Phase I/II Trial of Vandetanib and Bortezomib in Adults with Locally Advanced or Metastatic Medullary Thyroid Cancer

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TRIAL INFORMATION

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- Principal Investigator: Ann W. Gramza
- IRB Approved: Yes

LESSONS LEARNED

- Vandetanib at a dose of 300 mg orally every day plus bortezomib 1.3 mg/m² intravenously on days 1, 4, 8, and 11 could be administered safely.
- Assessing outcomes in 17 patients with medullary thyroid cancer, investigators considered the combination to be more difficult to administer than single-agent vandetanib and that achieving better outcomes was unlikely. Consequently, a planned phase II study was terminated early.

ABSTRACT

Background. The proto-oncogene RET (REarranged during Transfection) has a critical role in the pathogenesis of medullary thyroid cancer (MTC). Vandetanib (V), a multitargeted tyrosine kinase inhibitor approved for the treatment of MTC, is thought to inhibit RET in MTC. Supported by preclinical studies demonstrating that bortezomib (B) administration lowered RET mRNA and protein levels, we conducted a phase I study in advanced solid tumors of vandetanib in combination with bortezomib. The goal was to establish an RP2D (recommended phase II dose) for the combination of vandetanib plus bortezomib, a regimen envisioned as a dual strategy for targeting RET in MTC.

Methods. Patients with advanced solid tumors were treated with escalating doses of bortezomib or vandetanib to assess the safety and tolerability of daily oral vandetanib and intravenous (IV) bortezomib administered on days 1, 4, 8, and 11 of a 28-day cycle. Intrapatient dose escalation was allowed.

Results. Twenty-two patients were enrolled and received escalating mg/m² 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. Patients received a median of four cycles of bortezomib/vandetanib (range: 1–10), with 13 patients escalating to 1.3/200 and 10 to 1.3/300. G3 toxicities occurring in more than one patient included hypertension (24%), fatigue (19%), thrombocytopenia (10%), diarrhea (10%), and arthralgia (10%). There were no drug-related G4/5 toxicities. There was one dose-limiting toxicity, G3 thrombocytopenia, at bortezomib/vandetanib doses of 1.3/200 in cycle 2 that resolved without intervention. Four patients with a diagnosis of MTC (27%) had a partial response (PR).

Conclusion. The MTD of the combination was established as bortezomib, 1.3 mg/m² IV days 1, 4, 8, and 11 with vandetanib 300 mg p.o. daily. RECIST responses were observed in patients with a diagnosis of MTC. The Oncologist 2019;24:16–e14

DISCUSSION

Activating point mutations in RET kinase are present in nearly all hereditary MTC and at least 50% of sporadic MTC. RET has therefore been considered an attractive therapeutic target in MTC. Vandetanib, an oral inhibitor of vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor, and RET, was approved by the U.S. Food and Drug Administration (FDA) in April 2011 after a phase III trial demonstrated an improvement

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in median progression-free survival (PFS) compared with placebo (hazard ratio 0.45; 95% confidence interval [CI] 0.30–0.69; p < .001) and an overall response rate of 45% in patients with metastatic MTC. Cabozantinib, a tyrosine kinase inhibitor of hepatocyte growth factor receptor, VEGFR-2, and RET, has also demonstrated clinical activity in patients with MTC, albeit at a dose far in excess of that tolerable by patients. A phase III trial comparing cabozantinib at a starting dose of 140 mg reported a median PFS of 11.2 months for cabozantinib versus 4.0 months for placebo (hazard ratio 0.28; 95% CI 0.19–0.40; p < .001), a result that subsequently led to its approval by FDA in 2012 in patients with progressive metastatic MTC. However, toxicity limits its use and we lack evidence of its efficacy at lower doses and thus cannot know with certainty its benefit.

Preclinical studies demonstrating bortezomib administration reduced both RET mRNA and protein levels prompted this clinical trial to determine the optimal dose of bortezomib in combination with vandetanib. The ultimate goal was to use these two drugs in combination in a strategy targeting both the levels and the activity of the RET proto-oncogene. This study was designed to evaluate the safety and tolerability of combined daily oral vandetanib and on a days 1, 4, 8, and 11 every 28 days schedule to establish the optimal doses (recommend phase II doses) of the drug combination in adults with locally advanced or metastatic cancer, including MTC.

Twenty-two patients with advanced or metastatic cancer were enrolled, 17 of whom had a diagnosis of MTC. Four dose levels were explored, with patients receiving initial doses of bortezomib/vandetanib (mg/m² B/mg V) of 1/100 (3), 1.3/100 (6), 1.3/200 (6), and 1.3/300 (7). The MTD of the combination was established as oral vandetanib at a daily dose of 300 mg with bortezomib 1.3 mg/m² administered intravenously on days 1, 4, 8, and 11 every 28 days.

Vandetanib and cabozantinib are approved agents for the treatment of patients with progressive metastatic medullary thyroid carcinoma who are ineligible for surgery and who have disease that is growing or causing symptoms. Unfortunately, intrinsic or acquired resistance limit their effectiveness, and efforts are ongoing to seek new treatment options. This trial testing the combination of bortezomib and vandetanib established bortezomib 1.3 mg/m² administered intravenously on days 1, 4, 8, and 11 with oral vandetanib at a daily dose of 300 mg as the RP2D. Although the original plan called for a phase II study in patients with MTC using the RP2D, only one patient enrolled in the phase II portion, after which the study was terminated. The reason for study termination was the feeling that the activity of the combination was comparable to single-agent vandetanib but more difficult to tolerate and that prolonged administration would not be possible.

**Trial Information**

| Disease               | Thyroid cancer – medullary |
|-----------------------|----------------------------|
| Stage of Disease/Treatment | Metastatic/advanced       |
| Prior Therapy         | No designated number of regimens |
| Type of Study - 1     | Phase I                    |
| Type of Study - 2     | Phase I/II                 |
| Primary Endpoint      | Safety                     |
| Secondary Endpoint    | Efficacy                   |
| Additional Details of Endpoints or Study Design | The activity of vandetanib plus bortezomib in adults with MTC using RECIST 1.1. |
| Investigator’s Analysis | Level of activity did not meet planned endpoint |

Figure 1. RECIST response. Each patient’s percentage represents the best response by RECIST criteria. Abbreviations: ACC, adrenal cortical carcinoma; FTC, follicular thyroid cancer; NET, neuroendocrine tumors; MTC, medullary thyroid cancer.
**Drug Information**

**Drug 1**
- **Generic/Working Name**: Vandetanib (CAPRELSA; ZD6474)
- **Trade Name**: Vandetanib
- **Company Name**: AstraZeneca/SanoGenzyme
- **Drug Type**: Small molecule
- **Drug Class**: VEGF
- **Dose**: 100–300 mg per flat dose
- **Route**: p.o.
- **Schedule of Administration**: Administered daily

**Drug 2**
- **Generic/Working Name**: Bortezomib (Velcade, PS-341)
- **Trade Name**: Bortezomib
- **Company Name**: Small molecule
- **Drug Class**: Other: 26S proteasome inhibitor
- **Dose**: 1.0–1.3 mg/m²
- **Route**: IV
- **Schedule of Administration**: Days 1, 4, 8, and 11 of a 28-day cycle

**Dose Escalation Table**

| Dose level | Dose of drug: vandetanib (CAPRELSA; ZD6474) | Dose of drug: bortezomib (Velcade, PS-341) | Number enrolled | Number evaluable for toxicity |
|------------|---------------------------------------------|---------------------------------------------|-----------------|------------------------------|
| 1          | 100 mg daily                                | 1 mg/m² days 1, 4, 8, and 11               | 3               | 3                            |
| 2          | 100 mg daily                                | 1.3 mg/m² days 1, 4, 8, and 11             | 6               | 9                            |
| 3          | 200 mg daily                                | 1.3 mg/m² days 1, 4, 8, and 11             | 6               | 13                           |
| 4          | 300 mg daily                                | 1.3 mg/m² days 1, 4, 8, and 11             | 7               | 7                            |

**Patient Characteristics**

- **Number of Patients, Male**: 14
- **Number of Patients, Female**: 8
- **Stage**: Metastatic or advanced solid tumors with focus on hereditary or sporadic, locally advanced or metastatic MTC
- **Cancer Types or Histologic Subtypes**: Medullary thyroid cancer, 19; Adrenocortical cancer, 2; Neuroendocrine tumor (not otherwise specified), 1

**Primary Assessment Method**

- **Title**: Total patient population
- **Number of Patients Screened**: 22
- **Number of Patients Enrolled**: 22
- **Number of Patients Evaluable for Toxicity**: 21
- **Number of Patients Evaluated for Efficacy**: 22
- **Response Assessment CR**: $n = 0$
- **Response Assessment PR**: $n = 6$
- **Response Assessment SD**: $n = 11$
- **Response Assessment PD**: $n = 5$
- **Response Assessment OTHER**: $n = 0$
ADVERSE EVENTS

All Cycles

| Name                                   | NC/NA | 1  | 2  | 3  | 4  | 5  | All grades |
|-----------------------------------------|-------|----|----|----|----|----|------------|
| Alanine aminotransferase increased      | 0%    | 65%| 35%| 0% | 0% | 0% | 100%       |
| Aspartate aminotransferase increased    | 0%    | 65%| 35%| 0% | 0% | 0% | 100%       |
| Platelet count decreased                | 0%    | 82%| 6% | 12%| 0% | 0% | 100%       |
| Rash maculo-papular                     | 0%    | 27%| 73%| 0% | 0% | 0% | 100%       |
| Hypertension                            | 0%    | 43%| 21%| 36%| 0% | 0% | 100%       |
| Fatigue                                 | 0%    | 23%| 46%| 31%| 0% | 0% | 100%       |
| White blood cell decreased              | 0%    | 55%| 45%| 0% | 0% | 0% | 100%       |
| Electrocardiogram QT corrected interval prolonged | 0% | 28%| 67%| 6% | 0% | 0% | 101%       |
| Peripheral sensory neuropathy           | 0%    | 40%| 60%| 0% | 0% | 0% | 100%       |
| Diarrhea                                | 0%    | 53%| 33%| 13%| 0% | 0% | 99%        |

Abbreviation: NC/NA, no change from baseline/no adverse event.

DOSE-LIMITING TOXICITIES

| Dose level | Number enrolled | Number evaluable for toxicity | Number with a dose-limiting toxicity | Dose-limiting toxicity information |
|------------|----------------|------------------------------|-------------------------------------|-----------------------------------|
| 1          | 3              | 3                            |                                     |                                   |
| 2          | 9              | 9                            |                                     |                                   |
| 3          | 13             | 13                           | 1                                   | Grade 3 thrombocytopenia          |
| 4          | 10             | 10                           |                                     |                                   |

ASSESSMENT, ANALYSIS, AND DISCUSSION

Completion: Study completed

Investigator’s Assessment: Level of activity did not meet planned endpoint

Medullary thyroid cancer (MTC) is a neuroendocrine tumor of the parafollicular or C cells of the thyroid gland that derives from the neural crest and accounts for approximately 4% of thyroid carcinomas [1]. In about 20%–25% of cases, MTC presents as a part of an autosomal dominant inherited disorder, with sporadic tumor accounting for 75% of cases. Activating mutations of the RET (REarranged during Transfection) proto-oncogene are common, with germ-line activating RET mutations seen in familial MTC (FMTC) and multiple endocrine neoplasia (MEN) 2a/MEN2b [2–4]. Mutations in RET are also found in sporadic cases, with an estimated 50% of such tumors harboring RET mutations in the absence of germline changes [5–7]. MTC often produces immunoreactive calcitonin and carcinoembryonic antigen (CEA), which can be used as tumor markers [8, 9].

Calcitonin is an excellent tumor marker that correlates with tumor bulk [10, 11]. In patients with detectable serum calcitonin or CEA but without anatomic evidence of disease, careful observation is advised given clinical benefit has not been demonstrated with early therapeutic intervention. Empiric surgical interventions to remove all the lymph nodes of the neck and the mediastinum have been proposed, but results have been disappointing [12, 13]. These procedures often do not find tumor nor result in a biochemical remission. In contrast, patients with rapidly progressive disease by anatomic imaging or in whom a biochemical doubling time of calcitonin levels <2 years is detected should be considered for treatment, ideally in the context of a well-designed clinical trial [4, 14].

Metastatic MTC is the most common cause of death in patients with MEN 2a and MEN 2b, and the tumor is unresponsive to conventional doses of radiation therapy. For years, doxorubicin was the only U.S. Food and Drug Administration (FDA)-approved agent that was used for patients with advanced thyroid cancer; however, response rates in patients with MTC were < 20% often with toxicity [15–17]. In recent years, several tyrosine kinase inhibitors including axitinib, cabozantinib, gefitinib, imatinib, motesanib, sorafenib, sunitinib, and vandetanib have been evaluated in phase I, II, and III clinical trials in patients with advanced MTC [18–29]. Vandetanib, an inhibitor of vascular endothelial growth factor receptor (VEGFR), epidermal growth factor receptor, and RET [27, 30], was approved by the FDA in April 2011 at a dose of 300 mg per day after a phase III trial demonstrated improvement in median progression-free survival (PFS) compared with placebo (hazard ratio 0.45; 95% confidence interval [CI] 0.30–0.69; p < .001) and an overall response rate of 45% [31]. Cabozantinib, an inhibitor of hepatocyte growth factor receptor, VEGFR-2, and RET, also demonstrated clinical activity in patients with...
medullary thyroid cancer. A phase III trial that demonstrated a median PFS of 11.2 months for cabozantinib compared with 4.0 months for placebo (hazard ratio 0.28; 95% CI 0.19–0.40; p < .001) led to FDA approval in 2012 [32, 33]. The dose of cabozantinib employed in that study and approved by the FDA was 140 mg daily—a dose the FDA approval noted was not tolerated by 79% of patients—and substantially higher than currently administered doses of 40–60 mg daily. Unfortunately for the latter tolerable doses, we lack evidence of efficacy and thus cannot know with certainty the benefit, if any, in MTC.

Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins and is essential in regulating the intracellular concentration of proteins including multiple signaling cascades within the cell, leading to cell death. Bortezomib is approved for multiple myeloma and mantle cell lymphoma at a dose of 1.3 mg/m² given on days 1, 4, 8, and 11 of a 21-day cycle [34]. Moreover, preclinical studies indicate bortezomib reduces both mRNA and protein levels of RET in vitro [35], and published data reported that bortezomib inhibits growth of MTC cell lines and decreases RET expression in vitro [36]. This study was designed to evaluate the safety and tolerability of combined oral vandetanib and intravenous (IV) bortezomib on days 1, 4, 8, and 11 of an every-28-day cycle to establish a recommended phase II dose of the drug combination in adults with locally advanced or metastatic cancer, including MTC; and to assess the activity of vandetanib plus bortezomib in adults with MTC, using RECIST and tumor biomarkers including CEA and calcitonin as endpoints. Twenty-two patients were enrolled and received initial doses of bortezomib/vandetanib (mg/m² B/mg V) of 1/100 (3), 1.3/100 (6), 1.3/200 (6), and 1.3/300 (7). The maximum tolerated dose (MTD) of the combination was vandetanib 300 mg orally daily and bortezomib 1.3 mg/m² IV on days 1, 4, 8, and 11. Grade 3 toxicities reported were hypertension (24%), fatigue (19%), thrombocytopenia (10%), diarrhea (10%), and arthralgia (10%), with keratoacanthoma, hyperkalemia, pulmonary hemorrhage, edema, and prolonged QT each in one patient (5%). There were no drug-related grade 4/5 toxicities. There was one dose-limiting toxicity (DLT) of grade 3 thrombocytopenia with bortezomib and vandetanib doses of 1.3 and 200 in cycle 2. The toxicity resolved and the patient received cycle 3 and subsequent cycles at 1/100. No further DLTs were seen.

Of the 17 patients with MTC, 16 had previously had primary resection, 7 had prior radiation, 6 had prior systemic therapy, and 1 had undergone a craniotomy for metastatic disease. At the time of enrollment, all had metastatic disease. Although the decrease in calcitonin appeared to correlate with RECIST response, the correlation was limited (R² = 0.54). Importantly, no patient with stable disease duration of <6 months or progressive disease demonstrated a decrease in calcitonin.

In conclusion, the MTD of the combination therapy was vandetanib 300 mg orally daily and bortezomib 1.3 mg/m² intravenously on days 1, 4, 8, and 11. Although we established a recommended phase II dose for the combination, the activity observed in the 17 patients with MTC enrolled on study was not felt to be sufficient to continue pursuing this as a therapeutic option in MTC. For patients with MTC, many of whom will have an indolent course to their disease and require long-term therapy, the combination with bortezomib would likely not be sustainable much beyond six cycles. And although RECIST responses were achieved in 4/17 patients, it was felt this might not be better than single-agent vandetanib with some added toxicity. Thus, a planned phase II study was not pursued.

**Disclosures**

The authors indicated no financial relationships.

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