Amendment

Protocol Number: 09C0089-M **Reference Number:** 350638

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Protocol Title: A Targeted Phase I/II trial of ZD6474 (Vandetanib; CAPRELSA) Plus the Proteasome Inhibitor, Bortezomib (Velcade®), in Adults with Solid Tumors with a Focus on Hereditary or Sporadic, Locally Advanced or Metastatic Medullary Thyroid Cancer (MTC)

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** I have reviewed this research project and considered the NIH Policy for Inclusion of Women and Minorities in Clinical Research. Taking into account the overall impact that the project could have on the research field involved, I feel the current plans adequately includes both sex/gender, minorities, children, and special populations, as appropriate. The current enrollment is in line with the planned enrollment report for inclusion of individuals on the basis of their sex/gender, race, and ethnicity and is appropriate and of scientific and technical merit.

IRB Meeting Date: Expedited

DEC Clearance Date: 08/11/2015

Protocol Version Date: 07/28/2015

A Targeted Phase I/II trial of ZD6474 (Vandetanib; CAPRELSA) plus the proteasome inhibitor, bortezomib (Velcade®), in adults with solid tumors with a focus on hereditary or sporadic, locally advanced or metastatic medullary thyroid cancer (MTC)

Abbreviated Title: Phase I/II Vandetanib and Bortezomib
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Investigational Agent: Vandetanib (CAPRELSA; ZD6474; NSC 744325)
Investigational Agent: Bortezomib (Velcade, PS-341; NSC 681239)
IND number: 58443
This study will be filed under the CTEP IND for bortezomib 58443, and cross-filed to the vandetanib IND held by AstraZeneca.

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PRECIS

Background:

- Vandetanib (CAPRELSA; ZD6474) potently inhibits vascular endothelial growth factor receptor-2 (VEGFR-2), and shows additional inhibitory activity at sub-micromolar concentrations against the **RE**arranged during **T**ransfection (RET) receptor, Flt-4 and EGF receptor tyrosine kinases.
- Clinical trials have shown that vandetanib is active against medullary thyroid carcinomas (MTCs), but the activity is characterized by partial responses of variable duration, underscoring the need to develop active combinatorial regimens.
- Bortezomib (PS-341, Velcade®), a proteasome inhibitor, has been reported to have several putative mechanisms of action and it is likely that its toxcitiy is mediated by affecting more than one pathway or target. Bortezomib is reported to inhibit the NFκB pathway and regulate NF-κB-dependent expression of several other inhibitors of apoptosis.
- *In vitro* studies have shown bortezomib to be active against a broad range of thyroid cancer cell lines. Given this activity of bortezomib and the role of the proteasome in regulating diverse cellular pathways, this study proposes to combine bortezomib with vandetanib to treat patients with advanced solid tumors with a focus on patients with MTC.

Objectives:

- To assess the activity of vandetanib plus bortezomib in adults with MTC, using RECIST and tumor biomarkers including CEA and calcitonin as endpoints.
- To assess the safety and tolerance of vandetanib plus bortezomib in dose-seeking cohorts.
- To compare the combination bortezomib plus vandetanib versus vandetanib alone in adults with MTC by assessing the response rate and progression-free survival
- In exploratory analyses: (a) examine the correlation between genotype and response to therapy in patients with MTC; (b) examine the extent, if any, of RET inhibition in patients with MTC following the administration of vandetanib; and (c) examine the effect, if any, of bortezomib on microtubules.

Eligibility:

- Adults age 18 and older with unresectable, recurrent or metastatic solid tumors, including MTC.
- Disease must be evaluable by RECIST.

Design:

- Phase I dose-escalation study followed by randomized phase II trial.
- Maximum total number for planned enrollment: 117 - Dose-seeking cohorts of three to 6 patients until MTD/DLT reached [up to 24 patients] followed by a randomized phase II trial comparing the activity of the combination of bortezomib plus vandetanib with vandetanib alone [2:1 randomization 62 + 31 = 93 patients].
- The MTD and DLT will be determined based on toxicities during the first eight weeks of combined therapy.
- Cycle length will be four weeks. Response will be determined by RECIST every12 weeks.

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1 INTRODUCTION

1.1 Study Objectives

1.1.1 Primary Objective

1.1.1.1 Phase I: To assess the safety and tolerance of daily oral vandetanib and bortezomib on days 1, 4, 8 and 11 every 28 days schedule in adults with solid tumors (recurrent, metastatic, or primary unresectable) during dose escalations in order to establish the optimal doses (recommend phase II doses) of the drug combination in patients with locally advanced or metastatic cancer, including MTC.

1.1.1.2 Phase II: To determine the tumor response rate (RR) by RECIST in adults with a diagnosis of MTC treated with daily oral vandetanib and bortezomib on days 1, 4, 8 and 11 every 28 days schedule.

1.1.2 Secondary Objectives

1.1.1.3 To compare the response rate and progression-free survival of adults with a diagnosis of MTC treated with either of two regimens: (1) daily oral vandetanib and bortezomib on days 1, 4, 8 and 11 every 28 days schedule or (2) daily oral vandetanib.

1.1.1.4 To assess the activity of daily oral vandetanib and bortezomib on days 1, 4, 8 and 11 every 28 days schedule in adults with a diagnosis of hereditary MTC by measuring:

i. Change in tumor biomarkers (calcitonin and CEA) compared to baseline
ii. Change in tumor-related diarrhea (frequency and consistency) compared to baseline
iii. Determine the pharmacokinetics (PK) of bortezomib at the start of treatment and after vandetanib has reached steady state.
iv. Determine the PK of vandetanib at steady state before and after bortezomib.

1.1.1.5 Conduct exploratory analyses as follows:

i. Perform RET gene mutational analysis in tumor tissue obtained from patients with MTC prior to or at the time of enrollment and in peripheral blood mononuclear cells obtained prior to treatment and examine the correlation between genotype and response to therapy (See Appendix A).
ii. In patients with MTC who consent to two biopsies of a site of disease that is accessible without risk to the patient perform an exploratory analysis to examine the extent of RET inhibition, an important pharmacodynamic endpoint not yet explored in any clinical trial. In these patients a biopsy would be obtained prior to the start of therapy with the second biopsy obtained after at least 42 days of vandetanib administration (See Appendix A).
iii. In patients with a diagnosis other than MTC who consent to two biopsies of a site of disease that is accessible without risk to the patient perform a biopsy prior to the start of therapy and a second biopsy after the day 11 administration of bortezomib in cycle 1 or 2 to examine the changes in microtubule stabilization. The latter would provide evidence supporting the thesis that microtubule stabilization occurs following bortezomib administration and also provide pharmacodynamic evidence of an effect of bortezomib on the tumor (See Appendix A).
iv. Assess the expression and activation of RET, EGFR, MAPK and VEGFR by immunohistochemistry and or immunoblotting in tissue obtained prior to or at the time of enrollment on this protocol and examine the correlation between expression of these proteins and response to therapy (See Appendix A).

v. Assess gene expression by microarray in tumor biopsies obtained prior to and during treatment with vandetanib and bortezomib.

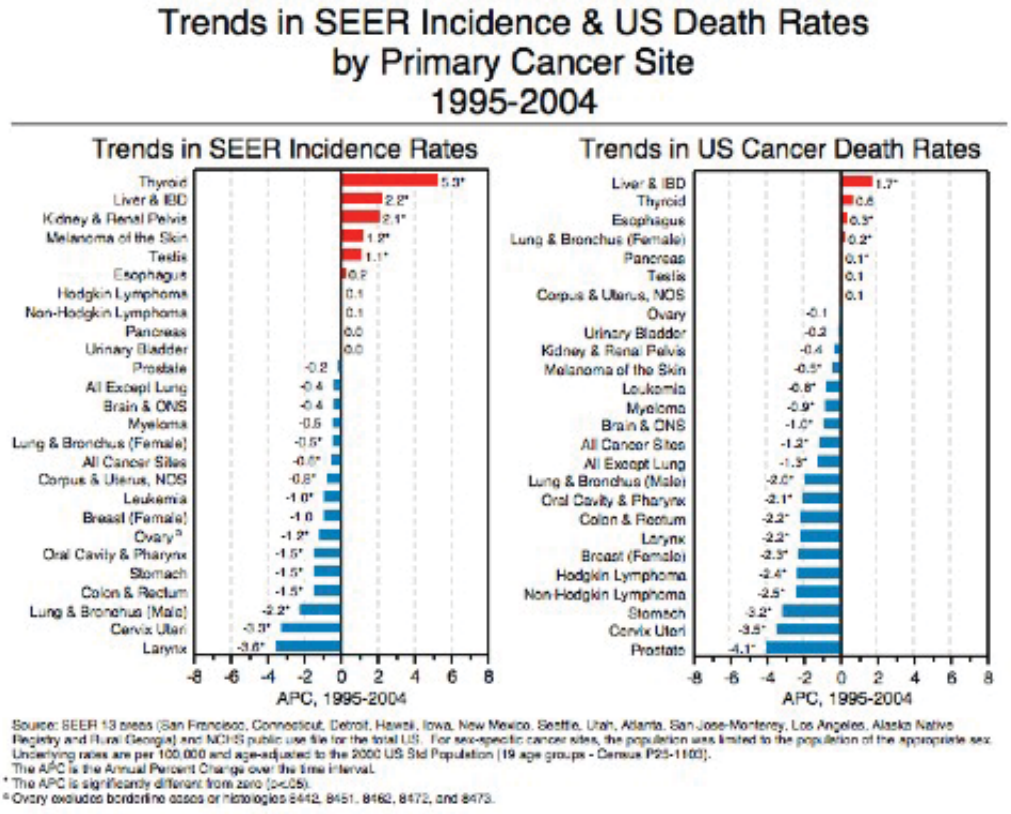
1.2 Background and Rationale

1.2.1 Thyroid Carcinoma

Over the last decade, the basic and clinical research of thyroid cancer has attracted increasing interest, since the incidence of thyroid cancer has increased at a rate more rapid than that of any solid organ malignancy. There has also been an increase in the incidence of thyroid cancer deaths exceeded only by deaths due to cancer of the liver and intra-hepatic bile ducts. (Figure 1) In 2007 there were an estimated 1530 deaths due to thyroid cancer.

The increased incidence is primarily of the papillary thyroid carcinoma (PTC) histologic subtype. The reasons for the increased incidence are unknown, however, it has been suggested that it is due to enhanced screening for thyroid nodules, resulting in more frequent detection of small, early stage PTCs[1]. Other investigators, however, have evidence that the incidence of larger thyroid tumors has also increased. Support for the latter is based on the fact that if the increased incidence were due to more frequent screening with ultrasound or other imaging procedures, one would expect a proportionate increase of all histologic types of thyroid cancer – and this has not occurred. Furthermore, there has been no organized national screening program to detect thyroid nodules.[2-4]

Figure 1



Despite the alarming increase in incidence, thyroid carcinoma is relatively rare. Data from the Surveillance, Epidemiology, and End Results (SEER)[5] and the American Cancer Society (ACS)[6]

estimate that there will be 33,500 new cases in the United States of America (USA) in 2007. The complete prevalence of thyroid cancer in the USA in January of 2003 was 347,420 (ACS), and in January of 2004 it was 366,466 (SEER). A more detailed analysis of the SEER data by stage, however, showed that the prevalence of patients with regional and distant thyroid cancer was less than 130,000 (Table 1).

Table 1

	29-year Limited Duration Prevalence *	Complete Prevalence #
Stage		-
-	195,058	-
Regional	108, 724	-
Distant	9,061	-
Unstaged	8,364	-
All stages	321,207	366,466
Regional/Distant/Unstaged	126,149	

* Number of people in the USA alive at 1/1/2004 and diagnosed with malignant thyroid cancer between 1975-2003

Number of people in the USA alive at 1/1/2004 and ever diagnosed with malignant thyroid cancer.

(Data analysis in Table 1 kindly provided by Dr. Lynn Ries and Dr. Angela Mariotto, Mathematical Statisticians at the National Cancer Institute, NIH, 6116 Boulevard, Suite 504, MSC 8317, Bethesda, MD 20892-8317; Telephone: 301.435.4923. E-mail: mariotta@mail.nih.gov). Dr. Elizabeth Ward, Executive Director of Cancer Surveillance, American Cancer Society, 1599 Clifton Road, Atlanta, GA 30329 provided the data from the ACS. Telephone: 404-929-6972. E-mail: Elizabeth.Ward@cancer.org)

Thyroid cancer occurs as one of four major histologic subtypes, with variable incidences: Papillary thyroid cancer [PTC] (70%), follicular thyroid cancer [FTC] (20%), MTC (5%) and anaplastic thyroid cancer [ATC] (5%)

The treatment of patients with thyroid carcinoma has changed little over the last 50 years. Surgical resection is the primary treatment of patients with PTC, FTC and MTC. In patients with PTC and FTC radioactive iodine is administered to treat persistent or residual disease. The long-term survival of patients with PTC and FTC is favorable, as approximately 90% of patients are living 10 years after thyroidectomy. Medullary thyroid carcinoma is distinctly more aggressive than PTC or FTC. Whether patients have hereditary or sporadic MTC, approximately 60% with a palpable tumor at the time of diagnosis have regional lymph node metastases.[7] Furthermore, most patients with sporadic MTC are incurable as evidenced by elevated plasma calcitonin [CTN] levels following thyroidectomy. Calcitonin has been routinely used as a tumor marker, as discussed below. Although incurable, the disease is sufficiently indolent in some patients that a substantial fraction survives 10 years. Thus, the 10-year survival rate in patients with MTC ranges from 40-80% and depends on several factors: patient age, tumor stage, capsular invasion, and male gender. Patients who have stage IV disease have a 5-year survival of 40%.[8-12] Anaplastic thyroid carcinoma has a poor prognosis as few patients are alive five years from the time of diagnosis.

1.2.2 Medullary Thyroid Carcinoma: Genetics of MEN 2 and MTC

Approximately 75% of cases of MTC are sporadic, while 25% are hereditary and present as one of three different but related syndromes: multiple endocrine neoplasia (MEN) 2a, MEN2b, or Familial Medullary Thyroid Carcinoma (FMTC). The MTC cells secrete the polypeptide hormone, CTN, and the glycoprotein, carcinoembryonic antigen (CEA), which serve as excellent tumor markers.

The MEN 2 syndromes are autosomal dominant inherited disorders caused by germline activating mutations in the RET (REarranged during Transfection) proto-oncogene, which has 21 exons.[13, 14] MEN 2 mutations are localized in exons 10, 11, and 13 to 16 (see Table 2 below). Missense mutations at one of six cysteine codons (609, 611, 618, 620, 630 at exon 10 and 634 at exon 11), which result in the substitution of any one of these extra-cytoplasmic cysteines by a different amino acid, are responsible for the majority of cases of MEN 2A (93–98%).[15, 16] In more than 95% of cases, MEN 2B is associated with a point mutation in the methionine residue in exon 16 (codon 918) in the intracellular tyrosine kinase receptor domain of RET.[17] Mutations are de novo in about 50% of MEN 2B cases; therefore, many patients with MEN 2B lack a family history of the disease and thus would not otherwise be targeted to undergo early screening and prophylactic thyroidectomy. These MEN 2B patients often experience a delay in diagnosis until signs of mucosal neuromas or palpable thyroid tumors are obvious.

Table 2

Domain	Exon	Codons	Syndrome
Cadherin-like			
Cysteine-rich	10	609, 611, 618, 620, 630	MEN 2A, FMTC
	11	634	MEN 2A, FMTC
Transmembrane			
Tyrosine kinase 1	13	768, 790, 791	MEN 2A, FMTC
	14	804, 844	MEN 2A, FMTC
Tyrosine kinase 2	15	883	MEN 2B
	16	918	MEN 2B

The RET proto-oncogene is located on chromosome 10 and encodes for a receptor tyrosine kinase module. The RET protein contains an extracellular ligand binding domain, a transmembrane region, and an intracellular tyrosine kinase region. The ligands known to interact with RET include Glial-derived neurotrophic factor (GDNF), neuturin, persephin, and artemin. There is also a family of membrane bound co-receptors termed GFRa-1, -2, -3, and -4. To activate RET, the ligand first binds with the requisite co-receptor, which then interacts on the cell membrane with the RET protein to cause receptor dimerization and initiation of intracellular signaling through the tyrosine kinase domains.[18] Because the mutations to RET in the MEN2 syndromes and sporadic MTC are activating, the RET RTK is a potential direct therapeutic target in this disease.

Recently, the genetic mutations or translocations causing most histological types of thyroid carcinoma have been discovered. For example, the large majority of PTCs have either BRAF mutations or RET/PTC translocations, while a minority has NTRK1 or AKAP9/BRAF translocation.[17-22] PAX8-PPARγ1 rearrangements and mutations of HRAS and NRAS have been reported with variable frequency in FTCs. [23,24] Mutations in the RET proto-oncogene are present

in the germline of virtually all patients with hereditary MTC and 30-50 percent of patients with sporadic MTC have somatic RET mutations.

Total thyroidectomy is the recommended treatment for primary MTC. Adjuvant radioactive iodine is not needed as the MTC cells derive from the neural crest, and are not composed of the follicular cells that take up iodine. In some patients who develop persistent or recurrent MTC following thyroidectomy surgeons have advocated repeat neck exploration with extensive resection of lymph nodes in the neck compartments, and occasionally the mediastinum. Approximately 10-15% of these patients have normalization of plasma CTN levels following re-operation, however, it has not been shown that overall survival is increased. [25-27] In patients with hereditary MTC genetic screening of family members at direct risk for developing MTC is critical as the majority of young children shown to have inherited a mutated *RET* allele can be cured by timely prophylactic thyroidectomy.[28]

Single base pair substitutions in one of five codons: 609, 611, 618, 620 (exon 10) or 634 (exon 11) are found in > 98% of MEN2A families.[29] Many of the same mutations responsible for MEN2A have also been found in FMTC. Substitutions of cysteine codons 609, 611, 618, 620, and 634 are found in more that 80% of FMTC families. Less commonly FMTC families have RET codon mutations in exons 13, 14 and 15. By comparison, patients with MEN2b most commonly (> 90%) have mutations in RET at codon T918T.[30] A very few patients with MEN2b have mutations in RET at codon A883F.[31]

Several studies have shown a strong correlation between the presence of a codon 634 mutation and the occurrence of pheochromocytoma and/or hyperparathyroidism (in association with MTC) in MEN2 families.[29, 32] This is direct evidence that different mutations have differing phenotypes. Furthermore, recently, a group of international scientists developed a risk analysis profile in families with hereditary MTC comparing the specific RET codon mutation to the biological aggressiveness of the MTC.[8] This is summarized in Table 3 below.

Table 3

Categorization of disease risk by RET proto-oncogene codon mutation and recommendation for prophylactic thyroidectomy

Risk level for MTC	1 - High	2 - Higher	3 - Highest
Codons	609, 768, 790, 791, 804, 891	611, 618, 620, 634	883, 918, or known MEN2B
Recommended age for prophylactic thyroidectomy	No consensus: By 5 to 10 years; or at first abnormal stimulated calcitonin	By 5 years	By 6 months; preferably within first month of life

Modified from Brandi ML, et al. 2001

Thus in the hereditary forms of the disease there is a correlation between genotype and phenotype, both as regards the clinical expression of diseases in the syndromes and the biological aggressiveness of the MTC. To date, a correlation between genotype and response to therapy has not been established. As will be discussed this study will allow for exploratory analyses that might shed preliminary light on this possibility.

Unfortunately, patients with locally advanced or metastatic MTC have a poor prognosis. There have been few clinical studies with standard regimens of systemic chemotherapy in patients with advanced MTC and most trials are single institution series and involve a small number of

patients. Partial response rates have ranged from 10-20% and are generally short lived (Table 4).[33-39]

Table 4

Efficacy of Systemic Chemotherapy in Patients with Advanced MTC

Study	N	Treatment	Response
Scherubl et al [33]	10	Adriamycin, cisplatin, vindesine	1 PR, 6 SD, 3 PD
Orlandi et al [34]	5	Dacarbazine, 5-FU	3 PR, 1 SD, 1 PD
Wu et al [35]	7	Dacarbazine, cyclophosphamide, vincristine	2 PR, 2 SD, 3 PD
Schlumberger et al [36]	20	5-FU + streptozocin or 5-FU + dacarbazine	3 PR, 11 SD, 6 PD
Di Bartolomeo et al [37]	7	Dacarbazine, 5-FU, epirubicin	1 PR
Bajetta et al [38]	1	5-FU, dacarbazine, epirubicin	1 PR
Petursson [39]	1	5-FU, dacarbazine	CR (10 months)

External beam radiotherapy (EXBRT) has a limited role in the treatment of MTC, and it is primarily indicated in the treatment of patients with metastases to bone or brain.[40] Thus, considering the relative ineffectiveness of chemotherapy and EXBRT, in patients with locally advanced or metastatic thyroid cancer of all histologic types, the availability of recently developed multi-targeted kinases has provided the opportunity to evaluate the therapeutic efficacy of these agents in clinical trials. To date there are early reports of clinical trials with several multi-targeted kinases for patients with PTC and FTC and MTC.

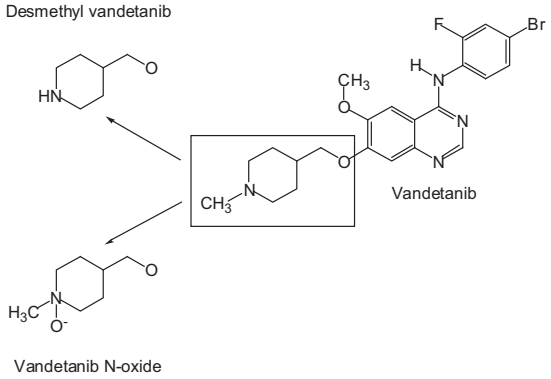
1.2.3 Biomarkers of MTC

The primary secretory product of thyroid C cells and MTC is calcitonin (CTN), which is an excellent tumor marker that correlates well with tumor bulk.[41-43] Basal or stimulated CTN values are almost always elevated in untreated patients with MTC.[8, 43] Elevated CTN values after surgery indicate persistent or recurrent disease. The physiologic role of CTN remains unclear.[44] It may play a role in calcium regulation through its effects on 3 target organs: bone (resorption), kidney (calcium excretion), and gastrointestinal (GI) tract.4[5] but an excess or deficiency of CTN does not appear to have a significant pathologic effect and some believe that it is vestigial and has no function. Extremely high levels (> 30,000 pg/ml) of serum CTN can cause symptomatic, intractable diarrhea and are usually associated with metastatic MTC.[46]

MTC cells also secrete CEA and several biogenic amines, in addition to CTN. As with CTN, CEA levels are generally proportional to tumor burden and, as a result, CEA is a useful, although nonspecific, tumor biomarker.[13]

1.2.4 Vandetanib (CAPRELSA, ZD6474, Figure 2)

Figure 2: Structure and metabolism of vandetanib



1.2.4.1 Mechanism of action

Vandetanib is a small molecule receptor tyrosine kinase (RTK) inhibitor (see Table 5 below) that potently inhibits vascular endothelial growth factor receptor-2 (VEGFR-2, KDR) tyrosine kinase activity (IC_{50} = 40 nM), and it also inhibits RET receptor tyrosine kinase (IC_{50} = 100 nM), Flt-4 (VEGF receptor-3: IC_{50} = 110 nM) and EGF receptor tyrosine kinases (IC_{50} = 500 nM).[47, 48] Vandetanib also inhibits the kinase activity of RET oncoproteins (although its affinity for all of the known mutated forms of RET in MEN 2A and 2B has not been studied) and blocks *in vivo* phosphorylation and signaling of the RET/papillary thyroid carcinoma and RET/MEN2B activated oncoproteins.[47, 49] Notably, RET/MEN2B phosphorylation and RET/MEN2B-dependent MAPK activation are inhibited by vandetanib *in vivo* at tolerable doses. The growth of cells expressing the RET/PTC oncoprotein is also inhibited *in vitro* and *in vivo*.[47]

Table 5

Vandetanib inhibition of VEGF receptor tyrosine kinase activity and selectivity profile[50, 51]

Kinase	Mean (± SE) IC_{50} (μM)*	Fold selectivity versus KDR†
KDR	0.04 ± 0.01	-
Flt-4	0.11 ± 0.02	2.7
RET	0.13	2.5
Flt-1	1.6 ± 0.4	40
EGFR	0.5 ± 0.1	12.5
PDGFRβ	1.1 ± 0.3	27.5
Tie-2	2.5 ± 1.2	62.5
FGFR1	3.6 ± 0.9	90
MEK	> 10	> 250
CDK2	> 10	> 250
c-Kit	> 20	> 500
ErbB2	> 20	> 500
FAK	> 20	> 500
PDK1	> 20	> 500
AKT	> 100	> 2500
IGF-1R	> 200	> 5000

*Data represent the mean ± SE of at least 3 separate determinations. IC_{50} values quoted as "greater than" denote the inability to reach an IC_{50} value with the highest concentration tested.

†Ratio for the IC_{50} obtained with a given kinase compared to that achieved versus KDR.

Vandetanib also has broad-spectrum antitumor activity *in vivo* in a range of models (subcutaneous or orthotopically implanted human tumor xenografts or syngeneic murine tumors) and histological types (lung, colon, breast, prostate, ovarian, vulval).[51] Vandetanib has also been shown to inhibit tumor metastases in liver, lung and lymph nodes with a variety of tumors types.[51] Reduced CD31 (endothelial cell) staining and increased tumor cell necrosis has been observed in human tumor xenografts from mice treated chronically with vandetanib (once-daily, orally, for 24 days), consistent with inhibition of angiogenesis and tumor vascular permeability. This is supported by dynamic contrast-enhanced MRI 24 hours post-vandetanib demonstrating a dose-dependent reduction in tumor k_{trans}, consistent with a reduction in vascular permeability, in mice bearing human prostate tumor xenografts.[52]

1.2.4.2 Preclinical toxicity

The preclinical safety evaluation of vandetanib revealed:

- Elevated plasma alanine transaminase (ALT), aspartate transaminase (AST), and GLDH activities; hepatocellular necrosis; and acute cholangitis were seen at the highest doses used in the rat 1-month and 6-month studies.
- Gastrointestinal tract toxicity (body weight loss, emesis, and diarrhea) was the dose limiting toxicity in dogs, but there were no associated histopathological findings.
- Renal papillary necrosis was observed at the higher doses in the 1-month rat study, but this finding was not seen in the 6-month rat study or in any dog study.
- Histopathological and ultrastructural changes, consistent with the induction of phospholipidosis, were observed in rats at the 1- and 6-month studies. No histological evidence of phospholipidosis was observed in dogs in any study. Vandetanib has physiochemical properties, which have been shown to induce excessive accumulation of intracellular phospholipids.
- The muzzle region of the skin of rats receiving the higher doses of vandetanib in the 1- and 6-month studies showed dose-related acute folliculitis and epidermal microabscess formation.
- As expected from its anti-angiogenic properties, vandetanib has shown significant effects on all stages of female reproduction in rats. These effects were characterized by the following:
    - Decreased numbers of corpora lutea in the ovaries of rats.
    - Increased estrus cycle irregularity and a dose-related increase in early intrauterine deaths, resulting in reduced number of live embryos and increased post-implantation loss.
    - Embryofetal developmental toxicity in the rat, indicated by embryofetal loss, delayed fetal development, heart vessel abnormalities and precocious ossification of some skull bones.
- A dose-dependent increase in the femorotibial epiphyseal zone of hypertrophy in growing rats when dosed daily with vandetanib for 14 days (an observation consistent with an ability to inhibit VEGF signaling and also angiogenesis *in vivo*).
- Elevated systolic and diastolic blood pressure in telemetered rats.

- Evidence of phototoxicity potential
- Vandetanib had no effect on male fertility in rats and no mutagenic or clastogenic potential.

1.2.4.3 Preclinical pharmacology

The pharmacokinetics and metabolism of vandetanib was studied in animals after oral and intravenous (IV) administration in the rat and dog and revealed:

- The bioavailability after oral dosing was high (>90% in the rat and >33% in the dog). There was evidence of slightly lower bioavailability in the rat at higher doses (72 to 78%). The absorption was not rapid, with peak concentrations occurring 3-8 hours post dose. At higher doses in rats and dogs, C x T profiles were flat, indicating prolonged absorption.
- After an IV dose of 5 mg/kg in rats, the clearance rate was 30 L/kg and the terminal half-life was 16 to 31 h. After a single IV dose (5 mg/kg) in dogs, the clearance was 85 ml/min/kg and the half-life was 8 h. The volume of distribution was 45 L/kg.
- Plasma protein binding ranged from 83% in rats to 90% in human plasma. Vandetanib was shown to bind to both human serum albumin and human α-1- acid glycoprotein.
- Toxicokinetic monitoring in rats showed dose proportional increases between 1 and 10 mg/kg, but a less than proportional increase in exposure between 25 and 75 mg/kg. Administration to rats for 6 months at 5 mg/kg resulted in a 3-fold increase in exposure (accumulation). There was evidence of a small degree of accumulation in the dog (13%) in the 1-month toxicity study that was confirmed in the 9-month toxicology study.
- After administration of ^{14}C-vandetanib to rats, radioactivity (parent drug + metabolites) was rapidly and extensively distributed, with the highest concentrations in the gastrointestinal tract, liver, spleen, adrenal glands and other glandular tissues.
- Two metabolites have been identified in samples from rats and dogs: the N-oxide of vandetanib and N-desmethyl vandetanib. These metabolites and a vandetanib glucuronide have been identified in humans. N-desmethyl vandetanib is primarily produced by CYP3A4 and N-oxide vandetanib by flavine-containing mono-oxygenase enzymes FMO1 and FMO3.
- Vandetanib had no inhibitory effect on the activity of human CYP1A2, 2C9, 2C19, or 3A4, but did inhibit 2D6 activity (k_i of 13 μg/ml).
- Urinary recovery of ^{14}C-vandetanib in rat and dog ranged from 4-12% of the dose. The majority of the radioactivity was recovered in the feces. Studies in rat demonstrated both biliary excretion and enterohepatic recirculation of vandetanib-related material.

1.2.4.4 Clinical trials

Vandetanib has been administered to over 500 adults who were enrolled in sixteen clinical trials, including two phase I trials in cancer patients, six phase I/pharmacokinetic studies in healthy volunteers, and eight phase II trials in non-s**m**all cell lung cancer (NSCLC), small cell lung cancer (SCLC), breast cancer, multiple myeloma (MM) and MTC (see Section 1.2.5.6). [53,54]

The recommended adult dose of oral vandetanib is 300 mg/d, administered continuously. The most common adverse events related to vandetanib are skin rash, diarrhea, hypertension, and asymptomatic prolongation of the electrocardiogram QTc interval. These events are dose-dependent. At a dose of 300 mg/d, QTc prolongation resulting in dose reduction has been seen in less than 15% of patients. One patient at the vandetanib 300 mg dose level experienced episodes of ventricular tachycardia, at least 1 of which was characterized as torsades-de-pointes, associated with prolongation of the corrected QT interval. Vandetanib was stopped and the patient recovered.

In the U.S. phase I trial conducted in adult patients with refractory solid tumors, patients received once-daily oral vandetanib (50-600 mg) in 28-day cycles. Seventy-seven patients were treated at doses of 50 mg (n=9), 100 mg (n=19), 200 mg (n=8), 300 mg (n=25), 500 mg (n=8), and 600 mg (n=8). Adverse events were generally mild. The most common drug-related adverse events were diarrhea (n = 29), rash (n = 26), nausea (n = 15), hypertension (n = 14), fatigue (n = 14), anorexia (n = 10), acneiform rash (n = 9), and maculopapular rash (n = 8). Drug-related adverse events that led to treatment discontinuation were congestive cardiac failure, follicular rash, folliculitis and prolonged QT interval (all n = 1). The most common dose-limiting toxicities (DLT) were diarrhea (n=4), hypertension (n=4), and rash (n=3). The incidence of most adverse events appeared to be dose-dependent. In the 500 mg/day cohort, 3/8 patients experienced DLT and this dose was therefore considered to exceed the maximum tolerated dose. Once-daily oral dosing of vandetanib at 300 mg/d was generally well tolerated in patients with advanced solid tumors, and this dose was recommended for subsequent phase II trials.[53]

In the largest monotherapy vandetanib study conducted to date comparing vandetanib to gefitinib in patients with lung cancer,[56] the most frequent adverse events observed with vandetanib were diarrhea (55.4%, grade 3 or 4, 8.4%), fatigue (36.1%), rash (27.7%, grade 3 or 4, 4.8%), nausea (24.1%), and grade 1 QTc prolongation (20.5%). Approximately 10% of subjects who received vandetanib developed hypertension, the majority of which was CTC grade 1 or 2. Three subjects developed CTC grade 3 hypertension and none were CTC grade 4. The median increase in systolic blood pressure for subjects who received vandetanib was 10 mmHg; the median increase in diastolic blood pressure was 6 mmHg. An increased incidence of SAEs was noted in subjects who received vandetanib compared to those who received gefitinib (44.6% vs. 35.3%). Cardiac disorders (6.0% vs. 1.2%), gastrointestinal disorders (6% vs. 2.4%, mainly diarrhea), and respiratory disorders (13.3% vs. 8.2%) did occur more frequently in subjects receiving vandetanib. The cardiac events included a variety of terms without any apparent pattern. Respiratory events were primarily those that would be anticipated in subjects with advanced lung cancer. Three subjects receiving vandetanib developed pulmonary embolism and three subjects developed interstitial lung disease, but cases were confounded by such factors as smoking, reduced mobility, infection, lung cancer progression and previous chemotherapy or radiation therapy. One subject in each arm developed a serious skin disorder. One subject who received vandetanib developed a hematologic event, as did two subjects who received gefitinib. No subjects who received vandetanib developed serious hepatotoxicity. Thirteen adverse events on study were followed by an outcome of death, seven in the vandetanib arm (ARDS, pneumonia, pneumonitis, dyspnea, interstitial lung disease, respiratory failure and carcinomatous meningitis) and six in the gefitinib arm (breathlessness, bone pain, cellulitis, acute respiratory failure (two cases) and pleural effusion). There were twelve subjects with confirmed QTc prolongation. Of these, six occurred in the first 28 days, and two in the following 28 days. The remaining four occurred sporadically, with the longest time to occurrence of 323 days. There were three events of reversible CTC grade 1 dizziness in subjects with a confirmed QTc prolongation occurring within the first 4 weeks. Subjects with dizziness had other events that might have caused dizziness and the events were not well correlated in time with the actual QTc prolongation. There were no other potentially relevant adverse events in subjects with confirmed QTc prolongation within the first 4 weeks, and no relevant adverse events in subjects whose first confirmed QTc prolongation occurred more than 4 weeks after randomization.

Evidence of an advantage for progression-free survival in NSCLC was seen with vandetanib 300 mg compared with gefitinib, and in the combination of vandetanib 100 mg and docetaxel

compared to docetaxel alone. These progression advantages did not translate into a corresponding advantage for overall survival in preliminary data. These observations have led to phase III trials of vandetanib in NSCLC.[50, 55]

Emerging Safety Profile

As a result of the updated Vandetanib (CAPRELSA, ZD6474) Investigator's Brochure, Edition 9, new clinical trial information has been included. Reported adverse events that may be related to vandetanib are listed below by body system:

- **Cardiovascular** – abnormal ECG (with or without QT prolongation; i.e. either T-wave or ST-segment changes consistent with repolarization abnormalities), torsade-de-pointes and ventricular tachycardia (both at 300 mg daily dose) and hypertension.
- **Central Nervous System** –headache, reversible Posterior Leukoencephalopathy Syndrome
- **Digestive** – constipation, diarrhea, nausea, vomiting
- **Hematologic and Lymphatic** – ecchymosis and thrombocytopenia
- **Investigations** – elevated liver function tests (generally CTC/CTCAE grade 1-2, preliminary data suggests these are reversible, in some cases while continuing therapy), weight loss
- **Metabolic and Nutritional** – dehydration, hypokalemia, hypomagnesemia, hypophosphatemia, anorexia
- **Skin and Appendages** – acneiform rash, pruritus, macular or macupapular rash (generalized or localized), localized and generalized erythema, photosensitivity reaction, sweating. On occasion (especially when given with chemotherapy) these have progressed to more serious conditions to include exfoliative dermatitis, skin desquamation, erythroderma, toxicoderma, toxic epidermal necrolysis, erythema multiforme
- **Respiratory** – interstitial lung disease, pulmonary embolism. A very small number of patients with lung cancer receiving vandetanib have developed shortness of breath and cough due to inflammation or scar tissue formation in the lungs (although this could be due to the underlying disease)
- **Renal** – proteinuria, hematuria
- **Vascular** – arterial ischaemic events (including myocardial infarction, stroke, peripheral ischaemia), venous thromboembolism. A small number of patients receiving vandetanib have developed blood clots affecting the legs or lungs (may have been due to the patient's cancer or other illness at the time, however it is considered possible that vandetanib might increase the risk for developing blood clots)
- **Psychiatric** – anxiety, depression, insomnia
- **General** – asthenia, fatigue

Note: Above text adapted from Vandetanib, ZD6474, Investigator's Brochure, Edition Number 9, March 2008. For additional details on vandetanib, please refer to the current Vandetanib Investigator's Brochure.

1.2.4.5 Human pharmacokinetics and metabolism

In healthy subjects, vandetanib absorption appeared to be relatively slow with a median t_{max} of 6 h (range, 4-10 h). From the C_{max}, plasma levels declined biexponentially with a terminal half-life of about 10 days. In population pharmacokinetic modeling, vandetanib was best described by a two-compartment, first order absorption, first order elimination with lag-time model, with a

CL/F of 14 L/h and a volume of distribution of 4590 L. After single doses over the dose range 300-1200 mg, exposure appeared to increase in proportion to the dose. There was no effect of food on the either AUC or C_{max}. There was no pharmacokinetic interaction with the potent inhibitor of CYP3A4 itraconazole or with the 5HT3 antagonist ondansetron.

The recovery of [^{14}C]-vandetanib was slow and both biliary (44%) and renal (25%) routes of excretion were important in its elimination. Vandetanib and its N-desmethyl and N-oxide metabolites were detected in the systemic circulation. Vandetanib, the N-oxide, the N-desmethyl, and a glucuronide metabolite were identified in urine and feces. The inhibitory activity of N-desmethyl and N-oxide metabolites of vandetanib, were examined in a growth factor stimulated HUVEC proliferation assay. N-desmethyl vandetanib retained similar potency against VEGFR and selectivity (versus EGF and bFGF) to the parent drug, where as the N-oxide of vandetanib had relatively weak activity in cells (IC_{50} > 3 μM) against the growth factor stimuli examined.

In patients the absorption of vandetanib appeared to be more variable and prolonged than in healthy subjects, with median t_{max} of 4-10 h and a larger range of 1-24 h.[53, 54] Population pharmacokinetic modeling showed a CL/F of 6.43 L/h, a volume of distribution of 6260 L, and an estimated terminal half-life of about 20 days. Over the dose range 100-600 mg, exposure appeared to increase in a dose-proportional manner. Trough levels indicate that a minimum of 28 days of daily dosing is required to achieve steady state plasma concentrations, with about a 10-fold (range, 3- to 30-fold) accumulation compared to a single dose.

1.2.4.6 Phase II Trial of Vandetanib in Adults with MTC

In preclinical studies vandetanib was first shown to be a potent inhibitor of KDR tyrosine kinase activity, and to have the ability to inhibit outgrowth of *RET/PTC* induced tumors in nude mice.[47] Subsequently in an open label phase II clinical trial of oral vandetanib in 30 patents with hereditary MTC, at the time of data cutoff (22 February 2008), 20% of patients in the ITT population who received ZD6474 300 mg had an objective response. A further 53% (16/30) of patients experienced SD ≥24 weeks and 20% (6/30) of patients experienced SD ≥8 and <24 weeks. Disease control was observed in 22 (77.3%) patients.[56]

Furthermore, the remissions were generally durable and even though the data analysis has not been completed no patient who experienced a partial remission has developed recurrent disease. In addition 24 patients showed a greater than a 50% decrease from baseline of the plasma CTN levels and 16 patients experienced a 50% decrease from baseline of plasma CEA levels.[49] Generally, side effects were mild with diarrhea the dose limiting toxicity as shown in Table 7.

Figure 3 Change in tumor size – waterfall plot (ITT analysis set)

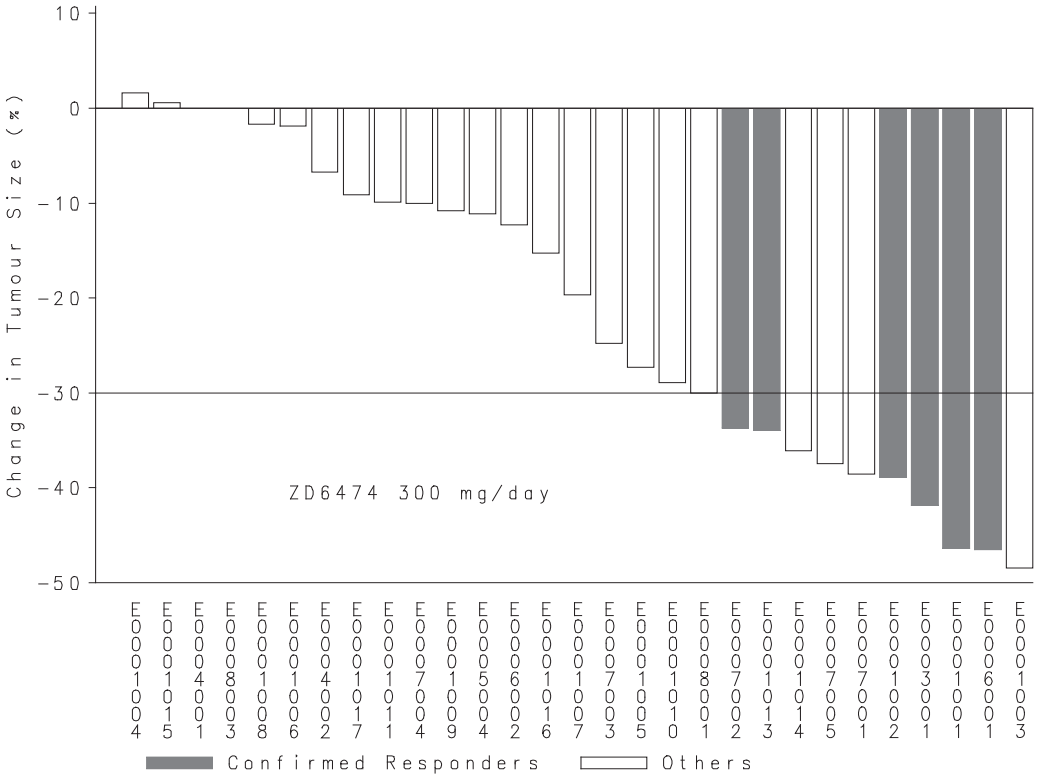


Table 6

Patient	Tumor Assessment: Best objective response (Largest % change in tumor size)[1]	Best CTN Response (% Change from baseline)[2]	Patient Status	Days on Study[3]
1	Confirmed PR (-46.4%)	PR (-95.7%)	Discontinued	115
2	Confirmed PR (-41.9 %)	PR (-92.4%)	Active	253
3	Confirmed PR (-39.8%)	PR (-72.8%)	Active	466
4	Confirmed PR (-38.9%)	PR (-99.5%)	Active	803
5	Confirmed PR (-34.0%)	PR (-84.8%)	Active	593
6	Confirmed PR (-50.0%)	PR (-86.6%)	Active	466
7	Confirmed PR (-39.5%)	PR (-81.2%)	Active	761
8	SD ≥ 24 weeks (-25.0%)	PR (-98.7%)	Active	284
9	SD ≥ 8 < 24 weeks (-24.8%)	PR (-30.2%)	Discontinued	105
10	SD ≥ 24 weeks (-24.6%)	PR (-95.5%)	Active	579
11	SD ≥ 24 weeks (-23.3%)	PR (-89.2%)	Active	243
12	SD ≥ 24 weeks (-20.6%)	PR (-81.3%)	Active	663
13	SD ≥ 24 weeks (-20.0%)	PR (-94.5%)	Active	218

[1]According to site review
[2]CTN Response; PR: At least -50% change from baseline in serum CTN levels maintained over a minimum of 4 weeks; SD: between +20% and -50%chnage in serum CTN levels maintained over a minimum of 8 weeks

[3]Total duration of time from first dose to last doe or data cutoff, including any dose interruptions
CTN: Calcitonin; PR: Partial Response; SD: Stable disease

Table 7

Number (%) of patients with the most commonly reported adverse events (≥10%), sorted by decreasing order of frequency (safety analysis set)

ZD6474 (vandetanib): 300 mg/day (N = 30)

Preferred term	Number (%) of patients who had an adverse event
Diarrhea	21 (70.0)
Rash	20 (66.7)
Fatigue	19 (63.3)
Nausea	19 (63.3)
Headache	14 (46.7)
Anorexia	13 (43.3)
Vomiting	12 (40.0)
Constipation	11 (36.7)
Dysgeusia	10 (33.3)
Hypertension	10 (33.3)
Dry skin	9 (30.0)
Dizziness	8 (26.7)
Electrocardiogram QT prolonged	8 (26.7)
Cough	7 (23.3)
Hypocalcemia	7 (23.3)
Edema peripheral	7 (23.3)
Urinary tract infection	7 (23.3)
Vision blurred	7 (23.3)
Abdominal pain	6 (20.0)
Acne	6 (20.0)
Anxiety	6 (20.0)
Asthenia	6 (20.0)
Dyspepsia	6 (20.0)
Insomnia	6 (20.0)
Esophagitis	6 (20.0)
Sinus congestion	6 (20.0)
Temperature intolerance	6 (20.0)

Preferred term	Number (%) of patients who had an adverse event
Alopecia	5 (16.7)

1.2.4.7 Phase III Trial of Vandetanib in Adults with MTC

The antitumor activity seen in the phase II trial of patients with MTC led to initiation of a double blinded, randomized phase III trial of vandetanib versus placebo for patients with advanced or metastatic MTC. This trial accrued 331 patients from December 2006 through November of 2007, with 231 patients randomized to vandetanib 300mg orally daily and 100 patients to placebo. At the time of data cutoff (July 31, 2009) in the ITT analysis, 45% of patients randomized to the vandetanib arm had a PR. This was statistically significant compared to placebo ($p < 0.0001$) despite unblinding and the option to crossover to vandetanib at the time of progression. The responses were durable, with the median duration of response not reached at 24 months of follow-up. PFS was also superior in the vandetanib arm in the ITT analysis with a HR of 0.46 (95% CI 0.31-0.69). The median PFS was not yet met at 24 months of follow-up for patients in the vandetanib arm; whereas the median PFS for patients in the placebo arm was 19.3 months. In general, the drug was safe and well-tolerated, permitting treatment with vandetanib for prolonged periods of time. In the randomized portion, the median duration of treatment with vandetanib was 90.1 weeks compared to 39.9 weeks in the placebo arm. The most frequent AEs (any grade) were diarrhea, rash, nausea, and hypertension. The most common grade 3+ AEs are listed in Table 8[71].

Table 8

Most common grade 3+ adverse events (>2% incidence in either arm)

	Vandetanib 300mg (n=231)	Placebo (n=99)
Diarrhea	25 (11%)	2 (2%)
Hypertension	20 (9%)	1 (1%)
ECG QT prolonged	18 (8%)	1 (1%)
Fatigue	13 (6%)	1 (1%)
Decreased appetite	10 (4%)	0
Rash	8 (3%)	1 (1%)
Asthenia	6 (3%)	1 (1%)
Dyspnea	4 (2%)	3 (3%)
Back pain	1 (0.4%)	3 (3%)
Syncope	0	2 (2%)

1.2.5 Bortezomib (Velcade®, PS-341)

As of May 2008, Bortezomib for Injection is FDA-approved and indicated for:
(1) The treatment of multiple myeloma patients who have received at least two prior therapies and have demonstrated disease progression on the last therapy [May 13, 2003].
(2) The treatment of patients with multiple myeloma who have received at least one prior therapy [March 25, 2005].
(3) The treatment of patients with mantle cell lymphoma who have received at least one prior therapy [December 8, 2006].

1.2.5.1 Mechanism of action

The 26S proteasome is a large ATP-dependent multimeric complex that degrades intracellular proteins that have been targeted for proteolysis by the process of ubiquitination. Several key regulators of transcription, growth and apoptosis, including nuclear factor-{kappa}B (NF-{kappa}B) inhibitor (I{kappa}B), p53, c-myc, and c-Jun N-terminal kinase (JNK), among others, are known substrates for proteasomal degradation. Proteasome inhibitors have shown evidence of preclinical activity against hematological malignancies and solid tumors and one proteasome inhibitor, bortezomib, has been approved by the Food and Drug Administration for use in relapsed refractory MM (MM). 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. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis that can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death. Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types in vitro. Bortezomib causes a delay in tumor growth in vivo in non-clinical tumor models, including MM. Bortezomib is currently undergoing extensive evaluation in a variety of other hematological and solid malignancies both as a single agent, but predominantly in combination with other chemotherapeutics. When bortezomib was shown to be active in the treatment of MM, emphasis was placed on its ability to inhibit the NF-{kappa}B pathway. Evidence indicated that proteasome inhibition abrogates degradation of and induces cytoplasmic accumulation of I{kappa}B, an inhibitor of NF-{kappa}B that acts by blocking the nuclear translocation and transcriptional activity of NF-{kappa}B. This may contribute to the cytotoxic effects of bortezomib in malignancies such as MM, in which NF-{kappa}B function is important for tumor cell proliferation and survival. However, this simplistic view of the agent's activity has been gradually replaced by a more in depth understanding that recognizes that bortezomib also regulates the NF-{kappa}B-dependent expression of several other inhibitors of apoptosis such as A1, cellular inhibitor of apoptosis protein-2, and X-linked inhibitor of apoptosis (XIAP); and also has a variety of other NF-{kappa}B-independent effects including stabilization of p53 protein and up-regulation of p53 mRNA, stabilization of c-myc, phosphorylation and activation of c-Jun, and activation of the Fas pathway, among many others.

1.2.5.2 Pharmacokinetics

Following intravenous administration of 1.3 mg/m^2 dose, the median estimated maximum plasma concentration of bortezomib was 509 ng/mL (range = 109-1300 ng/mL) in eight patients with MM and creatinine clearance values ranging from 31-169 mL/min. The mean elimination half-life of bortezomib after the first dose ranged from 9 to 15 hours at doses ranging from 1.45 to 2 mg/m^2 in patients with advanced malignancies. The pharmacokinetics of bortezomib as a single agent has not been fully characterized at the recommended dose in MM patients.

- Distribution: The distribution volume of bortezomib as a single agent was not assessed at the recommended dose in patients with MM. The binding of bortezomib to human plasma proteins averaged 83% over the concentration range of 100-1000 ng/mL.
- Metabolism: *In vitro* studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolized via cytochrome P450 enzymes, 3A4, 2D6, 2C19, 2C9, and 1A2. The major metabolic pathway is

deboronation to form two deboronated metabolites that subsequently undergo hydroxylation to several metabolites. Deboronated-bortezomib metabolites are inactive as 26S proteasome inhibitors. Pooled plasma data from 8 patients at 10 min and 30 min after dosing indicate that the plasma levels of metabolites are low compared to the parent drug.

- Elimination: The pathways of elimination of bortezomib have not been characterized in humans.

1.2.5.3 Drug Interactions

No formal drug interaction studies have been conducted with bortezomib. *In vitro* studies with human liver microsomes indicate that bortezomib is a substrate of cytochrome P450 3A4, 2D6, 2C19, 2C9, and 1A2. Bortezomib is a poor inhibitor of human liver microsome cytochrome P450 1A2, 2C9, 2D6, and 3A4, with IC50 values of > 30 μM (> 11.5 μg/mL). Bortezomib may inhibit 2C19 activity (IC50 = 18μM, 6.9 μg/mL) and increase exposure to drugs that are substrates for this enzyme. Bortezomib did not induce the activities of cytochrome P450 3A4 and 1A2 in primary cultured human hepatocytes.

Drug Interactions

In male Wistar rats bortezomib has been shown to inhibit the degradation of CYP2E1, a cytochrome P450 enzyme responsible for the biotransformation of many organic solvents and environmental pro-carcinogens oxidative and reductive.[57] *In vitro* experiments with human liver microsomes have shown that bortezomib is a poor inhibitor of cytochrome P450 CYP1A2, 2C9, 2D6, and 3A4. IC_{50} values were > 30 μmol/L (> 11.5 μg/mL). Bortezomib may inhibit CYP2C19 activity (IC_{50} = 18 μmol/L, 6.9 μg/mL) and increase exposure to drugs that are substrates for this enzyme. During clinical trials, hypoglycemia and hyperglycemia were reported in patients whose diabetes was controlled with oral hypoglycemic agents. Patients on oral anti-diabetic agents receiving bortezomib may require more frequent blood glucose monitoring and, if indicated, adjustment of anti-diabetic medication doses. [Velcade® product labeling, Oct. 2007. Millennium Pharmaceuticals, Inc., Cambridge, MA]

1.2.5.4 Bortezomib Adverse Events

Table 9

Bortezomib Adverse Events

Common Adverse Events	
Cardiovascular	Hypotension (11 – 12%)
Dermatologic	Rash (18 – 21%)
Gastrointestinal	Constipation (30 – 43%)
	Decrease in appetite (34 – 43%)
	Diarrhea (37% – 57%)
	Nausea (52 – 64%)
Hematologic	Anemia (26 – 48%%)
Musculoskeletal	Arthralgia (14 – 26%)
	N\Bone pain (14%)
	Cramp (12 – 14%)
	Myalgia (12 – 14%)
Neurologic	Asthenia (61 – 65%)
	Peripheral neuropathy (19 – 32%)

Common Adverse Events	
Ophthalmic	Blurred vision (11%)
Psychiatric	Mental disorder (35%)
Respiratory	Lower respiratory tract infection (15%)
Other	Fever (35 – 36%)

Serious Adverse Events	
Cardiovascular	Congestive heart failure, heart disease (15%)
Dermatologic	Toxic epidermal necrolysis
Gastrointestinal	Vomiting (35 – 36%)
Hematologic	Neutropenic disorder (19%)
	Thrombocytopenia (35%)
Hepatic	Hepatic failure, acute
Immunologic	Angioedema
Neurologic	Postherpetic neuralgia
	Transient ischemic attack
Respiratory	Acute respiratory distress syndrome (rare)
	Interstitial pneumonia (rare)
	Pneumonitis, acute (rare)

1.2.5.5 Clinical Studies (A very brief summary/history)

Clinical Studies in Relapsed and Refractory MM:

The safety and efficacy of bortezomib were initially evaluated in an open-label, single-arm, multicenter study of 202 patients who had received at least 2 prior therapies and demonstrated disease progression on their most recent therapy. Since then countless numbers of patients with a broad variety of cancer have been safely treated with bortezomib, albeit with some recurring but manageable toxicities. In the open-label, single-arm, multicenter study of 202 patients with MM, the median number of prior therapies was six. Baseline patient and disease characteristics are summarized in Table 9. An IV bolus injection of bortezomib 1.3 mg/m^2/dose was administered twice weekly for two weeks, followed by a 10-day rest period (21 day treatment cycle) for a maximum of eight treatment cycles. The study employed dose modifications for toxicity. Patients who experienced a response to bortezomib treatment were allowed to continue bortezomib treatment in an extension study.

Table 10

Velcade® in MM (N = 202)	
Summary of Patient Population and Disease Characteristics*	
Patient Characteristics	
Median Age in Years (Range)	59 (34,84)
Gender: Male/Female	60%/40%
Race: Caucasian/Black/Other	81%/10%/8%
Karnofsky Performance Status Score ≤ 70	20%
Hemoglobin < 100 g/L	44%
Platelet count < 75 x 10^9/L	21%
Disease Characteristics	

Type of myeloma (%): IgG/IgA/Light chain	60%/24%/14%
Median β2-microglobulin (mg/L)	3.5
Median Creatinine Clearance (mL/min)	73.9
Abnormal Cytogenetics	35%
Chromosome 13 Deletion	15%
Median Duration of MM Since Diagnosis	4.0 years
Previous Therapy	
Any Prior Steroids, e.g., dexamethasone, VAD	99%
Any Prior Alkylating Agents, e.g., MP, VBMCP	92%
Any Prior Anthracyclines, e.g., VAD, mitoxantrone	81%
Any Prior Thalidomide Therapy	83%
Received at Least 2 of the Above	98%
Received at Least 3 of the Above	92%
Received All 4 of the Above	66%
Any Prior Stem Cell Transplant /Other High-dose Therapy	64%
Prior Experimental or Other Types of Therapy	44%
*Based on number of patients with baseline data available	

Ninety-eight percent of study patients received a starting dose of 1.3 mg/m^2. Twenty-eight percent of these patients received a dose of 1.3 mg/m^2 throughout the study, while 33% of patients who started at a dose of 1.3 mg/m^2 had to have their dose reduced during the study (Table 10). Sixty-three percent of patients had at least one dose held during the study. In general, patients who had a confirmed CR received 2 additional cycles of VELCADE treatment beyond confirmation. The mean number of cycles administered was six. The median time to response was 38 days (range 30 to 127 days). The median survival of all patients enrolled was 16 months (range < 1 to 18+ months).

Table 11

Summary of Disease Outcomes
Response Analyses (VELCADE monotherapy) N = 188

Response	**N (%)**	**(95% CI)**
Overall Response Rate (Bladé) (CR + PR)	52 (27.7%)	(21, 35)
Complete Response (CR)[1]	5 (2.7%)	(1, 6)
Partial Response (PR)[2]	47 (25%)	(19, 32)
Clinical Remission (SWOG)[3]	33 (17.6%)	(12, 24)
Kaplan-Meier Estimated Median Duration of Response (95% CI)	365 Days	(224, NE)

[1] **Complete Response** required 100% disappearance of the original monoclonal protein from blood and urine on at least 2 determinations at least 6 weeks apart by immunofixation, and < 5% plasma cells in the bone marrow on at least two determinations for a minimum of six weeks, stable bone disease and calcium.
[2] **Partial Response** requires ≥ 50% reduction in serum myeloma protein and ≥90% reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks, stable bone disease and calcium.
[3]**Clinical Remission (SWOG)** required ≥ 75% reduction in serum myeloma protein and/or ≥ 90% reduction of urine myeloma protein on at least 2 occasions for a minimum of at least 6 weeks, stable bone disease and calcium.

Note: In this study, the response rate to VELCADE was independent of the number and types of prior therapies. There was a decreased likelihood of response in patients with either > 50% plasma cells or abnormal cytogenetics in the bone marrow. Responses were seen in patients with chromosome 13 abnormalities. A small dose-response study was performed in 54 patients with multiple myeloma who received a 1.0 mg/m^2/dose or a 1.3 mg/m^2/dose twice weekly for two out of three weeks. A single complete response was seen at each dose, and there were overall (CR + PR) response rates of 30% (8/27) at 1.0 mg/m^2 and 38% (10/26) at 1.3 mg/m^2.

Clinical Studies in Mantle Cell Lymphoma:

In addition, in December 2006, the FDA granted approval to bortezomib for the treatment of patients with mantle cell lymphoma who had received at least one prior therapy. An open-label, single-arm, multi-center study of 155 patients with progressive mantle cell lymphoma who had received at least one prior therapy was performed to assess response rate and duration (Table 11). Seventy-five percent had one or more extra-nodal disease sites and 77 percent were stage 4. In 91 percent of patients, prior therapy included an anthracycline or mitoxantrone, cyclophosphamide, and rituximab. Thirty-seven percent were refractory to their last prior therapy. Patients received bortezomib, 1.3 mg/m^2 intravenously, on days 1, 4, 8, and 11 of each three-week cycle. Response rates were determined according to the International Workshop Response Criteria (1999) and were based on an independent radiologic CT scan review. The overall response rate (CR plus CRu plus PR) was 31 percent and the median response duration was 9.3 months. The CR plus CRu response rate was 8 percent and the median response duration was 15.4 months. The median number of cycles in responding patients was eight. The median time to response was 40 days (range 31 to 204 days). Adverse events, irrespective of their relationship to bortezomib, were similar to those observed in the previously reported myeloma studies. The most commonly reported treatment-emergent adverse events were asthenic conditions (72%), peripheral neuropathies (55%), constipation (50%), diarrhea (47%), nausea (44%), and decreased appetite (39 percent). The most common adverse event leading to discontinuation was peripheral neuropathy.

Table 12: Mantle Cell Lymphoma[58]

Best Response to Treatment (N = 141) by Algorithm and by Investigator Assessment

	By Investigator			By Algorithm		
Response	#	%	95% CI	#	%	95% CI
CR + CRu + PR	47	33	26 to 42	57	40	32 to 49
CR + CRu	11	8	4 to 14	11	8	4 to 14
CR	9	6	3 to 12	8	6	2 to 11
PR	36	26	19 to 34	46	33	25 to 41
SD	47	33	26 to 42	46	33	25 to 41
PD	35	25	18 to 33	37	26	19 to 34
No post-baseline assessment	12	9	4 to 14	1	< 1	0 to 4

Abbreviations: CR, complete response; CRu, unconfirmed CR;

PD, progressive disease; PR, partial response; SD, stable disease.

Response, date of response, and PD were determined using a computer algorithm that applied the International Workshop Response Criteria (IWRC) with a minor modification

to correlate more closely with application of these criteria in clinical practice, and used tumor measurements from independent radiology review of patient scans. The IWRC modification was incorporated when it became clear that small changes in nodes smaller than 1 cm in size were assessed as PD by algorithm but not by investigator. The definition of PD, which required 50% or higher increase in the product of the longest perpendicular dimensions of any previously identified, measurable site of lymphoma, or 50% or higher increase in the longest dimension of any previously identified site of lymphoma that was larger than 1 cm in the longest transverse dimension (ie, measurable at baseline), was modified to specify that the lesion should be larger than 1 cm in both perpendicular dimensions at the time of PD and that the absolute increase in either dimension, or in the longest dimension, respectively, should be at least 0.5 cm. This better reflects the recently updated IWRC.

1.2.5.6 Clinical Studies: Bortezomib dose and schedules

The most widely used bortezomib regimen for MM employs 1.3 to 1.5 mg per square meter per dose on days 1, 4, 8 and 11. For example, in the registration trials for MM cited above, 98% of study patients received a starting dose of 1.3 mg/m^2. Twenty-eight percent of these patients received a dose of 1.3 mg/m^2 throughout the study, while 33% of patients who started at a dose of 1.3 mg/m^2 had to have their dose reduced during the study. Sixty-three percent of patients had at least one dose held during the study. In general, patients who had a confirmed CR received 2 additional cycles of bortezomib treatment beyond confirmation. The mean number of cycles administered was six. The median time to response was 38 days (range 30 to 127 days). The median survival of all patients enrolled was 16 months (range < 1 to 18+ months). A small dose-response study was performed in 54 patients with MM who received a 1.0 mg/m^2/dose or a 1.3 mg/m^2/dose twice weekly for two out of three weeks. A single complete response was seen at each dose, and there were overall (CR + PR) response rates of 30% (8/27) at 1.0 mg/m^2 and 38% (10/26) at 1.3 mg/m^2. The latter suggests that there may be more than one optimal dose and schedule for patients with MM and in cancer patients in general. Indeed, other schedules have been used. For example, a recently reported phase I and pharmacologic study of sequences of bortezomib in combination with paclitaxel and carboplatin in patients with advanced malignancies explored two schedules. The study identified the maximum tolerated dose and the recommended doses for future phase II trials as bortezomib 1.2 mg per square meter, paclitaxel 135 - 175 mg per square meter and carboplatin AUC = 6.[59] Pancreatic cancer patients were randomized to receive either 3-week cycles of bortezomib 1.5 mg per square meter on days 1, 4, 8 and 11 or bortezomib 1.0 mg per square meter on days 1, 4, 8 and 11 plus gemcitabine 1,000 mg per square meter on days 1 and 8. Twelve of 43 evaluable patients (28%) treated with bortezomib alone experienced at least one grade 4+ AE while eleven of 43 evaluable patients (26%) treated with the combination experienced at least one grade 4+ AE with one patient having grade 5 hypotension.[60] Finally, a recently reported phase I pharmacologic trial of two schedules of bortezomib in patients with advanced cancer administered the compound either twice weekly for 4 of 6 weeks or twice weekly for 2 of every 3 weeks and found dose-limiting thrombocytopenia at 1.6 to 1.7 mg per square meter as well as dose-limiting sensory neuropathy. The maximum tolerated dose for both schedules was 1.5 mg per square meter. Interestingly, reversible dose-dependent decreases in 20S proteasome activity in PBMCs were observed, with 36% inhibition at 0.5 mg per square meter, 52% at 0.9 mg per square meter, and 75% at 1.25 mg per square meter with accumulation of proteasome-targeted polypeptides detected in tumor samples after treatment with bortezomib.[61] The authors concluded that 1.5 mg per square meter

bortezomib twice weekly for 2 of every 3 weeks is well tolerated and should be further studied. From this and other data it seems clear that a dose of 1.5 mg per square meter twice weekly is likely too toxic to be sustained over a prolonged period of time, especially in patients receiving a TKI such as vandetanib who might continue treatment for a long time. It also seems probable that a dose of 1.0 mg per square meter would be a maximum tolerated dose in combination with another agent, even a "non-cytotoxic" agent such as vandetanib if either a three or four dose (twice-weekly) schedule of administration is used. However, it is clear that other dose schedules are under investigation and that there is no "hard evidence" that the schedules used to date are the only ones likely to be active.

In most solid tumors, bortezomib has not shown significant activity to date, although some combination studies are still ongoing and a final conclusion at to its activity or lack thereof in solid tumors cannot yet be reached. A few references are provided below.

Lung Cancer:
Lara PN Jr, Chansky K, Davies AM, Franklin WA, Gumerlock PH, Guaglianone PP, Atkins JN, Farneth N, Mack PC, Crowley JJ, Gandara DR. Bortezomib (PS-341) in relapsed or refractory extensive stage small cell lung cancer: a Southwest Oncology Group phase II trial (S0327). J Thorac Oncol, 1:996-1001 (2006).

Breast:
Engel RH, Brown JA, Von Roenn JH, O'Regan RM, Bergan R, Badve S, Rademaker A, Gradishar WJ. A phase II study of single agent bortezomib in patients with metastatic breast cancer: a single institution experience. Cancer Invest, 25:733-7 (2007)

Sarcomas:
Maki RG, Kraft AS, Scheu K, Yamada J, Wadler S, Antonescu CR, Wright JJ, Schwartz GK. A multicenter Phase II study of bortezomib in recurrent or metastatic sarcomas. Cancer, 103:1431-8 (2005).

Various:
Jatoi A, Dakhil SR, Foster NR, Ma C, Rowland KM Jr, Moore DF Jr, Jaslowski AJ, Thomas SP, Hauge MD, Flynn PJ, Stella PJ, Alberts SR. Bortezomib, paclitaxel, and carboplatin as a first-line regimen for patients with metastatic esophageal, gastric, and gastroesophageal cancer: phase II results from the North Central Cancer Treatment Group (N044B). J Thorac Oncol, 3:516-20 (2008).

1.2.5.7 A potential role for NF-κB in thyroid cancer and activity of bortezomib against thyroid cancer

Previous studies have shown that NF-κB is activated in TT cells, a human MTC cell line expressing MEN2a type RET. Inhibition of constitutive NF-κB activity in TT cells resulted in cell death and blocked focus formation induced by oncogenic forms of RET in NIH 3T3 cells. These studies suggest that RET-mediated carcinogenesis depends in part on I-κB Kinase (IKK) activity and subsequent NF-κB activation (Figures 4 and 5).[62]

Figure 4

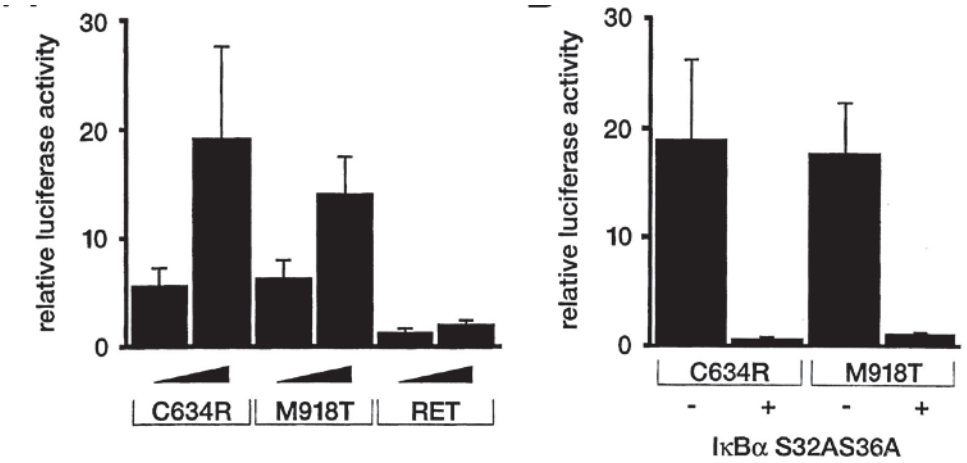


FIGURE 4: Oncogenic RET induces NF-B-dependent transcription. *Left panel*, HeLa cells were transiently transfected with the 3xBIFNßLuc reporter (5 µg/35-mm well) together with expression vectors encoding oncogenic RET mutants C634R and M918T or wild-type RET (1 or 3 µg, respectively). Forty-eight h after transfection, cells were lysed for luciferase assay. *Columns*, fold induction of luciferase activity relative to the reporter alone and represent means of four independent experiments performed in triplicate; *bars*, SE. *Right panel*, co-transfection of I□B□S32AS36A abolishes NF-B activation induced by oncogenic RET in HeLa cells. Cells were treated as described above. Three µg of the respective RET mutants were co-transfected with 3 µg of I□B□S32AS36A. Values represent means of two independent experiments performed in triplicate; *bars*, SE.[62]

Figure 5

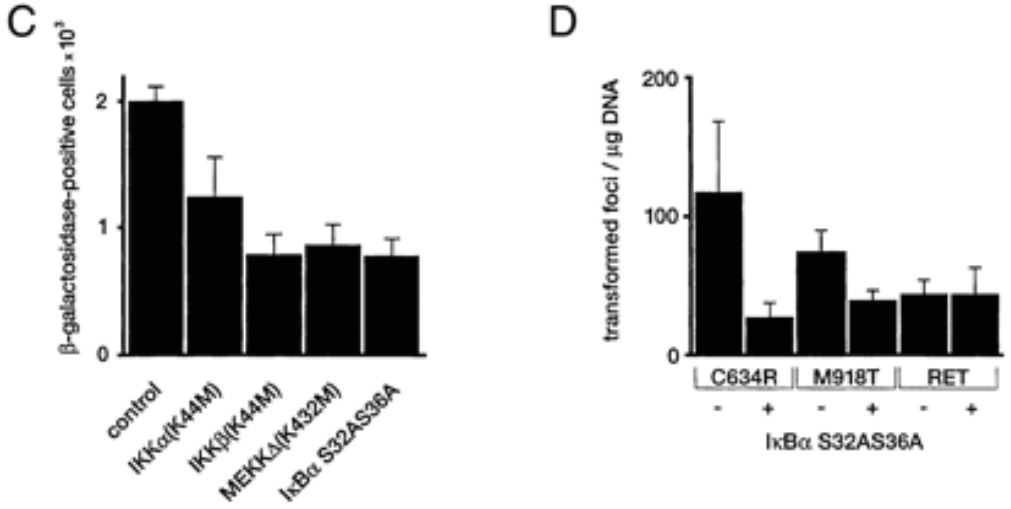


FIGURE 5: NF-κB inhibition affects viability of TT cells and blocks RET-induced transformation of NIH 3T3 cells. Left panel, Inhibition of NF-κB induces cell death of TT cells. TT cells were transiently transfected with the expression vectors listed on the X-axis containing the dominant-negative mutants of IKKα□□IKKβ□□MEKK, and IκBα (empty pcDNA as control) together with pCDNA3-LacZ. These mutants prevent NFKβ activation. Co-transfection of empty pCDNA3 with pcDNA3 -LacZ served as control. 72h after transfection, cells were fixed, stained and stained with X-gal, and counted in

each well. Values for β-gal-positive cells represent means of at least three independent transfections; *bars*, SE. Right panel, NF-κB is required for cellular transformation induced by oncogenic RET. NIH 3T3 cells were transfected with 1 mcg pCDNA-RET C634R, pCDNA-RET M918T or pcDNA-RET, together with empty pCDNA3(-) or the super repressor form of IκBα□ pCDNA-IκBα S32AS36A(+), and genomic DNA as carrier. Transformed foci were scored 14 - 21 days after transfection. Values represent means of at least three independent transfections; *bars*, SE.[62]

Additonal data suggests that bortezomib would be a reasonable agent to combine with vandetanib in treating patients with advanced MTC. This data includes experiments that showed that bortezomib induces apoptosis in both MTC and anaplastic thyroid carcinoma cells with IC50 values well within the range of clinically achievable concentrations and much lower than comprable IC50 values for other solid tumor malignancies (Table 12). Furthermore, the combination of bortezomib with chemotherapy (doxorubicin) was synergistic (Figure 6).[63]

Table 13

Bortezomib sensitivity *in vitro*

Cell line	Type	IC50 at 24 h (nM)
SW579	Papillary	> 100
NPA	Papillary	> 100
KAT5	Papillary	120
KAT1	Papillary	92
FRO	Anaplastic	10
DRO90–1	Anaplastic	14
BHT101	Anaplastic	19
KAT18	Anaplastic	561
SW1736	Anaplastic	> 1002
ARO	Anaplastic	> 1003
TT	**Medullary**	**8**
DRO81–1	**Medullary**	**16**
HRO85–1	**Medullary**	**19**
6-23	**Medullary**	**4.5**
WRO	Follicular	> 100
U87	Glioma	1,000
SW480	Colon	96
LN827	Glioma	375
CAKI-1	Renal	> 10,000
LNCaP	Prostate	100

Cell line	Type	IC50 at 24 h (nM)
SKOV3	Ovarian	131

Mitsiades et al. J Clin Endocrinol Metab. 2006. 91: 4013-21

Figure 6

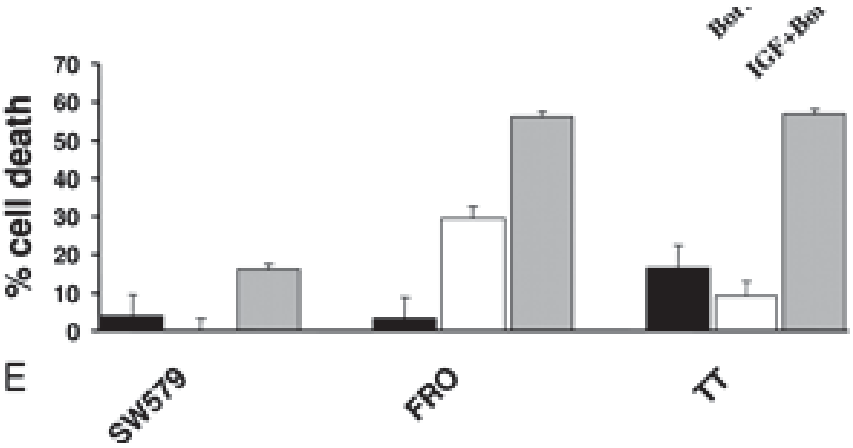


FIGURE 6: Sensitizing effect of bortezomib to conventional cytotoxic chemotherapy in thyroid carcinoma cells. SW579, FRO, and TT cells were treated with doxorubicin (0.25 μg/ml) for 48 h. During the last 24 h of that treatment, the cells were also exposed to bortezomib (2.5 nM) or vehicle. At the end of the 48-h incubation, percent cell death (mean ± SD) was quantified by MTT (*black bars*, bortezomib alone, *white bars*, doxorubicin alone, *gray bars*, doxorubicin + bortezomib). All experiments were repeated at least three times, and each experimental condition was repeated at least in quadruplicate wells in each experiment. Data reported are average values ± SD of representative experiments. Thyroid carcinoma cells are relatively resistant to cytotoxic chemotherapy, but treatment with a subtoxic concentration of bortezomib had a strong sensitizing effect on doxorubicin-induced cell death.[63]

1.2.5.8 **Proteasome inhibition. Bortezomib and microtubule stabilization**

Clinically bortezomib use has been hampered by peripheral neurotoxicity of unexplained etiology. Since proteasome inhibitors alter protein degradation, we speculated that proteins regulating microtubule (MT) stability may be affected after treatment and examined MT polymerization in cells by comparing the distribution of tubulin between polymerized (P) and soluble (S) fractions. We observed increased MT polymerization following treatment of SY5Y and KCNR [neuroblastoma], HCN2 [neural] and 8226 [MM] cells, using five proteasome inhibitors; the baseline proportion of total α-tubulin in polymerized fractions ranged from ~41-68%, and increased to ~55-99% after treatment with proteasome inhibitors (Table 13). Increased acetylated α-tubulin, a post-translational marker of stabilized MTs, was observed in the neural cell lines HCN1A and HCN2 (Table 14). Cell cycle analysis of SY5Y, KCNR and 8226 cells after treatment, showed decreases in G1 phase with ~50-75% increases in the G_2M phase, consistent with cell cycle arrest. Immunofluorescent studies of proteasome inhibitor treated cells did not reveal microtubule bundles in contrast to paclitaxel treated cells, suggesting MT

stabilization via a different mechanism. These data provide a plausible explanation for the neurotoxicity observed clinically. Given that proteasome inhibitors such as bortezomib have a plethora of cellular targets and effects, these results raise the possibility that microtubule stabilization contributes to cytotoxicity and provides a testable hypothesis that could be investigated in an exploratory manner in patient samples obtained before and after the administration of bortezomib [Proteasome inhibitors increase tubulin polymerization and stabilization in tissue culture cells. A possible mechanism contributing to peripheral neuropathy and cellular toxicity following proteasome inhibition.[64]]

TABLE 14

Percent of Polymerized Tubulin in Cell Lines Treated with Proteasome Inhibitors

Cell Line	Drug	Concentration	% Polymerized Tubulin Average ± Std Dev
SY5Y	None	-	41 ± 6.7
	Bortezomib	100 nM	65 ± 14.6
	MG132	50 mM	82 ± 17.1
	Lactacystin	5 mM	55 ± 2.1
	Epoxomycin	100 nM	56 ± 2.5
	PSI	10 mM	73 ± 15.6
KCNR	None	-	51 ± 3.4
	Bortezomib	100 nM	67 ± 6.8
	MG132	50 mM	63 ± 6.5
	Lactacystin	5 mM	61 ± 10.1
	Epoxomycin	100 nM	66 ± 4.3
	PSI	10 mM	93 ± 2.1
HCN2	None	-	68 ± 17.7
	Bortezomib	300 nM	93
	Bortezomib	100 nM	78 ± 14.8
	MG132	50 mM	91 ± 3.5
	Lactacystin	10 mM	92
	Lactacystin	5mM	97
	Epoxomycin	300 nM	87
	Epoxomycin	100 nM	85
	PSI	30 mM	99
	PSI	10 mM	80 ± 7.8

TABLE 15

Average Fold Increase in Acetylated a-Tubulin in HCN2 Cells Treated with Proteasome Inhibitors

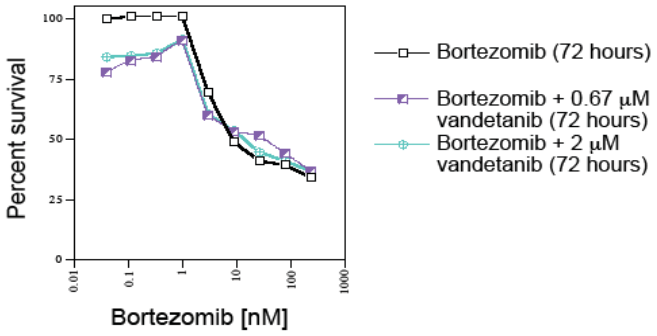
Cell Line	Drug	Concentration	Acetylated a-Tubulin*
HCN2	None	-	1
	Bortezomib	100 nM	2.2 ± 0.7
	MG132	50 mM	2.3 ± 0.3
	Lactacystin	30 mM	2.6
	Lactacystin	10 mM	2.1 ± 0.3
	Epoxomycin	300 nM	2.8
	Epoxomycin	100 nM	2.7 ± 0.7
	PSI	30 mM	4
	PSI	10 mM	2.9 ± 0.8

*Normalized to GAPDH

1.2.6 Study Rationale

This clinical trial will evaluate the combination of vandetanib and bortezomib, compounds with demonstrated activity against MTC cells, in a phase I/II clinical trial of patients with malignant solid tumors, including MTC. A clinical trial of a multi-targeted kinase inhibitor combined with a second therapeutic has not been conducted in thyroid cancer. If the specific aims of the study are achieved an active combinatorial therapeutic regimen will be available for the treatment of patients with a malignant thyroid cancer and possibly other cancers as well.
Pre-clinical studies indicate that the combination of bortezomib and vandetanib are not antagonistic (Figure 7). In the experiments performed using a cell line with a RET mutation established from a patient with a diagnosis of MTC, the activity of the combination is at least as active as the most active drug, be it bortezomib or vandetanib. There is no evidence that either drug antagonizes the efficacy of the other drug.

Figure 7



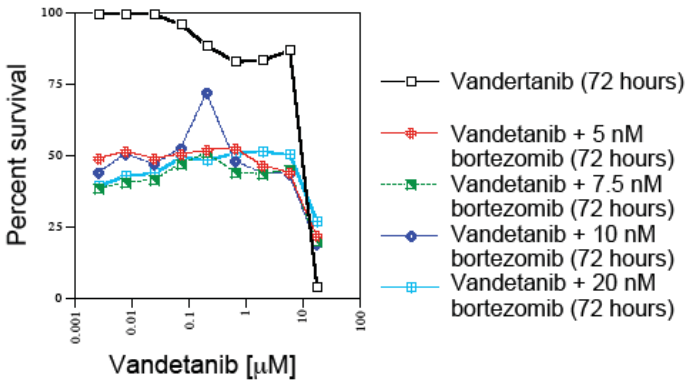


FIGURE 7: For the representative experiments shown, thyroid carcinoma (cell line TT) cells plated in 96 well dishes (~ 2000 - 4000 cells per well or 65 - 75% confluency) were grown for 24 - 48 hrs prior to removal of media [F112K + 10% FBS + penicillin/streptomycin + glutamine]. In triplicate, either no drug [media] or drugs were added to cells as follows: vandetinib alone [serial dilution range of 18 - 0.0027 □M]; bortezomib alone [serial dilution range of 243 - 0.04 nM]; combinations of the range of bortezomib + various concentrations of vandetanib [0.67 or 2 □M]; combinations of the range of vandetinib + various amounts of bortezomib [5, 10, 20 nM] for a period of 72 hrs. After these times either an MTS or an SRB assay analysis was performed and IC_{50} values were determined.

Three clinical trials of ZD6474 have been completed, however, the results have not been published in peer review journals and the drug has not been approved by the FDA – although ZD6474 (vandetanib) has been granted FDA and EU orphan drug status, and is on FDA fast track for an indication in hereditary medullary thyroid cancer. Data from the first clinical trial, described above, demonstrated that vandetanib has significant activity against MTC. In considering agents which might be combined with vandetanib in a clinical study bortezomib is appealing for several reasons. While bortezomib has been approved clinically only for the treatment of MM, preclinical studies indicates that it has a wide spectrum of activity. It is also a very interesting compound in that it has a specific target, the proteasome, which can have broad consequences, reminiscent of many of our active "cytotoxic compounds". It is felt that the combination of vandetanib with bortezomib has the potential to be clinically effective both in a

disease such as MTC, where vandetanib has already demonstrated gratifying activity as a single agent, as well as in a variety of cancers, including NSCLC, and MM, among others.

This study seeks to develop a clinical protocol of vandetanib in combination with the proteasome inhibitor, bortezomib, by first performing the phase I portion of the study to determine the optimal doses of this combination. While the toxicities of vandetanib and bortezomib are largely not overlapping we would propose to approach the combination cautiously in this portion of the trial. We propose that the starting dose for vandetanib will be 100 mg per day. This dose was well tolerated by patients in the recently reported phase II trial of single agent vandetanib in patients with hereditary MTC.[56] We would also note that 100 mg was the daily dose in the placebo-controlled phase II study of ZD6474 plus docetaxel in patients with previously treated non–small-cell lung cancer, in which the primary objective - a significant prolongation of PFS compared with docetaxel in relation to the pre-specified significance level – was reached.[65] The latter suggest that a dose of 100 mg daily may be sufficient to achieve a pharmacologic effect.

As for bortezomib, we would argue that the data suggest that several doses and schedules of administration are efficacious. In this regard we would note the following evidence: (1) In patients with MM, weekly bortezomib was as effective and more convenient than twice weekly doses;[66] (2) In first line treatment of patients with advanced solid tumors weekly bortezomib (1.0 mg per square meter) plus gemcitabine and cisplatin was recommended as the phase II dose over twice-weekly bortezomib based on a similar response and survival of NSCLC patients treated with twice-weekly or weekly bortezomib – with greater gastrointestinal toxicity as well as myelosuppression seen with the twice-weekly regimen;[67] (3) In patients with advanced solid tumors with an emphasis on NSCLC, weekly and twice weekly schedules were compared and both were recommended, with somewhat greater toxicities seen in the twice-weekly schedule (Note a weekly dose of 1.6 mg per square meter on days 1 and 8 was administered with 500 mg of pemetrexed every 21 days);[68] (4) In patients with relapsed or refractory follicular lymphoma and mantle cell lymphoma, the investigators concluded that weekly dosing may not be as effective as twice weekly administration.[69] We would propose as a starting point, a dose of 1 mg per square meter administered on days 1, 4, 8 and 11 every 28 days with escalation to 1.3 mg per square meter. The combination of bortezomib plus vandetanib will be administered for a minimum of six cycles. After the completion of the first six cycles depending on tolerability, and whether or not continued tumor reduction is occurring, bortezomib may be continued, or the patient may be treated with vandetanib alone. This approach recognizes that some patients with this MTC may continue therapy for a long time and also considers the difficulty of indefinitely continuing therapy on days 1, 4, 8, and 11 every 28 days.

We thus propose the following Phase I trial design:

- Level -2: 100mg vandetanib every other day (vandetanib only; toxicity reduction)
- Level -1: 100 mg vandetanib daily (vandetanib only; toxicity reduction)
- Level 1: 100 mg vandetanib daily + 1 mg/m^2 bortezomib on days 1, 4, 8 & 11 every 28 days
- Level 2: 100 mg vandetanib daily + 1.3 mg/m^2 bortezomib on days 1, 4, 8 & 11 every 28 days
- Level 3: 200 mg vandetanib daily + 1.3 mg/m^2 bortezomib on days 1, 4, 8 & 11 every 28 days
- Level 4: 300 mg vandetanib daily + 1.3 mg/m^2 bortezomib on days 1, 4, 8 & 11 every 28 days

Notes:

If levels 1, 2 or 3 are established as the MTD, two additional levels (levels 1A and 1B) will be tried:

- Level 1A: 200 mg vandetanib daily + 1 mg/m^2 bortezomib on days 1, 4, 8 & 11 every 28 days.
- Level 1B: 300 mg vandetanib daily + 1 mg/m^2 bortezomib on days 1, 4, 8 & 11 every 28 days.

Then:

- If level 1 is initially identified as the MTD, level 1A or 1B ***will*** be substituted as the level recommended for the phase II portion of the study, provided safety can be demonstrated.
- If levels 2 or 3 are initially identified as the MTD, level 1A or 1B ***can*** be substituted as the level recommended for the phase II portion of the study, provided safety can be demonstrated and ***only after all interested parties have discussed the available data and a decision is made as to which dose might be best to pursue***.

The doses of bortezomib and then vandetanib will be increased in cohorts of three patients. ***The MTD and DLT will be determined based on toxicities during the first eight weeks of combined therapy.*** Toxicities that arise after the first six weeks of combined therapy will be managed according to the following guidelines that consider the possible drug responsible for the observed toxicity: For all toxicities other than QTc prolongation, the dose of study treatment will be withheld for up to 3 weeks until the toxicity has resolved to CTCAE grade 1 or better; patients will be withdrawn from the study if toxicity does not resolve to ≤ CTCAE grade 1 within 3 weeks. When the toxicity resolves to ≤ CTCAE grade 1, study treatment may be restarted with an appropriate dose reduction dependent on the dose that is being administered and the drug determined to be responsible for the toxicity. If toxicity is determined to be secondary to vandetanib, then when the toxicity resolves to ≤ CTCAE grade 1, vandetanib should be restarted at one dose level lower than that administered at the time the toxicity developed (patients receiving the starting dose of 100 mg vandetanib will have their therapy discontinued). If toxicity is determined to be secondary to bortezomib, then when the toxicity resolves to ≤ CTCAE grade 1, bortezomib should be restarted at one dose level lower than that administered at the time the toxicity developed (patients receiving the starting dose of 1 mg/m^2 bortezomib will have bortezomib discontinued but can continue to receive vandetanib alone). If the drug responsible for the toxicity cannot be determined then when the toxicity resolves to ≤ CTCAE grade 1 both vandetanib and bortezomib should be restarted at one dose level lower for both drugs than that administered at the time the toxicity developed. If the toxicity does not recur at the reduced doses of both vandetanib and bortezomib, the dose of vandetanib may be increased one dose level to that which was being administered at the time the toxicity developed. If toxicity recurs following this increase, both vandetanib and bortezomib are held. When the toxicity resolves to ≤ CTCAE grade 1 bortezomib is continued at the same dose but vandetanib is restarted at one dose level lower than that administered at the time the toxicity recurred. Note than once the MTD is identified the combination will be examined in a randomized phase II and that these patients will receive the dose recommended for Phase II trials. In these patients the guidelines described in the preceding sentences apply.

Thus the design considers the fact that doses of 100 mg vandetanib appear to be active in some patients with MTC, and the fact that in a randomized, placebo-controlled phase II study of vandetanib plus docetaxel in previously treated NSCLC the primary objective was achieved with vandetanib 100 mg plus docetaxel. The evidence indicates that over a broad range increasing doses result in increased proteasome inhibition.

Rationale for translational studies:

RET sequencing and asseesment of the effect of vandetanib on RET activity and the effect of bortezomib on microtubules will be queried. These are justifed as follows:

1. In patients with a diagnosis of MTC we propose to examine in an exploratory analysis the correlation between genotype and response to therapy. As noted above, in the hereditary forms of MTC there is a correlation between genotype and phenotype, both as regards the clinical expression of diseases in the syndromes and the biological aggressiveness of the MTC. However, to date, a correlation between genotype and response to therapy has not been established. Evidence exists that RET inhibition leads to growth inhibition or apoptosis in MTC cells. However, individual RET mutations, especially those involving the intracellular tyrosine kinase domain, are likely to have different sensitivities to TKIs. A RET mutation at codon 804, associated mostly with FMTC, was recently shown to be associated with marked in vitro resistance to vandetanib (IC_{50} ~ 5 uM), whereas a second TKI, sorafenib, inhibited these mutants with IC_{50} in the 100 - 150 nM range vs. 49 nM for wt RET. Thus we propose as a secondary objective to examine in an exploratory analysis, the correlation between genotype and response to therapy in all patients with MTC. To accomplish this we propose to perform RET gene mutational analysis in tumor and peripheral blood mononuclear cells prior to treatment. The tumor to be assessed would most likely be tissue that has been previously obtained, or either be obtained at the time of study enrollment.
2. In patients with a diagnosis of MTC, we propose to examine the extent, if any, of RET inhibition following the administration of vandetanib. Specifically, we propose as an exploratory analysis to examine the extent of RET inhibition, an important pharmacodynamic endpoint not yet explored in any clinical trial. *It should be noted that despite the fact that over 380 patients with MTC have been treated with vandetanib to date and it is stated that vandetanib is active in this disease by virtue of its ability to inhibit RET, not a single patient has had the extent of RET inhibition examined in their tumors.* In MTC patients, the first biopsy would be obtained prior to the start of therapy, while the second biopsy would be obtained after 42 days of vandetanib administration. The purpose of these biopsies would be to examine the extent of RET inhibition (See Appendix A). Note: RET mutations will not be assessed in real time.
3. In patients without a diagnosis of MTC, we propose as an exploratory analysis, to perform a biopsy prior to the start of therapy and a second biopsy after the day 4 bortezomib (the same day or on day 5, but following the dose of bortezomib) administration to determine whether microtubule stabilization has occurred. Demonstration of the latter would provide *in vivo* documentation of the *in vitro* observations we have made demonstrating the occurrence of microtubule stabilization following proteasome inhibition. The latter would provide evidence supporting the thesis that microtubule stabilization might contribute to bortezomib cytotoxicity and also provide unequivocal evidence of an effect of bortezomib on the cancer cells – a pharmacodynamic effect. It is preferable to obtain these biopsies during the first cycle of the study. However, because occasionally biopsies cannot be scheduled to coincide with the start of the study these biopsies may be obtained before Cycle 2 day 1 bortezomib and on days 4 or day 5 after the day 4 bortezomib dose - a schedule that our experience indicates should not measurably affect the results.

<u>*Positive attributes of MTC as a platform for drug development:*</u>

1. Surgery is the only effective therapy.
2. There are no accepted adjuvant therapies.
3. There are only limited options for patients with disseminated disease.
4. Calcitonin is an exquisitely sensitive hormonal biomarker; CEA is a secondary marker.

5. It has orphan disease status.
6. It is attractive because of an outstanding molecular target, the RET proto-oncogene. Significant experimental proof-of-principle exists that RET inhibition leads to growth inhibition or apoptosis in MTC cells.

Considerations for trials in MTC:

1. Although vandetanib has been shown to have activity in MTC, the molecular basis for why intrinsic resistance exists or acquired resistance develops has not been explored. Preliminary evidence that individual RET mutations, especially those involving the intracellular tyrosine kinase domain, are likely to have different sensitivities to TKIs supports clinical trials that examine genetics of patients enrolled on trial. Similarly trials with sequential biopsies to discern the molecular basis of acquired resistance are needed.
2. Activated RET provides a host of docking sites to trigger activation of a number of other kinase pathways including ERK, JNK, p38 MAPK and FAK. Understanding the relative contributions of these different signaling outputs of RET in MTC cells will be important in assessing the efficacy of RET kinase inhibitors. Again this supports clinical trials that examine genetics of patients enrolled on trial, even in an exploratory manner

Arguments in favor of combination trials:

1. To date no single TK inhibitor has been able to bring about a sustained complete response let alone a cure in patients with solid tumors. Vandetanib has been shown to have activity in MTC, but there is much room for improvement.
2. The experience of unsuccessful Phase III combination trials, including EGFR inhibitors plus chemotherapy in NSCLC suggests the answer may not necessarily always lie in pairing targeted and cytotoxic agents and underscore the need to investigate combinations of targeted therapies.
3. As noted, activated RET triggers the activation of numerous other kinase pathways including ERK, JNK, p38 MAPK, FAK and NF-κB. The activation of these pathways supports the conduct of clinical trials using rational drug combinations – including drugs targeting more than one pathway.

Phase I Trial Results

The accrual to Phase I is complete and the MTD has been determined to be Dose Level 4 (Vandetanib 300mg orally daily and bortezomib 1.3mg/m^2 IV days 1, 4, 8, 11 of 28 day cycles). The first patient was enrolled on 3/5/09 and the final patient was enrolled 11/10/10. Twenty-one patients were enrolled; three were assigned to Dose Level 1, and six each to Dose Levels 2, 3, and 4. Seventeen patients had metastatic or advanced medullary thyroid cancer (MTC). The single DLT in the study was Grade 3 thrombocytopenia at Dose Level 3. The most common AEs felt to be at least possibly related to study drug(s) were: prolonged QTc (86%), transaminase elevation (81%), thrombocytopenia (81%), diarrhea (71%), rash/skin changes (71%), hypertension (67%), fatigue (62%), leukopenia (52%), neuropathy (48%). Most of the toxicities were grade 1 or 2. The most common Grade 3 toxicities were: lymphopenia (24%), hypertension (24%), fatigue (19%), diarrhea (9.5%), thrombocytopenia (9.5%), and hyperkalemia (9.5%). To date, there have been four PRs in assessable patients with MTC (27%). SD for > 6 months is the best response in 6 patients (43%). One MTC patient had PD (7%) as his best response. To date, patients with PR or SD > 12 months have all had decreases of calcitonin by $\geq$ 50%. Change in CEA did not correlate with response.

Phase II Trial Design

In accordance with the protocol and the results of the Phase I portion of the study, the Phase II design is thus proposed:

- A randomized phase II trial comparing the activity of the combination of bortezomib plus vandetanib with vandetanib alone [2:1 randomization 62 + 31 = 93 patients].
- The Phase II dose is established at the Phase I MTD, Dose Level 4: 300 mg vandetanib daily + 1.3 mg/m2 bortezomib on days 1, 4, 8 & 11 every 28 days for the combination arm, vs. 300 mg vandetanib daily for the single agent arm.

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 Eligibility Criteria

2.1.1 Inclusion Criteria

2.1.1.1 Pathologic confirmation of cancer by the Laboratory of Pathology, NCI

2.1.1.2 Phase I: Diagnosis of recurrent, metastatic or primary unresectable solid tumor that does not have curative standard treatment.

Phase II: Diagnosis of recurrent, metastatic or primary unresectable medullary thyroid cancer (MTC).

2.1.1.3 Measurable disease at presentation: Either by RECIST or by measurement of serum markers (calcitonin, CEA, PSA or CA-125) in the dose-finding portion of the study; with disease measurable by RECIST required only in the phase II cohort.

2.1.1.4 A life expectancy of at least 3 months and ECOG performance status 0 – 1.

2.1.1.5 Age ≥ 18 years

2.1.1.6 Last dose of chemotherapy or experimental therapy more than 4 weeks (6 weeks in the case of nitrosourea) prior to enrollment date; unless the last therapy consisted of an oral agent whose average half life is known to be less than 48 hours in which case only 2 weeks need to have elapsed. Regardless of the therapy, any toxicity greater than CTCAE grade 1 from previous anti-cancer therapy must have been resolved.

2.1.1.7 Last radiotherapy treatment 4 weeks prior to starting treatment with this protocol – with the exception of palliative radiotherapy – and there must be sites of measurable disease that did not receive radiation.

2.1.1.8 Organ and marrow function as defined:

- total bilirubin < 1.5 x upper limit of reference range (ULRR), unless the patient meets the criteria for Gilbert's Syndrome
- alanine aminotransferase (ALT), aspartate aminotransferase (AST) and alkaline phosphatase (ALP) all three < 2.5x ULRR, or < 5x ULRR if judged by the investigator to be related to liver metastases
- serum creatinine < 1.5 x ULRR or creatinine clearance ≥ 30 mL/minute (calculated by Cockcroft-Gault formula or measured in a timed urine collection)
- serum calcium below the CTCAE grade 1 upper limit (11.5mg/dL or 2.9 mmol/L). In cases where the serum calcium is below the normal range, the calcium adjusted for albumin is calculated and substituted for the measured value.
- Serum potassium greater than the LLN and < 5.5 mmol/L.
- Serum magnesium greater than the LLN and < 3.0 mg/dL or 1.23 mmol/L.
- absolute neutrophil count ≥ 1000/mm^3

- platelet count ≥ 100,000/mm3
- PT ≤ 4 seconds above ULN and PTT ≤ 10 seconds above ULN.

2.1.1.9 Ability to understand and sign an informed consent document.

2.1.1.10 Provision of informed consent prior to any study-related procedures

2.1.1.11 Negative pregnancy test for women of childbearing potential

2.1.1.12 Ability and willingness to follow the guidelines of the clinical protocol including visits to NCI, Bethesda, Maryland for treatment and follow up visits.

2.1.1.13 Because the effects of chemotherapy on the developing human fetus are potentially harmful, female patients must be one year post-menopausal, surgically sterile, or using an acceptable method of contraception during and continued after the last dose of study medications (oral contraceptives, barrier methods, approved contraceptive implant, long-term injectable contraception, intrauterine device or tubal ligation). Male patients must be surgically sterile or using an acceptable method of contraception during their participation in this study. Contraceptive use will continue for at least four months after the last dose of study medication.

2.1.2 Exclusion Criteria

2.1.2.1 Patients with cancer potentially curable by surgical excision alone or patients who have not received therapy that might be considered standard and potentially curable.

2.1.2.2 Evidence of severe or uncontrolled systemic disease or any concurrent condition – including, but not limited to symptomatic congestive heart failure, unstable angina pectoris, unstable hypertension, seizure disorder, or psychiatric illness – which in the Investigator's opinion makes it undesirable for the patient to participate in the trial or which would jeopardize compliance with the protocol.

2.1.2.3 Untreated brain metastases (or local treatment of brain metastases within the last 6 months) due to the poor prognosis of these patients and difficulty ascertaining the cause of neurologic toxicities.

2.1.2.4 During Phase II enrollment: Prior therapy with vandetanib.

2.1.2.5 Women who are currently pregnant or breast-feeding, due to the possible adverse effects on the developing fetus and infants.

2.1.2.6 The presence of a second malignancy within the last 2 years, other than squamous cell carcinoma of the skin or in situ cervical cancer because it will complicate the primary objective of the study. Cancer survivors who have been free of disease for at least two years can be enrolled in this study.

2.1.2.6.1 There is one other exception to the exclusion of secondary malignancies: MEN2 patients with concurrent medullary thyroid cancer and pheochromocytoma may be enrolled at the discretion of the Principal Investigator. In this case, response data will not be used as a measure of the primary endpoint, but data will continue to be collected for the secondary objectives.

2.1.2.7 Patients with evidence of a bleeding diathesis that cannot be corrected with standard therapy or factor replacement.

2.1.2.8 Any unresolved toxicity greater than CTCAE grade 1 (except alopecia) from previous anti-cancer therapy. Patients with grade 1 neuropathy will be evaluated on a case by case basis for entry into study. Baseline conditions will be taken into consideration.

2.1.2.9 Major surgery within 4 weeks, or incompletely healed surgical incision before starting study therapy.

2.1.2.10 Clinically significant cardiovascular event (e.g. myocardial infarction, superior vena cava syndrome (SVC), New York Heart Association (NYHA) classification of heart disease ≥ 2 (see Appendix C) within 3 months before entry; or presence of cardiac disease that, in the opinion of the Investigator, increases the risk of ventricular arrhythmia.

2.1.2.11 History of arrhythmia (multifocal premature ventricular contractions PVCs), bigeminy, trigeminy, ventricular tachycardia, or uncontrolled atrial fibrillation) which is symptomatic or requires treatment (CTCAE grade 3) or asymptomatic sustained ventricular tachycardia. Atrial fibrillation, controlled on medication is not excluded.

2.1.2.12 History (within the last 6 months) or presence of stroke/cerebrovascular accident.

2.1.2.13 QTc prolongation with other medications. If the medication can be discontinued and an alternative medicaiton started that does not cause QTc prolongation, the patient would be eligible. If no alternative medication is available and the medication can not be discontinued for medical reasons, then the patient would not be eligible.

2.1.2.14 Congenital long QT syndrome, or 1st degree relative with unexplained sudden death under 40 years of age.

2.1.2.15 Presence of left bundle branch block (LBBB).

2.1.2.16 QTc with Bazett's correction that is not measurable, or ≥ 480 msec on screening ECG. (Note: If a patient has a QTc interval ≥ 480 msec on screening ECG, the screen ECG may be repeated twice (at least 24 hours apart). The average QTc from the three screening ECGs must be < 480 msec in order for the patient to be eligible for the study). Patients who are receiving a drug that has a risk of QTc prolongation (see Appendix C) are excluded if QTc is ≥ 460 msec.

2.1.2.17 Concurrent medication that may cause QTc prolongation or induce Torsades de Pointes: Those medications in Group One of Appendix C will not be allowed. Those medications in Group Two of Appendix C will be allowed.

2.1.2.18 Hypertension not controlled by medical therapy (systolic blood pressure greater than 160 mm Hg or diastolic blood pressure greater than 100 mm Hg)

2.1.2.19 Currently active (uncontrolled) diarrhea ≥ CTCAE Grade 2 that may affect the ability of the patient to absorb the vandetanib or tolerate diarrhea. Antidiarrhea medications are allowed in patients with chronic diarrhea.

2.1.2.20 Concomitant medications that are potent inducers (rifampicin, rifabutin, phenytoin, carbamazepine, phenobarbital and St. John's Wort) of CYP3A4 function.

2.1.2.21 Major surgery within 4 weeks, or incompletely healed surgical incision before starting study medications. Biopsies, port placements, and dental work are examples of acceptable (non-major) surgery within the 4 week time frame.

2.1.2.22 Inability to take oral medications for whatever reason.

2.2 Research Eligibility Evaluation

Physical examination should be performed within 72 hours prior to enrollment on the trial unless otherwise stated.

- HISTORY AND PHYSICAL EXAMINATION including vital signs with blood pressure, height, weight, ECOG performance status, documentation of palpable, measurable disease (longest diameter and location), and a description of baseline signs and symptoms is required. A family history of endocrine neoplasia should also be recorded.
- Daily stool frequency over the prior 7 days and consistency (formed, loose or partially formed, watery) should be documented. The patient diary (Appendix B) can be used to collect daily stool history during the pretreatment evaluation period.
- **Pre-treatment blood tests** should be performed within 72 hours prior to enrollment on the trial unless otherwise stated.
- HEMATOLOGY: complete blood count, differential, platelet count, PT, PTT.
- CHEMISTRIES: ALT, AST, alkaline phosphatase, bilirubin (total and direct), BUN, creatinine, electrolytes, calcium, magnesium, phosphorus, uric acid, total protein, and albumin.
- Thyroid stimulating hormone
- BIOMARKERS: Serum CTN and CEA should be measured during screening and the day vandetanib starts (prior to the first dose). The baseline value for CTN and CEA is the average of these 2 pretreatment measurements. Serum CTN should be drawn after a 12 hour fast and placed on wet ice and sent to the chemistry lab immediately.
- URINE OR SERUM PREGNANCY TEST: required for females of childbearing potential.
- 12-lead ECG with Calculation of QTc - Use Bazett's correction ($QTc = QT/RR^{0.5}$) must be performed at screening. The QTc must be <480msec. Up to 3 ECGs may be obtained at screening, and then the mean QTc value used to determine eligibility.

Scans should be performed within one month prior to enrollment of the study.

- CT scans of the neck, chest, abdomen and pelvis
- Optional: MRI of the brain and neck
- Optional: ^{99m}Tc-Bone scan
- Optional biopsy for RET mutational analysis

2.3 Patient Registration and Treatment Assignment

Maureen Edgerly, RN (office 301-435-5604, pager 102-10728) must be notified prior to entering any patients on study.

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and faxed to 301-480-0757. After confirmation of eligibility at Central Registration Office, CRO staff will call pharmacy to advise them of the acceptance of the patient on the protocol prior to the release of any investigational agents.

During the phase II portion of the study CRO staff will perform randomization procedures following confirmation of eligibility. The phase II cohort randomization will be a 2:1 ratio as described in section **3.3.7**. Verification of Registration will be forwarded electronically via e-mail. Please note, it is very important for all registrars to acquire encrypted e-mail from NIH

Help Desk, since the verification of registration includes patient's information. A recorder is available during non-working hours.

3 STUDY IMPLEMENTATION

3.1 Study Design

This study is designed to assess the safety, tolerance and activity of daily oral vandetanib and bortezomib on days 1, 4, 8 & 11 every 28 days in adults. The Phase I portion involves dose escalations as described below, in order to establish the optimal doses of the drug combination in patients with locally advanced or metastatic cancer, including MTC. The primary objective of the Phase II portion examines the activity (response rate and progression-free survival) in adults with MTC receiving the combination of vandetanib plus bortezomib and compares this with a cohort receiving vandetanib alone. The design is that of a 2:1 randomization.

Note: In both the phase I portion of the study and in the patients randomized to the bortezomib plus vandetanib combination in the phase II portion of the study, patients will receive a minimum of 24 weeks of combination therapy (six cycles). After six cycles have been administered, the option to discontinue bortezomib and continue only with vandetanib will be considered in all patients at each re-assessment. This will be a clinical decision that will consider the tolerability of therapy to that point and the expected tolerability going forward with special attention given to toxicities such as neuropathy that are considered to be primarily secondary to the administration of bortezomib. The clinical decision will also consider the rate of change (decrease) in tumor burden in the assessment period leading just prior to the time of making the decision. As regards the latter the invstigators will consider whether there is evidence of continued tumor shrinkage or whether maximum shrinkage has been attained as evidenced by the lack of measurable shrinkage in the last assessment interval compared to the previous assessment interval. If a decision is made to discontune bortezomib the patient can remain on vandetanib alone and the vandetanib dose can then be adjusted in accordance with the dose levels under "3.3.7 Phase II cohort".

3.1.1 Dose escalation schema:

The doses of bortezomib and vandetanib will be increased in cohorts of three patients. ***A cycle is defined as a four week period with Day One defined as the day on which the first dose of bortezomib is administered.*** The MTD and DLT will be determined *based on toxicities during the first eight weeks (two cycles) of combined therapy*. Dose escalations may occur once two of the three patients in the ongoing cohort have completed eight weeks of treatment and the third patient has completed four weeks of treatment. In the event that one of the first three patients enrolled on a given dose level experiences DLT, an additional three patients will need to be enrolled at that dose level before the dose escalation can continue. In this case, if none of the additional three patients experience DLT, then the dose escalation may continue to the next dose level. If more than one additional patient experience DLT such that ≥ 2/6 patients experienced DLT then accrual will cease and the dose administered in the previous level will be designated the MTD.

Dose levels will be as follows:

- Level -2: 100 mg vandetanib every other day (vandetanib only; reduction for toxicity)
- Level -1: 100 mg vandetanib daily (vandetanib only; reduction for toxicity)
- Level 1: 100 mg vandetanib daily + 1 mg/m^2 bortezomib on days 1, 4, 8 & 11 every 28 days

- Level 2: 100 mg vandetanib daily + 1.3 mg/m^2 bortezomib on days 1, 4, 8 & 11 every 28 days
- Level 3: 200 mg vandetanib daily + 1.3 mg/m^2 bortezomib on days 1, 4, 8 & 11 every 28 days
- Level 4: 300 mg vandetanib daily + 1.3 mg/m^2 bortezomib on days 1, 4, 8 & 11 every 28 days

Notes:

If in the dose escalation portion of the study:

Levels 1, 2 or 3 are established as the MTD, two additional levels (levels 1A and 1B) will be tried:

- Level 1A: 200 mg vandetanib daily + 1 mg/m^2 bortezomib on days 1, 4, 8 & 11 every 28 d.
- Level 1B: 300 mg vandetanib daily + 1 mg/m^2 bortezomib on days 1, 4, 8 & 11 every 28 d.

If: Dose level 1 is established as the MTD, both levels 1A and 1B ***will*** be explored.
Dose level 2 is established as the MTD, both levels 1A and 1B ***can*** be explored.
Dose level 3 is established as the MTD, both levels 1A and 1B ***can*** be explored.

A decision will be made ***only after all interested parties have discussed the available data and a decision is made as to which dose might be best to pursue***.

Then:

- If level 1 is initially identified as the MTD, level 1A or 1B ***will*** be substituted as the level recommended for the phase II portion of the study, provided safety can be demonstrated.
- If levels 2 or 3 are initially identified as the MTD, level 1A or 1B ***can*** be substituted as the level recommended for the phase II portion of the study, provided safety can be demonstrated and ***only after all interested parties have discussed the available data and a decision is made as to which dose might be best to pursue***.

3.1.2 Intrapatient dose escalation:

Intra-patient dose escalation will be allowed once a patient has completed eight weeks of treatment at a given dose level without suffering a DLT. The dose for each patient may be escalated several times; depending at which dose level they enter the study. An individual patient will have the dose escalated to the next higher dose level after eight weeks at their current dose level. Once on the higher level for eight weeks, without DLT, the dose can be escalated again. Once the MTD is established, no patient will have the dose escalated beyond that level.

3.1.3 Determination of maximum tolerated dose (MTD) and dose-limiting toxicity (DLT):

The doses of bortezomib and then vandetanib will be increased in cohorts of three patients. The MTD and DLT will be determined based on toxicities during the first eight weeks of combined therapy. If a patient experiences any DLT during the first eight weeks of treatment, therapy will be withheld and the dose of study treatment will be withheld for up to 3 weeks until the toxicity has resolved to CTCAE grade 1 or better. Patients will be withdrawn from the study if toxicity does not resolve to ≤ CTCAE grade 1 within 3 weeks. When the toxicity resolves to ≤ CTCAE grade 1 study treatment may be restarted at one lower dose level. See Section 3.3 **Guidelines for dose modifications and management of toxicities following the first six weeks of therapy.** Guidelines for the management of toxicities and for supportive measures discussed therein apply also to the first eight weeks of therapy with the exception that dose reductions in every case will be by one dose level regardless of which drug is felt to be responsible for the toxicity. In all cases if a dose reduction is instituted for toxicity, the patient may subsequently be re-challenged with

that dose provided that at least one cycle has been completed at the reduced dose level without any dose limiting toxicity and in the opinion of the investigators such a re-challenge can be attempted without risk to the patient.

Note: A patient will be considered evaluable for toxicity after one cycle or four weeks and this is at least twenty doses of vandetanib and four doses of bortezomib.

Note: A DLT is attributed to a dose level not an individual drug dose.

Note: Patients who go off study for reasons other than toxicity will be replaced.

3.1.4 Definition of Maximum Tolerated Dose (MTD):

A MTD for the combination of vandetanib and bortezomib will be determined if DLT is observed in 2 or more pateints at one of the dose levels being evaluated. The MTD will be the dose level immediately preceeding the dose level at which DLT occurred.

3.1.5 Definition of Dose-Limiting Toxicty (DLT):

This study will utilize the NCI Common Terminology Criteria for Adverse Events Version 3.0 (CTCAE) for toxicity and Adverse Event grading and reporting until December 31, 2010. CTCAE version 4.0 will be utilized beginning January 1, 2011. A copy of the CTCAE version 3.0 can be viewed or downloaded from the CTEP website (http://ctep.info.nih.gov/reporting/ctcv30.html). A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov). An adverse event must be judged to be possibly, probably, or definitely related to vandetanib to be a dose-limiting toxicity.

Dose-limiting toxicity is defined as:

3.1.6 Hematologic Dose-Limiting Toxicity (H-DLT):

- Neutrophil count below 1,000/µL (grade 3) on 2 consecutive measurements drawn at least 72 hours apart (a Monday/Thursday or Tuesday/Friday schedule) OR a single neutrophil count below 500/µL (grade 4).
- Platelet count below 50,000/µL (grade 3) on 2 consecutive measurements drawn at least 72 hours apart (a Monday/Thursday or Tuesday/Friday schedule) OR a single platelet count below 25,000/µL (grade 4). A platelet transfusion administered when platelet count is below 50,000/µL is dose-limiting thrombocytopenia, unless the transfusion is being administered for peri-operative coverage.
- Grade 3 or 4 decrease in hemoglobin that can be corrected to at least 8.0 g/dl (grade 2) by transfusion of red blood cells is not a dose-limiting toxicity. However, grade 3 or 4 hemolysis is a dose-limiting toxicity if it is judged to be vandetanib-related.
- Grade 3 or 4 leucopenia is not a dose-limiting toxicity.
- Grade 3 or 4 lymphopenia is not a dose-limiting toxicity.

3.1.7 Non-Hematologic Dose-Limiting Toxicity (NH-DLT):

NH-DLT is any grade 3 or higher non-hematologic toxicity, with the exception of:

- Grade 3 nausea that is controlled by symptomatic treatment with anti-emetics (see Appendix C to avoid agents that can prolong the QTc) within 48 hours.

- Grade 3 vomiting that is controlled by symptomatic treatment with anti-emetics (see Appendix C to avoid agents that can prolong the QTc) within 48 hours.
- Any grade of diarrhea that is tumor-related (present at baseline and associated with elevated calcitonin levels) or grade 3 diarrhea that is related to vandetanib and is controlled by symptomatic treatment within 48 hours.
- Grade 3 serum transaminase elevation (ALT/AST) that returns to grade 2 or less within 7 days. The drug may be held until the transaminase elevation subsides, but if the grade 3 transaminase elevation recurs when the drug is re-instituted, this will be considered dose-limiting toxicity.
- Grade 3 electrolyte abnormalities that are asymptomatic and correctable to grade 2 or less within 48 hours.
- *Grade 3 infection, with neutropenia, without neutropenia, or with unknown ANC*
- *Grade 3 febrile neutropenia (fever with ANC ≤ 1000/μL)*
- *Grade 3 HTN* that is suboptimally treated

3.1.8 Dose-limiting hypertension:

This is defined as any grade 4 HTN or a grade 3 HTN that does not respond to treatment or requires more than 3 weeks to resolve to ≤ grade 1.

QTc Prolongation: Dose-limiting QTc prolongation is defined as:

- A single QTc value ≥ 550 msec OR an increase of ≥ 100 msec from baseline, OR
- Two consecutive ECG measurements, which are within 48 hours of one another and which meet either of the following criteria:
  i. QTc ≥ 500 msec but < 550 msec OR
  ii. A ≥ 60 msec but < 100 msec increase in the QTc from baseline QTc to a QTc value ≥ 480 msec.

3.2 Drug Administration

3.2.1 Vandetanib

3.2.1.1 Administration:

Vandetanib is administered orally, once daily continuously. A cycle of vandetanib is defined as 28 consecutive days starting with the first day of the treatment cycle. Treatment will be administered in an outpatient setting. Vandetanib and bortezomib will be given simultaneously on the first day of each cycle.

Notes:

i. Patients will receive their assigned dose of vandetanib once daily at the same time of the day. Vandetanib absorption is not affected by a meal so it need not be administered in the fasted state.[70] The tablet should be swallowed whole. If a patient misses a scheduled dose of vandetanib and less than 6 hours have passed since the scheduled dosing time, the dose should be taken immediately. If more than 6 hours have passed since the scheduled dosing time, the patient should not take the missed dose but should wait and take the next regularly scheduled dose.

ii. If the patient vomits within 15 minutes of taking vandetanib, then another dose can be administered. The dose may only be repeated once. If more than 15 minutes has passed from the time of oral dosing then no additional doses should be given.
iii. Patients or their guardians will keep a diary (Appendix B) to document the intake of each dose, concomitant medications, and any toxicity.

3.2.2 Bortezomib

3.2.2.1 Administration:

Bortezomib will be administered as a bolus intravenous injection on days 1, 4, 8 and 11 of a 28-day cycle followed by a 17-day rest period (days 12-28). This four-week period is considered a treatment cycle. Approximately 72 hours should elapse between consecutive doses of bortezomib. However, it is recognized that because of inadvertent delays a dose may be given more than 72 hours after the previous dose, and if plans have been made for airline travel, a delay of subsequent doses may adversely affect this. Consequently a period in excess of 66 hours is considered acceptable. Bortezomib is an antineoplastic. Caution should be used during handling and preparation. Proper aseptic technique should be used. Use of gloves and other protective clothing to prevent skin contact is recommended. In clinical trials, local skin irritation was reported in 5% of patients, but extravasation of bortezomib was not associated with tissue damage.

3.2.2.2 Administration precautions:

Bortezomib infusion is given by rapid IV push (usually into a running IV over 3 to 5 seconds). Compatibility studies have not been done; because the drug is reconstituted with 0.9% Sodium Chloride Injection, USP, that is the preferred solution for infusion flush following intravenous push. Administration via central or peripheral access is acceptable.

3.2.2.3 Administration locations:

Bortezomib will be administered at the NCI, CCR facility in Bethesda, MD during both phases of the study. Patients will NOT have the option of receiving bortezomib at their local physician's practice setting.

3.3 Guidelines for dose modifications and management of toxicities following the first eight weeks of therapy

DLTs that arise *after the first eight weeks* of ***combined therapy*** will be managed according to the guidelines below that identify drug doses for each dose level and consider the drug responsible for the observed toxicity.

Dose Level	Vandetanib Dose	Bortezomib Dose
Level –1	100 mg vandetanib daily	None (vandetanib only)
Level 1	100 mg vandetanib daily	1 mg/m^2 bortezomib on days 1, 4, 8 and 11
Level 1A	*200 mg vandetanib daily*	*1 mg/m^2 bortezomib on days 1, 4, 8 and 11*
Level 1B	*300 mg vandetanib daily*	*1 mg/m^2 bortezomib on days 1, 4, 8 and 11*
Level 2	100 mg vandetanib daily	1.3 mg/m^2 bortezomib on days 1, 4, 8 and 11
Level 3	200 mg vandetanib daily	1.3 mg/m^2 bortezomib on days 1, 4, 8 and 11
Level 4	300 mg vandetanib daily	1.3 mg/m^2 bortezomib on days 1, 4, 8 and 11

For example, a patient on dose level 3 who experiences toxicity can have the dose reduced to:

- Dose level 2 if the toxicity is determined to be due to vandetanib
- Dose level 1A if the toxicity is determined to be due to bortezomib or
- Dose level 1 if the toxicity is determined to be due to both drugs

In patients randomized to the vandetanib only arm of the study in the phase II portion as well those in whom bortezomib is discontinued for reasons of tolerability, the vandetanib dose can be escalated in 100 mg increments to a maximum of 300 mg per day provided that they are tolerating the therapy well. Dose adjustments in these patients will be as per the dose levels below. Given that about 42 days are needed to reach steady state, upward dose adjustments in vandetanib should be performed after every two cycles.

Dose levels for vandetanib alone
100 mg vandetanib every other day
100 mg vandetanib daily
200 mg vandetanib daily
300 mg vandetanib daily

3.3.1 Cutaneous Toxicity

Guidelines for making protocol decisions in patients with cutaneous toxicity

Note: The cutaneous toxicity should be graded/assessed by a physician as soon as possible according to the CTCAE cutaneous toxicity criteria and documented.

Rash ≥ grade 2	Both vandetanib and bortezomib should be held and ***immediate*** symptomatic treatment should be provided.
If treatment held for more than 3 weeks due to cutaneous toxicity	Therapy will be discontinued.
When toxicity resolves to ≤ grade 1	Both vandetanib and bortezomib should be restarted at one dose level lower for both drugs than that administered at the time the toxicity developed. Symptomatic treatment may continue indefinitely as a preventive measure.
If cutaneous toxicity grade 3/4 recurs at a reduced doses of vandetanib and bortezomib, and this level is other than level -1	Again hold both vandetanib and bortezomib until the toxicity resolves to ≤ grade 1 at which time both vandetanib and bortezomib or vandetanib alone should be restarted at one dose level lower for both drugs than that administered at the time the toxicity developed. Symptomatic treatment may continue indefinitely as a preventive measure.
If cutaneous toxicity grade 3/4 recurs at dose level -2	Therapy will be discontinued.
If with or without continued symptomatic treatment the cutaneous toxicity does not recur at the reduced doses of vandetanib and bortezomib	The dose of vandetanib may be increased one dose level to that which was being administered at the time the cutaneous toxicity developed. If toxicity recurs following this increase, then follow the guidelines above, with the exception that when drug is restarted only the vandetanib dose should be reduced one dose level.

3.3.2 Gastrointestinal (GI) Toxicity - Nausea/Vomiting

Guidelines for making protocol decisions in patients with nausea and/or vomiting

If the nausea and/or vomiting cannot be controlled with the preventive measures outlined in section 4, and their severity is grade 3/4 or persistent grade 2 (persistent defined as lasting for more than two weeks)	Both vandetanib and bortezomib should be held.
If vandetanib and bortezomib are held for more than 3 weeks and the nausea and/or vomiting do not resolve to ≤ grade 1	The patient will discontinue therapy on study.
If within three weeks of holding therapy the nausea and vomiting resolve to ≤ grade 1	Both vandetanib and bortezomib should be restarted at one dose level lower for both drugs than that administered at the time the toxicity developed.
If the nausea and/or vomiting that is grade 3/4 or persistent grade 2 (persistent defined as lasting for more than two weeks) recurs at the reduced doses of vandetanib and bortezomib, and this is higher than level -1	Again hold both vandetanib and bortezomib until the toxicity resolves to ≤ CTCAE grade 1 at which time both vandetanib and bortezomib or vandetanib alone should be restarted at one dose level lower for both drugs than that administered at the time the toxicity developed. Symptomatic treatment may continue indefinitely as a preventive measure.
If nausea and/or vomiting that is CTCAE grade 3/4 or persistent grade 2 (persistent defined as lasting for more than two weeks) recurs at dose level -2	The patient will discontinue therapy on study.
If with or without continued symptomatic treatment the nausea and vomiting do not recur at the reduced doses of vandetanib and bortezomib	The dose of vandetanib may be increased one dose level to that which was being administered at the time the nausea and vomiting developed. If toxicity recurs following this increase, then follow the guidelines above, with the exception that when drug is restarted only the vandetanib dose should be reduced one dose level.

3.3.3 Gastrointestinal (GI) Toxicity – Diarrhea

Guidelines for making protocol decisions in patients with diarrhea

Grade 1/2 diarrhea	Symptomatic treatment designed to resolve the diarrhea should be the focus. No dose modifications will be made for grade 1/2 diarrhea unless grade 2 diarrhea persists for more than two weeks,
If grade 2 diarrhea persists for more than two weeks	Then the guidelines below for grade 3/4 diarrhea should be followed.
If the diarrhea cannot be controlled with the preventive	Both vandetanib and bortezomib should be held. Also if persistent grade 2 diarrhea (persistent defined as

measures outlined, and is grade 3/4 or worsens by one grade level (grade 3 to grade 4) while on vandetanib and is not alleviated by symptomatic treatment within 48 h	lasting for more than two weeks) while on vandetanib is not alleviated by symptomatic treatment both vandetanib and bortezomib should be held.
If vandetanib and bortezomib are held for more than 3 weeks and the diarrhea does not resolve to ≤ grade 1	The patient will discontinue therapy on study.
If within three weeks of holding therapy the diarrhea resolves to ≤ grade 1	Both vandetanib and bortezomib should be restarted at one dose level lower for both drugs than that administered at the time the toxicity developed.
If diarrhea that is grade 3/4 or persistent grade 2 (persistent defined as lasting for more than two weeks) recurs at the reduced doses of vandetanib and bortezomib, and this is higher than level -1	Again hold both vandetanib and bortezomib until the toxicity resolves to ≤ CTCAE grade 1 at which time both vandetanib and bortezomib or vandetanib alone should be restarted at one dose level lower for both drugs than that administered at the time the toxicity developed. Symptomatic treatment may continue indefinitely as a preventive measure.
If diarrhea that is grade 3/4 or persistent grade 2 (persistent defined as lasting for more than two weeks) recurs at dose level -2	The patient will discontinue therapy on study.
Electrolytes should be closely monitored in the event of persistent diarrhea.	Vandetanib should be held in patients who develop electrolyte abnormalities from diarrhea until the electrolyte abnormalities are corrected because of the risk of QTc prolongation and subsequent arrhythmias.
If with or without continued symptomatic treatment the diarrhea does not recur at the reduced doses of vandetanib and bortezomib,	The dose of vandetanib may be increased one dose level to that which was being administered at the time the diarrhea developed. If toxicity recurs following this increase, then follow the guidelines above, with the exception that when drug is restarted only the vandetanib dose should be reduced one dose level.

3.3.4 Hypertension

Note: Patients will have their blood pressure checked once per week during their first 24 weeks of therapy or for any eight-week period after and adjustment is made in their vandetanib dose. They will call a member of the study team to report the blood pressure. If an adjustment is needed this may be made at the time of the call or alternately a referral to the local physician will be made

Guidelines for making protocol decisions in patients with hypertension

Grade 3 hypertension	Continue on therapy if blood pressure is controlled on antihypertensive medication. If blood pressure cannot be stabilized with increased

	antihypertensive medication, study treatment must be discontinued and cannot be resumed until blood pressure is controlled to baseline level.
Grade 4 hypertension:	Discontinue study treatment and do not resume therapy until blood pressure is controlled to baseline level. If study treatment must be interrupted for more than 3 weeks to allow for toxicity to resolve, the patient will discontinue therapy on study.

Treatment modification guidelines for vandetanib-induced hypertension

Toxicity Grade for Hypertension	**Definition**
G1	Asymptomatic, transient (< 24 hours) increase by > 20 mmHg (diastolic) or to > 150/100 if previously WNL; intervention not indicated
G2	Recurrent or persistent (> 24 hours) or symptomatic increase by > 20 mmHg (diastolic) or to > 150/100 if previously WNL; monotherapy may be indicated
G3	Requiring more than one drug or more intensive therapy than previously
G4	Life threatening (e.g., hypertensive crisis).

Adverse Event	**Treatment Modification**
G1	Continue vandetanib at same dose and schedule
G2 asymptomatic	Treat with anti-hypertensive medications and continue vandetanib at same dose and schedule
G2 symptomatic or persistent G2 despite anti-hypertensive medications or Diastolic BP > 110 mm/Hg or G3 hypertension	Treat with anti-hypertensive medications. Hold vandetanib (maximum 3 weeks until symptoms resolve and diastolic BP < 100 mm Hg); then continue vandetanib at one dose level lower *Note:* If vandetanib is held more than 3 weeks then discontinue therapy
G4	Discontinue therapy

3.3.5 Toxicities other than cutaneous, gastrointestinal, hypertension or QTc prolongation

If the toxicity cannot be controlled with the standard measures, and is CTCAE grade 3/4 or persistent grade 2 (persistent defined as lasting for more than two weeks)	Both vandetanib and bortezomib should be held. (Note: the decision to discontinue therapy for persistent grade 2 will depend on the toxicity and the opinion of the investigator)
If the toxicity has resolved to ≤ grade 1 within 3 weeks of holding the study medication	Study treatment may be restarted with an appropriate dose reduction dependent on the dose that is being administered and the drug determined to be responsible for the toxicity
If toxicity does not resolve to ≤ grade 1 within 3 weeks.	Patients will be withdrawn from the study

If toxicity is determined to be secondary to vandetanib	
when the toxicity resolves to ≤ grade 1	Vandetanib should be restarted at one dose level lower than that administered at the time the toxicity developed.
If toxicity that is grade 3/4 or persistent grade 2 (persistent defined as lasting for more than two weeks) recurs at the reduced dose of vandetanib, and this is higher than level -1	Again hold vandetanib until the toxicity resolves to ≤ grade 1 at which time vandetanib should be restarted at one dose level lower than that administered at the time the toxicity developed. Symptomatic treatment may continue indefinitely as a preventive measure.
If toxicity that is grade 3/4 or persistent grade 2 (persistent defined as lasting for more than two weeks) recurs at dose level -2	The patient will discontinue therapy on study.
If toxicity is determined to be secondary to bortezomib	
When the toxicity resolves to ≤ grade 1	Bortezomib should be restarted at one dose level lower than that administered at the time the toxicity developed.
If toxicity that is grade 3/4 or persistent grade 2 (persistent defined as lasting for more than two weeks) recurs at the reduced dose of bortezomib, and this is higher than level 1	Again hold bortezomib until the toxicity resolves to ≤ CTCAE grade 1 at which time bortezomib should be restarted at one dose level lower than that administered at the time the toxicity developed. Symptomatic treatment may continue indefinitely as a preventive measure.
If toxicity that is grade 3/4 or persistent grade 2 (persistent defined as lasting for more than two weeks) recurs at dose level 1 of bortezomib	The patient will discontinue therapy on study.
If the drug responsible for the toxicity cannot be determined	
When the toxicity resolves to ≤ CTCAE grade 1	Both vandetanib and bortezomib should be restarted at one dose level lower for both drugs than that administered at the time the toxicity developed.
If toxicity that is CTCAE grade 3/4 or persistent grade 2 (persistent defined as lasting for more than two weeks) recurs at the reduced doses of vandetanib and bortezomib, and this is higher than level -1	Again hold both vandetanib and bortezomib until the toxicity resolves to ≤ grade 1 at which time both vandetanib and bortezomib or vandetanib alone should be restarted at one dose level lower for both drugs than that administered at the time the toxicity developed. Symptomatic treatment may continue indefinitely as a preventive measure.
If toxicity that is grade 3/4 or persistent grade 2 (persistent defined as lasting for more than two weeks) recurs at dose level -2 of vandetanib	The patient will discontinue therapy on study.
If with or without continued symptomatic treatment the toxicity does not recur at the reduced doses of	The dose of vandetanib may be increased one dose level to that which was being administered at the time the toxicity developed. If toxicity recurs following

vandetanib and bortezomib	this increase, then follow the guidelines above, with the exception that when drug is restarted only the vandetanib dose should be reduced one dose level.

3.3.6 QTc prolongation

3.3.6.1 QTc monitoring:

Patients will have ECGs performed to monitor QTc interval (using Bazett's correction) as outlined in the study plan. The definition and management of QTc are as follows:

3.3.6.2 Definition of QTc prolongation:

- A single QTc value of ≥ 550 msec or an increase of ≥100 msec from baseline; **OR**
- Two consecutive QTc measurements, within 48 hours of one another, where either of the following criteria are met for both QTc values (the second being the mean of 3 consecutive ECGs):
  - A QTc interval ≥ 500 msec but < 550 msec, **OR**
  - An increase of ≥ 60 msec, but < 100 msec, from baseline QTc to a QTc value ≥ 480 msec.

Guidelines for making protocol decisions in patients with QTc prolongation

Vandetanib dose levels: 100 mg/day, 200 mg/day and 300 mg/day.	
For a single QTc value of ≥ 550 msec or an increase of ≥ 100 msec from baseline	Vandetanib must be withheld. ECGs and electrolytes should be followed 3 times a week until QTc recovers to < 480 msec or baseline, whichever is higher. Vandetanib treatment may be resumed at a lower dose level after the QTc recovers to < 480 msec or baseline.
For a QTc interval ≥ 500 msec, but < 550 msec, or an increase of ≥ 60 msec but < 100 msec from baseline QTc to a QTc value ≥ 480 msec,	Vandetanib may be continued but a **repeat ECG (in triplicate)** must be obtained within 48 hours. If QTc prolongation is confirmed at the **repeat ECG (performed in triplicate)**, vandetanib should be withheld. ECGs and electrolytes should be checked 3 times a week until QTc falls below 480 msec or baseline, whichever is higher.
After the QTc recovers to < 480 msec or baseline.	Vandetanib treatment may be resumed at a lower dose level
If the patient does not meet the criteria for QTc prolongation at the **repeat ECG (performed in triplicate)**	Then the patient should continue treatment and resume the ECG schedule as outlined in the Study Plan.

3.3.7 Phase II Cohort

Two cohorts will be added once the MTD is identified. Both cohorts will be restricted to patients with a diagnosis of MTC in order to assess the activity and tolerability in this patient population and to be able to perform correlative studies. The eligibilty criteria for these cohorts will be the same as for patients in the dose escaltion portion of the study with the exception of the diagnosis of MTC only in phase II cohorts. Patients will be randomized in a 2:1 ratio as follows:

Arm A: This arm will receive the combination of vandetanib and bortezomib at the identified MTD. Also, since this cohort will be begin at the MTD, the guidelines for dose modifications following the first eight weeks of therapy should be followed. See **3.3 Guidelines for dose modifications and management of toxicities following the first eight weeks of therapy**
Arm B: This arm will begin vandetanib alone at the MTD dose used in Arm A. In these patients the dose can be escalated in 100 mg increments to a maximum of 300 mg per day provided that they are tolerating the therapy well. See **3.3 - Guidelines for dose modifications and management of toxicities following the first eight weeks of therapy**

3.4 Correlative Studies

***Note:* Germline testing will not be done.** We will only be testing the tumor DNA. We will not be testing DNA from any normal tissue.

3.4.1 Exploratory analyses in patients with MTC and those with a diagnosis other than MTC (see Appendix A)

3.4.1.1 Exploratory analyses in patients with MTC:

1. Perform RET gene mutational analysis in tumor tissue obtained prior to (surgical or other procedure) or at the time of enrollment on this protocol (core biopsy) and examine the correlation between genotype and response to therapy. Research samples will be used to evaluate gene expression in the tumor and to sequence and identify mutations in the RET gene. These studies of the RET mutation status in tumor will not be used to determine protocol eligibility or inform clinical decisions on the trial. They will be used for research purposes only in exploratory analyses. Information about mutations in tumors that might affect vandetanib sensitivity is not currently available. (Dr. Fojo's laboratory; 301-496-6611 or 301 435-2278). These tests can be performed on samples from tissue blocks, fresh or frozen samples.
2. In patients with MTC who consent to two biopsies of a site of disease that is accessible with minimal risk to the patient we will perform an exploratory analysis to examine the extent of RET inhibition, an important pharmacodynamic endpoint not yet explored in any clinical trial. In these patients a biopsy would be obtained prior to the start of therapy with the second biopsy obtained after 42 days of vandetanib administration. (Dr. Fojo's laboratory; 301-496-6611 or 301 435-2278 → Dr. Figg's laboratory). These samples will be obtained during Cycle 3 or later, once a patient has received at least 42 consecutive days of vandetanib.This test will be perfomed on tissue from fresh samples.
3. Assess the expression of RET, EGFR and VEGFR by immunohistochemistry in tissue obtained prior to or at the time of enrollment on this protocol (obtained either by biopsy performed while on study or from a prior surgery or other procedure) and examine the correlation between expression of these proteins and response to therapy. (Dr. Fojo's laboratory; 301-496-6611 or 301 435-2278 → Dr. Figg's laboratory). These tests can be performed on samples from tissue blocks, fresh or frozen samples.

3.4.1.2 Exploratory analyses in patients with a diagnosis other than MTC:

In patients with a diagnosis other than MTC who consent to two core biopsies of a site of disease that is accessible with minimal risk to the patient we will plan to perform a core biopsy prior to the start of therapy and second core biopsy after the day 4 administration of bortezomib in cycle 1 or 2 to assess whether microtubule stabilization has occurred. The latter would provide evidence supporting the thesis that microtubule stabilization occurs following bortezomib

administration and also provide pharmacodynamic evidence of an effect of bortezomib on the tumor. Microtubule stabilization will be assessed both by immunohistochemistry and by immunoblotting using two antibodies that recognize post-translational modifications that occur on stable microtubules and thus provide a measure of the extent of microtubule stabilization. These antibodies recognize alpha tubulin that has been acetylated at lysine 40 by tubulin acetylase and alpha tubulin whose c-terminal residue is a glutamic acid (glu-tubulin) as a result of detyrosination or removal of the c-terminal tyrosine residue by tubulin carboxypeptidase. (Dr. Fojo's laboratory; 301-496-6611 or 301 435-2278 → Dr. Figg's laboratory)

3.4.2 Gene expression by microarray

Assess gene expression by microarray prior to and during treatment with vandetanib and bortezomib in core biopsy samples. Patients with MTC in both the phase I portion of the study as well as those in the randomized cohorts will be eligible for this analysis. (Dr. Fojo's laboratory; 301-496-6611 or 301 435-2278 → Dr. Meltzer's laboratory; and → Dr. Figg's laboratory)

3.4.3 Tumor Sample acquisition

When available, paraffin embedded tumor from diagnostic biopsies or prior surgical resections will be obtained and examined for the expression of RET, VEGFR and EGFR (and the phospho-forms of these proteins) and somatostatin receptor by immunohistochemistry (IHC). In the event that a biopsy or surgical procedure is performed for clinical indications or research purposes while a patient is on this study, tumor may also be obtained and examined for expression of these targets by IHC. Pathology report should accompany each specimen and the specimen should be labeled with the patient ID number. [Tumor should be shipped to: Ravi Madan, MD, Genitourinary Malignancies Branch, NCI, Building 10, Room 3-4460, 10 Center Drive, Bethesda, MD 20892, Phone: 301-496-3493, Fax: 301-480-5094, Page: 301-496-1121, E-mail: madanr@mail.nih.gov]

Patients with tumors that are accessible to percutaneous core needle (16 or 18 gauge) biopsy with minimal risk to surrounding vital structures will be asked to voluntarily undergo a core needle biopsy of the tumor under local anesthesia prior to the initiation of treatment and again during the first or second cycle. A portion of the biopsy will be processed for histologic and immunohistochemical evaluation by Dr. Maria Merino in the Laboratory of Pathology. The remainder will be snap frozen and divided into two. One of the two frozen samples will be sent to the laboratory of Dr. W. Doug Figg for processing, coding and storage. A second frozen sample together with a 5 ml blood sample in lithium heparin (green top tube) should also be obtained and sent with the frozen tumor tissue sample to Paul Meltzer, MD [Paul Meltzer, M.D., Bldg. 37/Rm. 6138, Bethesda, MD 20892, Phone: (301) 496-5266, Email: pmeltzer@mail.nih.gov]

3.4.4 Pharmacokinetics of vandetanib and bortezomib

Pharmacokinetic samples will only be done during the Phase One portion of the study.

3.4.4.1 Vandetanib Pharmacokinetic Studies

- Pharmacokinetic (PK) evaluation of vandetanib will be performed for each patient at the start of treatment cycle 3 (cycle 3, day 1 ± 3 days). See Appendix A for details of sample collection, handling, shipping, and PK Worksheet.
- At least 42 days of continuous vandetanib dosing is required to ensure that patients are at steady state at the time of the PK study. Therefore, patients who have their dosing of

vandetanib interrupted for toxicity during cycle 1 or 2 will have the PK sampling performed on a subsequent cycle.

- 3 mL blood samples will be collected in heparinized tubes prior to the dose and then 1, 2, 4, 6, 8, 10, and 24 hours after the dose. Plasma will be separated by centrifugation and the plasma sample will be stored and shipped frozen. An additional trough samples (24 h after the previous dose) will be drawn on day 9 of the same cycle.

3.4.4.2 Bortezomib Pharmacokinetic Studies

- Bortezomib pharmacokinetics will be obtained after the first dose (C1D1) and again at the start of treatment cycle 3 (cycle 3, day 1) to assess the effect, if any, of vandetanib at steady state on bortezomib PK.
- At least 42 days of continuous vandetanib dosing is required to ensure that patients are at steady state at the time of the 2nd PK series. Therefore, patients who have their dosing of vandetanib interrupted for toxicity during cycle 1 or 2 will have the PK sampling performed on a subsequent cycle.
- 3 mL blood samples will be collected in heparinized tubes prior to the dose and then 1, 2, 4, 6, 8, 10, and 24 hours after the dose. Plasma will be separated by centrifugation and the plasma sample will be stored. The bortezomib samples will be processed in the laboratory of Dr. Doug Figg (see **Appendix A: Laboratory Methodology**).

3.5 Study Calendar

3.5.1 Study Calendar for Combined Vandetanib and Bortezomib Therapy

Week	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**16**	**20**	**24, 28, etc**	**Post Study**
Day 1 of Cycle #	**1**				**2**				**3**				**4**	**5**	**6**	**7**	
Day	**1**	**8**	**15**		**29**				**57**				**85**	**113**	**141**	**159,**	
History &Physical	**X**	**X**			**X**				**X**				**X**	**X**	**X**	**X**	**X**
Assessment of toxicity	X	X			X				X				X	X	X	X	X
Vital signs & weight	X	X			X				X				X	X	X	X	X
Performance status	X	X			X				X				X	X	X	X	X
Urinalysis	X	X			X				X				X	X	X	X	X
Urine/Serum pregnancy test	X																
CBC with differential and platelets	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
PT,PTT	X	X	X		X				X				X	X	X	X	X
Acute Care Panel	X	X	X	X	X		X		X		X		X	X	X	X	X
Mineral Panel	X	X	X	X	X		X		X		X		X	X	X	X	X
LFTs	X	X	X	X	X		X		X		X		X	X	X	X	X
Total protein, albumin, GGT	X	X	X		X				X				X	X	X	X	X
TSH	X				X				X					X		Xb	
12-lead ECG with calculation of QTc	Xa	X			X				X				X	X	X	X	X

Week	0	1	2	3	4	5	6	7	8	9	10	11	12	16	20	24, 28, etc	Post Study
Day 1 of Cycle #	**1**				**2**				**3**				**4**	**5**	**6**	**7**	
Day	**1**	**8**	**15**		**29**				**57**				**85**	**113**	**141**	**159,**	
History &Physical	**X**	**X**			**X**				**X**				**X**	**X**	**X**	**X**	**X**
RECIST assessment with CT neck, chest, abdomen	Xe								X					X		Xb	X
Blood samples for CTN/CEA	X				X				X					X		Xb	X
Pharmacokinetics (see Appendix A) Phase I only	X								X	Xc							
Biopsies in pts with MTC	X								X								
Biopsies in pts with other than MTC	Xd				Xd												

a. ECG done prior to first dose of vandetanib then 4 and 8 hours after dose
b. done at completion of 6 cycles (cycle 7day 1) then q 3 cycles thereafter (Day 1 Cycles 10, 13, etc)
c. PK done day 9
d. cycle 1 day 4 or cycle 2 day 4
e. within 4 weeks prior to cycle 1 day 1

3.5.2 Study Calendar for Vandetanib Alone

For patients who are randomized to vandetanib alone (Arm B) in the Phase II portion of the trial, or for those who have discontinued bortezomib in either the Phase I or II portions of the trial, the study calendar below will be used.

Week	0	1	2	3	4	8	16	24, etc. visits every 12 weeks through 2 years; then every 6 months (f)	Post Study
Day 1 of Cycle #	**1**				**2**	**3**	**5**	**7**	
Day	**1**	**8**	**15**		**29**	**57**	**113**	**159**	
History &Physical	**X**	**X**			**X**	**X**	**X**	**X**	**X**
Assessment of toxicity	X	X			X	X	X	X	X
Vital signs & weight	X	X			X	X	X	X	X
Performance status	X	X			X	X	X	X	X
Urinalysis	X	X			X	X	X	X	X
Urine/Serum pregnancy test	X								
CBC with differential and platelets	X	X	X		X	X	X	X	X
PT,PTT	X	X	X		X	X	X	X	X
Acute Care Panel	X	X	X		X	X	X	X	X
Mineral Panel	X	X	X		X	X	X	X	X

Week	**0**	**1**	**2**	**3**	**4**	**8**	**16**	**24, etc. visits every 12 weeks through 2 years; then every 6 months (f)**	**Post Study**
Day 1 of Cycle #	**1**				**2**	**3**	**5**	**7**	
Day	**1**	**8**	**15**		**29**	**57**	**113**	**159**	
History &Physical	**X**	**X**			**X**	**X**	**X**	**X**	**X**
LFTs	X	X	X		X	X	X	X	X
Total protein, albumin, GGT	X	X	X		X	X	X	X	X
TSH	X				X	X	X	X	
12-lead ECG with calculation of QTc	Xa	X	X		X	X	X	X	X
RECIST assessment with CT neck, chest, abdomen	Xe					X	X	X	X
Blood samples for CTN/CEA	X				X	X	X	X	X
Biopsies in pts with MTC	X					X			
Biopsies in pts with other than MTC	Xd				Xd				

a) ECG done prior to first dose of vandetanib
b) done at completion of 6 cycles (cycle 7day 1) then q 3 cycles thereafter (Day 1 Cycles 10, 13, etc)
c) PK done day 9
d) cycle 1 day 4 or cycle 2 day 4
e) within 4 weeks prior to cycle 1 day 1
f) After 2 years of treatment, patients will follow-up at the Clinical Center every 6 months. They should be followed by the home oncologist at the interim 3-month intervals with labs and EKGs, but no scans.

3.6 Concurrent Therapies

3.6.1 Other Anti-cancer Agents

Patients may not receive other forms of cancer chemotherapy, immunotherapy or investigational agents while enrolled on this trial and receiving vandetanib and bortezomib.

3.6.2 Complementary and Alternative Therapies

All complementary or alternative therapies including herbal preparations, vitamins, and supplements should be discussed with the PI or an Associate Investigator. All agents, allowed by the investigators, will be recorded on the electronic case report forms.

3.6.3 Thyroid Replacement Therapy

Patients who are receiving thyroid replacement therapy at the time of enrollment onto the study should be maintained on thyroid replacement therapy. The dose should be adjusted to maintain the TSH within the normal range. Patients who have an elevated TSH at enrollment and who are not on thyroid replacement therapy should be started on replacement therapy and maintained on a dose that suppresses TSH into the normal range.

3.6.4 Anti-Hypertensive Therapy

Please refer to Section 4.4 for information on the use of enalapril for the management of vandetanib-related hypertension.

3.6.5 Agents that Prolong the QTc

3.6.5.1 Please refer to Appendix C prior to starting any new supportive care drugs. Concomitant use of medications generally accepted as having a risk of causing Torsades de Pointes (reference Appendix C, Table 1) are not allowed within 2 weeks of randomization or during study (at least 4 weeks for Levomethadyl). These drugs should also be avoided for up to 4 weeks following discontinuation of study treatment.

Effective with Amendment I, Appendix C has been updated to reflect additional drugs that are generally accepted by authorities to have a risk of causing Torsades de Pointes. If after reviewing the updated list of drugs in Table 1, Appendix C, the investigator finds that any ongoing patient is now taking a Group 1 drug, the investigator is to manage the patient immediately as follows:

- The investigator should switch the patient to an alternative drug as soon as possible.
- If it is not possible to switch the patient to an alternative drug, the patient will have to stop vandetanib.

3.6.5.2 Co-administration of drugs that in some reports might be associated with Torsades de Pointes but at this time lack substantial evidence of Torsades de Pointes (see Appendix C, Table 2) should be avoided within 2 weeks of randomization and during study. However, these drugs will be allowed, at the discretion of the Investigator, if considered absolutely necessary. In such cases, the subject must be closely monitored including regular checks of QTc and electrolytes. For patients who start on the drugs in this group while on the study treatment, the ECG must be checked within 24 hours of commencing the concomitant medication and then at least once per week while the patient remains on the medication. The frequency of ECG monitoring could revert to the standard schedule if no QTc prolongation has been noted during 4 weeks of co-administration of a drug from Appendix C, Table 2. The electrolytes should be maintained within the normal range using supplements if necessary.

Effective with Amendment I, Appendix C has been updated to reflect additional drugs that might be associated with Torsades de Pointes but at this time lack substantial evidence of Torsades de Pointes. If after reviewing the updated list in Table 2, Appendix C, the investigator finds that any ongoing patient is now taking a Group 2 drug, the investigator is to manage the patient immediately as follows:

- The investigator should switch the patient to an alternative drug as soon as possible.
- If it is not possible to switch the patient to an alternative drug, the investigator must begin monitoring the patient according to instruction provided in first paragraph of this section.

This monitoring includes additional ECGs and laboratory assessments of electrolytes to ensure the patient's safety.

3.6.5.3 Other medication than described in Sections 3.5.5.1 and 3.5.5.2 which is considered necessary for the patient's safety and well-being may be given at the discretion of the investigator.

Effective with Amendment I, Appendix C has been updated to reflect the most current list of drugs that Prolong the QT Interval and/or Induce Torsades de Pointes. If the patient is in need of a drug previously found on the Group 1 or Group 2 list (Appendix C) but the drug is no longer on either list on Appendix C, it is acceptable to prescribe such a drug to the patient after the Amendment approval.

Supportive care measures and symptomatic treatment for any treatment-associated toxicity may be instituted once the first signs of toxicity occur (see Section 3.3 and Section 4 for guidance on toxicity management).

3.7 Surgical Guidelines

Elective surgical procedures (dental extractions, mediport placement) for patients enrolled on study will be scheduled during the last week of a cycle in order to avoid the nadir periods for leukocytes and platelets. All procedures should be done only when counts are sufficiently recovered to lessen any risk of infection and or bleeding. Radio-frequency ablation (RFA) will be allowed for symptomatic relief of pain.

3.8 Radiation Therapy Guidelines

No concurrent radiation therapy will be allowed on study.

3.9 Off-Treatment Criteria

- **Toxicity:** Patients who develop a vandetanib and/or bortezomib-related DLT (Section 3.1) that does not recover to grade ≤ 1 in ≤ 14 days OR who develop a vandetanib and/or bortezomib-related DLT on dose level -1 doses will discontinue protocol therapy. See Sections 3.1 to 3.3 for criteria on discontinuation of vandetanib for hypertension, QTc prolongation, and skin toxicity.
- **Progressive Disease:** Patients with clinical or radiographic evidence of progressive disease will be removed from study (see Section 5.2). If possible, tumor progression should be documented radiographically.
  Note: At the discretion of the principal investigator in consultation with other physicians involved in the care of the patient, vandetanib may be continued after progressive disease has been documented and recorded as such in the research chart. Continuation of vandetanib will be possible if in the opinion of those involved in the care of the patient, the patient is tolerating therapy well and the pace of disease progression appears to be reduced when compared to that before therapy began. The reduction in the pace of disease must be considered meaningful such that it is felt the therapy is providing benefit to the patient, and might, if continued, provide further benefit. This policy recognizes that there are no other approved therapies for this disease, and if benefit is being achieved it might be in the best interest of the patient to continue receiving a therapy that is well-tolerated.

- **Other Medical Reason:**
  - The development of a concurrent serious medical condition that might preclude or contraindicate the further administration of vandetanib.
  - It is deemed in the best interest of the patient, as determined by the Principal Investigator. The reasons for discontinuation of study agents should be noted in the patient's medical record.
  - Protocol non-compliance or inability to follow protocol instructions as determined by the Principal Investigator.

3.10 Off-Treatment Evaluation:

The following tests or procedures should be performed, if possible, immediately prior to the time a patient comes off study regardless of the reason, unless the test or procedures have been performed within the past two weeks.

- Physical examination
- Performance status
- Assessment of clinical toxicity/adverse events
- Complete blood count with differential and platelet count
- Electrolytes, BUN, creatinine, calcium, magnesium, phosphorus, uric acid, ALT, total and direct bilirubin, alkaline phosphatase, albumin, and creatine kinase.
- Serum CTN and CEA drawn after a 12 hour fast, placed on ice and sent to the lab immediately.
- Radiographic evaluation of measurable or evaluable disease

3.11 Post-treatment Follow-Up

An objective of this study is to determine the progression-free survival and overall survival in adults treated with this combination of drugs. If a patient is removed from treatment for a reason other than disease progression, they will continue to be followed at 3 - 4 month intervals in order to assess their status. This follow-up may be conducted in person or remotely via phone calls and written records from the patient and their local physician. Follow-up will continue until such time that the patient has disease progression or death. These patients will remain ‘on-study’ but ‘off-treatment’ during this period of follow-up.

3.12 Off Study Criteria

- Patient withdrawal of consent. Reasons must be noted on the patient's medical record.
- Lost to follow up.
- Disease progression requiring treatment or death
  Note: Every attempt will be made to collect data on survival even if a patient has met “off-study” criteria.

Off-Study Procedure: Authorized staff must notify Central Registration Office (CRO) when a patient is taken off-study. An off-study form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and faxed to 301-480-0757.

4 SUPPORTIVE CARE ISSUES

4.1 Cutaneous

4.1.1 Preventive measures for cutaneous toxicity:

It is strongly recommended that all patients follow a program of sun protective measures while receiving study therapy and for 3 - 4 weeks after discontinuing study therapy. The aim is to reduce the risk of development of cutaneous toxicity, minimize its severity, and reduce the need for dose reduction of study therapy.

4.1.2 Suggested regimens for the management of cutaneous toxicities:

4.1.2.1 A variety of agents can be used to manage skin rashes. These include mild to moderate strength steroid creams, topical or systemic antibiotics, and systemic antihistamines. Topical antihistamines and retinoid creams are not recommended because of drying and/or irritating effects on the skin. They are only to be used with caution when necessary. Possible topical treatments include, but are not limited to those that contain dimethicone, which is a moisture barrier that reduces dry skin. Application of colloidal oatmeal lotions may be beneficial before moving to medication containing treatments.

4.1.2.2 Possible products include, but are not limited to topical hydrocortisone 1% or 2.5% cream, fluocinolone, Clindamycin 1% gel, Pimecrolimus 1% cream, Doxycycline, Minocycline or Tetracycline.

4.1.2.3 Consultation with Dermatology is encouraged to assist in the selection of treatment.

4.2 Gastrointestinal (GI) - Nausea/Vomiting

4.2.1 Preventive measures for nausea and/or vomiting:

4.2.1.1 The dose of vandetanib may be repeated if emesis occurs within 15 minutes of taking the dose.

4.2.1.2 Nausea, vomiting, or both may be controlled with antiemetic therapy. In subjects who have emesis and are unable to retain vandetanib, every attempt should be made to obtain control of nausea and vomiting using conventional antiemetic drugs. There is a risk that the use of 5HT-3 antagonists including ondansetron, granisetron, palonosetron and tropisetron may prolong QTc interval; therefore these agents are prohibited. See Appendix C for a list of agents that prolong the QTc. Agents that may be tried first include the following: prochlorperazine, metoclopramide, lorazepam or diphenhydramine

4.2.2 Suggested regimen for the management of nausea and/or vomiting:

4.2.2.1 Nausea and vomiting may be controlled with antiemetic therapy. There is a risk that the use of 5HT-3 antagonists including ondansetron, granisetron, palonosetron and tropisetron may prolong QTc interval; therefore these agents are prohibited. See Appendix C for a list of agents that prolong the QTc. Agents that may be tried first include the following: prochlorperazine, metoclopramide, lorazepam or diphenhydramine.

4.2.2.2 Electrolytes should be closely monitored in the event of persistent diarrhea. Vandetanib should be held in patients who develop electrolyte abnormalities from diarrhea until the

electrolyte abnormalities are corrected because of the risk of QTc prolongation and subsequent arrhythmias.

4.3 Gastrointestinal (GI) - Diarrhea

4.3.1 Preventive measures for diarrhea:

Diarrhea that occurs after initiation of vandetanib is likely to be treatment-related and should be treated symptomatically with standard medications to avoid dose modification or interruption, if possible. An increase in the frequency of stools such that the patient is having two additional stools per day above baseline and these are loose in character should prompt the institution of an anti-diarrheal regimen. Part of this regimen should include electrolyte supplementation with regular laboratory monitoring, when appropriate, to maintain electrolytes within normal limits and prevent an increased risk of QTc prolongation that might occur with vandetanib.

4.3.2 Suggested regimen for the management of diarrhea:

4.3.2.1 If diarrhea develops, and does not have an identifiable cause other than vandetanib or bortezomib therapy, administer loperamide 2 mg p.o. q 2 h while awake and loperamide 4 mg p.o q 4 h at night until the diarrhea stops. If the diarrhea recurs within 24 h of stopping loperamide, then restart and continue loperamide until the patient is free of diarrhea for 12 hours, at which time the loperamide will be discontinued. This regimen can be repeated for each diarrheal episode. The occurrence of liquid stools after a 24 h diarrhea-free period will be considered a new episode. NOTE: Although this dosage regimen may exceed the usual dosage recommendations (16 mg/day) for loperamide, it is the dosing regimen specified for diarrhea associated with irinotecan administration and has been successfully and safely utilized

4.3.2.2 If a patient develops blood or mucus in the stool, dehydration or hemodynamic instability, or if diarrhea persists > 48 h despite loperamide: discontinue loperamide and hospitalize the patient for treatment with IV fluids as needed.

4.3.2.3 For persistent diarrhea, other potentially helpful treatments may also be administered, such as somatostatin analogues, propantheline, tincture of opium etc.

4.3.2.4 Electrolytes should be closely monitored in the event of persistent diarrhea. Vandetanib should be held in patients who develop electrolyte abnormalities from diarrhea until the electrolyte abnormalities are corrected because of the risk of QTc prolongation and subsequent arrhythmias.

4.3.3 Management of MTC-Related Diarrhea

Because diarrhea may be a component of MTC with elevated CTN, no dose modifications will be made for pre-existing cases of diarrhea. Patients who are receiving symptomatic treatment for diarrhea at study entry can continue the treatment while on study. If CTN levels are elevated at study entry in these patients and the levels drop by > 50% on vandetanib therapy, an attempt should be made to taper or discontinue the symptomatic anti-diarrheal therapy. Adults with MTC and CTN-related diarrhea had improvement in diarrhea on vandetanib, so symptomatic treatment for MTC-related diarrhea should not be started after study entry for at least 2 weeks to determine whether vandetanib could alleviate the diarrhea.
Note: Patients should not be treated with short- or long-acting octreotide while on study because it may have an independent therapeutic effect on the biomarker endpoints (CTN and CEA).

4.4 Hypertension

4.4.1 Preventive measures for hypertension:

Patients who develop CTCAE grades 1 - 3 hypertension may continue on therapy if blood pressure is controlled on antihypertensive medication. If blood pressure cannot be stabilized with increased antihypertensive medication, study treatment must be discontinued and cannot be resumed until blood pressure is controlled to baseline level.

4.4.2 Suggested regimen for the management of hypertension:

Note: The recommendations below consider both the CTCAE grade of the hypertension as well as the patient's baseline blood pressure values

4.4.3 Single Agent Anti-Hypertensive Therapy

4.4.3.1 Patients with a persistently (> 72 h) elevated DBP that is < 100 mm Hg or ≤ 10 mm Hg above their baseline or with ≥ 2 of 3 DBP measurements on a single day that are 11 - 25 mm Hg above their baseline should be started on enalapril at a dose of 5.0 mg PO once daily.[40]

4.4.3.2 Blood pressure should be monitored 4 hours after the first dose (day 1), 24 hours after the first dose, and then every 48 hours until the DBP is ≤ 90 mm Hg or the patient's baseline x 2 measurements.

4.4.3.3 If the DBP remains elevated at ≤ 25 mm Hg above the patient's baseline and ≤ 110 mm Hg after 7 days of enalapril, the dose of enalapril can be doubled, if the patient has not experienced enalapril-related toxicity at the starting dose.

4.4.3.4 If the DBP remains elevated at ≤ 25 mm Hg above the above the patient's baseline and ≤ 110 mm Hg after 14 days of enalapril despite a doubling of the dose, a second anti-hypertensive agent may be added. If the DBP remains elevated at ≤ 25 mm Hg above the above the patient's baseline and ≤ 110 mm Hg after 14 days of two anti-hypertensive agents, then the vandetanib should be held (see Section 4.1.1).

4.4.3.5 If the DBP increases to > 25 mm Hg above the baseline or > 110 mm Hg on ≥ 2 of 3 measurements at any time during anti-hypertensive treatment or the patient develops grade 4 hypertension at any time, then the vandetanib should be held.

4.4.3.6 Antihypertensive therapy should be continued to maintain the DBP < 10 mm Hg or < the patient's baseline, and no more than 100 mm Hg or < 10 mm Hg above the patient's baseline.

5 DATA COLLECTION and EVALUATION

5.1 Data Collection

Clinical data will be entered into the NCI C3D electronic database at least once every 2 weeks when patients are enrolled on the trial. Protocol-specific electronic Case Report Forms (eCRFs) will be developed for this trial in C3D.

The PI will be responsible for overseeing entry of data into an in-house password protected electronic system and ensuring data accuracy, consistency and timeliness. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All human subjects personally identifiable information (PII) as defined in accordance to the Health Insurance Portability and Accountability Act, eligibility

and consent verification will be recorded. Primary data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

End of study procedures: Data will be stored in locked cabinets and in a password protected database until it is no longer of scientific value.

Loss or destruction of data: Should we become aware that a major breech in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

Data will not be distributed outside NIH without IRB notification.

Dr. Fojo will continue to have access to the data for purposes of data analysis and publication when he is at Columbia University. He will have access to the data via a secure flash drive. It is also possible that data will be sent to him via encrypted email.

5.1.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, patients' diaries or evaluation checklists, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, X-rays. The investigator will permit trial-related monitoring, audits, IRB review, and regulatory inspection(s), providing direct access to source documents.

5.1.2 Case Report Forms

Data may be entered from the source documents directly into eCRFs in C3D for each patient enrolled in this study.

The principal investigator or research nurse will review the eCRFs for completeness and accuracy. Independent audits may also be conducted by NCI personnel to ensure completeness and accuracy of data in C3D.

In addition to the eCRFs the following form will be completed:

- Eligibility checklist prior to enrollment (Faxed to the Central Registration Office).

5.1.3 Data Quality Assurance

The research team will monitor each patient’s data set throughout the study. Source document review will be made against entries on the eCRF and a quality assurance check will be performed to ensure that the investigator is complying with the protocol and regulations. In addition, after eCRFs are completed by the research team (data managers), review of the data will be conducted by a research nurse or physician.

5.2 Response Criteria

To be considered as evaluable for response, a patient should have completed 8 weeks of therapy (2 cycles) and this is at least 40 days of vandetanib and 4 doses of bortezomib.

MEN2 patients with concurrent medullary thyroid cancer and pheochromocytoma who were enrolled at the Principal Investigator’s discretion per Section 2.1.2.6.1 will not be evaluable for the primary endpoint.

5.2.1 RECIST

Baseline documentation of "Target" and "Non-Target" lesions

- All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.
- The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up.
- All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total, representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline.
- Target lesions should be selected on the basis of their size (lesions with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). Lesions that are calcified or have been previously irradiated will be excluded from the target lesions.
- A sum of the longest diameter (LD) for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.
- All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence or absence of each should be noted throughout follow-up. Non-target lesions may include non-measurable lesions, which include: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease.

Evaluation of Target Lesions

Complete Response (CR):	Disappea***rance of all targe***t lesions
Partial Response (PR):	At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD
Progressive Disease (PD):	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
Stable Disease (SD):	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of Non-Target Lesions

Complete Response (CR):	Disappearance of all non-target lesions and normalization of tumor marker level. Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.
Incomplete Response/ Stable Disease (SD):	Persistence of one or more non-target lesion(s) or maintenance of tumor marker level above the normal limits

Progressive Disease (PD):	Appearance of one or more new lesions or unequivocal progression of existing non-target lesions. Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

Confirmation of Response

- The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.
- To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.
- In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum 8 weeks from study entry.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Evaluation of Best Overall Response

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥ 4 weeks confirmation
CR	Non-CR/ Non-PD	No	PR	≥ 4 weeks confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	Documented at least once ≥ 4 weeks from baseline
PD	Any	Yes or No	PD	No prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

Duration of Response

Duration of overall response:	The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented, taking as reference for progressive disease the smallest measurements recorded since the treatment started. The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.
Duration of stable disease:	Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started. To be considered clinically relevant, the duration of stable disease must be ≥ 24 weeks.

Progression-Free Survival (PFS)
PFS is defined as the duration of time from start of treatment to time of progression.

5.2.2 Biomarker Response Criteria

See Section 3.6 for calcitonin (CTN) and CEA sampling time points. Only patients with average pre-treatment CTN and CEA levels that are > 2 times the ULN are evaluable for biomarker response. Response criteria for CEA and CTN are:

- **Complete Response (CR):** Normalization (≤ ULN) of CEA or CTN level following treatment, confirmed with a repeat CEA/CTN level at least 4 weeks apart.
- **Partial Response (PR):** A ≥ 50% decrease in the CEA or CTN level relative to the baseline level, confirmed with a repeat CEA/CTN level at least 4 weeks apart.
- **Progressive Disease (PD):** A ≥ 50% increase in the CEA or CTN relative to the baseline level, confirmed with a repeat CEA/CTN level at least 4 weeks apart.
- **Stable disease (SD):** < 50% increase or decrease in CTN or CEA level relative to the baseline level.

- To be assigned a status of biomarker PR or CR, changes in serum tumor biomarker level must be confirmed by repeat measurement, which should be performed ≥ 4 weeks after the criteria for PR or CR are first met.
- For stable disease, follow-up CEA/CTN levels must have met the stable disease criteria at least once after study entry at a minimum interval defined as 12 weeks.
- Each patient's **best CEA response and best CTN response** will be calculated from the average (of 2) baseline measurement and lowest measurement during treatment (confirmed by a second measurement ≥ 4 weeks later). Responders are those subjects with a best biomarker response of CR or PR.

5.2.3 Clinical Response Criteria (Symptomatic Diarrhea)

Patients who present with **diarrhea** attributable to elevated CTN will be followed for symptomatic response after treatment with vandetanib and bortezomib. Baseline stool frequency will be the average of daily stool counts during a 7-day period immediately prior to starting vandetanib and bortezomib. Baseline stool consistency (formed, loose or partially formed, watery) will be the consistency most frequently observed during a 7-day period immediately

prior to starting vandetanib. Only patients with a stool frequency of ≥ 5/day and a stool consistency of watery will be evaluable for clinical response. Symptomatic response will be determined from a change in stool consistency (watery, loose or partially formed, formed) and frequency using patient histories and patient diaries:

- **Complete Response (CR):** an average of 0 - 2 formed stools per day for a period of at least 4 weeks.
- **Partial Response (PR):** A ≥5 0% decrease in the average stool frequency relative to baseline and a change in stool consistency from watery to loose (partially formed) for a period of at least 4 weeks.
- **No Response (NR):** Criteria for CR or PR not met.
  - Information on stool frequency will be self-reported by the subject using the patient diary (Appendix D). Subjects will be asked to report their daily stool frequency and consistency.
  - Responders are those subjects who achieve a clinical response of CR or PR.

5.2.4 Statistics and Feasibility

Following completion of the phase I dose escalation portion of the trial, the primary objectives of this study are to determine 1) if vandetanib plus bortezomib will be associated with a modestly high response rate in patients with MTC which is greater than that of vandetanib alone; and 2) secondarily if vandetanib plus bortezomib will be associated with a modestly higher progression free survival in patients with MTC which is greater than that of vandetanib alone.

The trial will use a conventional 3 - 6 patient dose escalation scheme for a maximum of 4 dose escalation levels. Thus, depending on the number of patients identified with DLT at a given dose level, up to 24 patients may be required to be enrolled to determine the MTD.

Data from a phase II trial of patients with MTC using vandetanib alone found 7/29 (24%) of patients having a partial response; thus it would be desirable if this could be improved upon by the combination. Once the MTD of the combination has been determined, the next portion of the study using only MTC patients will be conducted as a randomized phase II trial. This trial will be conducted using a phase 2.5 design, which is intended to detect a difference with a one tailed 0.10 test. The goal of the study is to accrue 31 and 62 patients (93 total) to the vandetanib alone arm and vandetanib +bortezomib arm respectively. This number of patients would provide 80% power to detect a difference between a 25% response rate and 50% response rate using a two-tailed Fisher exact test at the one-sided 0.10 level.

The total number of patients to possibly enroll is thus 117. This is calculated from the following:

- Dose escalation cohorts of 3 - 6 patients x 4 levels = maximum of 24 patients
- 93 MTC patients at the MTD in the randomized phase II portion of the trial

Calcitonin levels will also be obtained on all patients and explored compared to baseline in order to determine if there is a change that may be associated with the use of this agent.

For all patients with MTC, progression free survival will be evaluated using Kaplan-Meier curves, as a secondary endpoint. This curve will be compared informally to results from vandetanib alone.

A number of biomarkers and other parameters will also be obtained and compared to clinical response. Levels of the following parameters at various time points at which they are obtained, as well as changes from baseline, will be compared between patients whose tumors are scored as

responding to therapy and those whose tumors are not scored as responding to treatment: RET, EGFR, VEGFR, somatostatin receptor, microtubule stabilization, RET inhibition. These analyses will be done using tumor samples from patients with a diagnosis of MTC treated at the MTD. Furthermore, these analyses will be done in an exploratory manner using a Wilcoxon rank sum test, without formal adjustment for multiple comparisons, although the results will be presented in the context of the exploratory nature of the analysis.

5.3 Multi-institutional guidelines

At the outset this is a single-institution study and the multi-institutional guidelines do not apply.

5.4 Data and Safety Monitoring Plan:

Adverse events observed in patients enrolled on the trial will be monitored in real time by the Principal, Adjunct Principal and Associate Investigators, and attribution of these events to vandetanib and or bortezomib will be determined at the end of each treatment cycle in each subject. The clinical research team (PI, adjunct PI, AIs, research nurses, data managers) will meet on a regular basis when patients are being actively treated on the trial to discuss each patient in detail and ensure that all events are graded appropriately, and that the attribution to study drug is correct. Decisions about dose level (escalation) and enrollment will be made based on the toxicity data from prior patients. Internal audits of the trial will be performed by an independent team of data managers to ensure compliance with the protocol and to ensure that the data recorded in the CRFs accurately reflects the data in the source documents. This trial will not require monitoring by a DSMB.

6 HUMAN SUBJECTS PROTECTION

6.1 Rationale for Subject Selection

Patients of both genders, from all racial and ethnic groups are eligible for this trial if they meet the eligibility criteria outlined in Section **2.1**. There is no clinical information that suggests differences in vandetanib or bortezomib metabolism, disposition or MTC response among racial or ethnic groups or between the genders, indicating that results of the trial will be applicable to all groups. This Phase I/II trial of vandetanib and bortezomib will be conducted in adults with solid tumors, including those with MTC. Efforts will be made to extend the accrual to a representative group from this population, but with a rare disease and with a limited accrual of patients, a balance must be struck between completing the trial in a timely fashion on the one hand and the need to explore gender, racial, and ethnic aspects of clinical research on the other. If differences in outcome that correlate to gender, racial, or ethnic identity are noted, accrual may be expanded or additional studies may be performed to investigate those differences more fully. We anticipate that accrual to this trial can be completed in 18 months to 2 years.

6.2 Participation of Children

There is currently an independent study in the Pediatric Oncology Branch examining vandetanib in children with hereditary MTC.

6.3 Evaluation of Benefits and Risks/Discomforts

The primary risk to patients participating in this research study is from toxicity of vandetanib and bortezomib.

In adults, vandetanib has been relatively well tolerated. The most common adverse events have been rash, diarrhea and asymptomatic QTc prolongation, which are reversible and generally can be alleviated by dose reduction. The starting dose is based on the results of previous adult phase I trials of vandetanib and planned dose escalation will not exceed the dosing range which demonstrated clinical benefit and which was tolerated in adults. The benefits of this molecularly targeted agent in hereditary MTC have been demonstrated in adults. The objective response rate (PRs) by RECIST is approximately 30% and the majority of patients have substantial reductions in serum calcitonin levels that are felt to contribute to MTC-related diarrhea.

Bortezomib is approved by the FDA for the treatment of patients with relapsed MM The most common adverse events have been sensory neuropathy, hypotension, gastrointestinal disturbances including nausea, diarrhea, constipation and vomiting, as well as thrombocytopenia. Both the individual doses as well as the total dose per cycle are substantially less than those approved by the FDA and now widely used in patients with MM.

The protocol administers vandetanib in combination with bortezomib and the possibility that unexpected toxicities may occur cannot be excluded, although a priori there is no reason to suspect this, not are the toxicities of these agents discernibly overlapping, with the exception of nausea, which is not expected to be a major toxicity. Toxicity data from the first dose level will be collected and reviewed in real time to ensure that there were no severe (dose-limiting) toxicities prior to escalating to the second dose level (intra-patient dose escalation will also be allowed provided the patient tolerates any given dose level without grade 3/4 toxicities).

The protocol incorporates percutaneous core needle biopsies of superficial tumors with minimal risk to surrounding vital structures in order to obtain tumor specimens for research purposes in patients who meet the eligibility criteria in Section **2.1**. These research specimens will be used to assess the mutational status of the RET gene mutations in the tumor (compared to germ line mutations) at the onset of treatment. These specimens will also be used to assess pharmacodynamic effects of bortezomib and may assess the effect of vandetanib (*in vivo*) on gene expression in tumors (see Section**3.4.**2 and **Appendix A: Laboratory Methodology**). There would be no immediate direct benefit to the subject who undergoes a biopsy on this trial. The most likely site for biopsies would be superficial lymph nodes or other sites in the neck.

6.4 Risks/Benefits Analysis

No children or adolescents will be entered on this trial. A primary risk to patients participating in this research study is from toxicity of vandetanib, an investigational agent, and also from bortezomib, an FDA-approved agent. The starting doses of both agents are below the level that experience has shown in well tolerated in adults. Cohorts will be escalated only after it has been determined via the current cohort, that the current level is tolerable.

One of the primary objectives of this trial is to assess the activity of daily oral vandetanib and a day 1, 4, 8 & 11 administration schedule for bortezomib in adults with solid tumors with an emphasis on patients with hereditary medullary thyroid carcinoma (MTC). Thus all patients entered will be treated with therapeutic intent and response to the therapy will be closely monitored. The potential benefits from this therapy are disease stabilization or shrinkage and a reduction in symptoms caused by the MTC, such as diarrhea, and possibly tumor shrinkage inpatient with other tumors. Therefore, although the phase I/II component of this protocol involves a greater than minimal risk, it presents the prospect for direct benefit to individual patients (Category 2).

The biopsies being performed to obtain tumor samples for research purposes will not provide immediate direct benefit to the participants but will potentially provide value data regarding the mechanisms of action of bortezomib and interaction between bortezomib and vandetanib.

6.5 Informed Consent/Assent Process and Documentation

The treatment consent will explain the investigational nature and research objectives of this trial, the procedures and treatment involved and the attendant risks, discomforts and benefits, and potential alternative therapies. For those patients with a superficial tumor that can be safely biopsied, the investigator will also explain the purpose, risks, and lack of direct benefit from participating in the series of biopsies, and the optional nature of the procedure will be explained (i.e., refusing participation will not impact on their eligibility to participate in the treatment component of the trial). These issues will be carefully explained to the patient and a signature will be obtained on the informed consent document prior to entry onto the study. Senior investigators from the GMB will lead this discussion. Patients will be allowed ample time to review the consent form and have all their questions answered. A copy of the signed consent form will be give to each patient.

Patients who agree to undergo biopsies will have a separate biopsy consent obtained by the physician performing the biopsy.

7 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

7.1 Definitions

7.1.1 Adverse Event

An adverse event is defined as any reaction, side effect, or untoward event that occurs during the course of the clinical trial associated with the use of a drug in humans, whether or not the event is considered related to the treatment or clinically significant. For this study, AEs will include events reported by the patient, as well as clinically significant abnormal findings on physical examination or laboratory evaluation. A new illness, symptom, sign or clinically significant laboratory abnormality or worsening of a pre-existing condition or abnormality is considered an AE. All AEs must be recorded on the AE case report form unless otherwise noted above in Section **5.1**.

All AEs, including clinically significant abnormal findings on laboratory evaluations, regardless of severity, will be followed until return to baseline or stabilization of event. Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of at least possibly related to the agent/intervention should be recorded and reported as per sections **7.3** and **7.4**.

An abnormal laboratory value will be considered an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Is associated with clinical signs or symptoms
- Requires treatment or any other therapeutic intervention
- Is associated with death or another serious adverse event, including hospitalization.
- Is judged by the Investigator to be of significant clinical impact

- If any abnormal laboratory result is considered clinically significant, the investigator will provide details about the action taken with respect to the test drug and about the patient's outcome.

7.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

7.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application. "Unexpected", also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

7.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

7.1.5 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.1.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

7.1.7 Life-threatening adverse drug experience

Any adverse event or suspected adverse reaction that places the patient or subject, in the view of the investigator or sponsor, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that had it occurred in a more severe form, might have caused death.

7.1.8 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

7.1.9 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

7.1.10 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and (b) the characteristics of the subject population being studied; **AND**

- Is related or possibly related to participation in the research; **AND**

- Suggests that the research places subjects or others at a *greater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

7.2 Adverse Event Reporting Criteria

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized until December 31, 2010 for AE reporting. CTCAE version 4.0 will be utilized beginning January 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

All data collection and reporting will be coordinated through:

Maureen Edgerly, RN
National Cancer Institute (NCI)
Building 10
Room 12N226
10 Center Drive
Bethesda, Maryland 20892
(301) 435-5604
edgerlym@pbmac.nci.nih.gov

7.3 NCI-IRB Reporting

7.3.1 NCI-IRB Expedited Reporting of Unanticipated Problems and Deaths

The protocol PI will report to the NCI-IRB:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All serious non-compliance

Reports must be received by the NCI-IRB within 7 working days of PI awareness via iRIS.

NCI, IRB contact information:
E-mail- nciirbadmin@mail.nih.gov
Mail-Building 82/Room 115,
9030 Old Georgetown Road
Bethesda, MD 20814
Fax 301-480-0106

7.3.2 NCI-IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NCI-IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:

- All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
- All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
- All Grade 5 events regardless of attribution;
- All Serious Events regardless of attribution.

NOTE: Grade 1 events are not required to be reported.

7.3.3 NCI-IRB Reporting of IND Safety Reports

Only IND Safety Reports that meet the definition of an unanticipated problem will need to be reported to the NCI IRB.

7.4 IND SPONSOR REPORTING CRITERIA: ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (and the characteristics of an observed AE will determine whether the event requires expedited (via CTEP-AERS) reporting **in addition** to routine (via CTMS or CDUS) reporting.

7.4.1 Comprehensive Adverse Events and Potential Risks (CAEPR) Lists

CAEPRs for CTEP-Supplied Investigational Agent(s)

Comprehensive Adverse Events and Potential Risks list (CAEPR)
for
PS-341 (Bortezomib, Velcade, NSC 681239)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2084 patients.* Below is the CAEPR for PS-341 (bortezomib, Velcade).
NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.5, June 30, 2014[1]

Adverse Events with Possible Relationship to PS-341 (Bortezomib, Velcade) (CTCAE 4.0 Term) [n= 2084]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***
CARDIAC DISORDERS			
		Heart failure	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 3)***
Constipation			***Constipation (Gr 3)***
Diarrhea			***Diarrhea (Gr 3)***
	Dyspepsia		***Dyspepsia (Gr 2)***
	Gastrointestinal hemorrhage[2]		
		Gastrointestinal perforation[3]	
	Ileus		***Ileus (Gr 3)***
Nausea			***Nausea (Gr 3)***
Vomiting			***Vomiting (Gr 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema limbs		***Edema limbs (Gr 3)***
Fatigue			***Fatigue (Gr 3)***
Fever			***Fever (Gr 3)***
INFECTIONS AND INFESTATIONS			

Adverse Events with Possible Relationship to PS-341 (Bortezomib, Velcade) (CTCAE 4.0 Term) [n= 2084]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
Infection[4]			***Infection[4] (Gr 3)***
INVESTIGATIONS			
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight loss		
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 3)***
	Dehydration		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		***Arthralgia (Gr 2)***
	Back pain		***Back pain (Gr 2)***
	Bone pain		***Bone pain (Gr 2)***
	Musculoskeletal and connective tissue disorder - Other (muscle spasms)		
	Myalgia		***Myalgia (Gr 3)***
	Pain in extremity		***Pain in extremity (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 3)***
	Headache		***Headache (Gr 2)***
		Leukoencephalopathy	
	Neuralgia		***Neuralgia (Gr 3)***
	Paresthesia		
Peripheral motor neuropathy			***Peripheral motor neuropathy (Gr 3)***
Peripheral sensory neuropathy			***Peripheral sensory neuropathy (Gr 3)***
		Reversible posterior leukoencephalopathy syndrome	
PSYCHIATRIC DISORDERS			
	Anxiety		
	Insomnia		***Insomnia (Gr 2)***
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
		Adult respiratory distress syndrome	
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Pharyngeal mucositis		***Pharyngeal mucositis (Gr 2)***
		Pulmonary hypertension	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Rash maculo-papular		***Rash maculo-papular (Gr 3)***
VASCULAR DISORDERS			
	Hypotension		***Hypotension (Gr 3)***

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[3]Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Also reported on PS-341 (bortezomib, Velcade) trials but with the relationship to PS-341 (bortezomib, Velcade) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (hematocrit low); Blood and lymphatic system disorders - Other (lymphadenopathy); Disseminated intravascular coagulation; Febrile neutropenia; Hemolytic uremic syndrome; Leukocytosis
CARDIAC DISORDERS - Acute coronary syndrome; Asystole; Atrial fibrillation; Atrial flutter; Atrioventricular block complete; Cardiac arrest; Cardiac disorders - Other (cardiac amyloidosis); Cardiac disorders - Other (cardiomegaly); Chest pain - cardiac; Left ventricular systolic dysfunction; Mobitz type I; Myocardial infarction; Palpitations; Pericardial effusion; Pericardial tamponade; Pericarditis; Right ventricular dysfunction; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia; Ventricular arrhythmia; Ventricular fibrillation; Ventricular tachycardia
EAR AND LABYRINTH DISORDERS - External ear inflammation; Hearing impaired; Tinnitus
ENDOCRINE DISORDERS - Hypothyroidism
EYE DISORDERS - Blurred vision; Conjunctivitis; Dry eye; Extraocular muscle paresis; Eye disorders - Other (chalazion); Eye disorders - Other (choroidal effusion); Eye disorders - Other (conjunctival hemorrhage); Eye disorders - Other (retinal hemorrhage with bilateral vision impairment); Keratitis; Watering eyes
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Bloating; Colitis; Dry mouth; Duodenal ulcer; Dysphagia; Enterocolitis; Esophagitis; Flatulence; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (colonic wall thickening); Gastrointestinal disorders - Other (early satiety); Gastrointestinal disorders - Other (eructation); Gastrointestinal disorders - Other (ileitis); Gastrointestinal disorders - Other (ischemic bowel); Gastrointestinal disorders - Other (mouth/tongue ulceration); Gastrointestinal disorders - Other (retching); Gastrointestinal pain; Gingival pain; Hemorrhoids; Mucositis oral; Oral pain; Pancreatitis; Small intestinal obstruction; Typhlitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (catheter related complication);General disorders and administration site conditions - Other (hepato-renal syndrome); Hypothermia; Injection site reaction; Malaise; Multi-organ failure; Non-cardiac chest pain; Pain; Sudden death NOS
HEPATOBILIARY DISORDERS - Hepatic failure; Hepatobiliary disorders - Other (hepatitis); Hepatobiliary disorders - Other (portal vein thrombosis); Hepatobiliary disorders - Other (VOD)
IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Cytokine release syndrome
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Fall; Fracture; Vascular access complication
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; CD4 lymphocytes decreased; CPK increased; Carbon monoxide diffusing capacity decreased; Cardiac troponin I increased; Cardiac troponin T increased; Cholesterol high; Creatinine increased; Ejection fraction decreased; GGT increased; INR increased; Investigations - Other (albumin); Investigations - Other (BUN); Investigations - Other (low chloride);

Investigations - Other (pancytopenia); Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight gain; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Metabolism and nutrition disorders - Other (hypoproteinemia); Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Avascular necrosis; Buttock pain; Chest wall pain; Generalized muscle weakness; Joint range of motion decreased; Muscle weakness lower limb; Musculoskeletal and connective tissue disorder - Other (cramping); Osteonecrosis of jaw
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Acoustic nerve disorder NOS; Akathisia; Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Dysphasia; Edema cerebral; Encephalopathy; Facial muscle weakness; Facial nerve disorder; Hypersomnia; Intracranial hemorrhage; Ischemia cerebrovascular; Lethargy; Memory impairment; Nervous system disorders - Other (autonomic neuropathy); Nervous system disorders - Other (Bell's palsy); Nervous system disorders - Other (cranial palsy); Nervous system disorders - Other (dysautonomia); Nervous system disorders - Other (L sided facial droop); Nervous system disorders - Other (paralysis); Nervous system disorders - Other (polyneuropathy); Nervous system disorders - Other (spinal cord compression); Nervous system disorders - Other (tongue paralysis); Presyncope; Seizure; Somnolence; Stroke; Syncope; Tremor; Vasovagal reaction
PSYCHIATRIC DISORDERS - Agitation; Confusion; Delirium; Depression; Personality change; Psychosis
RENAL AND URINARY DISORDERS - Bladder spasm; Chronic kidney disease; Cystitis noninfective; Hematuria; Proteinuria; Renal and urinary disorders - Other (bilateral hydronephrosis); Renal and urinary disorders - Other (calculus renal); Renal and urinary disorders - Other (glomerular nephritis proliferative); Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Aspiration; Atelectasis; Bronchopulmonary hemorrhage; Bronchospasm; Epistaxis; Hiccups; Hypoxia; Laryngeal edema; Mediastinal hemorrhage; Pharyngolaryngeal pain; Pleural effusion; Pleuritic pain; Pneumonitis; Postnasal drip; Pulmonary edema; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (obstructive airways disease); Respiratory, thoracic and mediastinal disorders - Other (pleurisy); Respiratory, thoracic and mediastinal disorders - Other (respiratory distress); Respiratory, thoracic and mediastinal disorders - Other (tachypnea); Tracheal mucositis; Tracheal stenosis; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Bullous dermatitis; Dry skin; Erythema multiforme; Erythroderma; Hyperhidrosis; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Pruritus; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (angioedema); Skin and subcutaneous tissue disorders - Other (leukoclastic vasculitis); Skin and subcutaneous tissue disorders - Other (Skin lesion NOS); Urticaria
VASCULAR DISORDERS - Capillary leak syndrome; Flushing; Hematoma; Hypertension; Thromboembolic event; Vascular disorders - Other (trach site); Vasculitis

Note: PS-341 (bortezomib; Velcade) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.4.2 Adverse Event List(s) for Vandetanib (CAPRELSA, ZD6474)

7.4.2.1 Emerging Safety Profile

As a result of the updated Vandetanib (CAPRELSA, ZD6474) Investigator's Brochure, Edition 9, new clinical trial information has been included. Reported adverse events that may be related to vandetanib are listed below by body system:

- **Cardiovascular** – abnormal ECG (with or without QT prolongation; i.e. either T-wave or ST-segment changes consistent with repolarization abnormalities), torsade-de-pointes and ventricular tachycardia (both at 300 mg daily dose) and hypertension.

- **Central Nervous System** – headache, reversible Posterior Leukoencephalopathy Syndrome
- **Digestive** – constipation, diarrhea, nausea, vomiting
- **Hematologic and Lymphatic** – ecchymosis and thrombocytopenia
- **Investigations** – elevated liver function tests (generally CTC/CTCAE grade 1-2 , preliminary data suggests these are reversible, in some cases while continuing therapy), weight loss
- **Metabolic and Nutritional** – dehydration, hypokalemia, hypomagnesemia, hypophosphatemia, anorexia
- **Skin and Appendages** – acneiform rash, pruritus, macular or macupapular rash (generalized or localized), localized and generalized erythema, photosensitivity reaction, sweating. On occasion (especially when given with chemotherapy) these have progressed to more serious conditions to include exfoliative dermatitis, skin desquamation, erythroderma, toxicoderma, toxic epidermal necrolysis, erythema multiforme
- **Respiratory** – interstitial lung disease, pulmonary embolism. A very small number of patients with lung cancer receiving vandetanib have developed shortness of breath and cough due to inflammation or scar tissue formation in the lungs (although this could be due to the underlying disease)
- **Renal** – proteinuria, hematuria
- **Vascular** – arterial ischaemic events (including myocardial infarction, stroke, peripheral ischaemia), venous thromboembolism. A small number of patients receiving vandetanib have developed blood clots affecting the legs or lungs (may have been due to the patient's cancer or other illness at the time, however it is considered possible that vandetanib might increase the risk for developing blood clots)
- **Psychiatric** – anxiety, depression, insomnia
- **General** – asthenia, fatigue

Note: Above text taken from Vandetanib, ZD6474, Investigator's Brochure, Edition Number 9,
March 200. For additional details on vandetanib, please refer to the current Vandetanib Investigator's Brochure.

7.4.2.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized until December 31, 2010 for AE reporting. CTCAE version 4.0 will be utilized beginning January 1, 2011. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).
- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' *(see Section X.1 above)* for expedited reporting purposes only. 'Expected' AEs (the ASAEL) are ***bold and italicized*** in the CAEPR *(Section X.1.1)*.
- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.

- Unlikely – The AE *is doubtfully related* to the study treatment.
- Unrelated – The AE *is clearly NOT related* to the study treatment.

7.4.3 Expedited Adverse Event Reporting

Expedited AE reporting for this study must use CTEP-AERS (CTEP Adverse Event Reporting System), accessed via the CTEP home page (http://ctep.cancer.gov). The reporting procedures to be followed are presented in the "CTEP, NCI Guidelines: Adverse Event Reporting Requirements" which can be downloaded from the CTEP home page (http://ctep.cancer.gov).

A 24-hour notification is to be made to CTEP by telephone at 301-897-7497 only when Internet connectivity is disrupted. Once Internet connectivity is restored, an AE report submitted by phone must be entered electronically into CTEP-AERS by the original submitter at the site.

This is a Phase I/II Study and during the Phase I portion of the study the following Phase I Expedited Reporting Guidelines will apply. Once the study moves into Phase II the Phase II Guidelines that follow will apply.

Expedited Reporting Guidelines – CTEP-AERS Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent on Phase 1 Trials

Phase 1 Trials

	Grade 1	Grade 2		Grade 3				Grades 4 & 5[2]
				Unexpected		Expected		
	Unexpected and Expected	Unexpected	Expected	Hospitalization				Unexpected and Expected
				Yes	No	Yes	No	
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	24-Hours; 5 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	24-Hours; 5 Calendar Days	24-Hours; 5 Calendar Days	10 Calendar Days	Not Required	24-Hours; 5 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**
CTEP-AERS 24-hour notification followed by complete report within 5 calendar days for:
- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 4 unexpected events
- Grade 5 expected events and unexpected events

[2] Although an CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

December 15, 2004

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or

prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

CTEP-AERS Reporting Requirements for Adverse Events that occur within 30 Days[1] of the Last Dose of the Investigational Agent on Phase 2 and 3 Trials

Phase 2 and 3 Trials

	Grade 1	Grade 2		Grade 3				Grades 4 & 5[2]	
	Unexpected and Expected	Unexpected	Expected	Unexpected Hospitalization		Expected Hospitalization		Unexpected	Expected
				Yes	No	Yes	No		
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hours; 5 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur greater than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**
CTEP-AERS 24-hour notification followed by complete report within 5 calendar days for:
- Grade 4 and Grade 5 unexpected events

CTEP-AERS 10 calendar day report:
- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although an CTEP-AERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

December 15, 2004

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause must be provided.
- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via CTEP-AERS within 24 hours of learning of the event followed by a complete CTEP-AERS report within 5 calendar days of the initial 24-hour report.
  - "10 calendar days" - A complete CTEP-AERS report on the AE must be submitted within 10 calendar days of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following

treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

7.4.4 Routine Adverse Event Reporting

Adverse Events **must** be reported in routine CDUS~~)~~ study data submissions. **AEs reported through CTEP-AERS must also be reported in routine study data submissions.**

AEs must be reported using the routine reporting requirements described in the table below. In general, CTEP defines routine AE reporting guidelines for Phase 1 and Phase 2 trials. During the Phase I and II portions of this study CDUS Complete Reporting will apply (based on CTEP's Coding Letter.

Clinical Data Update System (CDUS)
The CDUS is the primary repository of clinical data for CTEP, NCI.

CDUS Guidelines for Routine Adverse Event Reporting on Trials using Agent(s) under a CTEP IND

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			CDUS	CDUS	CDUS
Unlikely			CDUS	CDUS	CDUS
Possible	CDUS	CDUS	CDUS	CDUS	CDUS
Probable	CDUS	CDUS	CDUS	CDUS	CDUS
Definite	CDUS	CDUS	CDUS	CDUS	CDUS

7.4.5 Secondary AML/MDS

The AML/MDS events will be reported via CTEP-AERS (in addition to routine AE reporting mechanisms). In CTCAE v 4, the event(s) may be reported as either: 1) Leukemia secondary to oncology chemotherapy, 2) Myelodysplastic syndrome, or 3) Treatment related secondary malignancy.

7.4.6 Routine events that do not need to be recorded in C3D

The following AE do not need to be reported to CTEP or the IRB. They will not be recorded in C3D as well:
Lymphopenia, grade 1 or 2
Hypoalbuminemia, grade 1

7.5 Collaborative Agreement

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http:// ctep.cancer.gov/industry) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies

utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data".):
   a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
   b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
   c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order.. Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.
4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be

forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Regulatory Affairs Branch, CTEP, DCTD, NCI
Executive Plaza North, Suite 7111
Bethesda, Maryland 20892
FAX 301-402-1584
Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

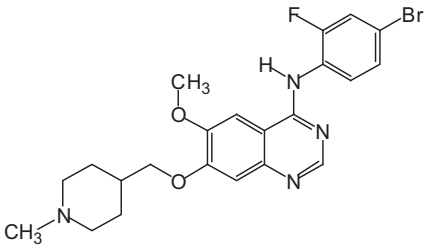
8 PHARMACEUTICAL AND INVESTIGATIONAL DEVICE INFORMATION

8.1 Vandetanib

8.1.1 Chemical Information

Chemical Name: (IUPAC): N-(4-bromo-2-fluorophenyl)-6-methoxy-7-[(1-methyl-4 piperidinyl)methoxy]-4-quinazolinamine
Other Names: ZD6474, vandetanib, CAPRELSA

Chemical Structure:



Molecular Formula: $C_{22}H_{24}BrFN_4O_2$
Molecular Weight: 475.36

8.1.2 Mechanism of Action

Vandetanib is a potent inhibitor of the tyrosine kinase activity of kinase insert domain-containing receptor (KDR), an endothelial cell receptor for vascular endothelial growth factor (VEGF), and also possesses activity against epidermal growth factor receptor (EGFR). Vandetanib is being developed clinically for its anti-angiogenic properties, but it also inhibits the enzymatic activity of RET-derived oncoproteins with an IC_{50} of 100 nM. RET inhibition is the basis for the use of vandetanib in MTC.

8.1.3 Source of Vandetanib

This study is filed under the CTEP IND for bortezomib 58443, and cross-filed to the vandetanib IND held by AstraZeneca. AstraZeneca will supply vandetanib directly to the Clinical Center.

8.1.4 Formulation of Vandetanib

The 100 mg tablets contain vandetanib, calcium hydrogen phosphate, microcrystalline cellulose, crospovidone, povidone, and magnesium stearate with a film coating containing methylhydroxypropylcellulose, polyethylene glycol 300 and titanium dioxide.

8.1.5 Storage and Stability

The tablets and bottles should be stored at room temperature in the original pack until use. Documentation indicating vandetanib was destroyed will be sent to AstraZeneca.

8.1.6 Vandetanib Administration

Vandetanib is administered orally, once daily continuously. Vandetanib can be taken without regard to food. See also Section 3.2.1 for more information. A cycle of vandetanib is defined as 28 consecutive days starting with the first day of treatment (day 1). Treatment will be administered in an outpatient setting.

8.1.7 Vandetanib Toxicity Profile

Percentage of patients with adverse events by system organ class and preferred term in vandetanib emerging safety profile.

Event	CIOMS†	Percentage of patients from study 6474IL/0003*
Cardiovascular		
QT prolongation	Very common	21%
Hypertension	Very Common	12%
Central Nervous System		
Headache	Very common	18%
Digestive		
Constipation	Very common	22%
Diarrhea	Very common	58%
Nausea	Very common	28%
Vomiting	Common	6%
Hematologic and lymphatic		
Ecchymosis	Uncommon	< 1%
Thrombocytopenia	Common	1%
Investigations		
Elevated liver function tests	Common	2 - 4%
Weight loss	Very common	12%
Metabolic		
Dehydration	Common	8%
Hypokalemia	Common	6%
Hypomagnesemia	Common	4%
Hypophosphatemia	Uncommon	< 1%
Skin/appendages		
Rash (variety of terms)	Very common	46%
Renal		
Proteinuria	Common	1%
Respiratory		
Interstitial lung disease (including pneumonitis)	Common	5%
Pulmonary embolism	Common	2%
Vascular		
Venous thromboembolism	Common	1%
General		
Asthenia	Common	8%

Event	CIOMS†	Percentage of patients from study 6474IL/0003*
Fatigue	Very common	40%

*The values reflect the frequency of events as a reported adverse event and do not include out-of-range laboratory values or abnormal vital signs. The events of hypophosphatemia and ecchymosis occurred in phase I studies, but did not occur in study 6474IL/0003; the frequency has therefore been set as <1%. The events of interstitial lung disease/pneumonitis, pulmonary embolism and venous thromboembolism occurred in study 6474IL/0003, but these events are heavily confounded by advanced cancer, previous radiation and chemotherapy, and disease progression.

†CIOMS Council for International Organization for Medical Sciences (subset of World Health Organization).

8.2 Bortezomib (Velcade, PS-341, NSC 681239)

Chemical Name: N-Pyrazinecarbonyl-L-phenylalanine-L-leucine boronic acid
Other Names: MLN341, LDP-341, Velcade®, bortezomib
Classification: Proteasome Inhibitor
CAS Registry #: 179324-69-7
Molecular Formula: $C_{19}H_{25}BN_4O_4$ **(**MW: 384.25)

8.2.1 Mechanism of action

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. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis that can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death**.** Experiments have demonstrated that bortezomib is cytotoxic to a variety of cancer cell types *in vitro*. Bortezomib causes a delay in tumor growth *in vivo* in non-clinical tumor models, including multiple myeloma.

8.2.2 Pharmacokinetics

Following intravenous administration of 1.3 mg/m^2 dose, the median estimated maximum plasma concentration of bortezomib was 509 ng/mL (range = 109-1300 ng/mL) in eight patients with MM and creatinine clearance values ranging from 31-169 mL/min. The mean elimination half-life of bortezomib after first dose ranged from 9 to 15 hours at doses ranging from 1.45 to 2.00 mg/m^2 in patients with advanced malignancies. The pharmacokinetics of bortezomib as a single agent has not been fully characterized at the recommended dose in MM patients.
Distribution: The distribution volume of bortezomib as a single agent was not assessed at the recommended dose in patients with MM. The binding of bortezomib to human plasma proteins averaged 83% over the concentration range of 100-1000 ng/mL.
Metabolism: In vitro studies with human liver microsomes and human cDNA-expressed cytochrome P450 isozymes indicate that bortezomib is primarily oxidatively metabolized via cytochrome P450 enzymes, 3A4, 2D6, 2C19, 2C9, and 1A2. The major metabolic pathway is deboronation to form two deboronated metabolites that subsequently undergo hydroxylation to several metabolites. Deboronated-bortezomib metabolites are inactive as 26S proteasome inhibitors. Pooled plasma data from 8 patients at 10 min and 30 min after dosing indicate that the plasma levels of metabolites are low compared to the parent drug.

Elimination: The pathways of elimination of bortezomib have not been characterized in humans.

8.2.3 How Supplied:

Bortezomib is commercially available and will be supplied to CTEP *by* Millennium Pharmaceuticals, Inc. 75 Sidney St. Cambridge, MA 02139 PS-341 (NSC 681239)

Chemical Name:	N-Pyrazinecarbonyl-L-phenylalanine-L-leucine boronic acid
Other Names:	MLN341, LDP-341, Velcade®, bortezomib
Classification:	Proteasome Inhibitor
CAS Registry #:	179324-69-7
Molecular Formula:	$C_{19}H_{25}BN_4O_4$ **(**MW: 384.25)
How Supplied:	PS-341 is supplied by the DCTD, NCI as a 3.5 mg vial for injection. Each sterile single use 10 mL vial contains 3.5 mg PS-341 as a lyophilized powder with 35 mg mannitol, USP.
Preparation:	When the 3.5 mg vial is reconstituted with 3.5 mL normal saline, USP, each milliliter of solution will contain 1 mg of PS-341 at a pH of approximately 5 to 6. The drug is to be given without further dilution as an IV bolus (over 3-5 seconds).
Storage:	Store intact vials at room temperature. Protect from light.
Stability:	Shelf life surveillance of the intact vials is ongoing. The solution as reconstituted is stable for 43 hours at room temperature. *CAUTION: The single-use lyophilized dosage form contains no antibacterial preservatives. Therefore, it is advised that the reconstituted product be discarded 8 hours after initial entry.*

Administration Route: Intravenous

8.2.4 Bortezomib administration

Bortezomib is administered intravenously on Days 1, 4, 8 and 11 of each cycle. See also Section 3.2.2 for more information. A cycle of bortezomib is defined as 28 consecutive days starting with the first day of treatment (day 1). Treatment will be administered in an outpatient setting.

8.2.5 Bortezomib toxicity profile

See CAEPR in section 7.4.1

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10 Appendix A: Laboratory Methodology

Screening for RET mutations

RET mutations will be screened according to a protocol described recently for EGFR (J*i H, Zhao X,* Yuza Y, et al. Epidermal growth factor receptor variant III mutations in lung tumorigenesis and sensitivity to tyrosine kinase inhibitors. Proc Natl Acad Sci U S A 2006; 103:7817–22). Briefly, cDNA is amplified by PCR with primers spanning exons 10, 11, and 13 - 16, after which PCR products are separated in a 5% polyacrylamide gel and visualized by ethidium bromide staining. PCR product is treated with shrimp alkaline phosphatase (Roche Diagnostics Corporation) and exonuclease I (U.S. Biochemical Corp.) to remove excess deoxynucleotide triphosphates and primers followed by sequencing on the ABI 3830XL genetic analyzer using ABI Big Dye Terminator v1.1 sequencing kit.

Determination of the Levels of Modified Tubulin

Proteins isolated as above are loaded on gels and Western blots probed with antibodies specific for total a-tubulin, glu-terminated or acetylated a-tubulin. Alternately, fresh patient core biopsies are Dounce homogenized at 22ºC in hypotonic lysis buffer [1 mM MgCl2, 2 mM EGTA, 0.5% Nonidet P-40, 20 mM Tris-HCl, pH 6.8, containing protease inhibitors] and vortexed vigorously. The lysates are then sonicated to clarity, prior to centrifugation for 1 min at 1000 rpm, removing unlysed debris**.** Total protein concentrations in the lysates are determined using the Biorad assay and equal amounts of protein are loaded on SDS-PAGE gels for each pair of pre- and post-treatment samples. The western blots are sequentially probed with antibodies to total and modified a-tubulins, and with an antibody to actin, the latter as a loading control for each pair and visualized using ECL and densitometry or simultaneously probed with antibodies and visualized using the Odyssey technology. It is expected that post-treatment biopsies will be obtained anywhere from 1 to 4 hours after the bortezomib dose. In practical terms clinically this was the best that can be done, but it is felt that this is not a detriment since the *in vitro* studies have shown that the bortezomib effect on microtubules is stable long after its removal. The variables of when the dose is given on the ward or outpatient clinic, and when the slot becomes available in the radiology suite results in a range of times.

Western blotting to detect RET inhibition

Tumor tissues are homogenized at 4°C for 15 s in 10 volumes of lysis buffer using an Ultra-Turrax (Model T25). The lysis buffer consists of 50 mmol/L of Tris-HCl (pH 7.5), 5 mmol/L of EGTA, 1% Triton X-100, 150 mmol/L of NaCl, 1 mmol/L of PMSF, 80 μg/mL of aprotinin, 50 μg/mL of leupeptin, and 200 μmol/L of sodium orthovanadate. Following 30 min of incubation on ice, the lysates are cleared by centrifugation and the supernatant collected and stored at –70°C. Before freezing, a sample aliquot is diluted at 1:2,000 in water for determination of the protein concentration with a commercially available protein assay kit using bovine serum albumin as standard (Pierce). Sixty micrograms of each sample are separated by SDS-PAGE and blotted onto polyvinylidene difluoride or nitrocellulose membrane (Amersham Biosciences). The following primary antibodies can be used used: polyclonal rabbit anti-RET (C-19; Santa Cruz Biotechnology) and anti-p905-RET (Cell Signaling). The antigen-antibody complexes are visualized using horseradish peroxidase–conjugated anti-mouse or rabbit IgG antibody (Santa Cruz Biotechnology) and enhanced chemiluminescence system (Amersham Biosciences). The membrane can be stripped using a Restore Western blot Stripping Buffer (Pierce), and re-probed

several times. For quantitation, gel images were captured using the Odyssey image capture system and the accompanying image analysis software. In addition we will also monitor he phosphorylation status of various proteins downstream RET, including MAPK (ERK) and Shc. This will be achieved by immunoblot with commercially available phosphospecific antibodies. However, the latter alone will not be considered sufficient evidence for RET inhibition, since they are downstream of other vandetanib-inhibitable targets, including VEGFR and EGFR.

Immunohistochemistry for RET, EGF, MAPK and VEGFR
Assess the expression and activation of RET, EGFR, MAPK and VEGFR by immunohistochemistry with commercially available phosphospecific antibodies and antibodies against unmodified proteins. This will examine tissue obtained prior to or at the time of enrollment on this protocol and will examine the correlation between expression of these proteins and response to therapy (NOTE: We have not yet had experience with the RET antibodies, and will make sure we can perform this before submitting the final version of the protocol).

Pharmacokinetics of bortezomib
These samples will be obtained during Cycle 1, Day 1 and Cycle 3, Day 1. 3ml samples will be obtained in heparinized tubes (green top) and placed on ice at time 0 (pre dose), then 1, 2, 4, 6, 8, 10 and 24hr after the infusion start time. Samples will be delivered to the laboratory of Dr. Doug Figg (5A01), where they will be separated by centrifugation and then plasma aliquots frozen and stored until batch analysis.

Pharmacokinetics of vandetanib
These samples will be obtained during Cycle 3 on Days 1 (± 3 days) and 9. On Day 1 3ml samples will be obtained in heparinized tubes (green top) and placed on ice at time 0 (pre dose), then hours 1, 2, 4, 6, 8, 10, and 24 hours after the oral dose is taken. On Day 9 a single sample (3ml green top) will be obtained 24hours after the previous day's dose and prior to the Day 9 dose, as a trough level. All these samples will be placed on ice and delivered to the laboratory of Doug Figg (Rm 5A01) for processing. Once received the samples will be separated by centriguation, plasma aliquots frozen and then batch mailing of frozen samples to AstraZeneca for analysis.

Storage, Tracking and Handling of Research Specimens
Specimens will be distributed to the following labs for assay:

- Slides from archival tissues blocks will be requested from each patient's referring medical team. These slides will be transferred to Dr. Maria Merino-Neumann in the Laboratory of Pathology for immunohistochemical staining (RET, VEGFR, EGFR, somatostatin receptor). Stained slides, which will be labeled with the patients study number, will be stored in the Lab of Pathology until the trial is completed. If unstained slides are available after planned studies are completed, these may be used for future research after getting an exemption form OHSR or approval from the IRB.
- Snap frozen biopsy specimens will be transferred to Dr. Doug Figg's laboratory for coding and storage and may be processed in Dr. Tito Fojo's laboratory if the intent is to estimate the extent of tubulin polymerization. A snap frozen biopsy specimen and a blood specimen may also be transferred to Dr. Paul Meltzer's lab for gene expression analysis (see section 3.4.2).

These specimens will be labeled with the patient's study number. Dr. Meltzer will retain residual specimens, which may be used for future research only if the patient has consent to future use.

The study will remain open and status of the trial (and specimens) will be reported to the NCI IRB until all samples have been analyzed, reported, destroyed, stripped of all identifiers and unlinked from the protocol database, or transferred to another protocol. Unintentional loss or destruction of any samples will be reported to the NCI IRB as part of annual continuing reviews. Any use of samples not outlined in Section 3.4 or 3.5 will require an exemption from OHSR or prospective NCI IRB review and approval.

Sample Handling for Research Samples Managed by Dr. Figg's Laboratory

Storage/Tracking

All data associated with samples is entered into the Clinical Pharmacology Program's "Patient Sample Database Management System" (PSDMS) - Labrador. This is a secure program that can only be accessed by authorized users in Dr. Figg's lab. PSDMS creates a unique barcode ID for every sample and sample box, which cannot be traced back to patients without PSDMS access. The data recorded for each sample includes the patient ID, name, trial name/protocol number, time drawn, cycle time point, dose, material type, as well as box and freezer location. There are patient demographics that can be obtained to correlate with the samples through the PSDMS system. For each sample, there are notes associated with processing method (delay in sample processing, storage conditions on the ward, etc.). Bar-coded samples are stored in bar-coded boxes in a locked freezer at either -20 or -85°C according to stability requirements. These freezers are located onsite in Dr. Figg's lab and offsite at NCI Frederick Central Repository Services (Fisher Bioservices) in Frederick, MD. Samples will be stored until requested by the researcher assigned to the protocol (however, those requests must come from a member of Dr. Figg's laboratory with PSDMS access/clearance). All requests are monitored and tracked in the PSDMS system. All researchers are required to sign a form stating that the samples are only to be used for research purposes associated with this trial (as per the IRB approved protocol – that protocol is stored in the PSDMS system) and that any unused samples must be returned to Dr. Figg's laboratory.

Protocol Completion/Sample Destruction:

Once primary research objectives for the protocol are achieved, intramural researchers can request access to remaining samples provided they have a IRB approved protocol and patient consent. Samples, and associated data, will be stored permanently unless the patient withdraws consent. If researchers have samples remaining once they have completed all studies associated with the protocol, they must be returned to Dr. Figg's laboratory. The PI will report destroyed samples to the IRB if samples become unsalvageable because of environmental factors (ex. broken freezer or lack of dry ice in a shipping container) or if a patient withdraws consent. Samples will also be reported as lost if they are lost in transit between facilities or misplaced by researchers. Dr. Figg's laboratory will report any freezer problems, lost samples or other problems associated with samples to the IRB, the NCI Clinical Director, and the office of the CCR, NCI.

11 Appendix B: Patient Diary

Directions: Please use this diary daily to record your medications and symptoms. Do not wait until the end of the week to complete the diary.

Cycle _____ Start Date _____

Day	Vandetanib taken (yes/no)	Comments/Symptoms	Name and dose of other medications taken and why they were taken
Sunday Date:			
Monday Date:			
Tuesday Date:			
Wednesday Date:			
Thursday Date:			
Friday Date:			
Saturday Date:			

Use this area for any other information related to the medications or your symptoms. If you make a mistake, cross through the incorrect information once and initial it with the date or make a comment here in this box explaining the error. Use the back of the form if more room is needed. Please return this diary at each visit.

12 Appendix C: Medications Known To Prolong the QT Interval and /or Induce Torsades De Pointes (TdP)

Appendix C updated 19 August 2011

It has been recognized for a number of years that certain prescription medications can prolong the QT/QTc interval and cause a form of acquired Long QT syndrome, known as drug induced LQTS. The drugs that prolong the QT interval and/or have a risk of inducing Torsades de Pointes (TdP) are listed below. We have divided these into two groups based on their known or perceived risk of causing TdP:

Group 1. Drugs that are generally accepted by authorities to have a risk of causing Torsades de Pointes

Concomitant use of these drugs is not allowed during the study or within 2 weeks of randomization (at least four weeks for levomethadyl). These drugs should also be avoided for up to 4 weeks following discontinuation of study treatment:

Table 1 Group 1 Drugs

Drug (Generic Names)	Drug Class (Clinical Usage)	Comments
Amiodarone	Anti-arrhythmic / abnormal heart rhythm	TdP risk regarded as low
Arsenic trioxide	Anti-cancer / Leukemia	
Astemizole	Antihistamine / Allergic rhinitis	No Longer available in U.S.
Bepridil	Anti-anginal / heart pain	
Chloroquine	Anti-malarial / malaria infection	
Chlorpromazine	Anti-psychotic/ Anti-emetic / schizophrenia/ nausea	
Cisapride	GI stimulant / heartburn	Restricted availability
Clarithromycin	Antibiotic / bacterial infection	
Disopyramide	Anti-arrhythmic / abnormal heart rhythm	
Dofetilide	Anti-arrhythmic / abnormal heart rhythm	
Domperidone	Anti-nausea / nausea	Not available in the U.S.
Droperidol	Sedative; Anti-nausea / anesthesia adjunct, nausea	

Table 1 Group 1 Drugs

Drug (Generic Names)	Drug Class (Clinical Usage)	Comments
Erythromycin	Antibiotic; GI stimulant / bacterial infection; increase GI motility	
Halofantrine	Anti-malarial / malaria infection	
Haloperidol	Anti-psychotic / schizophrenia, agitation	When given intravenously or at higher-than- recommended doses, risk of sudden death, QT prolongation and torsades increases.
Ibutilide	Anti-arrhythmic / abnormal heart rhythm	
Levomethadyl	Opiate agonist / pain control, narcotic dependence	
Mesoridazine	Anti-psychotic / schizophrenia	
Methadone	Opiate agonist / pain control, narcotic dependence	
Moxifloxacin	Antibiotic / bacterial infection	
Pentamidine	Anti-infective / pneumocystis pneumonia	
Pimozide	Anti-psychotic / Tourette's tics	
Probucol	Antilipemic / Hypercholesterolemia	No longer available in U.S.
Procainamide	Anti-arrhythmic / abnormal heart rhythm	
Quinidine	Anti-arrhythmic / abnormal heart rhythm	
Sotalol	Anti-arrhythmic / abnormal heart rhythm	
Sparfloxacin	Antibiotic / bacterial infection	
Terfenadine	Antihistamine / Allergic rhinitis	No longer available in U.S.

Table 1 Group 1 Drugs

Drug (Generic Names)	Drug Class (Clinical Usage)	Comments
Thioridazine	Anti-psychotic / schizophrenia	
Vandetanib (*Does not apply to this study)	Anti-cancer / Thyroid cancer	"CAPRELSA®" is the proposed brand name

Source: www.QTdrugs.org

Group 2. Drugs that in some reports may be associated with Torsades de Pointes but at this time lack substantial evidence of causing Torsades de Pointes.

Concomitant use of these drugs is not allowed within 2 weeks of randomization or during the study. These drugs will be allowed during the study, at the discretion of the Investigator, if considered absolutely necessary. In such cases, the patient must be closely monitored, including regular checks of QTc and electrolytes (reference section 5.6.2 of the protocol).

Table 2 Group 2 Drugs

Drug (Brand Names)	Drug Class (Clinical Usage)	Comments
Alfuzosin	Alpha1-blocker / Benign prostatic hyperplasia	
Amantadine	Dopaminergic/Anti-viral / Anti-infective/ Parkinson's Disease	
Atazanavir	Protease inhibitor / HIV	
Azithromycin	Antibiotic / bacterial infection	
Chloral hydrate	Sedative / sedation/ insomnia	
Clozapine	Anti-psychotic / schizophrenia	
Dolasetron	Anti-nausea / nausea, vomiting	
Dronedarone	Anti-arrhythmic / Atrial Fibrillation	
Escitalopram	Anti-depressant / Major depression/ Anxiety disorders	
Famotidine	H2-receptor antagonist / Peptic ulcer/ GERD	
Felbamate	Anti-convulsant / seizure	

Table 2 Group 2 Drugs

Drug (Brand Names)	Drug Class (Clinical Usage)	Comments
Flecainide	Anti-arrhythmic / abnormal heart rhythm	
Foscarnet	Anti-viral / HIV infection	
Fosphenytoin	Anti-convulsant / seizure	
Gatifloxacin	Antibiotic / bacterial infection	
Gemifloxacin	Antibiotic / bacterial infection	
Granisetron	Anti-nausea / nausea and vomiting	
Indapamide	Diuretic / stimulate urine & salt loss	
Isradipine	Anti-hypertensive / high blood pressure	
Lapatinib	Anti-cancer / breast cancer, metastatic	
Levofloxacin	Antibiotic / bacterial infection	
Lithium	Anti-mania / bipolar disorder	
Moexipril/HCTZ	Anti-hypertensive / high blood pressure	
Nicardipine	Anti-hypertensive / high blood pressure	
Nilotinib	Anti-cancer / Leukemia	
Octreotide	Endocrine / acromegaly, carcinoid diarrhea	
Ofloxacin	Antibiotic / bacterial infection	
Ondansetron	Anti-emetic / nausea and vomiting	
Oxytocin	Oxytocic / Labor stimulation	
Paliperidone	Antipsychotic, atypical / Schizophrenia	
Perflutren lipid microspheres	Imaging contrast agent / Echocardiography	

Table 2 Group 2 Drugs

Drug (Brand Names)	Drug Class (Clinical Usage)	Comments
Quetiapine	Anti-psychotic / schizophrenia	
Ranolazine	Anti-anginal / chronic angina	
Risperidone	Anti-psychotic / schizophrenia	
Roxithromycin*	Antibiotic / bacterial infection	*not available in the United States
Sertindole	Antipsychotic, atypical / Anxiety, Schizophrenia	
Sunitinib	Anti-cancer / RCC, GIST	
Tacrolimus	Immunosuppressant / Immune suppression	
Tamoxifen	Anti-cancer / breast cancer	
Telithromycin	Antibiotic / bacterial infection	
Tizanidine	Muscle relaxant /	
Vardenafil	phosphodiesterase inhibitor / vasodilator	
Venlafaxine	Anti-depressant / depression	
Voriconazole	Anti-fungal / anti-fungal	
Ziprasidone	Anti-psychotic (schizophrenia)	

Source: www.QTdrugs.org

INSTITUTE: National Cancer Institute

STUDY NUMBER: 09-C-0089 PRINCIPAL INVESTIGATOR: Ravi Madan, MD

STUDY TITLE**:**

A Targeted Phase I/II Trial of ZD6474 (Vandetanib; CAPRELSA) Plus the Proteasome Inhibitor, Bortezomib (Velcade®), in Adults with Solid Tumors with a Focus on Hereditary or Sporadic, Locally Advanced or Metastatic Medullary Thyroid Cancer (MTC)

Continuing Review Approved by the IRB on 06/08/15
Amendment Approved by the IRB on 08/18/15 (M) Date posted to web: 08/22/15

Standard

INTRODUCTION

We invite you to take part in a research study at the National Institutes of Health (NIH).

First, we want you to know that:

Taking part in NIH research is entirely voluntary**.**

You may choose not to take part, or you may withdraw from the study at any time. In either case, you will not lose any benefits to which you are otherwise entitled. However, to receive care at the NIH, you must be taking part in a study or be under evaluation for study participation.

You may receive no benefit from taking part. The research may give us knowledge that may help people in the future.

Second, some people have personal, religious or ethical beliefs that may limit the kinds of medical or research treatments they would want to receive (such as blood transfusions). If you have such beliefs, please discuss them with your NIH doctors or research team before you agree to the study.

Now we will describe this research study. Before you decide to take part, please take as much time as you need to ask any questions and discuss this study with anyone at NIH, or with family, friends or your personal physician or other health professional.

Why is this study being done?

The combination of oral vandetanib and intravenous bortezomib has not been used in humans. However both drugs have been studied separately. Bortezomib is approved by the Food and Drug Administration (FDA) for the treatment of 2 other types of cancer called multiple myeloma and mantle cell lymphoma. It is considered an "investigational drug" in this study because we are studying its use in another cancer. Bortezomib has been tested in many other types of cancer including lung, breast, bone and gastrointestinal cancers. In these studies, bortezomib did not show significant activity, but many studies are still ongoing. Since the

initial start of this study, Vandetanib has been FDA approved for the treatment of symptomatic or progressive medullary thyroid cancer in patients with unresectable locally advanced or metastatic disease.

This particular combination of medications was initially chosen for a few reasons. Vandetanib and bortezomib have both shown activity in cancer including medullary thyroid cancer. It is our hope that the combination of these two drugs will be better than either of them alone. Their side effects do not appear to overlap, although we will be carefully monitoring all patients receiving this combination. Tumors have distinct mechanisms or ways of signaling or triggering their own growth. We have been able to identify several of these mechanisms. These two drugs each work at a different point in the tumor growth signaling pathway. We hope to be able to stop the triggering of tumor growth signals with this combination of drugs.

The purpose of the study is to:

1. Determine if this combination treatment will be effective in decreasing the amount of cancer and, if it does, to determine how long the response will last.
2. Determine the side effects that may occur with this combination of treatments.
3. Determine what doses of each drug are well tolerated and safe when given together.
4. To analyze genetic mutations in tumors to help us understand how tumors grow and how these drugs interact with the mechanisms within the tumor.

Why are you being asked to take part in this study?

This is a study designed for patients with various types of cancer, including medullary thyroid cancer.

How many people will take part in this study?

Up to 117 people will take part in this study.

Description of Research Study

The study is divided into 2 parts. In the first part, treatment will consist of a combination of two anti-cancer agents; vandetanib and bortezomib. In the second part, treatment will be either both of these anti-cancer drugs or only one of them. This is explained in more detail on the following pages of this consent form. Vandetanib is a pill, which you will take by mouth, once each day and continue throughout the duration of the study. Bortezomib will be given through a catheter placed in one of your veins and will be given on the 1st, 4th, 8th, and 11th day of each cycle. The infusion takes less than 1 minute and is followed by a flush of intravenous fluid.

What will happen if you take part in this research study?

Before you begin the study

Prior to starting (or "enrolling") on the study, an evaluation will be done at the NIH Oncology Clinic to determine if this study is appropriate for you. This is called "screening" and a different consent form explains the tests required for screening.

If a pathology specimen is not available from previous surgery, a biopsy may need to be performed at the NCI to confirm your cancer. A separate informed consent will be given to you for this procedure, if needed.

During the study

This study is divided into two phases. In Phase I, patients with various types of cancer participated. Both of the study medications (vandetanib and bortezomib) were given at increasing doses. The first few patients received Level One of both drugs. The levels are listed below for reference. These patients were carefully monitored for at least 4 – 8 weeks. Since there were no severe toxicities or side effects at Level One, the next group of patients began at Level Two. Levels increased as long as no severe toxicities were seen. This continued until a decision was reached regarding what is the safest dose level. This level is called the Maximal Tolerated Dose (MTD). The Phase I portion of this study is now complete, and it has been determined that the MTD is Level 4 (300 mg vandetanib daily + 1.3 mg/m^2 bortezomib on days 1, 4, 8 & 11 every 28 days). This is the dose that will be used in the Phase II portion of the study.

- Level 1: 100 mg vandetanib daily + 1 mg/m^2 bortezomib on days 1, 4, 8 & 11 every 28 days
- Level 2: 100 mg vandetanib daily + 1.3 mg/m^2 bortezomib on days 1, 4, 8 & 11 every 28 days
- Level 3: 200 mg vandetanib daily + 1.3 mg/m^2 bortezomib on days 1, 4, 8 & 11 every 28 days
- Level 4: 300 mg vandetanib daily + 1.3 mg/m^2 bortezomib on days 1, 4, 8 & 11 every 28 days

Mg/m^2 is a way to calculate a dose based on your height and weight.

Two additional levels may be included in the design, depending on the side effects at various levels. These levels are:

- Level 1A: 200 mg vandetanib daily + 1 mg/m^2 bortezomib on days 1, 4, 8 & 11 every 28 days
- Level 1B: 300 mg vandetanib daily + 1 mg/m^2 bortezomib on days 1, 4, 8 & 11 every 28 days

In Phase II of the study, patients with a diagnosis of medullary thyroid cancer will participate. These patients will be randomly assigned (like flipping a coin) to one of the following two groups: Group A will receive both study medications (vandetanib and bortezomib) at the maximally tolerated dose level from the Phase I portion of the study (Level 4: 300 mg vandetanib daily + 1.3 mg/m^2 bortezomib on days 1, 4, 8 & 11 every 28 days). Group B will receive only vandetanib at the same dose as those in Group A (300 mg vandetanib daily). The randomization or assignment to Group A or B is done by a computer program. If you are in Phase II of the study you will not know which Group you will be assigned to until after you sign the consent form, are enrolled and then randomized. Once you are enrolled and randomized you will be told. There is no placebo in this study. You will know exactly what medication(s) you are receiving. It will either be both study medications or one study medication. The purpose of this design is to compare the effect on medullary thyroid cancer of the combination of medications to the single medication. The ratio of assignment to each arm is 2 to 1. This means that for every 2 patients assigned to Group A (both medications), 1 patient will be assigned to Group B (one medication). There is evidence that vandetanib alone has activity in MTC. This trial design will help us determine if the combination of bortezomib and vandetanib is as good as or better than vandetanib alone. It will also tell us what the side effects are of the combination compared to vandetanib alone.

The treatment itself will be done on an outpatient basis in most cases. The treatment will be repeated every 4 weeks. If you are in the Phase I portion of study, you will need to come into the Clinical Center for infusions on Day 1, 4, 8 and 11. If you are in the Phase II portion of the study, and you are in the group of patients that will receive both vandetanib and bortezomib, you will need to come into the Clinical Center for infusions on Day 1, 4, 8 and 11.

Vandetanib is an oral medication (pill) and will start on Cycle 1 Day 1. You may take vandetanib with or without food. You will take vandetanib daily without stopping (unless there are side effects from the vandetanib) throughout the entire treatment. In other words, you will not stop the vandetanib between cycles. If you are in the Phase I portion of the study, the dose of vandetanib may be increased after 6 weeks, as long as the side effects are tolerable. If you are in the Phase II portion of the study, the dose of vandetanib will stay the same.

Bortezomib is an anticancer drug that will be given on Day 1, Day 4, Day 8 and Day 11 of each cycle. It will be given through a venous catheter by an infusion from a syringe, followed by an intravenous flush of fluid. If you are in the Phase I portion of the study the dose of bortezomib may be increased after 8 weeks, as long as the side effects are tolerable. If you are in the Phase II portion of the study you will be assigned to either Group A or Group B. Group A patients will receive bortezomib as described above. Group B patients will not receive bortezomib.

One of the goals of the Phase I portion of the study is to determine what doses of each drug are safe to give together. Once these doses have been determined, your dose will not be increased

above this safe dose. Both drug doses may be decreased based on your symptoms. This is why we need to evaluate you frequently.

CT scans will be done after each 2nd cycle (Cycle 2, cycle 4 etc) to follow the cancer and see what effect the drugs are having. The treatment will continue as long as the cancer is stable or smaller, and you are tolerating it well, and the physician determines it is safe to continue. If all the cancer disappears, we will continue the treatment for 2 additional cycles. The cancer may shrink to the point where surgery is an option. If that is possible, we will stop the treatment so you may receive surgery. If the cancer grows, the treatment will be stopped, because it is not helping.

Millennium Pharmaceuticals, Inc will supply bortezomib to the National Cancer Institute. The National Cancer Institute will then supply bortezomib to the Clinical Center Pharmacy. AstraZeneca will supply the experimental drug, vandetanib to the Clinical Center Pharmacy for use in this study. The Clinical Center Pharmacy will supply any other medications.

Birth Control

If you are a woman who is breast feeding or pregnant, you may not take part in the study because we don't know how this medicine would affect your baby or your unborn child. If you are a woman who can become pregnant, or are the partner of a woman who can become pregnant, you will need to practice an effective form of birth control before starting study treatment, during study treatment, and for four months after you finish study treatment. If you think that you or your partner is pregnant, you should tell your study doctor or nurse at once.

Effective forms of birth control include:

- abstinence
- intrauterine device (IUD)
- hormonal [birth control pills, injections, or implants]
- tubal ligation
- vasectomy

Alternative Approaches or Treatments

Instead of being in this study, you have these options**:**

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly. Instead, it tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Please talk to your doctor about these and other options.

Risks or Discomforts of Participation

If you choose to take part in this study, there is a risk that:

- You may lose time at work or home and spend more time in the hospital or doctor's office than usual
- You may be asked sensitive or private questions which you normally do not discuss

The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- The study doctors do not know who will or will not have side effects.
- Some side effects may go away soon, some may last a long time, or some may never go away.
- Some side effects may interfere with your ability to have children.
- Some side effects may be serious and may even result in death.

Here are important points about how you and the study doctor can make side effects less of a problem:

- Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.
- The study doctor may be able to treat some side effects.
- The study doctor may adjust the study drugs to try to reduce side effects.

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

What side effects or risks can I expect from being in this study?

Possible Side Effects of Bortezomib

COMMON, SOME MAY BE SERIOUS In 100 people receiving bortezomib, more than 20 and up to 100 may have:
• Anemia which may require blood transfusion • Constipation, diarrhea, nausea, vomiting • Tiredness, fever

- Infection
- Bruising, bleeding
- Loss of appetite
- Muscle weakness
- Numbness, tingling or pain of the arms and legs

OCCASIONAL, SOME MAY BE SERIOUS

In 100 people receiving bortezomib, from 4 to 20 may have:

- Pain
- Heartburn
- Bleeding from multiple sites
- Internal bleeding which may cause black tarry stool, or blood in vomit
- A tear or hole in internal organs that may require surgery which may cause difficulty swallowing
- Chills
- Swelling of arms, legs
- Weight loss
- Dehydration
- Muscle spasms
- Dizziness, headache
- Feeling of "pins and needles" in arms and legs
- Worry
- Difficulty sleeping
- Cough, shortness of breath, sore throat
- Rash
- Low blood pressure which may cause feeling faint

RARE, AND SERIOUS

In 100 people receiving bortezomib, 3 or fewer may have:

- Heart failure which may cause shortness of breath, swelling of ankles, and tiredness
- A tear or hole in internal organs that may require surgery which may cause difficulty swallowing
- Damage to organs which may cause shortness of breath, or changes in thinking
- Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)
- Kidney damage which may cause swelling, may require dialysis

Possible Side Effects of Vandetanib

COMMON, SOME MAY BE SERIOUS
In 100 people receiving Vandetanib, more than 20 and up to 100 may have:
• Diarrhea, nausea, loss of appetite • Pain • Tiredness • Headache • Acne, rash • High blood pressure which may cause dizziness, blurred vision

OCCASIONAL, SOME MAY BE SERIOUS
In 100 people receiving Vandetanib, from 4 to 20 may have:
• Severe blood infection • Change in the heart rhythm • Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome) • Damage to the lungs which may cause shortness of breath • Entry of material into lung which may cause cough, infection • Scarring of the lungs • Severe skin rash with blisters and can involve inside of mouth and other parts of the body • Bleeding

RARE, AND SERIOUS
In 100 people receiving Vandetanib, 3 or fewer may have:
• Heart failure which may cause shortness of breath, swelling of ankles, and tiredness • Stroke which may cause paralysis, weakness

Possible Side Effects for the Combination of Bortezomib and Vandetanib

These two drugs have not been given together in humans, so we do not know all the possible side effects. Both drugs cause the platelet count to drop, so perhaps when given together that effect might be lower than either one separately. Both drugs cause gastrointestinal side effects (nausea, vomiting, diarrhea, constipation). Perhaps these effects might be more intense during the combination. We think that the same side effects seen with each drug separately will be present when used together. We will monitor you closely and ask you to help us by reporting your

symptoms and communicating with us. You will be asked to keep a diary of your symptoms and bring it with you to your appointments.

Lastly, diarrhea is a common symptom of some patients with thyroid cancer. Diarrhea is also a potential side effect of both study medications. If you experience diarrhea, either from your disease or from the study medications, you will be given medications to manage the diarrhea. A few anti-diarrhea medicines (octreotide and lanreotide) may affect your heart rhythm. This side effect may or may not occur if you receive either of these anti-diarrhea medications. In fact some medical literature has reported that these 2 medicines can improve the heart rhythm. If you have diarrhea and need to receive medicine to manage the diarrhea, we will monitor your heart rhythm with EKGs.

Risks Associated with Tests and Procedures

Blood samples will be taken during your treatment for laboratory research and to monitor your organ functions. The total amount of blood taken will be less than 320 milliliters in the first 6 weeks, which is 21 tablespoons. This will be the most that will be routinely drawn in any 6 week period and is significantly less than the maximum amount deemed safe. All the remaining weeks will have less blood draws. The risks of drawing blood include discomfort from the needle stick and dizziness if you stand up quickly. These blood tests are a required part of the study.

CT scans will be done following every second cycle to determine if the drugs are helping. CT scans involved radiation exposure. These scans would be done whether you were participating in a clinical trial or not, although perhaps not as frequently if you were not in a clinical trial.

This research study involves exposure to radiation from up to 2 CT-directed biopsies. This radiation exposure is not required for your medical care and is for research purposes only. The amount of radiation you will receive in this study is 0.26 rem which is below the guideline of 5 rem (or 0.5 rem in children) per year allowed for research subjects by the NIH Radiation Safety Committee. The average person in the United States receives a radiation exposure of 0.3 rem per year from natural sources, such as the sun, outer space, and the earth's air and soil. If you would like more information about radiation, please ask the investigator for a copy of the pamphlet, An Introduction to Radiation for NIH Research Subjects.

While there is no direct evidence that the amount of exposure received from participating in this study is harmful, there is indirect evidence it may not be completely safe. There may be a very slight increase in the risk of cancer.

Please tell your doctor if you have had any radiation exposure in the past year, either from other research studies or from medical tests or care, so we can make sure that you will not receive too much radiation. Radiation exposure includes x-rays taken in radiology departments, cardiac catheterization, and fluoroscopy as well as nuclear medicine scans in which radioactive materials were injected into your body.

Reproductive Risks

Women of child-bearing potential:
There might be unknown risks to the unborn child if you are or if you become pregnant during the study. A pregnancy test will be done to confirm that you are not pregnant before you take part in this study. If you are pregnant you will not be permitted to participate in this research study. If you are breast feeding and the protocol involves injection of radioactive material you will not be permitted to participate. It is best to avoid radiation exposure to unborn or nursing infants since they are more sensitive to radiation than adults. You must avoid becoming pregnant and use an acceptable method of birth control during this study**.**

If at any time during this study you think you might be pregnant, or later learn that you were pregnant during the study, you must contact the Study Doctor immediately for further instructions about your participation in this study and follow-up.

Male patients:
If you are a male patient, the study drugs used in this study could affect your sperm and could potentially harm a child that you may father while in this study. You must avoid unprotected sex with a pregnant partner (or woman of child-bearing potential not using birth control) or donating sperm during the study and for three months following the last dose, since the potential for problems with unborn children has not yet been thoroughly investigated. Men should use a condom during the trial and for three months following the last dose.

If your partner becomes pregnant, you must notify the study doctor of any outcomes of the pregnancy from the date of the first dose until 14 days after last dose.

Potential Benefits of Participation

Are there benefits to taking part in this study?

The aim of this study is to see if this experimental treatment will cause your tumors to shrink. We do not know if you will receive personal, medical benefit from taking part in this study. These potential benefits could include shrinking of your tumor or lessening of your symptoms, such as pain, that are caused by the cancer. Because there is not much information about the drug's effect on your cancer, we do not know if you will benefit from taking part in this study, although the knowledge gained from this study may help others in the future who have cancer.

Research Subject's Rights

What are the costs of taking part in this study?

If you choose to take part in the study, the following will apply, in keeping with the NIH policy:

- You will receive study treatment at no charge to you. This may include surgery, medicines, laboratory testing, x-rays or scans done at the Clinical Center, National Institutes of Health (NIH), or arranged for you by the research team to be done outside the Clinical Center, NIH if the study related treatment is not available at the NIH.
- There are limited funds available to cover the cost of some tests and procedures performed outside the Clinical Center, NIH. You may have to pay for these costs if they are not covered by your insurance company.
- Medicines that are not part of the study treatment will not be provided or paid for by the Clinical Center, NIH.
- Once you have completed taking part in the study, medical care will no longer be provided by the Clinical Center, NIH.

Will your medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), which are involved in keeping research safe for people.
- National Cancer Institute Institutional Review Board.
- The study Sponsor (Cancer Therapy Evaluation Program) or their agent(s), or Collaborators (Millennium Pharmaceuticals and AstraZeneca).

A description of this clinical trial will be available on http://www.Clinicaltrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most the Web site will include a summary of the results. You can search this Web site at any time.

Stopping Therapy

Your doctor may decide to stop your therapy for the following reasons:

- if he/she believes that it is in your best interest
- if your disease comes back during treatment
- if you have side effects from the treatment that your doctor thinks are too severe
- if new information shows that another treatment would be better for you

In this case, you will be informed of the reason therapy is being stopped.

You can stop taking part in the study at any time. However, if you decide to stop taking part in the study, we would like you to talk to the study doctor and your regular doctor first.

If you decide at any time to withdraw your consent to participate in the trial, we will not collect any additional medical information about you. However, according to FDA guidelines, information collected on you up to that point may still be provided to CTEP, AstraZeneca or Millennium Pharmaceuticals or designated representatives. If you withdraw your consent and leave the trial, any samples of yours that have been obtained for the study and stored at the NCI can be destroyed upon request. However, any samples and data generated from the samples that have already been distributed to other researchers or placed in the research databases can**not** be recalled and destroyed.

Conflict of Interest

The National Institutes of Health (NIH) reviews NIH staff researchers at least yearly for conflicts of interest. This process is detailed in a Protocol Review Guide. You may ask your research team for a copy of the Protocol Review Guide or for more information. Members of the research team who do not work for NIH are expected to follow these guidelines but they do not need to report their personal finances to the NIH.

Members of the research team working on this study may have up to $15,000 of stock in the companies that make products used in this study. This is allowed under federal rules and is not a conflict of interest.

The National Institutes of Health and the research team for this study are using drugs developed by AstraZeneca and Millennium Pharmaceuticals through a joint study with your researchers and the company. The company also provides financial support for this study.

Optional Biopsy

Tumor biopsy may be done, if you agree, before starting on the study medications, to help us better understand the cancer, but will not be of any clinical benefit to you. The tissue obtained from this biopsy may be used to determine the growth mechanisms (signaling pathways or triggers) in your tumor, to determine what genes are in your tumor tissue, and some of the tissue may be saved for possible future studies.

If you had prior surgery and there is frozen tumor tissue from that time, we may be able to use that sample, with your permission, to perform these tests.

A second tumor biopsy may be done, when possible, if you agree. In patients with thyroid cancer the 2nd biopsy will be done at the 6 week evaluation (approximately 42 days after beginning) to look at the tumor signaling pathways in thyroid tumors. In patients with cancer other than thyroid cancer, the 2nd biopsy will be obtained on Day 4 of either the 1st or 2nd cycle, after the bortezomib infusion. This biopsy is looking at the cell structure within the tumor to determine what effect bortezomib has had. You may participate in the study whether or not you have these biopsies.

Please note that we will only look in your tumor for mutations in the RET gene that is so important in MTC. We will not be looking in any normal cells from you and therefore will obtain no information on your genetic predisposition to this disease or whether you can pass it on. This latter information is often called "germ line testing," and we will not be doing this. If you would like we can give you more information on how to go about pursuing this.

The biopsy to be performed is exclusively for research purposes and will not benefit you. It might help other people in the future. Even if you sign "yes" to have the biopsy you can change your mind at any time. Please read each sentence below and think about your choice. After reading each sentence, circle and initial the answer that is right for you. The decision to participate in this part of the research is optional, and no matter what you decide to do, it will not affect your care.

I give permission (1) To use the pre-existing sample

(2) To have a biopsy if there is no previous sample prior to treatment

(3) To have a second biopsy after treatment starts.

YES ____ NO _____ Initials _____

Optional Studies

We would like to keep some of the specimens and data that are collected for future research. These specimens and data will be identified by a number and not your name. The use of your specimens and data will be for research purposes only and will not benefit you. It is also possible that the stored specimens and data may never be used. Results of research done on your specimens and data will not be available to you or your doctor. It might help people who have cancer and other diseases in the future.

If you decide now that your specimens and data can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens and/or data. Then any specimens that remain will be destroyed and your data will not be used for future research.

Please read each sentence below and think about your choice. After reading each sentence, circle and initial the answer that is right for you. No matter what you decide to do, it will not affect your care.

1. My specimens and data may be kept for use in research to learn about, prevent, or treat cancer or other health problems.

Yes No Initials_____

2. Someone may contact me in the future to ask permission to use my specimen(s) and/or data in new research not included in this consent.

Yes No Initials_____

OTHER PERTINENT INFORMATION

1. Confidentiality. When results of an NIH research study are reported in medical journals or at scientific meetings, the people who take part are not named and identified. In most cases, the NIH will not release any information about your research involvement without your written permission. However, if you sign a release of information form, for example, for an insurance company, the NIH will give the insurance company information from your medical record. This information might affect (either favorably or unfavorably) the willingness of the insurance company to sell you insurance.

The Federal Privacy Act protects the confidentiality of your NIH medical records. However, you should know that the Act allows release of some information from your medical record without your permission, for example, if it is required by the Food and Drug Administration (FDA), members of Congress, law enforcement officials, or authorized hospital accreditation organizations.

2. Policy Regarding Research-Related Injuries. The Clinical Center will provide short-term medical care for any injury resulting from your participation in research here. In general, no long-term medical care or financial compensation for research-related injuries will be provided by the National Institutes of Health, the Clinical Center, or the Federal Government. However, you have the right to pursue legal remedy if you believe that your injury justifies such action.

3. Payments. The amount of payment to research volunteers is guided by the National Institutes of Health policies. In general, patients are not paid for taking part in research studies at the National Institutes of Health. Reimbursement of travel and subsistence will be offered consistent with NIH guidelines.

4. Problems or Questions. If you have any problems or questions about this study, or about your rights as a research participant, or about any research-related injury, contact the Principal Investigator, Ravi Madan, M.D., Building 10, Room 3-4460, Telephone: 301-496-3493. Other researchers you may call are: Maureen Edgerly, RN, Telephone: 301-435-5604. You may also call the Clinical Center Patient Representative at 301-496-2626. If you have any questions about the use of your specimens or data for future research studies, you may also contact the Office of the Clinical Director, Telephone: 301-496-4251.

5. Consent Document. Please keep a copy of this document in case you want to read it again.

COMPLETE APPROPRIATE ITEM(S) BELOW:	
A. Adult Patient's Consent I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby consent to take part in this study. _____ _____ Signature of Adult Patient/ Legal Representative Date _____ Print Name	**B. Parent's Permission for Minor Patient.** I have read the explanation about this study and have been given the opportunity to discuss it and to ask questions. I hereby give permission for my child to take part in this study. (Attach NIH 2514-2, Minor's Assent, if applicable.) _____ _____ Signature of Parent(s)/ Guardian Date _____ Print Name
C. Child's Verbal Assent (If Applicable) The information in the above consent was described to my child and my child agrees to participate in the study. _____ _____ _____ Signature of Parent(s)/Guardian Date Print Name	
THIS CONSENT DOCUMENT HAS BEEN APPROVED FOR USE FROM JUNE 8, 2015 THROUGH JUNE 7, 2016. _____ _____ _____ _____ Signature of Investigator Date Signature of Witness Date _____ _____ Print Name Print Name	