Phase II Trial of Bortezomib and Vorinostat in Mantle Cell and Diffuse Large B-Cell Lymphomas

NCT00703664

Version 18.0

April 10, 2014

NCI Protocol #: 8064

Local Protocol #: MCC-8064

TITLE: Phase II Trial of Bortezomib and Vorinostat in Mantle Cell and Diffuse Large B-Cell Lymphomas

Coordinating Center: Southeast Phase II Consortium (SEP2C)
H. Lee Moffitt Cancer Center and Research Institute
University of South Florida
12902 Magnolia Drive, Tampa, FL 33612

Study Chair: Beata Holkova, MD
Massey Cancer Center
Virginia Commonwealth University
[redacted]

Co-Investigators: Dan Sullivan, MD (N01 PI – CM-62208)
H. Lee Moffitt Cancer Center and Research Institute
[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Statistician:

[redacted]

Correlative Studies:

[redacted]

Correlative Studies and Pathologist: [redacted]

Disease Entities	**SCD#**
Mantle Cell Lymphoma	10026799
Diffuse Large B-cell Lymphoma	10012820

NCI Supplied Agents: Bortezomib (Velcade) NSC# 681239; IND# 58,443
Vorinostat (Zolinza) NSC# 701852; IND# 71,976

Protocol Type / Version # / Version Date: Phase II, Version 18, Version Date 04/10/2014

SCHEMA

Phase II Study of Bortezomib and Vorinostat in Mantle Cell and Diffuse Large B-Cell Lymphoma.

Patient cohorts:

A: Mantle cell lymphoma - No prior bortezomib
B: Mantle cell lymphoma - Prior bortezomib *[closed with Protocol Version 8]*
C: Diffuse large B-cell lymphoma - No prior bortezomib *[closed 6/25/2013]*

Days	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
	V	V	V	V	V			V	V	V	V	V									
	B			B				B			B										

V = vorinostat 400 mg (total dose) po
B = bortezomib 1.3 mg/m^2/d iv

Vorinostat precedes bortezomib on days of concurrent administration.

Repeat every 3 weeks.

TABLE OF CONTENTS

1 OBJECTIVES

1.1 Primary Objective

Estimate the response rates of mantle cell and diffuse large B-cell lymphomas to bortezomib and vorinostat combination therapy.

1.2 Secondary Objectives

1.2.1 Assess the safety and tolerability of the study regimen

1.2.2 Observe progression-free survival and response durations

1.2.3 Observe relationship between pretreatment lymphoma cell nuclear relA and response.

2 BACKGROUND

2.1 Study Diseases

Mantle Cell Lymphoma (MCL)

From the National Comprehensive Cancer Network (NCCN) Physician Guidelines (v2.2007):

Mantle cell lymphoma has the worst characteristics of both indolent and aggressive non-Hodgkin's lymphomas. Like many of the more common indolent lymphoid neoplasms, mantle cell lymphoma appears to be incurable with conventional chemotherapy. However, mantle cell lymphoma does not have an indolent natural history; rather, it has the shorter disease-free and overall survivals more characteristic of aggressive lymphomas. Therefore, there is no established standard of care. In the absence of standard management for mantle cell lymphoma, patients with this disease should be referred for participation in prospective clinical trials. Few patients present with localized MCL and the available published literature on management is retrospective and anecdotal. Outside of a clinical trial the panel recommended either combined modality therapy or involved field radiation therapy though this was based on treatment principles as there was not data to guide these recommendations.

The overwhelming majority of patients with MCL will have advanced stage disease and require systemic therapy. For patients who do not have access to clinical trials for first line therapy, several regimens have shown significant activity including R-HyperCVAD (rituximab, cyclophosphamide, vincristine, doxorubicin, dexamethasone) alternating with methotrexate and cytarabine, R-CHOP, and REPOCH (rituximab, etoposide, prednisone, vincristine, cyclophosphamide, doxorubicin) though relapse is common with a median time of 15-18 months without adjuvant stem cell transplant (autologous or allogeneic).

Initial remission should be followed by stem cell transplantation (category 2B) in eligible patients as this has been associated with some evidence of durable remission. Allogeneic stem cell transplant alone or in the context of a clinical trial is considered as the first line consolidation therapy. The optimal approach to recurrent disease remains to be defined. For this reason, the entry of patients into clinical trials is strongly encouraged. Data has demonstrated a role for single agents such as cladribine and bortezomib. Combination such as cyclophosphamide and fludarabine, PCR (pentostatin, cyclophosphamide, rituximab), and FCMR (fludarabine, cyclophosphamide, mitoxantrone, rituximab) also have activity. Marked anti-tumor activity has been shown for rituximab plus thalidomide in patients with relapsed/refractory MCL. Patients who obtain only a

partial response to induction therapy are also appropriate candidates for clinical trials of high-dose therapy and additional therapeutic modalities. Radioimmunotherapy has shown to be active for both untreated and relapsed MCL.

Diffuse Large B-cell Lymphoma (DLBCL)

From the National Comprehensive Cancer Network (NCCN) Physician Guidelines (v2.2007):

The realistic goal of induction therapy for DLBCL is to cure the disease. In fact, almost half of the patients with DLBCL may be cured with conventional therapy. Approaches to the treatment of DLBCL differ between patients with localized (Ann Arbor stage I-II) and advanced (Ann Arbor stage III-IV) disease. In patients with localized disease, treatment approaches also differ between patients with non-bulky (<10 cm) disease and those with bulky (≥ 10 cm) and/or extranodal disease. Patients with non-bulky localized disease who do not have adverse risk factors such as an elevated LDH, stage II disease, age >60 or an ECOG performance status 2 have an extremely good prognosis and may be treated with an abbreviated course (three cycles) of RCHOP (rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone) combined with involved-field RT. For patients with any of the adverse features listed above, the recommendation is 6-8 cycles of CHOP+R. Patients could receive additional adjuvant RT (category 2B). Patients who present with bulky disease and/or local extranodal disease may be more effectively treated with a full course (six to eight cycles) of CHOP chemotherapy with rituximab and involved-field RT (category 1).

Treatment options for patients with advanced-stage disease vary depending on additional prognostic information provided by the Age-Adjusted International Index. Patients who fall into the low or low-intermediate risk category, as indicated by a normal LDH serum level and normal performance status (Eastern Cooperative Oncology Group [ECOG] 0 or 1) are appropriate candidates for full course anthracycline-based chemotherapy. This therapy would include six to eight cycles of R-CHOP for patients of all ages (category 1). An alternative is CHOP-14 (bi-weekly CHOP) for patient >60. However, participation in clinical trials of new regimens is recommended if available. In patients with bulky disease or impaired renal function, initial therapy should include monitoring and prophylaxis for tumor lysis syndrome (i.e., vigorous hydration and administration of allopurinol). Patients who fall into the IPI high-intermediate- or high-risk category have less than a 50% chance of being cured with standard therapy. For this reason, the consensus of the panel is that, if possible, these patients should be treated in the context of appropriate clinical trials. Most current trials are evaluating augmented chemotherapy in the form of up-front or consolidative high-dose therapy, with or without stem cell rescue, in this patient group. In patients who are not candidates for placement on a clinical trial protocol or who do not have access to a protocol, an alternative would be 6-8 cycles of CHOP (category 1) with rituximab.

Patients who are receiving induction therapy should undergo repeat radiographic evaluation, including all positive studies, after three to four cycles of treatment. This early restaging is performed to identify, at the earliest point possible, patients whose disease has not responded or has progressed despite induction therapy. Upon completion of induction therapy, all positive radiographic studies should be repeated. Functional imaging (gallium or PET scans) may be particularly useful in determining whether residual masses represent fibrosis or viable tumor. A repeat biopsy of residual masses is recommended if the masses remained positive on a functional imaging scan upon completion of induction therapy. For patients having complete response (CR) or complete response/unconfirmed (CRu), the planned course of treatment is completed. Consideration of autologous stem cell transplant or completing the course of therapy with a higher RT dose (40-45 Gy) is recommended for stage I-II patients with partial response (PR). Stage III-IV PR patients need to continue with R-CHOP to a total of 6-8 cycles. In addition, appropriate clinical trial is recommended for all the PR patients. If there is no response to treatment or progressive

disease is observed, patients are treated as relapsed. Patients who experience relapse following an initial complete response or have refractory disease and who are candidates for high-dose chemotherapy should be treated with a non-cross-resistant combination chemotherapeutic regimen, such as ICE±R (ifosfamide, carboplatin and etoposide), DHAP (dexamethasone, cytarabine [cytosine arabinoside], and cisplatin), MINE (mitoxantrone, ifosfamide, mesna, etoposide), miniBEAM (carmustine, etoposide, cytarabine, melphalan), and ESHAP (methylprednisolone, etoposide, cytarabine, cisplatin) in an attempt to achieve a second response. Patients who respond (CR or PR) to a non-cross-resistant chemotherapy regimen should be considered for further consolidation with high-dose therapy and stem cell support (category 1 for second response in relapse, category 2A for all others). There are multiple approaches to high-dose therapy with stem cell support; however, none of these has emerged as the preferred alternative. Additional RT can be given before or after stem cell transplant to sites of bulky disease. Pertinent clinical trials are considered another option in this case. Patients who achieve complete remission and are not eligible for high-dose therapy should be treated individually. Similarly, patients with disease recurrence following high-dose therapy should be treated in the context of a clinical trial or individually. However, patients with disease progression despite three successive chemotherapeutic regimens are not likely to benefit from currently available standard therapy, except for patients with a long disease-free interval.

2.2 Study agents

2.2.1 Bortezomib

Bortezomib (Velcade, PS-341), the prototypical clinically relevant proteasome inhibitor, is a dipeptidyl boronic acid derivative that has recently been approved for use in myeloma and mantle cell lymphoma and has also shown activity in other hematologic malignancies (1-3). Bortezomib inhibits the chymotryptic activity of the 20S proteasome, and in so doing, disrupts the proteasome-mediated degradation of diverse cellular proteins (4). Bortezomib activity has been postulated to reflect interference with NF-κB signaling secondary to inhibition of degradation of the NF-κB-inhibitory protein IκBα (5). However, multiple other mechanisms of lethality have been proposed, including increased generation of reactive oxygen species (ROS), which has been demonstrated in lung cancer and leukemia cells (6). Moreover, proteasome inhibitors have been shown to kill cells in association with induction of ER stress, presumably by interfering with the disposition of unfolded proteins. For reasons that are incompletely understood, proteasome inhibitors selectively induce apoptosis in tumor as compared with normal cells (7, 8).

2.2.2 Vorinostat

Vorinostat, a Class I/II histone deacetylase inhibitor (HDI), was the first approved agent of this class on the basis of activity in refractory cutaneous T cell lymphoma (9, 10). In phase I and phase II trials vorinostat also has elicited responses in acute leukemia, lymphoma, and a variety of solid tumors (11, 12).

HDIs are a chemically diverse group of compounds that share the ability to inhibit histone deactylases (HDs) and thereby promote acetylation of histones that in turn results in chromatin uncoiling and transcription of otherwise silenced genes (12). HDIs also promote acetylation of diverse non-histone proteins, and this may cause protein dysfunction (13). Downstream effects are diverse, and, in many or most cases, it is unclear whether these effects are due to promotion of gene expression or non-histone protein acetylation or the combination.

HDIs can induce apoptosis in leukemic cells through processes regulated by induction of the cyclin-dependent kinase inhibitor $p21^{CIP1}$ (14), generation of reactive oxygen species and Bid activation (15). Further, HDIs can inactivate cytoprotective signaling pathways (e.g., Raf/MEK/ERK and Akt) (16). Certain HDIs, including vorinostat, promote acetylation of HSP90, tubulin and dynein (17, 18). Acetylation and inactivation of Hsp90 induces increases in misfolded proteins that form protein aggregates. These protein aggregates are transported by dynein along a microtubule network to the aggresome where they are further processed for ultimate proteasomal degradation. HD6 is responsible for maintenance of deacetylation and proper functioning of dynein and other components of the aggresome. Disruption of HD6 results in dynein acetylation, aggresome dysfunction, and cell death manifested by the formation of dysmorphic perinuclear aggresomes. HDIs also can induce differentiation of tumor cells (9).

2.2.3 Bortezomib and Vorinostat in Combination

In preclinical studies involving both Bcr/Abl+ and Bcr/Abl- leukemia cells, including Bcr/Abl+ cells resistant to imatinib, we have shown synergistic cytotoxic interactions between bortezomib and vorinostat and other HDIs (19, 20). More recently, we have observed comparable synergistic interactions between bortezomib and vorinostat in continuously cultured human multiple myeloma cells as well as fresh CD138+ bone marrow cells (presumptive myeloma cells) from patients with multiple myeloma (21).

Three mechanisms have been proposed to explain synergism between these agents:

(1) HDI-mediated inhibition of class I, nuclear HDs may result in sustained activation of NF-κB, and lethal effects of HDIs may be intrinsically limited by this activation (22). Concurrent proteasome inhibition may disrupt NF-κB activation and thereby potentiate HDI antitumor activity (23, 24).

(2) Cell death resulting from HDI-mediated HSP90 and aggresome dysfunction may be potentiated by concurrent inhibition of the proteasome (25, 26).

(3) HDI-mediated accumulation of unfolded proteins in the endoplasmic reticulum may provoke an evolutionarily conserved adaptive response referred to as the unfolded protein response (UPR) (27, 28). It consists of multiple components that can be broadly characterized as alarm, adaptive, and apoptotic responses, including cell cycle arrest, chaperone protein synthesis, up-regulation of cytoprotective signaling pathways (including NF-κB), inhibition of protein translation, and enhanced protein degradation. When the UPR is overwhelmed, it triggers events that lead to apoptosis. Because proteasome inhibitors both promote accumulation of unfolded proteins and down-regulate NF-κB, it is plausible to propose that concurrent proteasome inhibition may potentiate the lethality of the UPR. Recent studies in pancreatic cancer cells implicate this mechanism in the enhanced lethality of proteasome/HDI regimens (29).

Recent preclinical studies from our laboratories in human U937 cells (derived from a patient with diffuse large B-cell lymphoma), T-lymphoblastic Jurkat cells, and primary AML blasts demonstrate a high degree of synergism between non-toxic concentrations of bortezomib and vorinostat. Similar results have been obtained in other lymphoma lines (e.g., SU-DHL 16, Karpas, and Raji). In each case, low, relatively non-toxic concentrations of bortezomib (e.g., 3-5 nM) and vorinostat (e.g., 1 μM), administered concurrently for 24 hrs resulted in a significant increase in apoptosis. The enhancement of lethality for the combination is at least as great as that previously reported in Bcr/Abl+ leukemia and in multiple myeloma

cells, raising the possibility that this strategy may be effective in lymphoproliferative malignancies such as lymphoma.

In an ongoing phase I trial of the combination of bortezomib iv days 1, 4, 8, and 11 and vorinostat po on days 4 through 11 on a 21 day cycle in patients with previously treated myeloma, maximum tolerated doses of bortezomib and vorinostat appear to be 1.3 mg/m^2/dose and 400 mg/dose, respectively (30). These doses are being confirmed in an expansion of the maximum tolerated dose patient cohort. Dose limiting toxicities were fatigue and QT interval prolongation. Other toxicities have included infections and thrombocytopenia. Toxicities appear to be cumulative, and schedule adherence in later cycles will be a focus in the ongoing study. Preliminary analysis suggests that the combination is active including activity in patients with bortezomib-refractory disease.

2.3 Study Design Considerations

Vorinostat typically displays cumulative toxicities and often is administered by an interrupted schedule. As the basis of this study is evidence of synergistic interactions between bortezomib and vorinostat, it seems appropriate to administer the two agents concurrently as much as feasible. Based upon the ongoing phase I trial it appears that 10 days of vorinostat is the most that is tolerated within a conventional bortezomib schedule (days 1, 4, 8, and 11 repeated every 21 days). In this study patients will receive two 5 day courses of vorinostat concurrent with twice weekly dosing of bortezomib.

After discussions with CTEP, it has been decided to target two entities within the spectrum of lymphoma: mantle cell lymphoma and diffuse large B-cell lymphoma. Mantle cell lymphoma is an attractive target as bortezomib has single agent activity against this entity and as there is a pressing need for better therapies for this usually lethal condition. Diffuse large B-cell lymphoma is another attractive target as with current therapy most patients are not cured of this most common of the aggressive lymphomas.

As the primary endpoint is disease response, patients must have measurable disease.

Presumably response rates that would be considered promising would differ depending upon whether patients had received prior bortezomib. Although it might be preferable to test the combination exclusively in patients who have not received prior bortezomib, the recent approval of bortezomib for the treatment of mantle cell lymphoma makes it unclear whether it would be feasible to enroll sufficient numbers of such patients with mantle cell lymphoma in a reasonable time frame. Therefore, we propose enrollment of 3 patient cohorts: mantle cell lymphoma, without prior bortezomib; mantle cell lymphoma, with prior bortezomib; and diffuse large B-cell lymphoma (without prior bortezomib). Should it become apparent during the course of the study that one or the other mantle cell lymphoma cohort is not likely to be completed, then that cohort will be closed to further enrollment.

Prior high dose therapy with autologous stem cell transplant raises similar issues with regard to promising response rates as well as tolerance for the combination regimen. Rather than establish separate cohorts for this parameter (potentially requiring 6 patient cohorts, each with different response rate targets), however, we propose to stratify patients according to this parameter in order to establish the appropriateness of an analysis of study outcomes on the basis of this factor.

Patients with persistent/recurrent lymphoma following prior allogeneic transplantation usually have resistant tumors and impaired host tolerance of further treatments. Inclusion of such patients might bias the study against an otherwise active regimen.

As the effects of bortezomib and vorinostat on the developing human fetus at the recommended therapeutic dose are potentially devastating, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation and to report pregnancy or suspected pregnancy while participating in the study. For similar reasons, women who are pregnant or nursing may not participate.

As there is no phase I experience with the combination in children, they are excluded.

2.4 Correlative Studies Background

Two of the three proposed mechanisms for synergistic interaction among the two agents involve interactions with NF-kappaB. Nuclear RelA by immunohistochemical staining is a semi-quantitative measure of NF-kappaB activation with which the investigators have prior experience (31). It is reasonable to propose that the combination of bortezomib and vorinostat might be more active in lymphomas in which there is baseline activation of NF-kappaB, and this is a testable hypothesis.

Lymphoma cell nuclear relA will be assayed in tumor samples obtained previously to confirm eligibility.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

- [redacted]

- [redacted]

[redacted]

- [redacted]

- [redacted]

- [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

3 PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Histologically confirmed mantle cell or diffuse large B-cell lymphoma. Histological material must be available for central pathological review. Unstained histological material -- slides or blocks -- must be available for correlative studies. Archived material from previous biopsies is acceptable, unless a patient's lymphoma has been known to undergo histological transformation in the past, in which case a repeat biopsy to confirm histology prior to enrollment is required. Availability of material must be confirmed at the time of registration, but material may be submitted subsequent to registration and initiation of study treatment.

3.1.2 Measurable disease according to the Revised Response Criteria for Malignant Lymphoma (35). This requires at least one lesion greater than 1.0 cm in diameter in both the long and short axis as measured by spiral CT scan or physical exam.

3.1.3 Prior allogeneic stem cell transplant is allowed provided that all of the following conditions are met:

- ≥ 6 months have elapsed since allogeneic transplant
- No Graft vs. Host Disease (GVHD) is present
- Not currently on immunosuppressive therapy

3.1.4 Prior therapy:

Mantle cell lymphoma:

- Previously treated or untreated.
- No prior bortezomib.

Diffuse large B-cell lymphoma:

- At least one prior systemic therapy.
- No prior bortezomib.

Note: Not intended for patients in first relapse who are candidates for high dose therapy with stem cell support.

3.1.5 Age ≥18 years. As no dosing or adverse event data are available for the combination of bortezomib and vorinostat in patients <18 years of age, children are excluded.

3.1.6 Life expectancy of greater than 3 months.

3.1.7 ECOG performance status 0, 1, or 2.

	ECOG Performance Status
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

3.1.8 Able to tolerate loperamide or other anti-diarrheal medications.

3.1.9 Adequate organ and marrow status:

○ absolute neutrophil count	≥ 1.5 x 10^9/L
○ platelets	≥ 75 x 10^9/L
○ total bilirubin	≤ 1.5 x ULN
○ AST(SGOT)/ALT(SGPT)	≤ 2.5 x institutional upper limit of normal
○ creatinine	within normal institutional limits or calculated creatinine clearance ≥ 60 mL/min according to the Cockcroft-Gault Formula

Calculated Creatinine Clearance (Cockcroft and Gault)
Creatinine clearance (mL/min) = {(140 - Age) * Wt in kg * G}/ (Creat * 72) G= 1 (males); G=0.85 (females)

3.1.10 For patients with known HIV infection, a CD4 count ≥ 0.5 x 10^9/L.

3.1.11 For patients whose last treatment included bendamustine or fludarabine, a CD4 count ≥ 0.4 x 10^9/L.

3.1.12 The effects of bortezomib and vorinostat on the developing human fetus at the recommended therapeutic dose are unknown. For this reason women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation and to report pregnancy or suspected pregnancy while participating in the study.

3.1.13 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Chemotherapy or large field radiotherapy within 3 weeks prior to entering the study.

3.2.2 Prior histone deactylase inhibitor as cancer treatment.

3.2.3 Concurrent treatment with other investigational agents.

3.2.4 Plans for other concurrent cancer treatment. If steroids for cancer control have been used, patients must be off these agents for ≥ 1 week before starting treatment. Exception: maintenance therapy for non-malignant disease with prednisone or steroid equivalent dose < 10 mg/day is permitted.

3.2.5 History of brain metastasis including leptomeningeal metastasis.

3.2.6 Grade ≥ 2 neuropathy, regardless of cause.

3.2.7 Unable to take oral medications.

3.2.8 History of allergic reactions attributed to compounds of similar chemical or biologic composition to bortezomib or vorinostat.

3.2.9 Not sufficiently recovered from previous treatment.

3.2.10 Medical or other condition (for example: uncontrolled infection; potentially life threatening changes on EKG) or concurrent treatment (for example, marrow suppressive agents such as zidovidine) that represents an inappropriate risk to the patient or likely would compromise achievement of the primary study objective. Note that bortezomib is a 1A2, 2C9, 2C19, 2D6, and 3A4 substrate. Therefore, patients should be closely monitored when given bortezomib in combination with the CYP3A4 inhibitors and inducers listed in Section 5.2.2.

3.2.11 Pregnant women are excluded from this study because bortezomib and vorinostat are potential teratogens. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with bortezomib and vorinostat, breastfeeding should be discontinued.

3.2.12 Active concurrent malignancy, except adequately treated non-melanoma skin cancer.

3.3 Inclusion of Women and Minorities

Both men and women and members of all races and ethnic groups are eligible for this trial.

4 REGISTRATION PROCEDURES

4.1 General Guidelines

Patients are registered on study centrally at the Moffitt Cancer Center.

Following registration, patients should begin protocol treatment within one week. Notify the SEP2C Administrator of longer delays or a decision not to initiate study treatment and document.

Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov).

4.2 Registration Process

To register a patient, the following should be faxed (813-745-5944) or e-mailed (SEP2C@moffitt.org) to the SEP2C Administrator:

- Copy of signed and dated eligibility form (attached in Oncore)

The SEP2C administrator will then complete the registration process by:

- Registering the patient to Cohort A: mantle cell lymphoma, no prior bortezomib (Cohorts B and C are closed)
- Assigning a registration number
- Assigning stratification
    - Stratum SG01: prior autologous transplant
    - Stratum SG02: no prior autologous transplant
- Transmitting the patient number to the participating site.

The research nurse or data manager must then enter subject registration information into Moffitt's Oncore prior to starting study treatment.

5 TREATMENT PLAN

5.1 Schedule and Dosing

Patients whose serum total bilirubin > 1.5 x ULN within 4 days prior to Cycle 1 Day 1 should not receive study treatment and must be taken off-study.

Vorinostat 400 mg (total daily dose as a single dose) days 1-5 and 8-12.

Bortezomib 1.3 mg/m^2/d iv days 1, 4, 8, and 11.

Vorinostat precedes bortezomib on days of concurrent administration.

Repeat every 3 weeks.

Minor modifications in schedule may be made to accommodate scheduling difficulties. Modification and cause should be documented. In any event, bortezomib doses should not be administered closer than 72 hours apart.

5.2 General Concomitant Medication and Supportive Care Guidelines

5.2.1 Agent Related Supportive Care

Advise patients that vorinostat may cause anorexia, dehydration, diarrhea, nausea and emesis.

Encourage and monitor for adequate fluid and food intake.

Prescribe anti-emetics as clinically indicated.

Instruct patients to begin loperamide (or similar anti-diarrheal agent) at the first signs of: 1) poorly formed or loose stool, 2) more bowel movements than usual in one day, or 3) unusually high volume of stool. Loperamide dose and schedule is 4 mg (generally, 2 tablets) at first onset of diarrhea, then 2 mg (1 tablet) after each unformed stool, but not to exceed 16 mg/day (8 tablets/day). Loperamide should not be taken prophylactically. Avoid loperamide if there is the presence of blood or mucus in the stool or if diarrhea is accompanied by fever. If grade 3 or 4 diarrhea develops, discontinue vorinostat.

Consider intravenous hydration with each infusion of bortezomib. Intravenous infusion of 1000 mLs of normal saline or D5W over 30-60 minutes is recommended, or, in patients with cardiac concerns or fluid overload issues, intravenous infusion of 500 mLs normal saline or D5W via over 60 minutes.

Prophylactic antiviral treatment is recommended for all patients receiving bortezomib. Acyclovir 400 mg po bid or a similar regimen is recommended. Prophylactic antiviral treatment is allowed for all patients at the discretion of the treating physician.

In general, because of the risk of confounding response assessments, corticosteroids are to be avoided concurrent with study participation with the following exceptions:

- Corticosteroids for nausea control are allowed.
- Topical, intra-articular, and eye drop steroids are allowed.

Steroids for other indications should be discussed with the study chair prior to use.

Provide other supportive care measures as clinically indicated.

5.2.2 CYP3A4 Inhibitors and Inducers

Co-administration of a strong CYP3A4 inhibitor may increase the exposure of the patient to bortezomib, while co-administration of a CYP3A4 inducer may reduce the efficacy of bortezomib. Therefore, patients should be closely monitored when given bortezomib in combination with the CYP3A4 inhibitors and inducers listed in the table below.

Strong CYP3A4 Inhibitors	**CYP3A4 Inducers**
indinavir neflinavir ritonavir clarithromycin itraconazole ketoconazole nefazodone	carbamazepine phenobarbital phenytoin pioglitazone rifabutin rifampin St. John's wort troglitazone
Source: http://medicine.iupui.edu/clinpharm/DDIs/ClinicalTable.aspx "Clinically Relevant Table", Updated November 14, 2011	

5.2.3 Concurrent Cancer Treatment

Concurrent non-study cancer treatment is not permitted. Non-prescription nutritional and dietary supplements are discouraged but not prohibited and, if used, should be documented.

5.3 Duration of Therapy

Continue treatment until:

- Disease progression or requirement of palliative irradiation
- Unacceptable toxicity
- Patient decision to discontinue treatment
- Investigator decision that treatment no longer is in the patient's best medical interest
- Study closure

Patients who experience a complete or partial response following at least one year of treatment may go off study treatment but remain on study and resume study treatment upon disease progression if the study remains open.

5.4 Duration of Follow Up

Continue disease status follow up until disease progression or initiation of another treatment.

Continue toxicity follow-up until resolution or stabilization of treatment related toxicity or initiation of another treatment that confounds ongoing toxicity evaluation.

5.5 Criteria for Removal from Study

Patients are off study when off treatment and disease status and toxicity follow up is complete. Certain subsequent events, however (for example, secondary malignancies) may remain subject to reporting if identified. See Section 7.

6 DOSING DELAYS/DOSE MODIFICATIONS

Scheduled agent doses are administered or omitted, not delayed, with the exception that initial doses of a new cycle are delayed pending resolution of dose-modifying toxicity. If dose-modifying toxicity requires treatment delay for longer than 3 weeks, consider whether patient should be taken off study treatment as per Section 5.3. If dose omission for toxicity, omit one or both agents according to clinical judgment with regard to attribution and severity.

Vorinostat and bortezomib have both overlapping and non-overlapping toxicities; for example, fatigue or sensory neuropathy might be due to either/both agents, but motor neuropathy most likely would be due to bortezomib. Investigators adjust the administration of either/both agents according to the nature, severity, and attribution of toxicity in the suggested sequences.

Dose Level Modifications for Toxicities			
See following tables for independent dose adjustments of drugs.			
Hematologic		Non-hematologic (excluding bortezomib-induced neuropathy and excluding hyperbilirubinemia) *See instructions below	
Grade	Action	Grade	Action
Grade ≥ 3	Omit; resume dosing at next lower dose level upon resolution to Grade ≤ 2.	Grade 2, optional. Grade ≥ 3, required.	Omit; resume dosing at next lower dose level upon resolution to Grade ≤ 2 (Grade 1 preferred).

Vorinostat Dose/Schedule Reduction Schema	
1	Reduce vorinostat to 300 mg/dose
2	Reduce vorinostat to 200 mg/dose
3	Reduce vorinostat to 100 mg/dose
4	Discontinue vorinostat

Bortezomib Dose/Schedule Reduction Schema, excluding neuropathy[1]	
1	Reduce bortezomib dose to 1.0 mg/m^2
2	Reduce bortezomib dose to 0.7 mg/m^2
3	Reduce bortezomib dosing to once weekly (in weeks 1 & 2 of cycle)
4	Reduce bortezomib dosing to once per cycle
5	Discontinue bortezomib[2]

Bortezomib-Induced Hyperbilirubinemia Dose Reduction Schema
Patients with mild hepatic impairment (bilirubin ≤ 1.5 × ULN) do not require a starting dose adjustment. Please note that patients with bilirubin levels > 1.5 ULN are excluded from enrollment in this protocol. If a patient develops moderate or severe hepatic impairment with bilirubin ≥ Grade 2 (> 1.5 X ULN) while on study, the investigator should hold bortezomib until the toxicity returns to < Grade 2. Restarting bortezomib at the next lower dose level could be considered at the Investigator's discretion following exclusion of bortezomib-induced liver impairment and careful consideration of liver disease due to other causes, such as, but not limited to, active infection. Bortezomib doses may be re-escalated subsequently at the discretion of the investigator, but not to levels higher than the patient's initial dose.

Bortezomib-Induced Neuropathy Dose/Schedule Reduction Schema[1]	
Grade 1 (paresthesias and/or loss of reflexes) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (interfering with function but not with activities of daily living)	Reduce bortezomib dose by one dose level, according to table above
Grade 2 with pain or Grade 3 (interfering with activities of daily living)	Withhold bortezomib therapy until toxicity resolves to Grade 1 or less, then resume at 0.7 mg/m^2 and change treatment schedule to once per week (in weeks 1 & 2 of cycle); except if already at 0.7 mg/m^2 once per week, then discontinue bortezomib.[2]
Grade 4 (disabling)	Discontinue bortezomib[2]

[1] If both bortezomib dose/schedule reduction schemas apply, administer lower/less frequent bortezomib dose/schedule.

[2] If bortezomib must be discontinued due to dose reductions and vorinostat is tolerable, patient may continue on vorinostat alone at treating physician's discretion until next scheduled response assessment. At that time, if patient continues without evidence of progression or intolerable vorinostat toxicity, patient may continue on vorinostat alone.

7 ADVERSE EVENT LIST AND REPORTING REQUIREMENTS

7.1 Comprehensive Adverse Events and Potential Risks List (CAEPR)

Adverse events will be categorized in terms of nature, severity, and attribution and documented according to the NCI CTCAE v4.0 beginning April 1, 2011 (http://ctep.cancer.gov).

7.2 CAEPR - Bortezomib

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

The Comprehensive Adverse Event 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 via CTEP-AERS (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 2042 patients. Below is the CAEPR for bortezomib (PS-341).

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 2.4, February 26, 2013[1]

Adverse Events with Possible Relationship to Bortezomib (PS-341) (CTCAE 4.0 Term) [n= 2042]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)** (formerly known as ASAEL)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***
	Febrile neutropenia		
EYE DISORDERS			
	Blurred vision		
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 2)***
Fatigue			***Fatigue (Gr 3)***
Fever			***Fever (Gr 2)***
INFECTIONS AND INFESTATIONS			
Infection[4]			***Infection[4] (Gr 3)***
	Infections and infestations - Other (Opportunistic infection associated with >= Grade 2 Lymphopenia)		
INVESTIGATIONS			
	Lymphocyte count decreased		
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	White blood cell decreased		
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)***
	Generalized muscle weakness		
	Myalgia		***Myalgia (Gr 2)***
	Pain in extremity		***Pain in extremity (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 3)***
	Headache		***Headache (Gr 2)***
		Leukoencephalopathy	
	Neuralgia		***Neuralgia (Gr 3)***
Peripheral motor neuropathy			***Peripheral motor neuropathy (Gr 3)***
Peripheral sensory neuropathy			***Peripheral sensory neuropathy (Gr 3)***
		Reversible posterior leukoencephalopathy syndrome	
	Syncope		
PSYCHIATRIC DISORDERS			
	Anxiety		
	Insomnia		***Insomnia (Gr 2)***
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		
	Epistaxis		
	Pharyngeal mucositis		***Pharyngeal mucositis (Gr 2)***
	Pleural effusion		
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 bortezomib (PS-341) trials but with the relationship to bortezomib (PS-341) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (lymphadenopathy); Disseminated intravascular coagulation

CARDIAC DISORDERS - Asystole; Atrial fibrillation; Atrial flutter; Cardiac disorders - Other (cardiac amyloidosis); Heart failure; Left ventricular systolic dysfunction; Myocardial infarction; Pericardial effusion; Right ventricular dysfunction; Sinus bradycardia; Ventricular tachycardia

EAR AND LABYRINTH DISORDERS - Hearing impaired

EYE DISORDERS - Conjunctivitis; Dry eye; Extraocular muscle paresis; Eye disorders - Other (conjunctival hemorrhage); Watering eyes

GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Dry mouth; Dysphagia; Esophagitis; Flatulence; Gastritis; Gastrointestinal disorders - Other (ischemic bowel); Gastrointestinal disorders - Other (eructation); Mucositis oral; Oral pain; Pancreatitis; Small intestinal obstruction

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Gait disturbance; General disorders and administration site conditions - Other (hepato-renal syndrome); Injection site reaction; Non-cardiac chest pain; Sudden death NOS

HEPATOBILIARY DISORDERS - Hepatobiliary disorders - Other (portal vein thrombosis)

IMMUNE SYSTEM DISORDERS - Allergic reaction

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Fracture

INVESTIGATIONS - Activated partial thromboplastin time prolonged; Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; CPK increased; Creatinine increased; GGT increased; INR increased; Serum amylase increased; Weight gain; Weight loss

METABOLISM AND NUTRITION DISORDERS - Hypercalcemia; Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (hypoproteinemia); Metabolism and nutrition disorders - Other (failure to thrive); Tumor lysis syndrome

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Buttock pain

NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysgeusia; Dysphasia; Intracranial hemorrhage; Ischemia cerebrovascular; Memory impairment; Nervous system disorders - Other (spinal cord compression); Nervous system disorders - Other (cranial palsy); Nervous system disorders - Other (dysautonomia); Seizure

PSYCHIATRIC DISORDERS - Agitation; Confusion; Depression; Psychosis

RENAL AND URINARY DISORDERS - Bladder spasm; Hematuria; Proteinuria; Renal and urinary disorders - Other (calculus renal); Renal and urinary disorders - Other (bilateral hydronephrosis); Renal and urinary disorders - Other (glomerular nephritis proliferative); Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract pain

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Atelectasis; Bronchopulmonary hemorrhage; Bronchospasm; Hiccups; Hypoxia; Pharyngolaryngeal pain; Pneumonitis; Pulmonary hypertension; Respiratory, thoracic and mediastinal disorders - Other (obstructive airways disease); Voice alteration

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Pruritus; Purpura; Skin and subcutaneous tissue disorders - Other (leukoclastic vasculitis); Urticaria

VASCULAR DISORDERS - Capillary leak syndrome; Flushing; Hematoma; Thromboembolic event

Note: Bortezomib (PS-341) 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.

7.3 CAEPR - Vorinostat

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Vorinostat (SAHA, NSC 701852)

The Comprehensive Adverse Event 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 via CTEP-AERS (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 702 patients.* Below is the CAEPR for vorinostat (SAHA).

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 2.8, December 18, 2013[1]

Adverse Events with Possible Relationship to Vorinostat (SAHA, Zolinza) (CTCAE 4.0 Term) [n= 1076]			**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)***
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
	Constipation		***Constipation (Gr 2)***
Diarrhea			***Diarrhea (Gr 2)***
	Dry mouth		***Dry mouth (Gr 2)***
	Dyspepsia		***Dyspepsia (Gr 2)***
Nausea			***Nausea (Gr 2)***
Vomiting			***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
	Fever		
INFECTIONS AND INFESTATIONS			
	Infection[2]		
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***

	Blood bilirubin increased		
	Creatinine increased		***Creatinine increased (Gr 2)***
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 3)***
	Weight loss		***Weight loss (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 4)***
METABOLISM AND NUTRITION DISORDERS			
Anorexia			***Anorexia (Gr 2)***
	Dehydration		***Dehydration (Gr 2)***
	Hyperglycemia		***Hyperglycemia (Gr 2)***
	Hypocalcemia		
	Hypokalemia		
	Hypophosphatemia		***Hypophosphatemia (Gr 3)***
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Muscle weakness[3]		***Muscle weakness[3] (Gr 2)***
NERVOUS SYSTEM DISORDERS			
	Dizziness		***Dizziness (Gr 2)***
	Dysgeusia		***Dysgeusia (Gr 2)***
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Alopecia		
		Skin and subcutaneous tissue disorders - Other (skin necrosis)	

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

[3]Muscle weakness includes Generalized muscle weakness, Muscle weakness left-sided, Muscle weakness lower limb, Muscle weakness right-sided, Muscle weakness trunk, and Muscle weakness upper limb under the MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS SOC.

[4]Prolongation of prothrombin time and International Normalized Ratio have been observed in patients using vorinostat concomitantly with coumarin-derivative anticoagulants.

Also reported on vorinostat (SAHA, Zolinza) trials but with the relationship to vorinostat (SAHA, Zolinza) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Febrile neutropenia

CARDIAC DISORDERS - Atrial fibrillation; Atrial flutter; Cardiac disorders - Other (supraventricular arrhythmia); Chest pain - cardiac; Left ventricular systolic dysfunction; Myocardial infarction; Palpitations; Pericardial effusion; Sinus bradycardia; Sinus tachycardia; Ventricular fibrillation

EAR AND LABYRINTH DISORDERS - Tinnitus; Vertigo

EYE DISORDERS - Blurred vision; Eye disorders - Other (retinal tear)

GASTROINTESTINAL DISORDERS - Abdominal distension; Anal hemorrhage; Bloating; Cheilitis; Colitis; Dysphagia; Esophageal hemorrhage; Esophagitis; Flatulence; Gastric hemorrhage; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (duodenitis); Lower gastrointestinal hemorrhage; Mucositis oral; Oral hemorrhage; Oral pain; Small intestinal obstruction; Stomach pain; Upper gastrointestinal hemorrhage

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Gait disturbance; General disorders and administration site conditions - Other (failure to thrive); Malaise; Multi-organ failure; Non-cardiac chest pain; Pain

HEPATOBILIARY DISORDERS - Hepatic failure

IMMUNE SYSTEM DISORDERS - Immune system disorders - Other (angioedema)

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Vascular access complication; Wound dehiscence

INVESTIGATIONS - Activated partial thromboplastin time prolonged4; Alkaline phosphatase increased; Cardiac troponin I increased; Electrocardiogram QT corrected interval prolonged; GGT increased; INR increased4; Investigations - Other (increased lactate dehydrogenase); Lipase increased

METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperkalemia; Hypermagnesemia; Hyperuricemia; Hypoalbuminemia; Hyponatremia; Metabolism and nutrition disorders - Other (decreased total protein); Tumor lysis syndrome

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Chest wall pain; Musculoskeletal and connective tissue disorder - Other (muscle spasms); Musculoskeletal and connective tissue disorder - Other (myositis); Myalgia; Neck pain; Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor hemorrhage); Tumor pain

NERVOUS SYSTEM DISORDERS - Abducens nerve disorder; Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysphasia; Encephalopathy; Facial muscle weakness; Facial nerve disorder; Headache; Intracranial hemorrhage; Ischemia cerebrovascular; Lethargy; Memory impairment; Nervous system disorders - Other (Guillain-Barre syndrome); Nervous system disorders - Other (head injury); Nervous system disorders - Other (polyneuropathy); Paresthesia; Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Somnolence; Stroke; Syncope; Tremor

PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Euphoria; Personality change; Psychosis

RENAL AND URINARY DISORDERS - Acute kidney injury; Hematuria; Proteinuria; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract pain

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Irregular menstruation; Pelvic pain; Uterine hemorrhage; Vaginal hemorrhage

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Epistaxis; Hypoxia; Pharyngeal mucositis; Pleural effusion; Pleuritic pain; Pneumonitis

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Dry skin; Hyperhidrosis; Nail loss; Palmar-plantar erythrodysesthesia syndrome; Purpura; Rash maculo-papular; Skin and subcutaneous tissue disorders - Other (brittle nails)

VASCULAR DISORDERS - Flushing; Hematoma; Hot flashes; Hypertension; Hypotension; Thromboembolic event; Visceral arterial ischemi

Note: Vorinostat (SAHA, Zolinza) 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 Adverse Event Characterization

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting beginning April 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 Sections 7.2 and 7.3 above) for expedited reporting purposes only. 'Expected' AEs (the ASAEL) are ***bold and italicized*** in the CAEPR (Sections 7.2 and 7.3).

- **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.

7.5 Expedited Adverse Event Reporting

7.5.1 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). These requirements are briefly outlined in the table below (Section 7.5.3).

In the rare event when Internet connectivity is disrupted, a 24-hour notification is to be made to NCI by telephone at: 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of internet connection.

7.5.2 CTEP-AERS is programmed for automatic electronic distribution of reports to the following individuals: SEP2C Administrator (SEP2C@moffitt.org), Study Chair, and the local treating physician. CTEP-AERS provides a copy feature for other e-mail recipients.

7.5.3 **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 2 and 3 Trials

Phase 2 and 3 Trials									
	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unex-pected	Expected	with Hospitali-zation	without Hospitali-zation	with Hospitali-zation	without Hospitali-zation	Unex-pected	Expected
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-Hour; 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 a 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.

7.6 Routine Adverse Event Reporting

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

7.7 Secondary Malignancy

A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (*e.g.*, acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via routine reporting.

7.8 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

8 PHARMACEUTICAL INFORMATION

8.1 Bortezomib (NSC 681239)

Chemical Name: N-Pyrazinecarbonyl-L-phenylalanine-L-leucine boronic acid

Other Names: MLN341, LDP-341, PS-341, Velcade®

Classification: Proteasome Inhibitor

CAS Registry Number: 179324-69-7

Molecular Formula: $C_{19}H_{25}BN_4O_4$

M.W.: 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.

Route of Administration: Intravenous

Potential Drug Interactions: Substrate for CYP450 isoenzymes 1A2, 2C9, 2C19, 2D6, and 3A4. Bortezomib is provided to the NCI under a Collaborative Agreement between Millennium Pharmaceutics, Inc. and the DCTD, NCI (see Section 12.5).

8.2 Vorinostat (NSC 701852)

Chemical Name: N-hydroxy-N'-phenyl-octane-1,8-diotic acid diamide; N-hydroxyl-N'-phenyl (9CI) octanediamide; suberoylanilide hydroxamic acid

Other Names: SAHA, L-001079038, WIN 64652, MSK390, AP390, Zolinza®

Classification: Antineoplastic

CAS Registry Number: 149647-78-9

Molecular Formula: $C_{14}H_{20}N_20_3$

M.W.: 264.32

Approximate Solubility: Water ≤ 5 mg/mL

Description: Histone deacetylase (HDAC) inhibitor

Mode of Action: Histone deacetylases (HDACs) are a family of enzymes that regulate chromatin remodeling and gene transcription via the dynamic process of acetylation and deacetylation of core histones. Vorinostat, a potent inhibitor of HDAC activity, binds directly to the catalytic pocket of HDAC enzymes. It causes G1 or G2 phase cell-cycle arrest, apoptosis, or differentiation in cultured transformed cells.

How Supplied: Supplied by Merck and Co., Inc. and distributed by the CTEP, DCTD, NCI as a white, opaque gelatin, size 3 capsule, containing 100 mg of vorinostat. The inactive ingredients contained in each capsule are microcrystalline cellulose, sodium croscarmellose, and magnesium stearate. Vorinostat 100 mg capsules are supplied in bottles containing 120 capsules.

Storage: Store at room temperature, 15 to 30 ºC (59 to 86 ºF). Do not store above 30ºC. Avoid exposure to excessive moisture.

Stability: Shelf life stability studies of the intact bottles are on-going.

Route of Administration: Orally

Method of Administration: Unless otherwise stated in the protocol, vorinostat capsules must be administered whole. Administer doses of vorinostat with food, if possible.

Potential Drug Interactions: The major pathways of vorinostat metabolism involve glucuronidation and β-oxidation. As vorinostat is not eliminated via CYP450 pathways, no drug-drug interactions are expected with known CYP450 inhibitors or inducers. Prothrombin time and INR prolongations have been reported in patients taking vorinostat concomitantly with coumarin derivative anticoagulants. Monitor these patients more frequently for alterations in their coagulation parameters.

Special Handling: Vorinostat is an anticancer drug. Clean powder spills from broken or damaged vorinostat capsules carefully minimizing inhalation. Wash spill area at least 3 times with ethyl alcohol, followed by water.

Vorinostat is provided to the NCI under a Collaborative Agreement between Merck Pharmaceutics, Inc. and the DCTD, NCI (see Section 12.5).

8.3 Agent Ordering

NCI-supplied agents may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that the agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained). The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), Curriculum Vitae, Supplemental Investigator Data Form (IDF), and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution.

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov.

8.4 Agent Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the CTEP home page at http://ctep.cancer.gov for the Procedures for Drug Accountability and Storage and to obtain a copy of the DARF and Clinical Drug Request form.)

9 CORRELATIVE STUDIES

Baseline nuclear relA expression as a predictive marker of response to the combination of bortezomib and vorinostat in the treatment of mantle cell and diffuse large B-cell lymphoma.

The rationale is described in Section 2.4.

Directions for obtaining and submitting tissue samples for correlative studies are found in Section 12.1.

Before subjecting the samples to immunohistochemical evaluation,the available histological material will undergo central pathological review [redacted] at the Moffitt Cancer Center.

The expression of Rel A protein will be evaluated by immunohistochemistry using a specific antibody for testing on paraffin slides. We will use a mouse monoclonal anti-NF-κB antibody, p65 subunit (Chemicon International, Temecula CA, clone 12H11). This antibody is selective to the activated

form of NF-κB. This monoclonal antibody recognizes an epitope overlapping the nuclear localization signal (NLS) of the RelA/p65 transactivation subunit.

Briefly, pretreatment for antigen retrieval is performed using the DAKO Antigen Retrieval kit (Cat#S1700). Samples are preheated to 98°C for 15 min. After cooling for 20 min @ room temperature in solution, the samples are washed in milliQ-water for 4-5 min. The samples are incubated in quenching buffer for 10 min, washed in milliQ-water for 4-5 min, and incubated for 10 min with Avidin blocking buffer (Vector Labs Cat#SP-2001). After washing with PBS for 5 min, the slides are blocked with Biotin blocking buffer, and placed in blocking buffer (1% BSA, 0.2% Milk) for an hour. This is followed by incubation with the anti-NF-kB primary antibody (2 ug /mL) in blocking buffer overnight at 4°C. After rinsing with PBS for 5 min, the slides are incubated with a biotinylated goat anti-mouse secondary antibody, diluted in blocking buffer (0.334 ug/mL) for 1 hr at room temperature. After washing with PBS for 5 min, the slides are incubated with streptavidin–HPR diluted in blocking buffer 1:100 for 30 min (Invitrogen TSA Kit #21 cat# T20931), and washed again. The slides are next incubated in biotin –XX tyramide (in kit amplification buffer/0.0015% H_2O_2) for 10 min. After an additional washing, the sample is incubated with ABC for 30 min (Vector labs Cat# PK-6100) and developed with 3,3-diaminobenzidine (DAB) for 1-7 min (Vector labs Cat# SK-4100). All of the slides are lightly counterstained with hematoxylin for 10s before dehydration and mounting. Immunostaining is observed with a Leitz Orthoplan 2 microscope and images are captured by a CCD camera with the Smart Capture Program (Vysis, Downers Grove, IL*). Positive controls will be run with each set of slides according to the manufacturer's instructions.* Negative controls will be included by omitting the primary antibody during the primary antibody incubation.

The stained slides will be read by [redacted], MD in a blinded fashion, and scored for the presence of Rel A protein. The positive antibody reaction will consist in a nuclear dark-brown stain. The stain will be scored into four grades, according to the intensity of the staining: 0, 1+, 2+, and 3+. The percentages of positive cells will also be scored into four categories: 0 (0%), 1 (1-33%), 2 (34-66%), and 3 (67-100%). The product of the intensity and the percentage scores will be used as the final score.

To define the B cell immunophenotype (germinal center B cell-like or activated B cell-like) we will subject the samples to immunostains with CD10 and CD23. To identify germinal center B cells we will use a mouse monoclonal anti CD10 Ab (abCam Inc., Cambridge, MA; clone 56C6, dilution1: 25), and for the detection of activated B cell-like we will use a mouse monoclonal Ab to CD23 (abCam Inc., Cambridge, MA; clone 1B12; dilution1:10). In addition the samples will be stained for CD20 using a mouse monoclonal Ab (abCam Inc., Cambridge, MA; clone L26; dilution 1:300). All of the immunostains will be performed as described above.

10 STUDY CALENDAR

	BASELINE	WHILE ON STUDY TREATMENT	FOR PATIENTS OFF-TREATMENT & STILL ON STUDY	OFF-STUDY
H&P	A	Every cycle		
Vorinostat Tablet Counts and Concurrent Meds	A	Every cycle	End of treatment	
Adverse Events Assessment	A	Twice weekly during treatment weeks	End of treatment and at least every 12 weeks(K)	X
CBC with differential	A	Twice weekly during treatment weeks		
Comprehensive Metabolic Panel	B, I	Every cycle		
LDH	B			
CD_4	B, H			
Serum Pregnancy Test	C	C		
Tumor Measurements (G)	D	Every 9 weeks (E)	End of treatment and at least every 12 weeks (L)	
Bortezomib (F)		Days 1, 4, 8, 11; repeat every 3 weeks		
Vorinostat (F)		Days 1 thru 5 and 8 thru 12; repeat every 3 weeks.		
EKG, 12 lead	J			

A Update within one week of start of treatment.
B Within two weeks of start of treatment.
C Advise patients of pregnancy related risks prior to enrollment. Advise patients who might become pregnant that they may request pregnancy test upon first suspicion of pregnancy.
D Within one month of start of treatment.
E By calendar, not by treatment cycle (cycles may deviate from every 3 weeks as per protocol); weeks may be adjusted ± 1 week for convenience.
F Days may be adjusted ± 1 for convenience; however, bortezomib may not be administered on consecutive days. Following 3 cycles, patients may take “drug holidays” of up to 3 weeks.
G By spiral CT or physical exam; bone marrow if needed to follow disease status; PET recommended but not required (see Section 11).
H CD4 testing required in subjects known to be HIV positive, or any patient whose last treatment included either bendamustine or fludarabine.
I Serum total bilirubin must be repeated within 4 days of Cycle 1 Day 1.
J For patients with a known cardiac history.
K In general, subjects should be followed for adverse event resolution, stabilization, or onset until 30 days following the last dose of study drug or until a new regimen begins (whichever comes first). Occasionally, study treatment

related AEs which are felt by the treating physician or study chair to be significant may need to be followed longer if not stabilized or resolved.

L Unless started on other anticancer treatment, the response status should be followed every 12 weeks for those patients who go off-treatment with stable disease, a partial response, or a complete response.

11 MEASUREMENT OF EFFECT

Response will be assessed according to the Revised Response Criteria for Malignant Lymphoma (35). These criteria with reference to mantle cell and diffuse large B-cell lymphoma are summarized and modified for this study according to the following two tables; otherwise, see the publication. These criteria stipulate that each measureable lesion be evaluated by the bi-dimensional measurements and that the sum of the product of the diameters be reported in case report forms.

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥ 50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		
Relapsed disease or PD	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥ 50% increase in SPD of more than one node, or ≥ 50% increase in longest diameter of a previously identified node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

Abbreviations: CR, complete remission; FDG, [^{18}F]fluorodeoxyglucose; PET, positron emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

Recommended Timing of PET (PET/CT) Scans

Histology	Pretreatment	Mid-Treatment	Response Assessment	Post-Treatment Surveillance
DLBCL	Yes*	Optional	Yes§	No
MCL	Yes*	Optional	Yes*§	No

Abbreviations: PET, positron emission tomography; CT, computed tomography; FDG, [^{18}F]fluorodeoxyglucose; DLBCL, diffuse large B-cell lymphoma; HL, Hodgkin's lymphoma; NHL, non-Hodgkin's lymphoma; MCL, mantle-cell lymphoma; ORR, overall response rate; CR, complete remission.

* Recommended but not required.

§ Not recommended if pretreatment study negative.

Centralized Radiology Review

Radiologic images to determine response status (baseline and subsequent exams) will be transmitted to the Study Chair's site for centralized review and confirmation of response assessment when a subject goes off treatment.

Images should be copied onto CDs in Dicom format.

All CDs should be anonymized, i.e., patient-specific information will be removed - site information and date/type of image can remain, at the treating site prior to submission.

Site personnel should use a soft-tipped permanent marker to note the following information on each CD submitted:

- Study: NCI 8064/MCC 15428
- Subject Initials
- Subject's Sequence Number

Each CD may contain multiple exams for a single study subject, but must not contain exams for multiple subjects.

Each CD submitted must be accompanied by a completed Radiology Exam Transmission Notification form (Appendix A).

Submit CDs and completed Radiology Exam Transmission Notification forms to:

[redacted]
VCU Massey Cancer Center
[redacted]

Send CDs and forms via traceable mechanism (Federal Express, DHL, other).

12 SUBMISSION OF MATERIALS FOR CORRELATIVE STUDIES, CENTRAL PATHOLOGICAL REVIEW, DATA REPORTING, AND REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7 (Adverse Events: List and Reporting Requirements).

12.1 Submission of Materials for Correlative Studies and Pathological Review

Submission of slides or blocks is acceptable. If slides are submitted, send at least 10 unstained tissue sections on positively-charged glass slides. Slides will NOT be returned to the send; tissue blocks will be returned if requested.

Choice of material for submission:

- If the patient's disease process has been known to undergo histological transformation in the past, the submitted tissue should be obtained relatively recently and must be obtained subsequent to the most recent systemic treatment. In some cases this may necessitate a repeat biopsy.

- If the patient's disease has NOT been known to undergo histological transformation in the past, any archival tissue suffices. If there are multiple archival samples, the most recent (not the initial diagnostic) sample should be submitted. The rationale for this is that the purpose of the biopsy is to correlate NF-κB expression with response. If NF-κB is variable within the lifespan of a tumor, the most recent tissue sample is more likely to reflect the on-study status of NF-κB expression.

At least 24 hours PRIOR to tissue sample submission, email the following individuals to alert them to sample submission:

[redacted]

Samples should be shipped Monday through Thursday and not the day before a holiday.

Samples must be shipped by a traceable mechanism, e.g., Federal Express, UPS, DHL. Phone contact for shipping: [redacted]

The Tissue Notification Form (Appendix B) must accompany all sample submissions.

Material must be submitted to [redacted] of the Moffitt Cancer Center Department of Pathology for correlative studies and central pathological review at the address below.

[redacted]

Be sure to mark on the package: "ATTENTION: [redacted], STUDY SPECIMEN."

12.2 Data Reporting

12.2.1 Method

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using CDS application can be found on the CTEP web site (http://ctep.cancer.gov). **Note**: **All** adverse events that have occurred on the study, including those reported through CTEP AERS, must be reported via CDS.

12.2.2 Responsibility for Data Submission

Study sites are responsible for entering data at least monthly in the Coordinating Center's Oncore™ database to allow time for Coordinating Center compilation and Study Chair review prior to monthly safety teleconferences.

The Southeast Phase Two Consortium (SEP2C) leadership committee has identified that the Study Chair is the appropriate individual to be responsible for compiling and submitting CDUS data to CTEP for all participants on his study, as he is actively monitoring the protocol and evaluating the data. The Study Chair and related staff will work closely with the coordinating center (Moffitt Cancer Center) to ensure that logistical barriers related to CTEP reporting are removed.

12.3 Data and Safety Monitoring

12.3.1 Safety Updates

The SEP2C Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

12.3.2 Monitoring

The Study Chair and the Massey research team will monitor the data and submit reports to the SEP2C Steering Committee at least monthly.

12.3.3 Auditing

The trial will be audited in a manner consistent with the SEP2C guidelines.

12.4 CTEP Multicenter Guidelines

This protocol will adhere to the policies and requirements of the CTEP Multicenter Guidelines. The specific responsibilities of the Protocol Chair and the Coordinating Center (Study Coordinator) and the procedures for auditing are found in CTEP's Investigator Handbook (http://ctep.cancer.gov/handbook/index.html).

- The Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports received from CTEP to all participating institutions for submission to their individual IRBs for action as required.

- Except in very unusual circumstances, each participating institution will order DCTD-supplied agents directly from CTEP. Agents may be ordered by a participating site only after the initial IRB approval for the site has been forwarded by the Coordinating Center to the CTEP PIO (PIO@ctep.nci.nih.gov) (except for Group studies).

12.5 Cooperative Research and Development Agreement (CRADA)/Clinical Trials Agreement (CTA)

The agents supplied by CTEP, DCTD, NCI in this protocol are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the NCI Division of Cancer Treatment and Diagnosis and Merck and Company and Millennium Pharmaceuticals, Inc (herein referred to as Collaborator(s)). The agents that will be supplied in this protocol are vorinostat and bortezomib, respectively. 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.

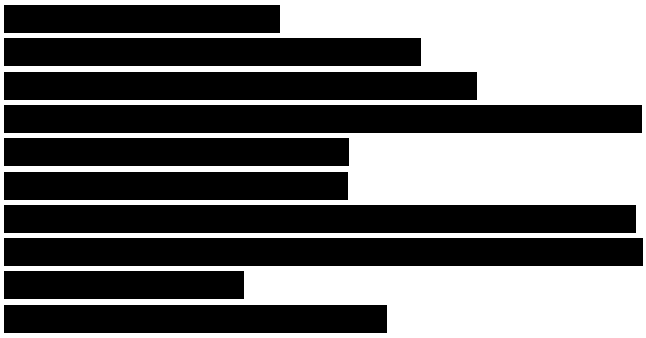
   c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

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:



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.

13 STATISTICAL CONSIDERATIONS

13.1 Mantle Cell Lymphoma

No prior bortezomib (Cohort A):

Patients will be accrued to the protocol according to a two-stage minimax design (36). Based on patient response (CR + PR), we will either conclude that the therapy is effective or ineffective. The two-stage design has the smallest sample size with the following two properties:

(1) if the true response rate is less than or equal to 30%, we will conclude that the therapy is ineffective with probability of at least 90% (alpha = .10), and

(2) if the true response rate is at least 50%, we will conclude that the therapy is effective with probability at least 90% (beta = .10).

At least 8 of 28 patients must respond in the first stage to proceed to the second stage. At any point when it is realized that this cannot happen, the study will be stopped and the therapy will be considered ineffective. Under the null hypothesis, this would occur with 36% probability. If the protocol proceeds to the second stage, at least 16 of 39 patients overall must respond for the therapy to be considered effective.

Prior bortezomib (Cohort B – closed with Protocol Version 8.0, 3/17/10):

Patients will be accrued to the protocol according to a two-stage minimax design (2). Based on patient response (CR + PR), we will either conclude that the therapy is effective or ineffective. The two-stage design has the smallest sample size with the following two properties:

(1) if the true response rate is less than or equal to 10%, we will conclude that the therapy is ineffective with probability of at least 90% (alpha = .10), and

(2) if the true response rate is at least 25%, we will conclude that the therapy is effective with probability at least 90% (beta = .10).

At least 3 of 27 patients must respond in the first stage to proceed to the second stage. At any point when it is realized that this cannot happen, the study will be stopped and the therapy will be considered ineffective. Under the null hypothesis, this would occur with 48% probability. If the protocol proceeds to the second stage, at least 7 of 40 patients overall must respond for the therapy to be considered effective.

13.2 Diffuse Large B-cell Lymphoma

(Cohort C – closed 6/25/2013)

Patients will be accrued to the protocol according to a two-stage minimax design. Based on patient response (CR + PR), we will either conclude that the therapy is effective or ineffective. The two-stage design has the smallest sample size with the following two properties:

(1) if the true response rate is less than or equal to 10%, we will conclude that the therapy is ineffective with probability of at least 90% (alpha = .10), and

(2) if the true response rate is at least 25%, we will conclude that the therapy is effective with probability at least 90% (beta = .10).

At least 3 of 27 patients must respond in the first stage to proceed to the second stage. At any point when it is realized that this cannot happen, the study will be stopped and the therapy will be considered ineffective. Under the null hypothesis, this would occur with 48% probability. If the protocol proceeds to the second stage, at least 7 of 40 patients overall must respond for the therapy to be considered effective.

13.3 Stratification Factors

For each tumor type, patients will be stratified according to prior or no prior autologous stem cell transplant. This stratification will not affect the assessment of the primary aim, treatment response. However, it will be used as a variable in the correlative studies logistic regression analysis described below, as well as to gauge whether it significantly affect the progression-free survival in any of the three treatment arms in Cox regression analysis.

13.4 Correlative Studies

The two correlative studies will be conducted by pooling the data across the three treatment arms (with the use of dummy variables for two of the treatment arms as offsets); to adjust for multiple testing, the Bonferroni-Holm procedure will be used to have an overall alpha of .05. The sample size for this protocol was determined for the primary endpoint. It is unclear whether this will be sufficient for these secondary aims, especially the second one which requires pre- and post-

treatment biopsies, which may not be performed in all patients. Also, one or more of the treatment arms may be terminated early. However, this testing plan provides the possibility of a statistically significant result if the hypothesized association is quite strong and could have data from as many as 116 patients, if all three treatment arms completely accrue. Prior to analysis with the dependent variable, response (and while blinded to its possible association), a power transformation of the independent variable (nuclear relA expression) will be considered, with the powers 1 (raw data), ½ (square root), and 0 (log transformation) examined. The Anderson-Darling test for normality will be the principal measure of ideal transformation, with the lowest value being the best. Slight preference will be given to both the raw and log transformations over the square root based upon their more facile interpretation (when examining change, a difference in raw values represents an additive change, while a difference in log values represents a multiplicative change). After the transformation has been determined and agreed upon by the PI and statistician, the main tests will be conducted. These will be logistic regression analyses, with three independent variables: nuclear relA expression, and dummy variables for the two mantle cell lymphoma groups (with the diffuse large cell lymphoma arm arbitrarily selected as the referent group).

14 REFERENCES

1. VelcadeTM Prescribing Information. Cambridge, MA: Millennium Pharmaceuticals Inc; 2003.; December 2006.
2. Richardson PG, Barlogie B, Berenson J, Singhal S, Jagannath S, Irwin D, Rajkumar SV, Srkalovic G, Alsina M, Alexanian R, Siegel D, Orlowski RZ, Kuter D, Limentani SA, Lee S, Hideshima T, Esseltine DL, Kauffman M, Adams J, Schenkein DP, Anderson KC. A phase 2 study of bortezomib in relapsed, refractory myeloma. *N Engl J Med*. 2003; 348:2609-2617.
3. Strauss SJ, Maharaj L, Hoare S, Johnson PW, Radford JA, Vinnecombe S, Millard L, Rohatiner A, Boral A, Trehu E, Schenkein D, Balkwill F, Joel SP, Lister TA. Bortezomib therapy in patients with relapsed or refractory lymphoma: potential correlation of in vitro sensitivity and tumor necrosis factor alpha response with clinical activity. *J Clin Oncol*. 2006; 24:2105-2112.
4. Almond JB, Cohen GM. The proteasome: a novel target for cancer chemotherapy. *Leukemia*. 2002; 16:433-443.
5. Cusack JC, Jr., Liu R, Houston M, Abendroth K, Elliott PJ, Adams J, Baldwin AS, Jr. Enhanced chemosensitivity to CPT-11 with proteasome inhibitor PS-341: implications for systemic nuclear factor-kappaB inhibition. *Cancer Res*. 2001; 61:3535-3540.
6. Ling YH, Liebes L, Zou Y, Perez-Soler R. Reactive oxygen species generation and mitochondrial dysfunction in the apoptotic response to Bortezomib, a novel proteasome inhibitor, in human H460 non-small cell lung cancer cells. *J Biol Chem*. 2003; 278:33714-33723.
7. Marks P, Rifkind RA, Richon VM, Breslow R, Miller T, Kelly WK. Histone deacetylases and cancer: causes and therapies. *Nat Rev Cancer*. 2001; 1:194-202.
8. An B, Goldfarb RH, Siman R, Dou QP. Novel dipeptidyl proteasome inhibitors overcome Bcl-2 protective function and selectively accumulate the cyclin-dependent kinase inhibitor p27 and induce apoptosis in transformed, but not normal, human fibroblasts. *Cell Death Differ*. 1998; 5:1062-1075.
9. Zolinza Prescribing Information. Merck & Co. Inc.; 2006.
10. Olsen E, Kim YH, Kuzel T, Pacheco TR, Foss F, Parker S, Wang JG, Frankel SR, Lis J, Duvic M. Vorinostat (suberoylanilide hydroxamic acid, SAHA) is clinically active in advanced cutaneous T-cell lymphoma (CTCL): Results of a phase IIb trial. *Journal of Clinical Oncology*. 2006; 24:422s-422s.
11. O'Connor OA, Heaney ML, Schwartz L, Richardson S, Willim R, MacGregor-Cortelli B, Curly T, Moskowitz C, Portlock C, Horwitz S, Zelenetz AD, Frankel S, Richon V, Marks P, Kelly WK. Clinical experience with intravenous and oral formulations of the novel histone deacetylase inhibitor suberoylanilide hydroxamic acid in patients with advanced hematologic malignancies. *J Clin Oncol*. 2006; 24:166-173.
12. Marks PA. Discovery and development of SAHA as an anticancer agent. *Oncogene*. 2007; 26:1351-1356.
13. Glozak MA, Sengupta N, Zhang X, Seto E. Acetylation and deacetylation of non-histone proteins. *Gene*. 2005; 363:15-23.
14. Rosato RR, Wang Z, Gopalkrishnan RV, Fisher PB, Grant S. Evidence of a functional role for the cyclin-dependent kinase-inhibitor p21WAF1/CIP1/MDA6 in promoting differentiation and preventing mitochondrial dysfunction and apoptosis induced by sodium butyrate in human myelomonocytic leukemia cells (U937). *Int J Oncol*. 2001; 19:181-191.
15. Ruefli AA, Ausserlechner MJ, Bernhard D, Sutton VR, Tainton KM, Kofler R, Smyth MJ, Johnstone RW. The histone deacetylase inhibitor and chemotherapeutic agent suberoylanilide hydroxamic acid (SAHA) induces a cell-death pathway characterized by cleavage of Bid and production of reactive oxygen species. *Proc Natl Acad Sci U S A*. 2001; 98:10833-10838. PMCID: PMC58560.
16. Nimmanapalli R, Fuino L, Bali P, Gasparetto M, Glozak M, Tao J, Moscinski L, Smith C, Wu J, Jove R, Atadja P, Bhalla K. Histone deacetylase inhibitor LAQ824 both lowers expression and promotes proteasomal degradation of Bcr-Abl and induces apoptosis of imatinib mesylate-

sensitive or -refractory chronic myelogenous leukemia-blast crisis cells. *Cancer Res*. 2003; 63:5126-5135.
17. Bali P, Pranpat M, Bradner J, Balasis M, Fiskus W, Guo F, Rocha K, Kumaraswamy S, Boyapalle S, Atadja P, Seto E, Bhalla K. Inhibition of histone deacetylase 6 acetylates and disrupts the chaperone function of heat shock protein 90: a novel basis for antileukemia activity of histone deacetylase inhibitors. *J Biol Chem*. 2005; 280:26729-26734.
18. Kawaguchi Y, Kovacs JJ, McLaurin A, Vance JM, Ito A, Yao TP. The deacetylase HDAC6 regulates aggresome formation and cell viability in response to misfolded protein stress. *Cell*. 2003; 115:727-738.
19. Yu C, Rahmani M, Conrad D, Subler M, Dent P, Grant S. The proteasome inhibitor bortezomib interacts synergistically with histone deacetylase inhibitors to induce apoptosis in Bcr/Abl+ cells sensitive and resistant to STI571. *Blood*. 2003; 102:3765-3774.
20. Dai Y, Rahmani M, Dent P, Grant S. Blockade of histone deacetylase inhibitor-induced RelA/p65 acetylation and NF-kappaB activation potentiates apoptosis in leukemia cells through a process mediated by oxidative damage, XIAP downregulation, and c-Jun N-terminal kinase 1 activation. *Mol Cell Biol*. 2005; 25:5429-5444. PMCID: PMC1156999.
21. Pei XY, Dai Y, Grant S. Synergistic induction of oxidative injury and apoptosis in human multiple myeloma cells by the proteasome inhibitor bortezomib and histone deacetylase inhibitors. *Clin Cancer Res*. 2004; 10:3839-3852.
22. Mayo MW, Denlinger CE, Broad RM, Yeung F, Reilly ET, Shi Y, Jones DR. Ineffectiveness of histone deacetylase inhibitors to induce apoptosis involves the transcriptional activation of NF-kappa B through the Akt pathway. *J Biol Chem*. 2003; 278:18980-18989.
23. Chen LF, Mu Y, Greene WC. Acetylation of RelA at discrete sites regulates distinct nuclear functions of NF-kappaB. *EMBO J*. 2002; 21:6539-6548. PMCID: PMC136963.
24. Chen L, Fischle W, Verdin E, Greene WC. Duration of nuclear NF-kappaB action regulated by reversible acetylation. *Science*. 2001; 293:1653-1657.
25. Hideshima T, Bradner JE, Wong J, Chauhan D, Richardson P, Schreiber SL, Anderson KC. Small-molecule inhibition of proteasome and aggresome function induces synergistic antitumor activity in multiple myeloma. *Proc Natl Acad Sci U S A*. 2005; 102:8567-8572. PMCID: PMC1150844.
26. Catley L, Weisberg E, Kiziltepe T, Tai YT, Hideshima T, Neri P, Tassone P, Atadja P, Chauhan D, Munshi NC, Anderson KC. Aggresome induction by proteasome inhibitor bortezomib and alpha-tubulin hyperacetylation by tubulin deacetylase (TDAC) inhibitor LBH589 are synergistic in myeloma cells. *Blood*. 2006; 108:3441-3449. PMCID: PMC1895432.
27. Xu C, Bailly-Maitre B, Reed JC. Endoplasmic reticulum stress: cell life and death decisions. *J Clin Invest*. 2005; 115:2656-2664. PMCID: PMC1236697.
28. Wu J, Kaufman RJ. From acute ER stress to physiological roles of the Unfolded Protein Response. *Cell Death Differ*. 2006; 13:374-384.
29. Nawrocki ST, Carew JS, Pino MS, Highshaw RA, Andtbacka RH, Dunner K, Jr., Pal A, Bornmann WG, Chiao PJ, Huang P, Xiong H, Abbruzzese JL, McConkey DJ. Aggresome disruption: a novel strategy to enhance bortezomib-induced apoptosis in pancreatic cancer cells. *Cancer Res*. 2006; 66:3773-3781.
30. Badros A. Personal Communication June 6 2007.
31. Grant S. Protocol NCI 6413: Phase I Trial of Bortezomib (PS-341; NSC 681239) and Flavopiridol (NSC 649890) in Patients with Recurrent or Refractory Indolent B-cell Neoplasms.
32. Belch A, Kouroukis CT, Crump M, Sehn L, Gascoyne RD, Klasa R, Powers J, Wright J, Eisenhauer EA. A phase II study of bortezomib in mantle cell lymphoma: the National Cancer Institute of Canada Clinical Trials Group trial IND.150. *Ann Oncol*. 2007; 18:116-121.
33. Kath R, Blumenstengel K, Fricke HJ, Hoffken K. Bendamustine monotherapy in advanced and refractory chronic lymphocytic leukemia. *J Cancer Res Clin Oncol*. 2001; 127:48-54.
34. Alamdari HS, Pinter-Brown L, Cassarino DS, Chiu MW. Severe cutaneous interface drug eruption associated with bendamustine. *Dermatol Online J*. 2010; 16:1.

35. Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, Coiffier B, Fisher RI, Hagenbeek A, Zucca E, Rosen ST, Stroobants S, Lister TA, Hoppe RT, Dreyling M, Tobinai K, Vose JM, Connors JM, Federico M, Diehl V. Revised response criteria for malignant lymphoma. *J Clin Oncol*. 2007; 25:579-586.
36. Simon R. Optimal two-stage designs for phase II clinical trials. *Control Clin Trials*. 1989; 10:1-10.

Radiology Exam Transmission Notification Form

Instructions:

- Send a Radiology Exam Transmission Notification form with each compact disk submitted
- Send CDs & forms via traceable mechanism (Federal Express, DHL, other)
- Be sure that exams are DE-IDENTIFIED prior to burning on CD
- Do NOT send exams on more than 1 subject on the same CD
- Use soft-tipped permanent marker to note the following on each CD submitted
  - Study: NCI 8064/MCC 15428
  - Subject Initials
  - Subject's Sequence #

Protocol:NCI 8064 (Moffitt Protocol MCC 15428)
Subject Initials: ________________________
Subject Sequence #: ________________________

The above patient has been enrolled in an IRB-approved clinical trial. The patient has signed the proper Informed Consent and Research Authorization documents.

Radiology Exam Details (note: exams required at baseline & every 9 weeks)
For each exam burned on enclosed CD, please note the following:

Study Timepoint (circle one)	Date of exam	Type of exam (circle all that apply)
Baseline Week 9 18 27 36 Other: ________		CT: head neck chest abdomen pelvis other:______ PET or PET/CT
Baseline Week 9 18 27 36 Other: ________		CT: head neck chest abdomen pelvis other:______ PET or PET/CT
Baseline Week 9 18 27 36 Other: ________		CT: head neck chest abdomen pelvis other:______ PET or PET/CT
Baseline Week 9 18 27 36 Other: ________		CT: head neck chest abdomen pelvis other:______ PET or PET/CT
Baseline Week 9 18 27 36 Other: _________		CT: head neck chest abdomen pelvis other:______ PET or PET/CT

Sender's Information:

Name: ____

Site: ____

Telephone #: ____

Email: ____

Tissue Notification Form

Subject Initials: _____

Sequence #: _____

Collection Date / Time: _____

Protocol MCC #: NCI 8064/MCC 15428

Sample Collection Details: _____

The above patient has been recruited to a research protocol. The patient has signed the proper Informed Consent and Research Authorization documents.

Sender's Information:

Name: _____

Title: _____

Telephone #: _____