Abstract

Vandetanib (ZD6474, Caprelsa, AstraZeneca), an oral small-molecule tyrosine kinase inhibitor (TKI) that targets the rearranged during transfection receptor (RET), vascular endothelial growth factor receptor (VEGFR2-3) and epidermal growth factor receptor (EGFR), is the first systemic therapy approved by the U.S. Food and Drug Administration (FDA) for the treatment of symptomatic or progressive advanced medullary thyroid cancer (MTC). In a randomized phase III trial of patients with unresectable, locally advanced or metastatic MTC, vandetanib improved progression free survival compared to placebo (hazard ratio (HR) 0.46; 95% confidence interval (CI): 0.31-0.69; p<0.001). However the benefits in delaying disease progression need to be balanced against the associated and potentially serious toxicities, including diarrhea, hypertension and QTc prolongation. Here, we review the clinical development of vandetanib leading to its integration into the current treatment paradigm and highlight the ongoing and future challenges in TKI use in MTC.

Introduction

Medullary thyroid carcinoma (MTC), a neuroendocrine tumor arising from the parafollicular cells of the thyroid, is characterized by hypersecretion of calcitonin. The majority of cases of MTC are sporadic (75%), whereas the remaining 25% are hereditary and comprise one of three autosomal dominant hereditary syndromes: multiple endocrine neoplasia (MEN) 2A, MEN 2B or familial medullary thyroid carcinoma (FMTC). Patients who present with distant metastases at diagnosis have a 10 year survival rate of 40%. Traditional treatment modalities such as external beam radiation therapy and chemotherapy are largely ineffective in unresectable or metastatic MTC. The limited treatment options highlight the unmet medical need for new therapeutic approaches in MTC.

Mutations in the RET proto-oncogene are key pathogenic events in the majority of patients with MTC. Virtually all patients with the hereditary MTC carry a germline RET
mutation. Approximately 65-80% of sporadic MTC tumors harbor a somatic RET mutation. Almost all (98%) MEN2A cases involve point mutations affecting the extracellular cysteine-rich domain. About 95% of MEN2B cases possess the kinase domain mutation, M918T. Up to 80% of sporadic MTC cases harbor a somatic M918T mutation which is associated with poorer prognosis.(1) RET receptor tyrosine kinase activation leads to signaling through multiple pathways including Ras/ERK, PI3K, SRC, phospholipase C, JNK and STAT3. In addition to RET, other kinase pathways are also important as evidenced by overexpression of VEGFR and EGFR in MTC.

Consequently targeting these signaling pathways using small molecule TKIs has eagerly been explored. Recent phase II studies in patients with advanced MTC have shown varying response rates as shown in Table 1.(2),(3)(4)(5)(6)(7)(8) Vandetanib is the first TKI to complete phase III testing and is currently the only systemic therapy to be approved by the U.S. FDA for MTC.

**Early Clinical Development**

Vandetanib was initially developed as an oral small-molecule inhibitor of the VEGFR2 tyrosine kinase (IC$_{50}$=40nmol/l), and was also found to inhibit VEGFR3 (IC$_{50}$=110nmol/l) and EGFR (IC$_{50}$=500nmol/l).(9) Subsequent preclinical studies showed that vandetanib inhibited RET mutant forms (MEN2A, MEN2B) and RET translocations found in papillary thyroid cancer.(10) Three phase I trials of single-agent vandetanib in patients with treatment-refractory solid tumors confirmed the recommended phase II dose of 300mg/day with dose limiting toxicities (DLTs) of diarrhea, hypertension and rash.(11-13) Two of the studies reported asymptomatic QTc prolongation.(11, 12) In one trial of 36 patients, only one partial response was observed (this patient had MTC).(13) Taken together, the phase I and preclinical studies provided rationale for the clinical development of vandetanib in MTC.
Two phase II single-arm, open-label studies of vandetanib confirmed efficacy in hereditary MTC. The first phase II study enrolled 30 patients with hereditary, unresectable or metastatic MTC to receive vandetanib at 300 mg/day. Six partial responses (20%) were observed and 53% of patients had stable disease; median PFS was 27.9 months. The majority of patients experienced at least one adverse event (AE) (diarrhea, rash, fatigue and nausea). A second phase II study with similar eligibility criteria enrolled 19 patients to receive vandetanib at 100mg/day with allowance for post-progression escalation to 300mg/day. Partial response rate was 16% and stable disease rate was 53%, thus confirming the anti-tumor activity of low dose vandetanib.

Late-Stage Development

The pivotal ZETA trial led to the approval of vandetanib for advanced progressive MTC by the U.S. FDA in April 2011. This international, randomized, double-blind phase III trial evaluated 331 patients with unresectable, locally advanced or metastatic MTC (hereditary or sporadic). Patients were randomized 2:1 to receive vandetanib 300 mg daily (n=231) or placebo (n=100) until disease progression. The primary end point was progression-free survival (PFS) and secondary end points were objective response rate (ORR), disease control rate (DCR) at 24 weeks, duration of response, overall survival, biochemical response, time to worsening of pain, safety and tolerability. Eligibility criteria did not include disease progression but required measurable tumor at baseline and a calcitonin level of at least 500pg/ml. Most patients who enrolled had non-hereditary MTC (90%) and metastases (95%). Forty percent had received prior systemic therapy. Calcitonin or carcinoembryonic antigen (CEA) doubling time of ≤24 months, a marker associated with more aggressive disease, was present in 51% of patients with respect to calcitonin and 31% of patients for CEA.

Efficacy

Vandetanib demonstrated efficacy in all evaluable end points in the ZETA trial except survival. At a median follow-up of 24 months, median PFS was not reached with
vandetanib (estimated ~30 months) and was 19.3 months with placebo (HR 0.46; 95%CI: 0.31-0.69; p<0.001). The 6 month PFS rate was 83% in the vandetanib group and 63% in the placebo group. Vandetanib demonstrated a higher ORR compared to placebo (45% vs 13%; p<0.001) and higher DCR (87% vs 71%; p=0.001). Of the 13 patients in the placebo arm who responded, 12 did so after treatment with open-label vandetanib. Overall survival data was immature at the time of analysis and revealed no significant difference (HR 0.89; 95%CI: 0.48–1.65). Final survival assessment is likely to be confounded by post-progression cross over from placebo to open-label vandetanib. The biochemical response rate (complete response defined as normalization of serum levels; partial response defined as ≥50% decrease from baseline in serum calcitonin and CEA for ≥4 weeks) was better for vandetanib compared to placebo (69% vs 3% for calcitonin; p<0.0001) (52% vs 2% for CEA; p<0.0001). Vandetanib was associated with a delay in time to worsening of pain (HR 0.61; 95%CI 0.43-0.87; p=0.006), however other health-related quality of life measures were not evaluated.

**Efficacy by mutation status**

A tremendous effort was made to correlate RET genotype with response to vandetanib in the ZETA trial. Tissue was obtained for RET genotyping in 297 of 298 patients with sporadic MTC. Somatic RET mutations were identified in 155 patients (52%) and somatic RET mutations were absent in 8 patients (2.7%). Unfortunately, a large proportion of patients were classified as RET mutation status ‘unknown’ (n=135; 45.3%) due to insufficient tumor DNA to fulfill stringent testing criteria, making subgroup analysis by RET mutation status for PFS and ORR in ZETA inconclusive. Interestingly, patients with sporadic MTC tumors harboring a somatic M198T mutation had a higher response rate to vandetanib (54.5%; 55/101) compared to patients with sporadic MTC tumors without a somatic M918T mutation (32%; 33/103). Vandetanib appeared active in all pre-specified subgroups.

**Safety and tolerability**

The most common and serious AEs in ZETA are listed in table 2. Vandetanib was associated with higher treatment discontinuation rate (12% vs 3%) and dose reductions...
due to AEs or QTc prolongation (36% vs 3%) compared to placebo. However median duration of treatment was much longer for vandetanib (90.1 weeks vs 39.9 weeks). Vandetanib at 300mg/day was associated with QTc prolongation (mean 35 ms) but there were no reports of torsades de pointes in ZETA.

Integration of Vandetanib into the Medullary Thyroid Cancer Treatment Paradigm

Few treatment options exist for patients with unresectable or metastatic MTC. In metastatic disease, a watch-and-wait approach is feasible in asymptomatic patients with low tumor burden, and no evidence of tumor progression on periodic restaging as patients with indolent metastatic disease may survive for years without systemic therapy. For patients with progressive or symptomatic metastatic disease and high tumor burden, the National Comprehensive cancer Network (NCCN) encourages clinical trial enrollment. In the absence of trial enrolment, systemic therapy with TKIs is preferred over cytotoxic chemotherapy which is associated with high toxicity and low efficacy. Vandetanib is currently the first-line systemic therapy of choice. If a patient is not a candidate for vandetanib or progresses on vandetanib, NCCN guidelines recommend the use of commercially available TKIs such as sorafenib or sunitinib, although these agents are not FDA approved for the treatment of thyroid cancer and their phase II trials specifically excluded patients with prior vandetanib therapy.

In practice, deciding when to initiate vandetanib therapy is less clear. The use of vandetanib should be restricted to symptomatic or rapidly progressive MTC, which is determined by clinical judgment since neither were part of the ZETA inclusion criteria. No validated predictors of response to vandetanib exist to guide patient selection. Subgroup analyses suggest that there may be a greater chance of benefit in patients with sporadic MTC tumors harboring the aggressive M918T mutation, and in patients with CEA doubling times ≤24 months compared to those with longer doubling times (54% vs 37%).

Judicious evaluation of the treatment risk-to-benefit ratio and close monitoring for toxicities is critical. Due to the potential of QT prolongation, torsades de pointes, and
sudden death, vandetanib is currently only available through the FDA Vandetanib Risk Evaluation Mitigation Strategy (REMS) Program. The goal of the program is to educate prescribers about the risk, appropriate monitoring and management of QT prolongation and to minimize the occurrence of torsades de pointes and sudden death associated with vandetanib. To prescribe vandetanib, providers must complete provider training and enroll in the vandetanib REMS program. ECG and serum potassium, calcium, magnesium and thyroid-stimulating hormone levels should be closely monitored and corrected. Concomitant use of drugs that prolong the QT interval or are associated with torsades de pointes should be avoided, recognizing that the risk for torsades de pointes may be protracted given the drug’s long half-life (t_{1/2} 19 days). Other common side effects (table 2) including diarrhea, rash and hypertension can usually be managed with early recognition, supportive measures, and dose reductions or interruptions for grade≥3 severity. (17) Most patients treated with vandetanib will have a rise in thyroid-stimulating hormone (78%) and ~50% will require increases in thyroid replacement dose. Given the toxicity profile, vandetanib is clearly unjustified for asymptomatic, indolent disease.

The MTC treatment schema is quickly evolving as clinical trials inform on new therapies. Cabozantinib, an oral kinase inhibitor of VEGFR2, RET and hepatocyte growth factor receptor (MET) is the only other TKI with randomized phase III data (EXAM trial) in progressive, advanced MTC showing a PFS benefit (primary endpoint) compared to placebo (median PFS 11.2 months vs 4.0 months; HR 0.28; 95%CI: 0.19–0.40; p<0.0001) and an ORR of 28% vs 0%. (18) Unlike ZETA, the EXAM trial eligibility criteria included disease progression by RECIST criteria within 14 months of screening. Similar to ZETA, very few patients were considered RET mutation-negative, thus subgroup analysis by RET mutation status for PFS was inconclusive. Toxicities associated with VEGF inhibition led to deaths in 1.9% of patients in the cabozantinib arm (3 cases of fistula formation and 1 hemorrhage). (18) In the future, cabozantinib may be an alternative first-line treatment option to vandetanib particularly for patients with rapidly progressive disease or high risk for torsades de pointes, or cabozantinib may be a second-line option post-progression after vandetanib, however the toxicities related to VEGF inhibition must be weighed (table 2). Future trials of head to head upfront comparison of TKIs and sequential approaches are
needed to inform. Uncertainty exists regarding the optimal treatment strategy when resistance to TKI therapy develops. It is unclear how many patients in the ZETA trial received prior TKI. In the EXAM trial, ~20% of patients had received prior TKI therapy and response was seen regardless of prior TKI treatment. Evidence to support the use of sorafenib or sunitinib after vandetanib progression is largely anecdotal.

**Future Challenges**

Vandetanib, represents a paradigm shift in the treatment of MTC by validating the efficacy of TKIs in advanced MTC. However challenges remain in optimizing patient selection, mitigating treatment toxicities and identifying strategies to overcome resistance as these therapies are currently not curative. Mechanisms of primary and acquired resistance to vandetanib require investigation. Presently, RET mutations cannot be used clinically to predict response to TKIs, although correlations may be strengthened in the future as TKI use and genetic testing in sporadic MTC increases. Comparison of sequential tumor biopsies pre/post treatment and upon resistance may provide insight into clinical mechanisms of resistance.

Characterization of anti-tumor activity of vandetanib and other TKIs against specific RET mutant and RET wild-type tumors may help to better select patients for therapy. ZETA confirms the clinical efficacy of vandetanib in patients with sporadic MTC tumors harboring the M918T mutation. Prior studies hinted that somatic M918T mutations may confer sensitivity to RET TKIs; in patients with somatic M198T mutations, 12/15 had durable responses or stable disease in the phase I trial of cabozantinib(7) and 5/8 patients had responses to sunitinib.(3) However the clinical efficacy of vandetanib in patients harboring other RET mutations such as those associated with MEN2A is less apparent. In vitro studies comparing the activity of four TKIs (vandetanib, axitinib, sunitinib and cabozantinib) in MEN2B, MEN2A and RET/PTC1 (papillary thyroid cancer) cell lines reported that vandetanib was the most potent inhibitor in MEN2B, and cabozantinib was the most effective in MEN2A and PTC,(19) suggesting that mutation-specific therapies may be
beneficial. Additionally, to avoid maleficence, identification of a subset of patients for whom vandetanib therapy is futile is important. For example, *in vitro* studies pinpointed the RET V804M and V804L gatekeeper mutations confer resistance to vandetanib.(20) Although rare, these mutations occur in sporadic and hereditary MTC, either alone or in combination with other RET mutations, and thus could result clinically in primary or acquired resistance to vandetanib. TKIs such as sorafenib have demonstrated activity against the V804 mutant in *in vitro* studies.(21) Finally, in patients with RET wild-type tumors, it remains to be seen if Ras mutations, identified in 60-80% of RET-negative sporadic MTC,(22) confer clinical resistance to vandetanib. *In vitro* studies using cell lines with acquired resistance to vandetanib have demonstrated persistent activation of the Ras/Raf/MEK pathway which can be partly abrogated by sorafenib.(23)

Ultimately it remains unclear if the activity of vandetanib is predominantly due to inhibition of RET, EGFR, VEGFR or other kinases. For example, dual inhibition of RET and EGFR may contribute to the efficacy of vandetanib,(24) however EGFR inhibition alone with gefitinib has not produced clinical responses in MTC.(25) All clinically tested RET inhibitors are non-selective, multi-kinase inhibitors that also inhibit VEGFR signaling, however VEGFR inhibition alone (axitinib) has demonstrated a response rate <20%.(5) The clinical efficacy of targeting VEGFR without RET inhibition is being evaluated in MTC in a single-arm phase II trial of pazopanib (GW786034, Votrient, GlaxoSmithKline; VEGFR1-3, PDGFRα/β, KIT inhibitor) in advanced thyroid cancer (NCT00625846). Interestingly, in a phase II trial of lenvatinib, there was no difference in treatment response according to RET mutation status, however high baseline levels of VEGF and sVEGFR3 correlated with greater tumor shrinkage, and low levels of ANG2, sTie-2, HGF and IL-8 were associated with tumor shrinkage and prolonged PFS.(6) This distinction is important as the main serious AEs associated with the current RET TKIs are related to anti-VEGFR or anti-EGFR effects. Greater understanding of the mechanism of activity of vandetanib will permit rational exploration of sequential or combination approaches with other therapies in the future including clinical development in the neoadjuvant or adjuvant setting.

**Conclusions**
Vandetanib demonstrated clinical efficacy and PFS benefit in advanced MTC thus validating small molecule TKIs as a valid therapeutic strategy in this disease. However the toxicities, some serious including QTc prolongation, need to be carefully weighed and managed. Vandetanib is unjustified in the setting of indolent and asymptomatic MTC. The risk-benefit assessment must take into account the toxicity risks, prolonged treatment administration and potential indolent course of advanced MTC. The MTC treatment paradigm is rapidly changing as future TKI studies continue to inform. Work is needed to further characterize appropriate patient selection, optimize management upon resistance, and examine novel sequential or combination treatment approaches.
Tables and Figures

Table 1. Response rates of TKIs in recent Phase II studies in advanced MTC

Table 2. Summary of common adverse events occurring with an incidence of ≥25% and Grade 3+ adverse events occurring with an incidence of ≥5% on either arm in phase III trials in advanced MTC.

Figure 1. Activated tyrosine kinase receptors targeted by vandetanib in MTC.
References:


Table 1. Response rates of TKIs in recent Phase II studies in advanced MTC

<table>
<thead>
<tr>
<th>TKI</th>
<th>Sorafenib(2)</th>
<th>Sunitinib(3)</th>
<th>Motesanib(4)</th>
<th>Axitinib(5)</th>
<th>Lenvatinib(6)</th>
<th>Cabozantinib(7)</th>
<th>Vandetanib(8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nevaxar, Bayer</td>
<td>Sutent, Pfizer</td>
<td>AMG-706, Amgen/Takeda</td>
<td>Inlyta, Pfizer</td>
<td>E7080, Eisai</td>
<td>XL-184, Exelixis</td>
<td>Caprelsa, Astra Zeneca</td>
<td></td>
</tr>
<tr>
<td>Main targets</td>
<td>RET</td>
<td>RET</td>
<td>RET</td>
<td>RET</td>
<td>RET</td>
<td>RET</td>
<td>RET</td>
</tr>
<tr>
<td>VEGFR2-3</td>
<td>VEGFR2</td>
<td>VEGFR1-3</td>
<td>VEGFR1-3</td>
<td>VEGFR2</td>
<td>VEGFR2</td>
<td>VEGFR2-3</td>
<td></td>
</tr>
<tr>
<td>RAF, KIT, PDGFR-β</td>
<td>KIT, PDGFR-β, FLT-3</td>
<td>PDGFR, KIT</td>
<td>PDGFR-β, KIT</td>
<td>FGFR1-4, KIT, PDGFR-β</td>
<td>MET, KIT, FLT1-3, Tie-2</td>
<td>EGFR</td>
<td></td>
</tr>
<tr>
<td>Response Rate</td>
<td>6%</td>
<td>33%</td>
<td>2%</td>
<td>18%</td>
<td>36%</td>
<td>29%</td>
<td>20%</td>
</tr>
</tbody>
</table>
Table 2. Summary of common adverse events occurring with an incidence of ≥25% and Grade 3+ adverse events occurring with an incidence of ≥5% on either arm in phase III trials in advanced MTC

<table>
<thead>
<tr>
<th></th>
<th>ZETA Trial (15)</th>
<th>EXAM Trial (18)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Vandetanib (n=231)</td>
<td>Placebo (n=99)</td>
</tr>
<tr>
<td><strong>Adverse events all grades in decreasing order of frequency</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Event (all grades)</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>130</td>
<td>56</td>
</tr>
<tr>
<td>Rash</td>
<td>104</td>
<td>45</td>
</tr>
<tr>
<td>Nausea</td>
<td>77</td>
<td>33</td>
</tr>
<tr>
<td>Hypertension</td>
<td>73</td>
<td>32</td>
</tr>
<tr>
<td>Headache</td>
<td>59</td>
<td>26</td>
</tr>
<tr>
<td>Fatigue</td>
<td>55</td>
<td>24</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse events Grade ≥3 in decreasing order of frequency</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse Event (Grade ≥3)</td>
<td>N</td>
<td>%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>25</td>
<td>11</td>
</tr>
<tr>
<td>Hypertension</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td>ECG QT prolonged</td>
<td>18</td>
<td>8</td>
</tr>
<tr>
<td>Fatigue</td>
<td>13</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Figure 1:

RET (activating mutations) → EGFR (overexpression) → VEGFR-2 (overexpression)

- PI3K → RAS → RAF → MEK → mTOR → Gene transcription
  → Cell cycle activation

- AKT → mTOR → Gene transcription
  → Cell cycle activation

Survival → Growth → Proliferation → Metastases → Angiogenesis

Vandetanib

© 2012 American Association for Cancer Research
Vandetanib for the Treatment of Medullary Thyroid Cancer

Nicole G Chau and Robert I Haddad

*Clin Cancer Res* Published OnlineFirst December 11, 2012.

Updated version
Access the most recent version of this article at:
doi:10.1158/1078-0432.CCR-12-2353

Author Manuscript
Author manuscripts have been peer reviewed and accepted for publication but have not yet been edited.

E-mail alerts
Sign up to receive free email-alerts related to this article or journal.

Reprints and Subscriptions
To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions
To request permission to re-use all or part of this article, contact the AACR Publications Department at permissions@aacr.org.