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Vandetanib in Children and Adolescents with Multiple Endocrine Neoplasia Type 2B Associated Medullary Thyroid Carcinoma

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Abstract

Purpose—Medullary thyroid carcinoma (MTC) is a manifestation of multiple endocrine neoplasia type 2 (MEN2) syndromes caused by germline, activating mutations in the *RET* proto-oncogene. Vandetanib, a VEGF and EGF receptor inhibitor, blocks *RET* tyrosine kinase activity and is active in adults with hereditary MTC.

Experimental Design—We conducted a phase I/II trial of vandetanib for children (5–12 years) and adolescents (13–18 years) with MTC to define a recommended dose and assess anti-tumor activity. The starting dose was 100 mg/m^2 administered orally, once daily, continuously for 28 day treatment cycles. The dose could be escalated to 150 mg/m^2/d after 2 cycles. Radiographic response to vandetanib was quantified using RECIST(v1.0), biomarker response was measured by comparing post-treatment serum calcitonin and carcinoembryonic antigen (CEA) levels to baseline, and a patient reported outcome was used to assess clinical benefit.

Results—Sixteen patients with locally advanced or metastatic MTC received vandetanib for a median (range) 27 (2–52) cycles. Eleven patients remain on protocol therapy. Diarrhea was the primary dose-limiting toxicity. In subjects with M918T *RET* germline mutations (n=15) the confirmed objective partial response rate was 47% (exact 95%CI, 21%, 75%). Biomarker partial response was confirmed for calcitonin in twelve subjects and for CEA in eight subjects.

Conclusion—Using an innovative trial design and selecting patients based on target gene expression, we conclude that vandetanib 100 mg/m^2/d is a well tolerated and highly active new treatment for children and adolescents with MEN2B and locally advanced or metastatic MTC.

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Keywords

MEN2B; Medullary Thyroid Carcinoma; Phase 1/2 Trial; Rare Disease; Vandetanib

Introduction

Medullary thyroid carcinoma (MTC) is a rare cancer arising from neural crest derived parafollicular C-cells within the thyroid gland. In childhood, the age adjusted incidence of MTC is < 0.5 cases per million per year. (1) Hereditary MTC is a manifestation of multiple endocrine neoplasia (MEN) type 2A and MEN2B, genetic cancer predisposition syndromes caused by germline, activating mutations in the *RET* (*REarranged during Transfection*) proto-oncogene.(2–4) MEN2B is associated with a point mutation in exon 16 (codon 918) in more than 95% of cases; (5) the associated MTC is characterized by a younger age of onset and a more aggressive clinical course.(1)

Preventive thyroidectomy is recommended for patients known to have MEN2B;(6–8) but patients with *de novo* germline mutations are not recognized early in life and present with locally advanced or metastatic MTC. MTC is the leading cause of death in patients with hereditary MTC, however, patients with locally advanced or metastatic disease can survive for years.(9–12)

MTC secrete the polypeptide hormone, calcitonin and the glycoprotein carcinoembryonic antigen (CEA), which are biomarkers that reflect tumor burden.(13–15) Elevated serum calcitonin or other polypeptides may be associated with secretory diarrhea.(16), (17, 18)

Vandetanib (Caprelsa®, AstraZeneca Pharmaceuticals, Macclesfield, UK) is a small molecule receptor tyrosine kinase inhibitor of vascular endothelial growth factor receptor 2 (VEGFR2), epidermal growth factor receptor (EGFR), and *RET* tyrosine kinase activity as well as the mutated *RET* oncoproteins.(19–21) In a randomized, placebo controlled trial in adults with MTC, vandetanib 300 mg daily significantly prolonged progression-free survival and 45% of patients had objective responses. Adverse events included diarrhea, rash, nausea, hypertension and headache.(22) In adults receiving vandetanib 300 mg daily, the area under the concentration curve ($AUC_{0-\infty}$) after a single dose was 14 mcg•h/mL, half-life 109±30 h, and apparent clearance was 4.7 L/h/m^2. The plasma concentration at steady state (C_{ss}) was 1 mcg/mL.(23) Based on the randomized trial, the FDA has approved vandetanib for symptomatic or progressive MTC in adults with unresectable advanced or metastatic MTC.(22)

In a phase 1 trial in children with pontine gliomas, the recommended dose of vandetanib was 145 mg/m^2/day. The median [range] duration of treatment was 212 [3–674] days. Toxicities included hypertension, posterior reversible encephalopathy, photosensitivity, diarrhea, and prolonged QTc interval.(24)

We designed a trial of vandetanib for children and adolescents with hereditary MTC to define the dose, toxicity profile, pharmacokinetics and anti-tumor activity. This is the first clinical trial of a RET inhibitor in children and adolescents with MTC. Utilizing intra-patient

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dose escalation meant that all patients with this very rare cancer were also evaluable for response and a therapeutic effect could be used to define the recommended dose.

MATERIALS and METHODS

Patients

Patients 5 to 18 years of age with measurable, locally advanced or metastatic, hereditary MTC were eligible. Other eligibility criteria are provided as Supplemental Data. Protocol-specific exclusion criteria included elevated plasma metanephrines (evidence of pheochromocytoma); prolonged QTc, or requirement for medications known to prolong QTc (See Supplemental Data); hypertension defined as diastolic blood pressure above the 95th percentile for sex and age. The NCI Institutional Review Board approved the trial. Consent and assent were obtained.

Study design

The primary objectives this Phase 1/2 trial were to assess the drug's safety, tolerance, and pharmacokinetics at two dose levels within the 100–300 mg/d dose range used in adults and to assess the anti-tumor activity of vandetanib in children and adolescents with measurable hereditary MTC.

Vandetanib was supplied by AstraZeneca Pharmaceuticals as 50 and 100 mg tablets and as a 10 mg/mL oral solution. The starting dose was 100 mg/m^2/d (equivalent to 180 mg in an adult) administered orally, once daily, continuously for 28-day cycles. Because of the limited safety data available in the pediatric population, adolescents (13–18 years) were enrolled prior to children (5–12 years) using a 3+3 design in each age group. To ensure safety and tolerance at steady state drug concentrations, toxicity was monitored during the initial 2 cycles of vandetanib prior to dose escalation. For individual patients, if dose-limiting toxicity (DLT) was not observed during cycles 1 and 2, intra-patient escalation to 150 mg/m^2/d (equivalent to an adult fixed dose of 270 mg) occurred on cycle 3. Intra-patient dose escalation was performed first in adolescents. Once 100 mg/m^2/d was demonstrated to be safe (≤ 33% DLT) during cycle 1 and 2 in at least 3 adolescents, children were enrolled at the 100 mg/m^2/d dose level. Children were not considered for intra-patient dose escalation until this dose was proven to be tolerable in adolescents. The starting dose level on cycle 1 could be escalated to 150 mg/m^2/dose if DLT was ≤33% during cycles 1 and 2 in each age group. In the absence of DLT, patients remained on treatment until there was radiographic evidence of tumor progression.

Toxicity Assessment and Definition of DLT

The CTEP Common Terminology Criteria for Adverse Events Version 3.0 (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm) was used for quantifying the severity of adverse events. Toxicity monitoring included physical exams, laboratory tests including thyroid stimulating hormone, blood pressure monitoring, and serial MRIs of the knee to quantify growth plate volume and monitor for potential bone toxicity from VEGFR inhibition.(25) Frequency of each observation is included in supplemental data.

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Hematologic DLT included grade 3 neutropenia or thrombocytopenia on 2 consecutive measurements at least 72 hours apart OR a single episode of grade 4 neutropenia or thrombocytopenia. Non-hematologic DLT included any grade 3 or higher non-hematologic toxicity, except for transient grade 3 nausea, vomiting, or electrolyte abnormalities that could be ameliorated within 48 hours and grade 3 serum transaminase elevation (ALT/AST) that returned to grade ≤2 within 7 days. Calcitonin-related diarrhea present at baseline, or vandetanib-related grade 3 diarrhea controlled by loperamide within 48 h, were not considered dose-limiting. Hypertension was graded and managed as previously described.(26) Dose-limiting QTc prolongation was defined as a single QTc value ≥550 msec OR an increase of ≥100 msec from baseline, OR two consecutive ECG measurements with QTc ≥500 msec but <550 msec OR ≥60 msec but <100 msec increase from baseline within 48 hours.

The maximum tolerated dose was the dose level at which <33% of patients in each age-based cohort (13–18 yr and 5–12 yr) experienced DLT during the first two treatment cycles. The recommended dose was based on overall tolerability and tumor response.

Pharmacokinetics

Vandetanib steady state pharmacokinetics were studied at the end of cycle 2. Vandetanib was measured using a validated HPLC tandem mass spectrometry assay.(23) Pharmacokinetic parameters were calculated using non-compartmental methods.

Response Assessment

Radiographic response, quantified using RECIST (v1.0), was the primary endpoint to assess activity.(27) Patients were evaluated prior to the start of treatment and after cycles 2, 4, 6 and 8 and then after every 4 cycles.

Biomarker response was quantified using serum calcitonin and CEA. Serum calcitonin was measured with a chemiluminescence immunoassay by Mayo Medical Laboratories (Rochester, MN). Serum CEA was measured with Axsym Analyzer (Abbott Laboratories, Abbott Park, IL) until 8/4/08 and then with the Immulite CEA method (Diagnostic Products Corp., Los Angeles, CA). Axsym results were converted to Immulite equivalents (1.255•Axium result+0.29), and CEA data are presented as Immulite equivalents. Baseline biomarkers levels >2-fold above the upper limit of normal were required to be evaluable for biomarker response. A complete biomarker response was normalization of serum calcitonin or CEA level confirmed with a repeat measurements ≥4 weeks later, and a partial response was a ≥50% decrease from baseline confirmed ≥4 weeks later.

Clinical benefit was evaluated using a patient reported outcome in patients with calcitonin-related diarrhea. Patients completed a daily diary including the number and consistency (formed, loose, or watery) of stools. Patients with 5 or more watery stools per day at baseline were evaluable for this endpoint. A complete response was defined as an average of 0–2 formed stools per day for a period of ≥4 weeks, and a partial response was defined as a ≥50% decrease in the average stool frequency relative to baseline and a change in stool consistency from watery to loose or formed for a period of ≥4 weeks.

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Statistical Methods

The phase 2 objective was to determine whether the response rate to vandetanib in children and adolescents with hereditary MTC was comparable to the preliminary response rate of 30% in adults.(28) If there were five objective responses among up to 21 patients, using an exact binomial test (one-sided alpha=0.1), the single stage design provided 80% power to rule out a response rate of <10% in favor of a response rate of 30%. Adverse events, pharmacokinetics, biomarker and clinical response rates are reported as median (range) values. The Wilcoxon signed rank test was used to compare height and weight percentiles for age at baseline and last evaluation; reported p-values are two-tailed and have not been adjusted for multiple comparisons.

RESULTS

Patient Characteristics

Between July 2007 and July 2011, 16 patients were accrued to this study at the NIH Clinical Center, 10 in the adolescent cohort (age 13–18 years) and 6 in childhood cohort (age 5–12 years). Patient characteristics are presented in Table 1. All patients harbored a germline *RET* mutation in codon 918 except patient 03 who had a polymorphism (G691S) in the *RET* proto-oncogene. All patients except subject 15 had *de novo RET* mutations with no family history of MEN2B or MTC. All subjects were evaluable for toxicity and response (Figure 1).

Toxicity

Three adolescents were enrolled at the 100 mg/m^2/d dose level, none had DLT in cycle 1 or 2, the protocol was then open to both children and adolescents at this dose level. Overall, nine adolescents enrolled at the 100 mg/m^2/d; none had DLT in cycle 1 or 2. Six children were enrolled at the 100 mg/m^2 dose level, one had dose-limiting diarrhea during cycle 2. One adolescent enrolled at starting dose of 150 mg/m^2/d required enalapril for hypertension during cycle 1 and had a dose reduction to 100 mg/m^2/d for bradycardia in cycle 3. No additional subjects were enrolled at a starting dose of 150 mg/m^2/d.

Seven adolescents met criteria for intra-patient dose escalation to 150 mg/m^2/d, one experienced dose-limiting diarrhea in cycle 3 and was dose reduced to 100 mg/m^2/d then reduced to 67 mg/m^2/d in cycle 6 due to intolerable diarrhea. Two adolescents did not intrapatient dose escalate. Subject 03 with the G691S *RET* polymorphism discontinued vandetanib after cycle 2 due to progressive disease and subject 07 declined intra-patient dose escalation due to non-dose-limiting diarrhea (grade 2) and hypertension requiring enalapril during cycle 2. Subject 07 subsequently required dose reduction to 67 mg/m^2/d in cycle 3 due to dose-limiting diarrhea.

As of July 2011, 392 cycles of vandetanib were administered at 150 mg/m^2/d (n=144 cycles), 100 mg/m^2/d (n=153 cycles), or doses ≤70 mg/m^2/d (n=95 cycles). The median number of cycles administered per subject was 27 (range, 2–52). Diarrhea was the primary DLT. No grade 4 toxicities attributable to vandetanib were observed.

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Adverse events attributed to vandetanib are presented in Figure 2. Common non-dose-limiting toxicities included prolonged QTc, hypertension, diarrhea, rash and TSH elevation necessitating an increase in levothryroxine dosage in athyrotic patients who were previously on a stable dose.

The median (range) baseline QT_C was 438 (352–472) msec. During therapy, 387 ECGs were performed in 16 subjects. No subject had dose limiting prolongation of QTc. The median (range) QT_C increase was 38 msec (11–71). Subject 10 receiving 100 mg/m^2/d, had a baseline QT_c =438 msec, a QT_C=509 msec on cycle 3, and a QT_C =500 msec on cycle 13. These asymptomatic QT_C prolongations were not verified on repeat ECG performed within 24 hours.

Four patients required enalapril to control hypertension. In patients receiving levothyroxine at enrollment (n=13), the levothroxine dose increased by 15% during cycles 1 and 2 and by 75% (0–175%) during all vandetanib courses. Thirteen patients developed vandetanib-associated rash that responded to topical therapy with hydrocortisone, flucinolone acetonide, dapsone, or clindamycin. Three patients required oral minocycline or tetracycline for acneiform rash. All patients required loperamide intermittently for diarrhea.

Serial MRI measurements of growth plate volume were completed in 13 subjects. Subjects 04, 08, 11 had increases in growth plate volume of 240%, 39%, and 52%, respectively. Despite an increase in growth plate volume, height increased 6.5, 6.2 and 5.2 cm/year, respectively. All children and adolescents demonstrated linear growth while receiving vandetanib. The median percentile of height for age at baseline was 30 (<3–96)%, and increased to 55 (<3–96)% at the last evaluation (P=0.03). The median percentile of weight for age at baseline was 9 (<3–96)% and increased to 20 (<3–91)% at last evaluation (P=0.48).

Pharmacokinetics

Steady state pharmacokinetic sampling was completed in eleven subjects receiving vandetanib 100 mg/m^2/dose. The median (range) apparent clearance was 5.9 (3.9–7.3) L/h/m^2; the area under the concentration-time curve was 16 (13.5–23.3) mcg•h/mL. All subjects achieved steady state. The average ± standard deviation C_{ss} was 0.73±0.14 mcg/mL (Supplemental Figure 1). The small sample size, low frequency of toxicity and progression of disease precluded formal correlations.

Response

All 15 subjects with M918T *RET* germline mutations experienced a decrease tumor size (Figure 3 and 4), and 7/15 achieved a confirmed partial response (objective response rate 47%; 95%CI, 21%, 73%). The overall objective response rate was 7/16 (44%; 95% CI, 20%, 70%). The number of cycles to achieve a partial response was 6 (6–20). Two patients who achieved PR (subject 01 and 04) subsequently had progressive disease after 44 or 48 cycles of vandetanib, one patient with best response of stable disease (subject 07) developed a new metastatic lesion in bone after 28 cycles. One patient discontinued therapy with 25% decrease in tumor diameter (stable disease) after 29 cycles. For seven patients with

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confirmed partial responses, only one had bone metastases. Eleven patients remain on protocol therapy.

Subject 03 with a *RET* polymorphism was enrolled on the trial 2 months after initial diagnosis of widely metastatic MTC. Compared to baseline, he had increased CEA and calcitonin during initial 2 cycles of vandetanib and clinical progression of disease in cervical vertebral bodies requiring surgery and discontinuation of vandetanib. He died from progression of disease 8 months after initial diagnosis.

Serum calcitonin and CEA are presented in Figure 5. Fifteen of 16 patients had a rapid decline in calcitonin. The decrease in calcitonin from baseline was 59 (35–84)% during cycle 1. Biomarker partial response in calcitonin was confirmed in 12 subjects at median (range) 3 (3–5) cycles. CEA was more variable, in part, because of the clinical laboratory change in the assay methodology during the study. Three subjects had baseline CEAs that were not evaluable for biomarker response. Two subjects (03 and 05) had increases in CEA, two had <50% reduction in CEA, eight had confirmed partial biomarker response in CEA by cycle 5 (3–17). No subject achieved a complete biomarker response (normalization of calcitonin or CEA).

Baseline performance status was 90 (80–100) and did not change significantly during therapy. Two patients had calcitonin-mediated diarrhea (≥5 watery stools per day) at enrollment, none achieved a complete response. Subject 07 presented with Cushing's syndrome and ectopic secretion of ACTH (urine cortisol 745 mcg/24h; serum ACTH 95 pg/mL). The Cushing's syndrome resolved, urine cortisol and serum ACTH normalized within 4 weeks of starting vandetanib.

DISCUSSION

MTC associated with activating germline mutations of *RET* is a rare cancer in children and adolescents. Conducting sequential phase 1 and 2 trials to define the dose and anti-tumor activity was impractical. We developed an innovative trial design to simultaneously determine the recommended dose using intra-patient dose escalation and anti-tumor activity of vandetanib, and restricted enrollment to patients with mutated *RET* proto-oncogene and measureable MTC. Dose escalation was limited to 2 dose levels with evidence of activity in adults with MTC. Safety was maintained by enrolling adolescents prior to children and by requiring DLT evaluation period to extent for 2 cycles to ensure steady state drug concentrations had been achieved and tolerated.

In adults with advanced solid tumors receiving vandetanib for 2.7 (0.1–14) months, the maximum tolerated and recommended dose of vandetanib was 300 mg daily. In the randomized phase 3 trial in adults with MTC, the median duration of vandetanib administration was 22.5 months, 35% required dose reductions for toxicity and one-third discontinued therapy due to an adverse event.(22) Vandetanib 100 mg/d (~55 mg/m^2/d) daily has demonstrated activity in adults with MTC with fewer and less severe toxicities, and a lower frequency of dose reductions during 8.7 (0.03–16.7) months of therapy.(29)

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In our study, the toxicity profile in adolescents and children was similar to adults. Vandetanib did not impair linear growth. The vandetanib C_{ss} in children receiving 100 mg/m^2/d is similar to the C_{ss} in adults receiving 300 mg/d fixed dose. Durable responses were achieved in children and adolescents at 150 mg/m^2/d (n=2, duration 40–52 cycles), 100 mg/m^2/d (n=4, duration 20–44 cycles) and 67 mg/m^2/d (n=1, 48 cycles). Therefore, based on a therapeutic endpoint and long-term tolerability, we recommend vandetanib 100 mg/m^2/d for children with locally advanced or metastatic MTC.

Vandetanib is active in adults with sporadic and hereditary MTC,(22, 28, 30) The objective response rate in children and adolescents with germline M918T *RET* mutations is comparable to adults with hereditary MTC and adults with sporadic MTC harboring the M918T in the tumor.(22) In our study, the subject with *RET* polymorphisms G691S, S836S had rapid progression of disease. The role of the *RET* variant allele G691S in MTC has been controversial. A recent metanalysis concluded that the G691S increases the risk of several cancers including MTC via a recessive mechanism of action. (31) Evidence that *RET* variants G691S, L769L, S836S and S904S are disease modifiers in sporadic MTC remains inconclusive.(32) The compelling anti-tumor activity of vandetanib in children with germline M918T *RET* mutations may reflect a *RET*-specific response to the drug. However, vandetanib is an inhibitor of VEGFR and EGFR, and inhibition of these targets may contribute to the clinical responses. In addition, the direct effect of *RET* kinase inhibitors on the secretion of calcitonin may contribute to the rapid reduction in calcitonin, and perhaps other hormones,. Resolution of Cushing's syndrome (subject 07) occurred prior to a decrease in tumor size.(33) In our study the TSH elevations in athyrotic subjects cannot be attributed to a decrease in thyroid hormone production, suggesting that vandetanib, like other VEGFR inhibitors may antagonize or increase metabolism of thyroid hormone.(34)

Although we observed a high response rate, the responses have been partial and 3 children have experienced progression after an initial decrease in tumor size. Disease control rather than cure may be a more realistic goal of molecularly targeted anticancer drugs. The development of resistance to vandetanib through somatic mutations in *RET* is the likely explanation for tumor progression after an initial response. Other *RET* inhibitors are currently in clinical development.(35)

Using an innovative trial design and selecting patients based on target gene expression, we conclude that vandetanib 100 mg/m^2/d is a well-tolerated, active treatment for children and adolescents with MEN2B and locally advanced or metastatic MTC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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STATEMENT OF TRANSLATIONAL RELEVANCE

Ninety-five percent of children and adolescents with the cancer predisposition syndrome Multiple Endocrine Neoplasia Type 2B (MEN2B) harbor a germline mutation in the RET proto-oncogene (exon 16 codon 918). All individuals with MEN2B develop medullary thyroid carcinoma (MTC); metastatic or locally advanced MTC is unresponsive to cytotoxic chemotherapy or radiation. Vandetanib is an oral inhibitor of tyrosine kinases including RET. This clinical trial of vandetainb in children and adolescents with MEN2B and MTC used a novel trial design and molecular selection of subjects to simultaneously and efficiently establish the recommended dose, tolerability of chronic dosing, and activity of vandetanib in this very rare population. The recommended dose is based on tolerability, pharmacokinetics, as well as biomarker and objective responses. Detailed pharmacokinetics at steady state support labeling in children. Therefore, this is an ideal dose finding method for development of molecularly targeted agents in rare tumors.

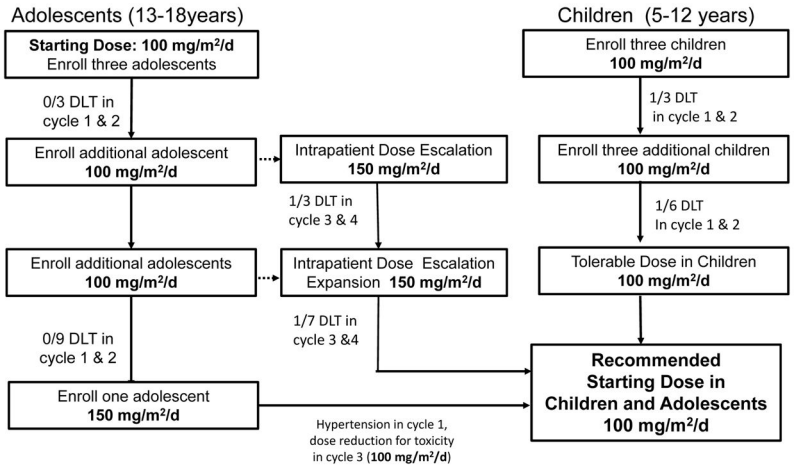

Figure 1. Clinical Trial Flow Diagram

The starting dose of vandetanib was 100 mg/m^2/d. Adolescents (age 13–18 years of age) were enrolled at the starting dose (100 mg/m^2/d) prior to children. Enrollment of the younger age cohort (Children age 5–12 years old) and intrapatient dose escalation in adolescents to 150 mg/m^2/d commenced after vandetanib 100 mg/m^2/d was demonstrated to be tolerable in adolescents (<33% dose limiting toxicity during cycle 1 and 2). Because of dose limiting diarrhea in subsequent cycles (cycle 5+) in adolescents, intrapatient dose escalation was not permitted in children. One adolescent was enrolled at the starting dose of 150 mg/m^2/d, that subject had hypertension and was dose reduced to 100 mg/m^2/d in cycle 3. The recommended dose of vandetanib (100 mg/m^2/d) was determine based on extended tolerability, pharmacokinetics, and demonstration of activity (objective response).

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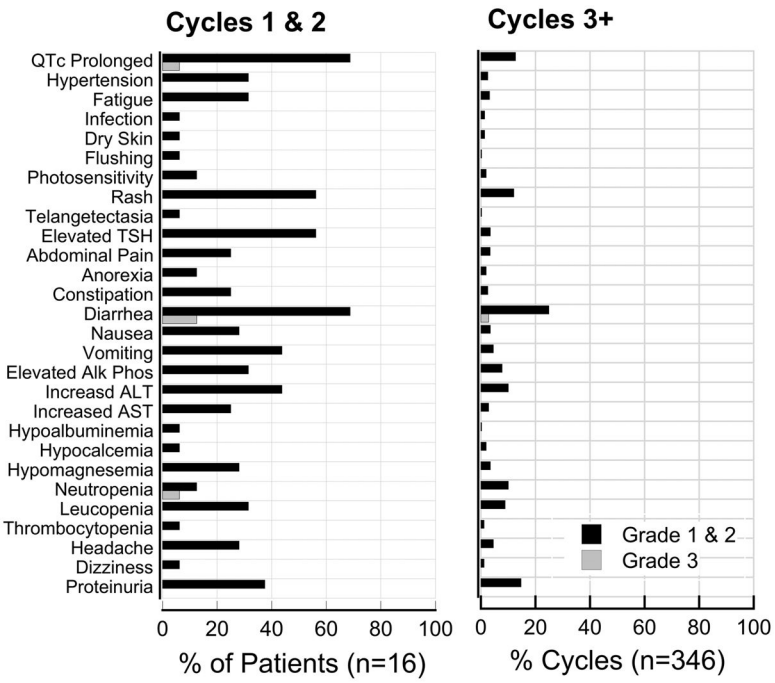

Figure 2. Adverse Events Attributed to Vandetanib

The percent of patients (n=16) experiencing grade 1 or 2 (solid black) or grade 3 (shaded grey) toxicity during cycle 1 and 2 is presented on left. The percent of cycles (n=346) in which grade 1 or 2 (solid black) or grade 3 (shaded grey) toxicity were reported is presented on the right. For each toxicity in each patient, the highest grade of toxicity during that cycle was recorded. No grade 4 toxicities possibly, probably or definitely related to vandetanib were observed.

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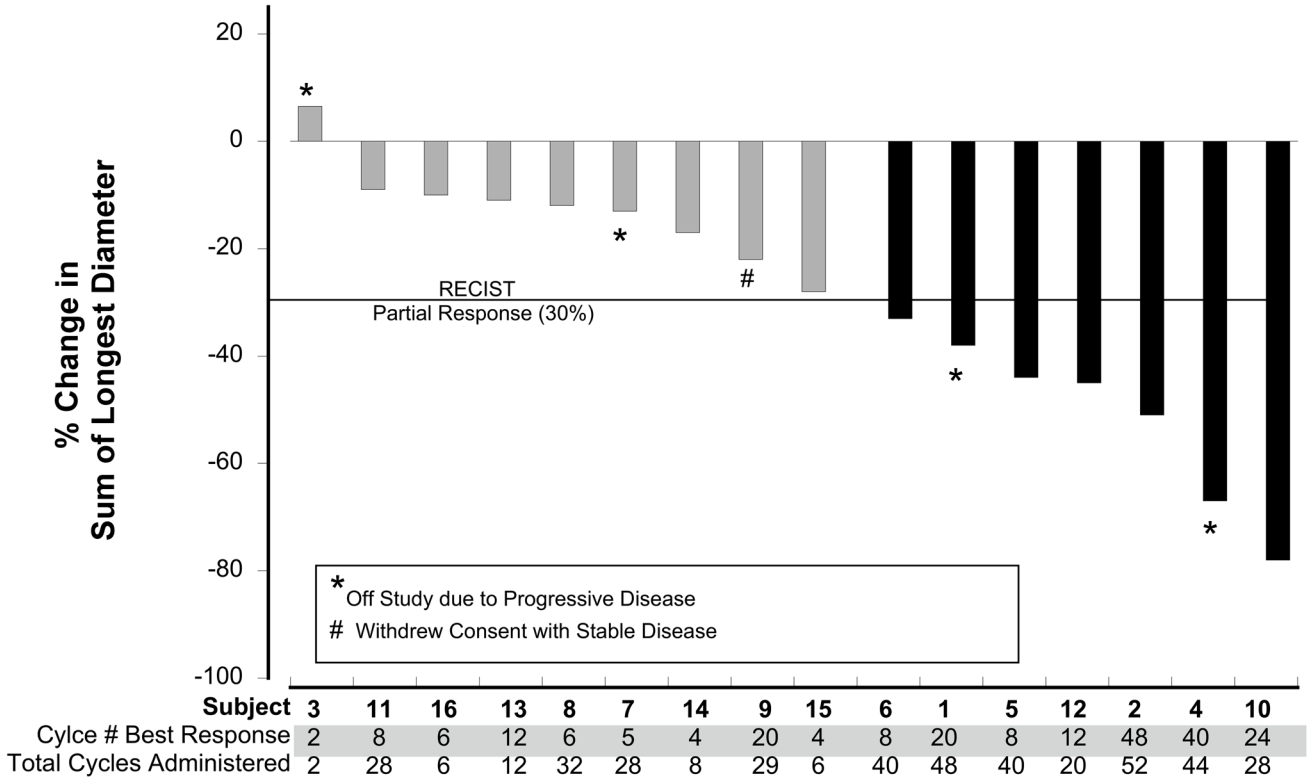

Figure 3. Waterfall Plot

Best Overall Response by RECIST v 1 is presented as percent change in the sum of the longest diameter of target lesions for each patient. Black bars indicate radiographic responses that were confirmed >4 weeks after documentation of partial response. The X-axis identifies the corresponding patient number, the cycle number when best response was initially documented and the total number of cycles administered for each patient.

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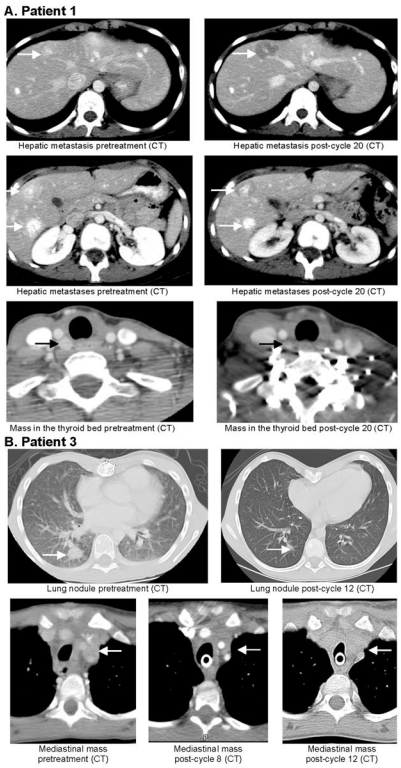

Figure 4. Radiographic Objective Responses in Adolescents and Children with MEN2B and MTC

(A) CT of chest and neck in Patient 1 (15 year old female) and (B) CT Chest in Patient 4 (11 year old male).

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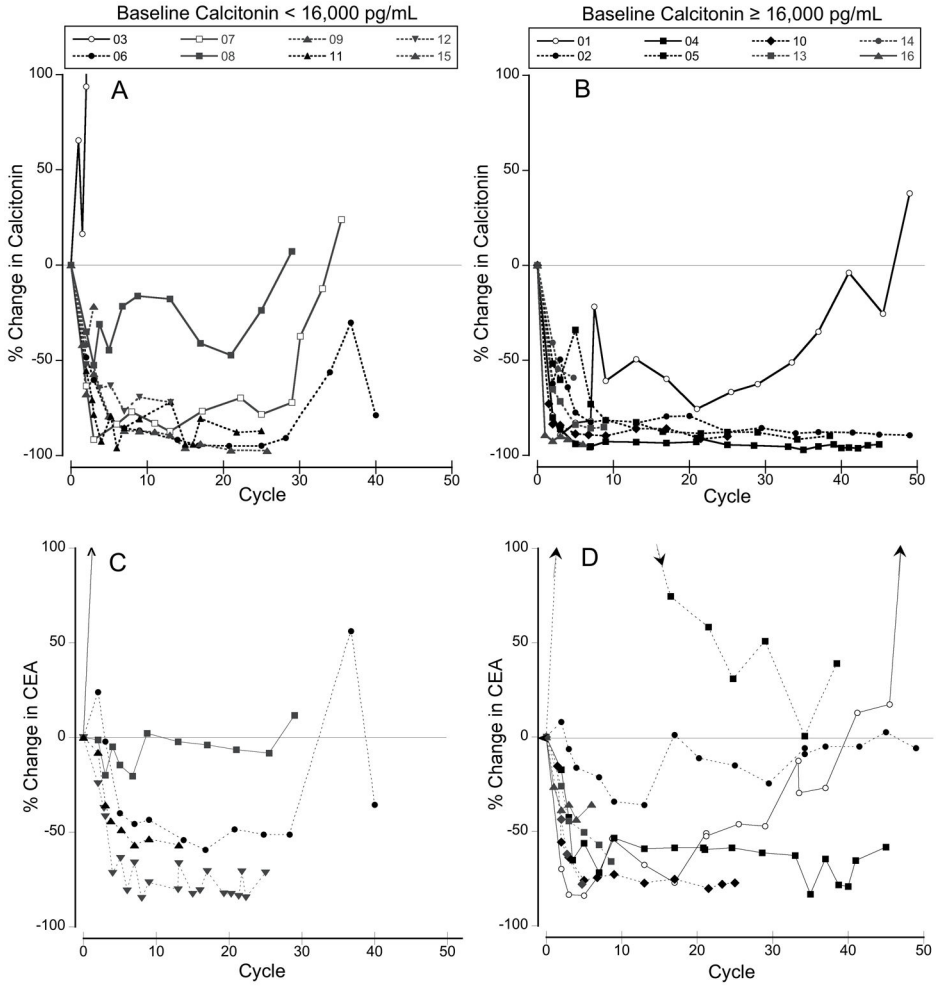

Figure 5. Biomarker Response

The percent change from baseline in calcitonin (top) or CEA (bottom) is presented for each evaluation point in each patient. Patients with baseline calcitonin less than the median (< 16,000 pg/mL) are on the left, patients with baseline calcitonin greater than the median (≥ 16,000 pg/mL) are on the right. Open symbols represent patients who had progression of disease by RECIST, black represents patients who maintain confirmed partial responses by RECIST, and grey represents patients with stable disease by RECIST. Dashed lines indicate patients who continue to received vandetanib as protocol therapy, solid lines are patients who have discontinued protocol therapy for any reason. Three subjects (07, 09, 15) had baseline CEA ≤ 2x ULN and were not evaluable for CEA biomarker response.

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Table 1

Patient Characteristics at Enrollment

Patient	Age (y)	Sex	Weight/ Height Percentile for age	PS	*RET* mutation	Disease sites at enrollment	Calcitonin (pg/mL)†	CEA (ng/mL)†	Diarrhea	Prior therapy
1	15	F	4%/67%	80	M918T	LN, neck, liver, lung	18,300	341.1	None	Surgery
2	17	M	3%/36%	90	M918T	LN, neck, bone, liver, lung	67,100	130.6	3/day (loose)	Surgery, imatinib, interferon-α
3	16	M	96%/96%	80	G691S, S836S*	Thyroid, LN, liver, bone	4,500	444.2	5–10/day (loose)	None
4	11	M	3%/3%	80	M918T	LN neck, lung	25,900	247.1	4–8/day (watery)	Surgery
5	9	F	32%/25%	100	M918T	LN, neck, lung	18,900	60.2	1–2/day (loose)	Surgery
6	16	F	53%/87%	80	M918T	LN, neck	4,600	17.7	None	Surgery
7	17	M	62%/22%	90	M918T	Lung, bone	2,000	6.8§	1–3/day (loose)	Surgery, radiation (mediastinum/neck)
8	12	M	6%/36%	100	M918T	LN, neck, lung	3.500	115.5	None	Surgery, Radiation to brain metastasis
9	16	F	6%/11%	100	M918T	LN	500	8.1§	None	Surgery
10	11	F	<3%/<3%	80	M918T	LN	57,800	801.3	2–3/day (loose)	Surgery
11	13	M	<3%/25%	100	M918T	Lung, bone	13,300	133.4	None	None
12	12	F	25%/40%	100	M918T	LN brain	6,900	28.4	None	Surgery, Radiation to brain metastasis
13	16	F	<3%/5%	90	M918T	LN, lung	24,200	244.5	4–5/day (loose)	Surgery
14	13	F	12%/77%	100	M918T	Thyroid, LN, liver	21,400	84	2–3/day (loose)	None
15	11	M	26%/88%	100	M918T	LN, lung	800	5.4§	None	Surgery
16	16	M	15%/<3%	100	M918T	Thyroid, LN, lung	47,700	60	4–5/day (watery)	Surgery (partial thyroidectomy)

Abbreviations: PS, performance score (Karnofsky for patients >10 years and Lansky for children ≤10 years); CEA, carcinoembryonic antigen; F, female; M, male; LN lymph node.

† Average of two pretreatment measurements.

§ Not evaluable for CEA response (upper limit of normal 4.6 ng/mL)

* RET polymorphism