcitonin, carcinoembryonic antigen), prior therapies, and disease type] were used to estimate PFS and OS. Nine patients experienced disease progression after about 2.1 years considering the median follow-up of 5.2 years, while the others had ongoing disease control (5 PR and 4 SD). Eight/nine patients with PD died from MTC after about 3.5 years from the beginning of the treatment. A pretherapeutic $SUV_{mean}>4.0$ predicted a significantly shorter PFS (1.9 vs 5.2 years, $P$=0.04). Moreover, sustained high $^{18}$F-FDG uptake at 3 months with an $SUV_{mean}>2.8$ predicted an unfavorable prognosis, with a PFS of 1.9 years ($P$=0.3). It was concluded that a low tumor metabolism with an $SUV_{mean}<4.0$ before treatment is associated with a longer PFS.[41]

The prognostic value of intratumoral textural features (TF) and volumetric parameters (total lesion glycolysis, TLG) derived by pre-therapeutic $^{18}$F-FDG PET was investigated in 18 patients with progressive MTC.[42] The TF complexity and TLG evaluated before vandetanib initiation successfully differentiated between low- and high-risk patients. A total of 10/18 patients were assigned to the high-risk group with an OS of 3.3 years by the complexity (vs low-risk group, $P$=0.03). A total of 11/18 patients were allocated to the high-risk group (OS=3.5 years vs low-risk group, $P$=0.005) by the evaluation of baseline TLG. The hazard ratio for cancer-related death was 6.1 for complexity (TLG, 9.5). The obtained results led to conclude that TF complexity and the volumetric parameter TLG are both independent parameters for OS prediction.[42]

A systematic review and a meta-analysis adopting standardized RECIST criteria as end-points have recently evaluated the efficacy of vandetanib.[43] Among the 487 screened articles, 10 (2 randomized controlled trials and 8 observational longitudinal studies) were included. No data were available for OS. No heterogeneity nor publication bias was recorded in the pooled rate of complete response (0.7%) and stable disease (47%). Vandetanib should be considered as a promising treatment in advanced MTC, even if data based on RECIST endpoints do not provide clear evidence on its efficacy.[43]

A study (Nbib1496313) evaluated the benefit-risk of 2 starting doses of vandetanib in patients with symptomatic or progressive MTC.[44] Patients received vandetanib 150 or 300 mg daily for up to 14 months (Part A). Then, they could enter an open-label phase (Part B) investigating vandetanib 100, 150, 200, and 300 mg daily doses. Eighty-one patients were randomized in Part A and 61 patients entered Part B, of whom 37 (60.7%) received 2 years of treatment. OR was in 25% of the patients at 14 months [OR rate, 0.29 [95% confidence interval (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 frequent AEs were asthenia, QTc prolongation, diarrhea, hypocalcemia, keratopathy, and hypokalemia, generally higher with the dose of 300 mg. 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 versus 150 mg as initial dose. It was concluded that 300 mg vandetanib is the most appropriate starting dose.[44]

A review evaluated the clinical effectiveness and safety of cabozantinib and vandetanib, the incremental cost-effectiveness of cabozantinib and vandetanib versus each other and best supportive care.[45] Moreover, the paper aimed to identify key areas for primary research and estimate the overall cost of these treatments in England. It was reported that cabozantinib and vandetanib improve PFS more than the placebo, even if significant OS benefits were not shown. The economic analysis reports that within the EU-label population, the incremental cost-effectiveness ratios

(ICERs) for cabozantinib and vandetanib are superior to £138,000 per quality-adjusted life-year (QALY) gained, and for vandetanib higher than £66,000.[45]

Actually, a first phase IV randomized trial is underway to investigate disparities in response to vandetanib in MTC patients administered with 300 mg versus 150 mg/day Table 1.[46]

## Pediatric MTC

Vandetanib has been studied also in a phase I/II trial which enrolled children (5–12 years) and adolescents (13–18 years) affected by metastatic or locally advanced MTC: the 16 participants took a dose of 100 mg twice daily and it was well tolerated and highly effective.[47]

In recent times, a case report describing a child affected by MEN2B with advanced, metastatic MTC and treated with vandetanib showed SD for almost 4 years characterized by fall in CT levels and shrinkage of tumor, lymphatic, and pulmonary metastasis.[48]

A paper evaluated toxicities and disease status in 17 patients (of whom 16 with a RET p.Met918Thr germline mutation) taking vandetanib for hereditary, advanced MTC.[49] The treatment lasted 6.1 (0.1–9.7+) years and has been continued in 9 patients. PR was shown in 10, SD in 6, and PD in 1 patient. Duration of response was 7.4 (0.6–8.7+) and 4.9 (0.6–7.8+) years in patients with PR and SD, respectively. Six patients died 2.0 (0.4–5.7) years after progression. Median PFS was 6.7 years (95% CI: 2.3 years-undefined) and 5-year OS was 88.2% (95% CI: 60.6%-96.9%). Among the 16 patients with a RET p.Met918Thr mutation, PFS was 6.7 years (95% CI: 3.1-undefined) and 5-year OS was 93.8% (95% CI: 63.2%-99.1%). DNA sequencing in 11 tissue samples showed an increase in copy number alterations across the genome suggesting a potential mechanism of drug resistance. The authors concluded that vandetanib is safe with sustained responses in children and adolescents with hereditary MTC.[49]

The case of a pediatric patient with metastatic MTC secondary to MEN2B, treated with vandetanib, has been described.[50] At presentation, he had an inoperable primary tumor, with carotid encasement, and pulmonary metastases. After the treatment with vandetanib, CT and CEA levels fell significantly, primary tumor maximal diameter decreased by 68%, and pulmonary metastases were no longer detectable, permitting the surgical resection of the primary tumor. The patient remained stable up to 6 years after the treatment, with no toxicity.[50]

All these data encourage the administration of vandetanib also among pediatric MTC cases Table 2.

## Vandetanib in MTC-related ectopic Cushing syndrome (ECS)

ECS is an uncommon clinical manifestation of MTC and bilateral adrenalectomy is mandatory in the majority of these patients. However, vandetanib could be considered a promising alternative medical therapy for ECS as it has been reported in one MTC patient for the first time.[51]

Similarly, a second paper reported the case of a 17-year-old adolescent affected by MEN2B and metastatic MTC complicated with ECS, who has been treated with vandetanib achieving subsequent decline of serum cortisol level and amelioration of clinical symptoms.[52]

Further, a woman with 16 years history of sporadic MTC complicated with lymph node and liver metastases was diagnosed with ECS. A dose of 300 mg/day vandetanib was then administered and biochemical and clinical remission was achieved 1 month later. No improvement of the tumor was seen instead.[53]

Therefore, vandetanib seems to represent a valid medical therapeutic option for ECS complicating MTC.

Recently it has been described the case of a 58-year-old man with MTC and CS, resistant to various combined anti-cortisolic drugs.[54] After the beginning of the treatment with vandetanib, a reversal of the hypercortisolism was shown, with no changes in tumor size. The treatment was interrupted 2 times, the first for 45 days owing to side effects and the second for 10 days to schedule surgical debulking. Plasma cortisol and CT levels rose after the interruption of the treatment and lowered upon its reintroduction. Before the therapy with vandetanib, a strong ACTH increase after desmopressin stimulation was shown, as reported in other cases of CS linked to MTC. On the other hand, during the vandetanib treatment, a mild ACTH response to desmopressin was reported, suggesting a TKI anti-secretory action. No signs of recurrence of hypercortisolism were reported after 3 years and 8 months from the beginning of the therapy, indicating the long-term effectiveness of vandetanib in maintaining the control of hypercortisolism in MTC-related CS.[54]

## CT, CEA, miRNA for monitoring vandetanib treatment

The first 2 phase II trials of vandetanib in MTC detected lower levels (more than 50%) of CT and CEA, even if only

**Table 1** Clinical trials with vandetanib in MTC adult patients

| No. of pts | CR% | PR % | SD % | PD% | PFS (months) | Ref |
|---|---|---|---|---|---|---|
| 30 | 0 | 20 | 53 (≥24 weeks) | 3 | 27.9 | Wells SA Jr et al[34] |
| 19 | 0 | 16 | 53 (≥24 weeks) | 16 | Not determined | Robinson BG et al[35] |
| 331 pts (231 treated with vandetanib, 100 with placebo) | Not evaluable/ unknown | Not evaluable/ unknown | Not evaluable/ unknown | Not evaluable/ unknown | 30.5 vs 19.3 months ($P$<0.001) in patients treated with vandetanib vs placebo | Wells SA Jr et al[36] |
| 62 pts (11 with MTC treated with vandetanib) | | 36 | 27 (≥24 weeks) | 9 | NR | Massicotte MH et al[38] |
| 60 | 1.7 | 20 | 55 | 12 | 16.1 months | Chougnet CN et al[39] |
| 14 (1 patient discontinued treatment because of a serious adverse event) | | 38 | 62% (≥12 weeks) | 31% | 85% at 12 months | Uchino K et al[40] |
| 18 | 5.6 | 44.4 | 44.4 | 50 | A pretherapeutic $SUV_{mean}$ >4.0 predicted a significantly shorter PFS (1.9 vs 5.2 years, $P$=0.04). A $SUV_{mean}$ >2.8 predicted an unfavorable prognosis (PFS of 1.9 years; $P$=0.3). It was concluded that a low tumor metabolism with an $SUV_{mean}$ <4.0 before treatment is associated with a longer PFS. | Werner RA et al[41] |

**Abbreviations:** CR, complete response; MTC, medullary thyroid cancer; NR, not reached; PD, progressive disease; PR, partial response; SD, stable disease; PFS, progression-free survival; pts, patients; No., number.

**Table 2** Clinical trials with vandetanib in pediatric MTC

| No. of pts | CR % | PR % | SD % | PD% | PFS (months) | Ref |
|---|---|---|---|---|---|---|
| 16 (15 with M918T RET germline mutations) | | 47 | 1 pt discontinued therapy with 25% decrease in tumor diameter after 29 cycles | 2 pts who achieved PR (subject 01 and 04) subsequently had PD after 44 or 48 cycles of vandetanib | | Fox E et al[47] |
| 17 (16 had a RET p.Met918Thr germline mutation) | | 59 | 35.3 | 5.9 | 80.4 (in the 16 pts with a RET p.Met918Thr germline mutation) | Kraft IL et al[49] |

**Abbreviations:** CR, complete response; MTC, medullary thyroid cancer; NR, not reached; PD, progressive disease; PR, partial response; SD, stable disease; PFS, progression-free survival; pts, patients; No., number.

CEA, and not CT, seemed to correlate better with the tumor response.[34,35]

To better explore the real value of CT and CEA levels during the treatment follow-up, 21 patients with advanced MTC and under vandetanib (3000 mg per os) therapy were investigated.[55] To reassess the disease stage, the patients underwent total body computed scan every 3 months along with a blood sample, drawn to check the CT and CEA levels. At the beginning of follow-up [range, 97–1140 days], dropping levels of both CT and CEA ware observed in 71.4% and 61.9% of the patients. Later, the rise in CT≥40% between 2 subsequent measurements was associated with a PD (71% sensitivity, 83% specificity, and 82% accuracy). Fluctuations in CEA circulating levels were not significant for PD instead. Thus, a new relevant (≥40%) increment of CT levels during vandetanib therapy might be considered a predictor of PD.[55]

However, it is necessary to collect more data to establish the accurate role that CT and CEA levels can play in the follow-up and the decision-making process during the treatment of MTC with vandetanib.

Lastly, the measurement of the miRNA miR-375 levels has been suggested as a novel marker of sensitivity and subsequent eligibility for vandetanib therapy, since a recent study reported that MTC samples with decreased cell proliferation and augmented response to vandetanib were distinguished by higher levels of miR-375 (and lower expression of SEC23A).[56]

## Adverse events

More than 20% of the patients treated with vandetanib use to suffer at least of one of the following: diarrhea, fatigue (of at least grade 3), nausea, abdominal pain, headache, rash and folliculitis, reduced appetite, and acne; more severe side effects are hypocalcemia, hypertension crisis, and QTc prolongation.[34–36,47,57,58]

The half-life of vandetanib is 19 days, and this must be taken into account in the management of AEs.[59,60]

In the case of AEs grade 1 or 2, they may ameliorate reducing the dose of vandetanib, while for AEs grade 3 or 4, it is recommended to stop the treatment till the resolution of AEs is reached; later the therapy can be restarted at a lower dose.[35]

### Dermatological AEs

The ZETA trial reported dermatological AEs in 45% of the patients.[36]

As EGFRs are highly expressed in epidermis and its annexes, a papulopustular eruption is often caused by vandetanib, due to EGFR inhibition, leading to hyperkeratosis, follicle obstruction and inflammation of the pilosebaceous follicle.[61]

Other dermatological AEs are photosensitivity, paronychia, xerosis, finger clefts, genital skin reactions, subungual splinter hemorrhages, blue-dots, and hair changes.[61]

A systematic review and meta-analysis aimed to evaluate the incidence and risk of developing a rash in 2961 MTC patients administered with vandetanib, showing a frequency of new cases of all-grade and high-grade rash of 46.1% and 3.5%, respectively.[62]

Photoallergic dermatitis is another possible AE that can ameliorate by discontinuation of vandetanib, and the use of topical and oral steroid administration.[63]

Rare AEs are pruritus, mucositis, and erythrodysesthesia; one case of Stevens–Johnson syndrome has been shown.[64]

In children, dermatological AEs are similar as in adults.[65]

Even if dermatological AEs are manageable, their incidence is quite elevated, and for this reason, their early detection and early control are crucial to diminish the risk to reduce the dose of the treatment or interrupt it.

## Gastrointestinal AEs

A recent meta-analysis evaluated the relative risk and incidence of vandetanib-associated gastrointestinal AEs in 22 trials with 6382 patients with cancer. The incidences of all-grade gastrointestinal AEs were anorexia 24%, constipation 17%, diarrhea 46%, nausea 29%, and vomiting 17%.[66]

The most frequent gastrointestinal AEs reported by the ZETA trial were diarrhea (56% of the patients), reduced appetite (21%), nausea (33%), abdominal pain (14%), and vomiting (14%),[36] leading to the interruption of the therapy. It is important to educate patients with dietary measures.

As the elevated hormone production by MTC may accelerate the intestinal transit, diarrhea is frequent, and the treatment with vandetanib can ameliorate it. Diarrhea treatment is based on correct hydration and possibly loperamide.

A systematic review and meta-analysis of 13 clinical trials evaluated the total risks of all-grade and high-grade diarrhea during vandetanib administration in 3264 patients.[67] The overall incidences of all-grade and high-grade diarrhea were 52.1% (CI, 48.3%–55.8%) and 5.6% (95% CI, 4.4%–76.7%), respectively. The risk ratios of the all-grade and high-grade diarrhea in vandetanib-treated patients versus controls were 1.932 (95% CI, 1.746–2.138; $P<0.001$) and 3.190 (95% CI, 2.061–4.938; $P<0.001$), respectively. The highest incidence of all-grade diarrhea (78.85%) and high-grade diarrhea (17.31%) was reported in patients with small-cell lung cancer, while the lowest in patients with hepatocellular carcinoma and non-small-cell lung cancer, respectively.[67]

The administration of 5-HT3 antagonists (as ondansetron) is discouraged to treat nausea for the risk of prolongation QTc interval,[68] and metoclopramide should be administered carefully. Palonosetron is another option in antiemetic therapy.[69]

Gastrointestinal (GI) AEs occurring with the anti-angiogenic activity of multikinase inhibitors (MKIs) that target VEGFR include hemorrhage, and intestinal perforation and GI and non-GI (as tracheal or esophageal) fistula.[59,70,71] Vandetanib can cause mild and moderate bleeding events in 14% of the patients and intestinal perforation in about 0.4%, even if serious bleeding and intestinal perforation were not reported in the phase III study.[36,69] The risk of intestinal perforation with MKIs is higher in patients with a history of bowel liabilities (as diverticulitis or colitis).

Owing to these serious and potentially fatal events, patients with a recent history of hemorrhage or significant hemoptysis should not receive vandetanib and those treated should be monitored for possible perforation or fistula.[70–73] Using MKI treatment, perforation usually occurs at sites of prior surgery or earlier irradiation.[74] In the case of perforation, the therapy should be interrupted, and the patient should be monitored for a possible reparative surgery. An altered wound healing can derive from decreased perfusion.[71,74] MKI treatment should be interrupted more than 2–4 weeks before undergoing major surgery (and more than 10 days before any surgery), and it should be resumed postsurgery according to clinical judgment of adequate wound healing, even if no major bleeding complications have been reported after emergent surgery of patients who had not withhold the drug.[74]

In the case of severe GI AEs, vandetanib should be stopped until the amelioration of the symptoms.

## Cardiovascular AEs

Vandetanib is associated also with cardiovascular AEs, as arterial thrombosis, hypertension, ventricular dysfunction,

bleeding, fatal cardiac failure, and QTc interval prolongation.[75,76]

The incidences of all-grade and high-grade hypertension have been investigated in 3154 patients, showing to be 24.2% [CI, 18.1–30.2%] and 6.4% (95% CI, 3.3–9.5%).[77] Hypertension is much more common among patients treated for MTC.[77] Appropriate blood pressure monitoring is needed and, if necessary, ACE inhibitors are suggested as first-line therapy, whereas calcium antagonist and beta-blockers can be added secondly.

One case of sudden cardiac death after 14 months of vandetanib therapy has been reported. The autopsy revealed diffuse signs of drug-induced cardiotoxicity with marked myocyte degeneration especially at the subendocardial zones and papillary muscles.[75]

Another similar case of drug-induced cardiotoxicity has been described.[39]

QTc prolongation along with other arrhythmia is potential AEs of TKI, included vandetanib. During the ZETA trial, QTc higher than 500 ms was diagnosed in 14% of the patients under vandetanib therapy and 2 patients with QTc more than 550 ms died, 1 for sepsis and the other because of heart failure.[60]

Before starting vandetanib, it is recommended to perform an electrocardiogram (ECG) and a cardiac ultrasound. The therapy should not be initiated if the QTc is more than 450 ms (US) or 480 ms (EU) and, during treatment, the concurrent use of other drugs known to prolong the QTc interval should be avoided. In addition, strict monitoring of electrolyte and circulating thyroid-stimulating hormone (TSH) levels is necessary as well. At approved dosage, vandetanib causes only a mild QTc prolongation with limited clinical impact,[76] but considering the risk of torsades de pointes and sudden death, vandetanib distribution is limited through a CAPRELSA Risk Evaluation and Mitigation Strategy (REMS) Program.[78]

Prolongation of the QTc interval is a serious complication deriving from the drug's interactions with the myocardial potassium ion channel that takes part in cardiac repolarization.[69,79] In a phase III study of vandetanib, 14% of the patients had QTc prolongation, and this event was of grade 3 or 4 severity in 8% of the patients.[36] QTc prolongation more than 500 ms was not reported in the phase III study of cabozantinib.[73] The treatment with vandetanib can cause torsades de pointes, ventricular tachycardia, and sudden death,[69] but these ones have not been shown in the vandetanib phase III trial.[36] In presence of congenital long QT syndrome, a history of torsades de pointes, bradyarrhythmias, or uncompensated heart failure, a pretherapy QTc interval higher than 450 ms (more than 480 ms in the European Union), hypomagnesemia, hypocalcemia, or hypokalemia, vandetanib should not be administered. If a patient develops a QTc interval higher than 500 ms, vandetanib should be interrupted until it returns inferior to 450 ms; then vandetanib could be resumed at a lower dose. Of note, owing to the 19-day half-life of vandetanib, a prolonged QT interval may not be solved rapidly.[69]

An ECG, circulating electrolyte and TSH levels, should be performed at baseline, at 2–4 weeks, and 8–12 weeks after the beginning of the therapy, and then every 3 months, in particular in patients with diarrhea. Moreover, they should be done also after any reduction or interruption of vandetanib lasting more than 2 weeks. Hypocalcemia, hypomagnesemia, or hypokalemia should be corrected before the beginning of the treatment with vandetanib. Furthermore, it should not be administered with agents that prolong the QT interval (as methadone, amiodarone, chloroquine, granisetron, clarithromycin).

QTc prolongation and advanced MTC are both fatal, and the risks and benefits of vandetanib must be carefully considered.

## Thyroid dysfunctions

Alongside other TKI, thyroid dysfunctions are observed also in patients treated with vandetanib.[80]

One study enrolled 19 patients on vandetanib therapy (100 mg) for locally advanced or metastatic hereditary MTC. They were already on thyroid hormone replacement because of prior thyroidectomy. Baseline TSH data were available for 17 patients, and in these patients, TSH levels increased [5.1-fold (mean) and 7.3-fold (median) increases over baseline]. Although no symptomatic hypothyroidism occurred, 2 patients needed an increase of levothyroxine (L-T4) therapy.[35]

Furthermore, the thyroid function has been also investigated in 13 pediatric patients affected by MEN2B with MTC.[81] After more than 6 months of vandetanib therapy, 11 (85%) patients, who had prior total thyroidectomy, showed higher TSH level. The peak was achieved after a median time of 1.8 months (0.3–9.3). The dose of L-T4 was increased from a baseline of 91 mcg/m(2)/day (±24) to 116 mcg/m(2)/day. The other 2 patients with intact thyroid had normal free T4 and TSH values throughout the study. These data support the hypothesis that

vandetanib may impair the pituitary sensitivity for TSH or the peripheral metabolism of thyroid hormones in patients with prior thyroidectomy. Thus, a watchful approach for thyroid function is recommended in patients on TKI, especially in children, since the adjustment of levothyroxine dose might be needed during the first period of vandetanib therapy as it has been demonstrated by the study mentioned above.[81]

## Other AEs

Hypocalcemia, increased transaminase levels, headache, hypoglycemia, and fatigue are other common side effects.[80]

The basal and stimulated adrenal function in 12 patients with advanced radioiodine-refractory (RAI-R) DTC and MTC treated with lenvatinib or vandetanib, respectively, was evaluated.[82] Among the 12 patients, 10 had fatigue and a progressive ACTH increase with normal cortisol levels. After ACTH stimulation, 6/10 patients had a slight cortisol response, confirming the diagnosis of primary adrenal insufficiency (PAI). Patients with PAI were administered with cortisone acetate replacement therapy, with a significant amelioration of fatigue, indicating that the occurrence of PAI may be a frequent cause of fatigue during the treatment with lenvatinib and vandetanib.

An open-label, multicenter, phase III study evaluated whether more common contact with vandetanib-treated patients reduced AEs of Common Terminology Criteria for Adverse Events (CTCAE) grade 2 or higher.[83] Patients with locally advanced or metastatic MTC were randomized to a patient outreach program (outreach; n=103) or a standard AE monitoring schedule (vandetanib control, who received vandetanib at 200 or 300 mg/day, according to the creatinine levels at screening; n=102) for 52 weeks. Patients in the outreach arm were contacted every 2 weeks for specific AE questioning related to diarrhea, nausea, vomiting, fatigue, headache, and rash. The mean percentage of time needed to experience at least one AE of grade 2 or higher was higher for the outreach group (51.65%) than for the vandetanib control group (45.19%), even if not significantly different. The most common AEs were diarrhea (56.9% for the outreach group vs 46.6% for the vandetanib controls), hypertension (36.3 vs 31.1%), rash (25.5 vs 24.3%), and nausea (25.5% vs 18.4%), and the most common AEs of grade 2 or higher were hypertension (33.3 vs 23.3%), diarrhea (26.5 vs 24.3%), and dermatitis acneiform (11.8 vs 9.7%). The reported data showed that further outreach to vandetanib-treated patients did not impact the rate or severity of AEs in comparison to the standard AE monitoring schedule.[83]

# Drug resistance

Although TKIs therapy is generally well tolerated, once AEs are diagnosed the therapy must be stopped. Furthermore, TKIs are cytostatic and they are not able to shrink the tumor mass. There are divergent data from clinical trials about the role of TKIs on advanced DTC and this can be attributed to some form of drug resistance, which allows the malignant cells to keep on proliferate through other signals.[84] Administering in the same patient and at the same time more than one TKIs with different molecular targets could be a promising new therapeutic strategy, which is already under investigation.

However, potential resistance mechanism to vandetanib has been already studied. Specific RET mutations seem not to be relevant in predicting the outcome of certain therapy in MTC patient.[85]

Moreover, the ZETA trial demonstrated the vandetanib efficiency in patients with M918T mutation, whereas the results are not so persuasive in case of different mutations.

Both sporadic and familial MTC cases, harboring the less common RET V804M and V804L mutations, seem to show less sensitivity to vandetanib,[86] as it is supported by in vitro studies. Sorafenib shows activity against the V804 mutant in vitro instead.[87]

More studies are required to understand if Ras mutations, detected in 60–80% of the RET-negative sporadic MTC12, are necessary to develop resistance to vandetanib. But cell lines with known resistance to vandetanib show in vitro perpetual activation of the Ras/Raf/MEK pathway (that sorafenib is able to inhibit).[84]

Testing in vitro TC cells derived directly from the patients with the aim to predict the response to TKIs may represent a new therapeutic approach as in vitro drug screening with human primary tumor cells has a 60% positive predictive and a 90% negative predictive value of clinical response in vivo.[88,89] Fine-needle aspiration (FNA) can be used over surgery as a preferred source of primary TC cell, including those of ATC, which can be then tested in vitro for their sensitivity to several chemotherapies.[89–94]

# Combination studies

Studies evaluating the synergistic action of different chemotherapies have already been performed.[95]

The synergic activity of vandetanib plus irinotecan has been also investigated. Also, therapy based on vandetanib plus irinotecan has been proposed since colon cancer cell lines proliferation has been inhibited in vitro by vandetanib administered subsequently to irinotecan.[96] These data are supported by another preclinical study where mice, grafted with vandetanib-pretreated human colon cancer, received irinotecan achieving higher effectiveness of the chemotherapies.[97]

Moreover, vandetanib, irinotecan, and radiotherapy together were able to limit cancer growth in human LoVo colorectal cell.[98]

PI3K/Akt/mTOR signaling pathway is probably involved in the carcinogenesis of many neuroendocrine tumors including MTC, and it acts enhancing the oncogenic effect of RET mutations. Thus, it could be considered a new chemotherapic target for advanced MTCs.

A recommended phase II dose (RP2D) for the combination of vandetanib and bortezomib (for targeting RET in MTC) was performed.[99] Twenty-two patients with advanced MTC were enrolled and received escalating mg/m$^2$ bortezomib and mg vandetanib (number of patients) at initial doses of 1 and 100 (3), 1.3 and 100 (6), 1.3 and 200 (6), and 1.3 and 300 (7), respectively, administered on days 1, 4, 8, and 11 of a 28-day cycle. Patients received a median of 4 cycles of bortezomib/vandetanib (range 1–10), with 13 patients escalating to 1.3/200 and 10 to 1.3/300. AEs grade 3, present in more than 1 patient, were fatigue (19%), hypertension (24%), thrombocytopenia (10%), arthralgia (10%), and diarrhea (10%). No AEs grade 4/5 occurred. There was 1 dose-limiting toxicity, thrombocytopenia grade 3, at bortezomib/vandetanib doses of 1.3/200 in cycle 2 that resolved without intervention. Four patients (27%) had a PR. The maximum tolerated dose was bortezomib, 1.3 mg/m$^2$ IV days 1, 4, 8, and 11 with vandetanib 300 mg p.o. daily. RECIST responses were observed in MTC patients.[99]

## Conclusion

Between 2011 and 2012, vandetanib gained the authorization from both FDA and EMA for the treatment of metastatic MTC. These approvals were carried out because the drug demonstrated, during phase II and III trials, significant prolongation of PFS (30.5 vs 19.3 months in the placebo group). More advantages have been noticed in patients with sporadic RET-positive-MTC, but a good response has also been established in those with M918T-negative tumors or RET unknown status.

Vandetanib demonstrated efficacy also in adolescents and in children with metastatic or locally advanced MTC, without significant increase over adults of the AEs. The drug seems to be also appropriate to treat the ECS, a paraneoplastic syndrome that can occur in patients affected by advanced MTC.

Regarding the CT and CEA circulating levels, data are still lacking to establish the role of their serum levels during the follow-up and their usefulness as a prognostic tool.

It is well known that vandetanib can provoke gastrointestinal, cardiovascular, dermatological, endocrine, and other systemic AEs. Those of grade 1 or 2 may improve at lower doses, while in case of AEs grade 3 or 4, it is recommended to withhold the therapy, which may be resumed, at lower dose, after the resolution of the AEs.

Vandetanib has also been co-administered together with other chemotherapies trying to enhance its antineoplastic effect and to overcome potential forms of resistance. In the era of tailored therapies, attempts have been made to personalize TKIs therapy in each patient with MTC or aggressive DTC; by this way, the percentage of treatment success should increase and the administration of worthless, but potentially dangerous, drugs be avoided. For this reason, recently, it has been even suggested the possibility to evaluate the sensitivity in vitro to different TKIs of primary aggressive DTC or MTC cells from each subject, on the basis of the molecular profile of single tumor.

Finally, vandetanib should be considered a valid weapon against advanced, symptomatic, or metastatic MTC, where it improves the PFS and these advantages may be achieved also in patients affected by aggressive DTC (a phase III trial is still ongoing). Anyway the effort to try to find out novel targeted chemotherapies, aiming to ameliorate the prognosis and the quality of life of oncological patients, should be carried on, encouraged by the deepening knowledge on molecular mechanisms of carcinogenesis and host response to it.

Until nowadays, surgery is the cornerstone of treatment for localized tumors, but most patients with neuroendocrine neoplasms (NENs) are diagnosed after the occurrence of metastases, and they need a chronic medical management according to a multidisciplinary approach. Owing to the high heterogeneity of these types of tumors in the clinical aggressiveness and response to the therapy, the clinical efficacy of current treatment options is limited.

For these reasons, a precision medicine (PM)-based strategy could be useful for the management of NENs.[100]

Several preclinical models have been considered as encouraging platforms for the development of PM applications. Primary cultures obtained from solid tumors have gained significant importance in personalized cancer therapy.[101]

Recently, CANscript™, a human platform technology, has been developed to predict the response to anti-cancer therapies in patients with head and neck squamous cell carcinoma. Moreover, patient-derived xenografts in mice are considered the strongest and most evaluated experimental platform for the development of PM applications.[100]

In particular, Pauli et al published a paper about the development of a precision cancer care platform, that integrates whole exome sequencing with a living biobank, that permits to conduct high throughput drug screening on patient-derived tumor organoids. The authors showed that for advanced cancer patients in whom genomics does not indicate a certain approved targeted therapy, in vitro drug testing could permit the assessment of additional possibilities, to identify effective therapeutic strategies and helping in the choice of clinical trials for individual patients.[102]

Further evaluations are needed to investigate the predictive potential of these innovative applications, and their translatability into the clinical practice, to ameliorate the quality of life and survival in oncological patients.

## Author contributions

All authors contributed toward data analysis, drafting and revising the paper, gave final approval of the version to be published and agree to be accountable for all aspects of the work.

## Disclosure

The authors declare no conflicts of interest in this work.

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