



**Memorial Sloan-Kettering Cancer Center
IRB Protocol**

IRB#: 08-045A(6)

**A Multi-Center Phase I/II Trial Of Vorinostat In Combination With Cyclophosphamide,
Etoposide, Prednisone And Rituximab For Elderly Patients With Relapsed Diffuse Large
B-Cell Lymphoma (DLBCL)**

MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

Principal Investigator/Department: David J. Straus, M.D. Medicine

**Co-Principal
Investigator(s)/Department:** Paul A. Hamlin, M.D. Medicine



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Investigator(s)/Department:

John F. Gerecitano, M.D.,Ph.D	Medicine
Craig H. Moskowitz, M.D.	Medicine
Alison Moskowitz, M.D.	Medicine
Ariela Noy, M.D.	Medicine
M. Lia Palomba, M.D.	Medicine
Carol S. Portlock, M.D.	Medicine
Andrew D. Zelenetz, M.D.,Ph.D.	Medicine
Matthew Matasar, M.D	Medicine
Steven Horwitz, M.D.	Medicine
Ephraim Casper, MD	Medicine - Basking Ridge
Deena Atieh Graham, MD	Medicine - Basking Ridge
Audrey Hamilton, MD	Medicine - Basking Ridge
Mila Gorsky, MD	Medicine - Basking Ridge
Magi Khalil, MD	Medicine - Basking Ridge
Shilen Patel, MD	Medicine - Basking Ridge
Han Xiao, MD	Medicine - Basking Ridge
Stefan Berger, MD	Medicine - Basking Ridge
Julie Fasano, MD	Medicine - Commack
John Fiore, MD	Medicine - Commack
Stuart Lichtman, MD	Medicine - Commack
Philip Schulman, MD	Medicine - Commack
Marni Sheren-Manoff, MD	Medicine - Commack
Steven Sugarman, MD	Medicine - Commack
Frank Y. Tsai, MD	Medicine - Commack
Arlyn Apollo, MD	Medicine - Commack
Pamela Drullinsky, MD	Medicine – Rockville Centre
Zoe Goldberg, MD	Medicine - Rockville Centre
Kenneth Ng, MD	Medicine - Rockville Centre
Tiffany Troso-Sandoval, MD	Medicine - Rockville Centre
Michelle Boyar, MD	Medicine - Rockville Centre
Philip Caron, MD, PhD	Medicine – Sleepy Hollow
Nancy Mills, MD	Medicine - Sleepy Hollow
Stephanie Smith-Marrone, MD	Medicine – Sleepy Hollow
Carolyn Wasserheit-Lieblich, MD	Medicine – Sleepy Hollow
Alexia Iasonos, Ph.D.	Epidemiology and Biostatistics
Otilia-Liana Dumitrescu, M.D.	Radiology



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**Consenting
Professional(s)/Department:**

David J. Straus, M.D	Medicine
Paul A. Hamlin	Medicine
John F. Gerecitano, M.D.,Ph.D	Medicine
Alison Moskowitz, M.D.	Medicine
Craig H. Moskowitz, M.D.	Medicine
Ariela Noy, M.D.	Medicine
M. Lia Palomba, M.D.	Medicine
Carol S. Portlock, M.D.	Medicine
Andrew D. Zelenetz, M.D., Ph.D.	Medicine
Matthew Matasar, M.D	Medicine
Steven Horwitz, M.D.	Medicine
Ephraim Casper, MD	Medicine – Basking Ridge
Deena Atieh Graham, MD	Medicine - Basking Ridge
Audrey Hamilton, MD	
Mila Gorsky, MD	Medicine - Basking Ridge
Magi Khalil, MD	Medicine - Basking Ridge
Shilen Patel, MD	Medicine - Basking Ridge
Han Xiao, MD	Medicine - Basking Ridge
Julie Fasano, MD	Medicine - Basking Ridge
Stefan Berger, MD	Medicine - Commack
John Fiore, MD	Medicine - Commack
Stuart Lichtman, MD	Medicine - Commack
Frank Y. Tsai, MD	Medicine - Commack
Philip Schulman, MD	Medicine - Commack
Marni Sheren-Manoff, MD	Medicine - Commack
Steven Sugarman, MD	Medicine - Commack
Arlyn Apollo, MD	Medicine - Commack
Pamela Drullinsky, MD	Medicine – Rockville Centre
Zoe Goldberg, MD	Medicine – Rockville Centre
Kenneth Ng, MD	Medicine – Rockville Centre
Tiffany Troso-Sandoval, MD	Medicine – Rockville Centre
Michelle Boyar, MD	Medicine – Rockville Centre
Philip Caron, MD, PhD	Medicine – Sleepy Hollow
Nancy Mills, MD	Medicine – Sleepy Hollow



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Carolyn Wasserheit-Lieblich, MD	Medicine – Sleepy Hollow
Stephanie Smith-Marrone, MD	Medicine – Sleepy Hollow
	Medicine – Sleepy Hollow

Medicine – Sleepy Hollow
Medicine – Sleepy Hollow
Medicine – Sleepy Hollow

Please Note: A Consenting Professional must have completed the mandatory Human Subjects Education and Certification Program.

Collaborating Institution:	PI's Name	Site's Role
Northwestern University Medical School Evanston Northwestern Healthcare	David Cella, Ph.D.	Data Analysis: Appendix V global rating of change scale
Weill Cornell Medical College 520 East 70th Street, Starr Pavilion New York, NY 10021 Phone: 212-746-2063 Fax: 212-746-3844 Email: ree2001@med.cornell.edu	Rebecca Elstrom, M.D.	Data Collection



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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

Study Title: A multicenter phase I/II trial of vorinostat in combination with cyclophosphamide, etoposide, prednisone and rituximab for elderly patients with relapsed diffuse large B-cell lymphoma (DLBCL)

Patient Population:

Relapsed/refractory DLBCL patients ≥ 60 years of age and not candidates for autologous stem cell transplantation

Design: This is a phase I/II, open-label, single arm trial. The goals are to determine the optimal dose of vorinostat when given in combination to rituximab, cyclophosphamide, etoposide and prednisone. In addition, we hypothesize that this regimen will increase the response rate and one-year progression free survival for elderly patients with relapsed or refractory DLBCL who are not candidates for autologous stem cell transplantation with the addition of a new chemotherapeutic agent, vorinostat, to rituximab, cyclophosphamide, etoposide and prednisone. As this is a palliative regimen, quality of life measurements will be another important endpoint.

Rituximab 375 mg/m² intravenously day one. Cyclophosphamide 600 mg/m² intravenously days 1 and 8, etoposide 70 mg/m² day 1 intravenously, then 140 mg/m² days 2 and 3 orally, vorinostat orally days 1-10 (see below), prednisone 60 mg/m² days 1-10. The regimen will be repeated every 4 weeks for 6 cycles unless there is disease progression or intolerance of the regimen due to toxicity.

The starting dose of vorinostat will be 300 mg orally days 1-10. All other agents will be held constant at the above doses. Three patients will be enrolled at this dose. If 0/3 experience DLT then the dose will be increased to 400 mg orally days 1-10. If 1/3 patient experiences a DLT then 3 more patients will be added at the 300 mg dose. If ≥ 2 patients experience DLT at 300 mg, the trial will be discontinued because of excessive toxicity. If ≤ 1 out of 6 patients experience a DLT at 300 mg then we will escalate to 400 mg and follow the same scheme. If 2 or more experience a DLT at 400 mg and only 3 patients were treated at 300 mg, then we will de-escalate to 300 mg and 3 additional patients will be added. If ≤ 1 out of 6 patients experience a DLT at 400 mg, then 400 mg will be the MTD for the Phase II part of the study. DLT is defined as any grade 3 or 4 non-hematological toxicity or grade 4 thrombocytopenia seen in the first cycle of treatment.

FACT-Lym will be administered at baseline, on first day of each treatment cycle and at all followup visits in first year of followup.



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2.0 OBJECTIVES AND SCIENTIFIC AIMS

Phase I:

1. To determine the maximum tolerated dose (MTD) of vorinostat given orally for 10 days in combination with cyclophosphamide, etoposide, prednisone and rituximab for elderly patients with relapsed diffuse large B-cell lymphoma

Phase II:

1. To determine the complete response rate to rituximab and a combination of vorinostat with cyclophosphamide, etoposide, and prednisone in elderly patients with relapsed diffuse large B-cell lymphoma who are not candidates for autologous stem cell transplantation.
2. To determine the overall response rate (complete and partial).
3. To estimate the one-year progression-free and overall survival
4. To estimate the quality of life for these patients at baseline, during and at completion of treatment.

3.0 BACKGROUND AND RATIONALE

Diffuse large B-cell lymphoma comprises 30-40% of non-Hodgkin lymphomas in adults. The median age is in the seventh decade. Approximately 50% of newly-diagnosed patients ages 60 years and older will achieve durable un-maintained remissions following treatment with rituximab, cyclophosphamide, vincristine, doxorubicin and prednisone (R-CHOP)¹. The standard treatment for relapsed and refractory patients is salvage chemotherapy and high-dose chemotherapy with peripheral stem cell support. This results in durable remissions in approximately 30-40% of patients². Some patients in their 60s and most patients above age 70 are not candidates for this type of program. These patients are treated for palliation and not with the goal of durable remissions or cures. There are few clinical trials that have addressed the treatment of this population of patients for whom tolerance of treatment and quality of life during treatment are as important issues as tumor response. Effective treatment of this population can thus be considered an unmet need and an opportunity for clinical research.

A combination of cyclophosphamide, etoposide, procarbazine and prednisone (CEPP) is used by many clinicians for palliative treatment of relapsed DLBCL, although there is little published literature on its efficacy. An overall response rate of 77% (17/22) and CR rate of 36 % (8/22) was reported with CEPP in a small number of patients with recurrent diffuse large cell lymphoma³.

Remission durations with salvage chemotherapy alone without consolidation autologous stem cell transplantation for relapsed and refractory aggressive lymphomas have been short. The median time to progression following CEPP was 7 months³. The median duration of response in a phase II trial in a similar patient population with a combination of pixantrone with cyclophosphamide, vincristine and prednisone was 10.3 months⁴. The one-year progression-free survival of patients with relapsed/refractory DLBCL treated with gemcitabine, cisplatin and



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methylprednisolone (GEM-P) was 27%. The addition of rituximab to combination chemotherapy may increase remission duration. The one-year progression-free survival of patients treated with GEM-P with rituximab was 51%. Only a minority of these patients received consolidation autologous stem cell transplants⁵.

Vorinostat or suberoylanilide hydroxamic acid (SAHA) was synthesized in the laboratory of Dr. Ronald Breslow at Columbia University and developed in the laboratory of Dr. Paul Marks at Memorial Sloan-Kettering Cancer Center. Vorinostat was approved by the US Food and Drug Administration (FDA) on 6-Oct-2006 for the treatment of cutaneous manifestations in patients with cutaneous T-cell lymphoma (CTCL) who have progressive, persistent or recurrent disease on or following two systemic therapies. Phase I studies demonstrated a signal of activity of the drug in patients with relapsed/refractory non-Hodgkin lymphomas. The proto-oncogene BCL-6, which is constitutively expressed in many B-cell lymphomas, suppresses genes involved in the control of lymphocyte activation, differentiation and apoptosis. Promotion of acetylation of BCL-6 by vorinostat could result in inactivation of this suppressive effect and reactivation of genes involved with these desirable cellular activities in the tumor cells^{6,7}. A preclinical study demonstrated enhanced cell death with combination of vorinostat and etoposide in the MCF-7 breast cancer cell line⁸.

Convenience of drug dosing, tolerance of treatment and overall quality of life are important issues in the treatment of elderly patients with relapsed DLBCL. The Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym) is an instrument that has been recently developed for assessment of quality of life in patients receiving chemotherapy for lymphoma and is now available for clinical chemotherapy trials⁹.

In this study, vorinostat, the novel oral histone deacetylase inhibitor, will be substituted for procarbazine in the CEPP regimen. Procarbazine is associated with significant toxicity including carcinogenesis in animal and in humans in the MOPP combination, nausea and vomiting, pancytopenia, neurologic symptoms including neuropathy and confusion, hypersensitivity reactions and stomatitis. The toxicity of vorinostat is described in Section 11.1. Rituximab, an important agent with little toxicity will also be added. Its toxicity is described in Section 11.3.

Quality of Life Component

Quality of life is an important consideration in the treatment of these patients with the most likely expectation of palliation rather than cure. With this goal, it is important that this regimen will be associated with reasonably mild side effects that will not severely affect comfort or ability to function. To measure quality of life in this study we will use the Functional Assessment of Cancer Therapy – Lymphoma (FACT-Lym) questionnaire. The FACT-Lym was developed as part of the FACIT Measurement System to meet the growing need for a disease-specific quality of life (QOL) questionnaire for patients with non-Hodgkin's lymphoma¹⁰ (www.facit.org). The 15-item Lymphoma subscale was constructed to complement the existing subscales of the FACT-G questionnaire¹¹. The FACT-Lym (FACT-G + lymphoma subscale) is formatted for



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self-administration and utilizes a 5-point Likert rating scales (0= Not at all; 1= A little bit; 2= Somewhat; 3= Quite a bit; 4= Very Much). Subscale scores are calculated by reversing negatively stated items and then summing individual item scores. A total score is derived by summing subscale scores. A Trial Outcome Index (TOI) can be calculated by summing the PWB, FWB, and Lymphoma subscale scores. The TOI is an efficient summary index of physical/functional outcomes and a common endpoint used in clinical trials because it is responsive to change in physical/functional outcomes, sometimes more than a total (overall) multidimensional aggregated score that includes social and emotional well-being.

The FACT-Lymphoma was developed with input from experts and the literature. An extensive item-generation and scale construction process generated 176 candidate items from interviews and item ratings on frequency and relevancy from 17 expert healthcare providers and the published literature describing quality of life in NHL. Data summaries, including median NHL symptom relevancy ratings ≥ 2 , disease-specificity, and clinical relevance were used to support retention of 22 items for testing. Cognitive debriefing with 75 NHL patients ensured content validity of the final scale^{9,12}.

The 22-item subscale was validated on a sample of 84 NHL patients. Patients completed the FACT-Lym and other measures at baseline (T1), 3-7 days (T2), and 8-12 weeks (T3). Item correlations, expert relevancy ratings, and patient input on content helped shorten the lymphoma subscale from 22 to 15 items. Patient interviews confirmed item relevance and comprehensiveness. The validation sample included 44% male, 60% with indolent disease, and 85% currently receiving treatment. Internal consistency coefficients (alpha) for the 15-item subscale (.79, .85, .84) and test-retest stability (.84) indicate good reliability at each assessment. Correlations between the subscale and the SF-36 physical ($r=.62$) and mental ($r=.48$) summary scores reflect concurrent validity. Responsiveness to ECOG performance status rating and treatment status (on vs. off) equaled or exceeded that of the more established FACT subscale scores. From T1 to T3, subscale scores declined (-6.8, effect size= -0.87) in 14 patients who reported themselves as worsened, increased (4.5, effect size= 0.58) in 35 patients who reported themselves as improved, and did not change (-0.1, effect size= -0.01) in 21 patients who reported themselves as unchanged^{9,12}. These results support the validity of the lymphoma subscale and suggest that it will be a useful targeted endpoint in trials where lymphoma-specific concerns are paramount.

Global Rating of Change Scale (adapted from Jaeschke et al, 1989):

The global rating of change scale (GRC) is a patient-reported measure used as the criterion against which actual change scores could be compared and calibrated. To align GRC ratings to the subscales of the FACT-Lym, each FACT dimension (PWB, SWB, EWB, FWB, the “additional concerns”, and total HRQL) was briefly summarized, and then patients rated whether they experienced no change, a worsening, or an improvement in that area. If they experienced a worsening or improvement, they rated the degree of change on a 7 point scale ranging from -3 (a great deal worse) through 0 (no change) to +3 (a great deal better). Patients will complete this at every first year visit other than baseline.



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3.1 VORINOSTAT

3.1.1 Histone deacetylases and HDAC Inhibitors

Histone deacetylases (HDAC) are enzymes that catalyze the removal of acetyl groups from the lysine residues of proteins, including histones and transcription factors. HDAC inhibitors can induce tumor cell growth arrest, differentiation, or apoptosis *in vitro* and inhibit tumor growth in animals^{13,14}. The transcription of genes is regulated at least in part by acetylation of nucleosomal histones¹⁵. The core nucleosomal histones are the most widely studied of the proteins that become acetylated following inhibition of HDAC activity¹⁵. In some cancer cells, there is an over expression of HDACs, or an aberrant recruitment of HDACs to oncogenic transcription factors causing hypo acetylation of core nucleosomal histones. Hypo acetylation of histones is associated with a condensed chromatin structure and repression of gene transcription. Inhibition of HDAC activity allows for the accumulation of acetyl groups on the histone lysine residues resulting in an open chromatin structure and transcriptional activation.

3.1.2 Mechanism of Action of Vorinostat

Vorinostat is a potent inhibitor of HDAC activity and binds directly to the catalytic pocket of HDAC enzymes. Vorinostat, at low nanomolar concentrations, inhibits the enzymatic activity of HDAC1, HDAC2 and HDAC3 (Class I) and HDAC6 (Class II)^{14,16,17}. Concentrations of vorinostat that cause the accumulation of acetylated histones also induces cell cycle arrest, differentiation or apoptosis of transformed cells¹⁶.

Vorinostat induces apoptosis in a wide variety of transformed cells in culture, including cutaneous T-cell lymphoma (CTCL) cell lines, circulating atypical T-cells derived from patients with CTCL, human lymphoma cell lines and murine erythroleukemia (MEL) cells. Vorinostat also inhibits proliferation of cultured transformed human cells derived from leukemias, non-small cell lung carcinomas, colon carcinomas, central nervous system tumors, melanomas, ovarian carcinomas, renal cell carcinomas, prostate and breast cancers. In cultured human transformed cell lines, vorinostat has synergistic or additive activity in combination with other cancer therapies, including radiation, kinase inhibitors, cytotoxic agents and differentiating agents^{16,18-24}.

In vivo, vorinostat demonstrates anti-neoplastic activity in a variety of rodent tumor models including xenograft models of human prostate, breast and colon carcinoma.

While it has been assumed that the effects of vorinostat on histone acetylation underpin its biological activities, a number of other proteins are regulated by histone acetyltransferases (HATs) and HDACs and may be targeted by vorinostat²⁵. Several non-histone proteins, (e.g., tubulin, Hsp90 and p53) are known to be reversibly acetylated on lysine residues and undergo hyper acetylation following exposure to vorinostat²⁶⁻²⁸. Acetylation of these proteins may also contribute to the antitumor activity of vorinostat.



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Please refer to the vorinostat Confidential Investigator's Brochure (CIB) for detailed information.

3.1.3 Non Clinical Pharmacology of Vorinostat

Vorinostat is approximately 71% bound to human plasma proteins over the range of concentrations of 0.5 to 50 µg/mL.

Vorinostat has a low propensity to cause or be affected by drug-drug interactions. In animal models and in vitro human systems, the major pathways of metabolism of vorinostat involve glucuronidation and hydrolysis followed by β-oxidation. Additionally, the glucuronidation of vorinostat is mediated by multiple uridine diphosphate glucuronosyltransferase isozymes (UGTs), making it less susceptible to drug interactions through modulation of UGTs. Vorinostat is not recovered intact in urine to any appreciable extent. Therefore, compounds known to affect renal elimination are not expected to affect the pharmacokinetics of vorinostat.

Vorinostat is not an inhibitor of CYP drug metabolizing enzymes in human liver microsomes at steady state C_{max} of the 400 mg dose (C_{max} of 1.2 µM vs. IC_{50} of >75 µM). Gene expression studies in human hepatocytes detected some potential for suppression of CYP2C9 and CYP3A4 activities by vorinostat at concentrations higher (≥ 10 µM) than pharmacologically relevant. Thus, vorinostat is not expected to affect the pharmacokinetics of other agents metabolized by CYP enzymes. As vorinostat is not eliminated via the CYP pathways, it is anticipated that vorinostat will not be subject to drug-drug interactions when co-administered with drugs that are known CYP inhibitors or inducers. However, no formal clinical studies have been conducted to evaluate drug interactions with vorinostat.

Please refer to the vorinostat CIB for detailed information.

3.1.4 Non Clinical Toxicology of Vorinostat

Vorinostat has been investigated in non-clinical acute and oral repeated-dose toxicity studies, reproductive, developmental toxicity studies, and genetic toxicity studies to support oral administration of this compound to humans.

The main toxicities observed in animal models were weight loss and inappetence, apparent hemolytic anemia (rats only at 3.8 times the equivalent 400 mg human dose), leukopenia (rats only at 1.3 times the equivalent 400 mg human dose), thrombocytopenia (male rats only, statistically significant change at 0.5 times the equivalent 400 mg clinically effective human dose, but within normal range at all doses), and gastrointestinal tract irritation (dogs only, at 8.5 times the equivalent 400 mg human dose). Although statistically significant and dose-dependent, many of the clinical pathology findings were within normal historical ranges indicating that they should not have major toxicological consequences. The toxicities appeared to be rapidly reversible within 12 to 14 days. There has been no evidence of cardiac toxicity based on



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electrocardiogram (ECG, dogs only), blood pressure (dogs only), heart rate (dogs only), creatinine kinase, organ weight, gross pathology, or histopathology assessments in studies up to one month duration. No serious, irreversible damage to any vital organ has been observed. Importantly, toxicities in rats and dogs were predictive of adverse effects in humans (anorexia, weight loss, fatigue). Toxicities present in animals would be manageable in the clinic, and the onset of serious toxicity is readily forecast by prodromal symptoms. The non clinical toxicity profile of vorinostat is acceptable for an oncology drug.

Vorinostat rapidly crossed the placenta in both the rat and rabbit, following administration of a dose of 15 mg/kg/day and 150 mg/kg/day, respectively (<1 times the human exposure based on AUC₀₋₂₄) and reached transplacental equilibrium within 30 minutes post-dose.

Vorinostat was evaluated in a panel of genetic toxicity assays; in vivo and in vitro assays were found to be positive. No human safety data for the use of vorinostat during pregnancy are available.

Please refer to the vorinostat CIB for detailed information.

3.1.5. Clinical Pharmacokinetics of Vorinostat

The pharmacokinetics of vorinostat following 400-mg single-dose in a fasted state; and 400 mg single- and multiple-doses in a fed (high-fat meal) state were evaluated in 23 patients in a Phase I study with relapsed or refractory advanced cancer using a validated assay. See Table A.



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Table A

PK Parameters of vorinostat following oral administration of single or multiple doses of 400 mg			
	400 mg single-dose Fasted	400 mg single-dose fed	400 mg q.d. multiple-dose fed
$AUC_{0-\infty}$, $\mu M \cdot hr^{\ddagger}$	3.87	5.33	6.46
C_{max} , μM^{\ddagger}	1.12	1.02	1.13
T_{max} , $hr^{\#}$	1.50	4.00	4.21
Apparent $t_{1/2}$, $hr^{\dagger\dagger}$	1.74	1.44	1.34
\ddagger Geometric mean $\#$ Median $\dagger\dagger$ Harmonic mean			

Vorinostat is eliminated predominantly through metabolism with less than 1% of the dose recovered as unchanged drug in urine, indicating that renal excretion does not play a role in the elimination of vorinostat. Recovery of two pharmacologically inactive metabolites, *O*-glucuronide of vorinostat (OG-V) and 4-anilino-4-oxobutanoic acid (4A4OA), in urine was more substantial.

Please refer to the vorinostat CIB for detailed information.

3.1.6 Summary of Clinical Experience with Vorinostat

Vorinostat has been studied in Merck Research Labs (MRL) sponsored studies, Investigator Initiated Study Protocols (IISP) and National Cancer Institute (NCI) sponsored studies. Vorinostat has been orally administered in Phase I, Phase II and Phase III clinical studies in patients with advanced solid tumors and hematologic malignancies. Vorinostat has been studied both alone and in combination with other chemotherapy agents.

Please refer to the vorinostat CIB for detailed information

3.1.7 Safety of Vorinostat

The types of adverse experiences observed in clinical trials of vorinostat were those usually associated with chemotherapy. The most common drug-related adverse experiences in patients treated with vorinostat could be classified into four symptom complexes: gastrointestinal symptoms (diarrhea, nausea, anorexia, weight decrease, vomiting, and constipation), constitutional symptoms (fatigue, chills), hematologic abnormalities (thrombocytopenia, anemia) and taste disorders (dysgeusia, dry mouth). Most of the adverse experiences were manageable. In fact, most of the very common adverse experiences were reversible and could be managed using conventional supportive care for chemotherapy. Overall, treatment with oral vorinostat was well tolerated.



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Adverse experiences considered by the Investigators to be at least possibly related to vorinostat in $\geq 10\%$ of patients across all Merck & Co., Inc. sponsored vorinostat clinical studies include (in descending frequency): fatigue, nausea, diarrhea, anorexia, vomiting, blood creatinine increased, hyperglycemia, weight decreased, thrombocytopenia, dysgeusia, constipation, dehydration, hemoglobin decreased, platelet count decreased, anemia, hypocalcemia, alanine aminotransferase increased, white blood cell count decreased, dyspnea, hyponatremia, aspartate aminotransferase increased, hypokalemia, dry mouth, alopecia, and muscle spasms.

The tolerability of vorinostat appears to be determined by total daily dose, frequency and the number of consecutive days of dosing. The results of an initial Phase I study of vorinostat in patients with advanced solid tumors and hematologic malignancies determined that the maximum tolerated dose (MTD) for continuous daily dosing without a rest period is 400 mg daily (q.d.) or 200 mg twice daily (b.i.d.). The MTD for intermittent dosing has been established as 300 mg b.i.d. x 3 consecutive days per week, or 250 mg 3 times daily (t.i.d.) x 14 consecutive days followed by a 7-day rest period²⁹. Therefore, the maximum tolerable total daily dose may range as high as 750 mg (250 mg P.O. t.i.d.) x 14 consecutive days followed by a 7-day rest period rather than 400 mg (given as q.d. or 200 mg b.i.d.) with continuous daily dosing or 600 mg when given as 300 mg b.i.d. for 3 consecutive days each week followed by a 4-day rest period. In a Phase I study in Japanese patients with solid tumors, MTD was established as 200 mg b.i.d. and 500 mg q.d. for 14 consecutive days followed by a 7-day rest.

Dose-limiting toxicities (DLTs) have been mainly non-hematologic. The majority of these DLTs occurred within the first month on vorinostat. At continuous daily dosing of 600 mg q.d., 300 mg b.i.d., and 400 mg b.i.d., doses that exceeded the established MTD, the pattern and severity of DLTs were similar. The DLTs were manageable because these toxicities resolved quickly after drug administration was interrupted. Hematologic events were primarily anemia, leukopenia, and thrombocytopenia. Generally, these events were rapidly reversible after study drug interruption.

Serious clinical adverse experiences (SAEs) regardless of causality have been reported in approximately 39% of the first 350 patients treated with vorinostat in Merck & Co., Inc. sponsored studies. This overall high incidence may reflect the underlying conditions of patients in this group. Of the patients who had a serious adverse experience, approximately 16% were considered by the Investigator to be related to study medication. Serious laboratory adverse experiences were uncommon, occurring in 3% or fewer of patients in the various populations. By contrast, to patients with solid tumors, the incidence of serious adverse experiences was higher in patients with hematologic malignancies.

Pulmonary embolism and deep vein thrombosis have been reported.

QT prolongation has been observed.

Please refer to the vorinostat CIB and **ZOLINZA™ (vorinostat)** package insert in Attachments for additional information.

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3.1.8. Efficacy of Vorinostat (See Appendix VI)

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This is a phase I/II, open-label, single arm trial. The goals are to determine the optimal dose of vorinostat when given in combination to rituximab, cyclophosphamide, etoposide and prednisone. In addition, we hypothesize that this regimen will increase the response rate and one-year progression free survival for elderly patients with relapsed or refractory DLBCL who are not candidates for autologous stem cell transplantation with the addition of a new chemotherapeutic agent, vorinostat, to rituximab, cyclophosphamide, etoposide and prednisone. As this is a palliative regimen, quality of life measurements will be another important endpoint.

Rituximab 375 mg/m² intravenously day one. Cyclophosphamide 600 mg/m² intravenously days 1 and 8, etoposide 70 mg/m² day 1 intravenously, then 140 mg/m² days 2 and 3 orally, vorinostat orally days 1-10 (see below), prednisone 60 mg/m² days 1-10. The regimen will be repeated every 4 weeks for 6 cycles unless there is disease progression or intolerance of the regimen due to toxicity.

Drug	Day 1	2	3	4	5	6	7	8	9	10
Ritux. (IV)	375 mg/m ²									
CTX (IV)	600 mg/m ²							600 mg/m ²		
Vorin. (PO)	See below x	x	x	x	x	x	x	x	x	x
Pred. (PO)	60 mg/m ² x	x	x	x	x	x	x	x	x	x
Etop.	70 mg/m ² (IV)	140 mg/m ² (PO)	140 mg/m ² (PO)							

The starting dose of vorinostat will be 300 mg orally days 1-10. All other agents will be held constant at the above doses. Three patients will be enrolled at this dose. If 0/3 experience DLT then the dose will be increased to 400 mg orally days 1-10. If 1/3 patient experiences a DLT then 3 more patients will be added at the 300 mg dose. If ≥2 patients experience DLT at 300 mg, the trial will be discontinued because of excessive toxicity. If ≤1 out of 6 patients experience a DLT at 300 mg then we will escalate to 400 mg and follow the same scheme. If 2 or more experience a DLT at 400 mg and only 3 patients were treated at 300 mg, then we will de-escalate to 300 mg

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and 3 additional patients will be added. If ≤ 1 out of 6 patients experience a DLT at 400 mg, then 400 mg will be the MTD for the Phase II part of the study. DLT is defined as any grade 3 or 4 non-hematological toxicity or grade 4 thrombocytopenia seen in the first cycle of treatment. Once the patient has been assigned a dose level, that dose will not change for that patient's treatment on protocol. If another cohort is opened, new patients may be accrued to a new dose level. However, previous patients will remain at their assigned dose level.

Growth factor support will start on day 11 (+/- 2 days) with either peg-filgrastim or filgrastim for at least 5 days. On day 1 of each cycle, drugs will be held for at least 1 week if absolute neutrophil count < 1000 /mm, platelet count < 50000 /mm or for any other non-hematological grade 3 or 4 toxicity. On day 8 of each cycle, vorinostat will be discontinued and the cyclophosphamide dose held for 1 week if absolute neutrophil count < 1000 /mm, platelet count < 50000 /mm or for any other non-hematological grade 3 or 4 toxicity. The subsequent cycle will begin 3 weeks after the second cyclophosphamide dose. In the phase II portion, the following dose modifications will be permitted if patients require admission for fever and with or without documented infection in the previous cycle of chemotherapy: reduction of cyclophosphamide dose by 25% on days 1 and 8 and omission of oral etoposide in subsequent cycles. If delays greater than 1 week are required, the Principal Investigator should be notified.

FACT-Lym will be administered at baseline, on first day of each treatment cycle and at all followup visits in first year of followup.

Estimated duration of accrual:
Three years

4.2 Intervention

Patients will be treated with 6 cycles of rituximab, cyclophosphamide, etoposide, prednisone and vorinostat every 4 weeks. Quality of life determinations will be obtained at the beginning of each cycle of chemotherapy and at each visit during the first year of followup.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

All agents are FDA approved. Vorinostat is approved for treatment of cutaneous T-cell lymphoma. Vorinostat will be supplied by the manufacturer for this trial at no cost to the patients.

Product Description of Vorinostat

Vorinostat (N-hydroxy-N'-phenyl-octane-1, 8-dioic acid diamide, N hydroxy-N'-phenyl (9CI) octane diamide, suberoylanilide hydroxamic acid, also known as SAHA, or MK-0683), is an orally available HDAC inhibitor. The physical and chemical properties of vorinostat are listed in Table 4.



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Table B

Properties of Vorinostat

Molecular Formula	C₁₄H₂₀N₂O₃
Molecular Weight	264.32
Physical Appearance	White to light orange powder
Solubility	Water (pH = 11.2) ≤5 mg/mL
Moisture (Karl Fischer)	≤1%
Melting Point	159.5 to 160.5°C
pK_a	8.5 and 11.1
Hygroscopicity	None
Hydrates	None
Chirality	None

The oral formulation of vorinostat is available as a 100-mg capsule. Earlier studies of vorinostat were performed with formulation strengths of 50 mg and 200 mg. Currently no additional dose images other than the 100 mg strength is manufactured. Each 100 mg vorinostat capsule for oral administration contains 100 mg vorinostat and the following inactive ingredients: microcrystalline cellulose, sodium croscarmellose and magnesium stearate. The capsule shell excipients are titanium dioxide, gelatin and may contain sodium lauryl sulfate.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

1. MSKCC or Weill Cornell biopsy confirmation of relapsed/refractory diffuse large B-cell lymphoma. Patients with large cell transformation of a low-grade B-cell lymphoma will be eligible.
2. One or two prior chemotherapy regimens not including autologous stem cell transplantation.
3. Age ≥ 60 years.
4. Not a candidate for autologous stem cell transplantation.
5. Patient must have performance status of ≤2 on the ECOG Performance Scale.
6. Measurable disease (see Section 12).



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7. Adequate organ and bone marrow function: ANC \geq 1000/mm³, platelet count \geq 50,000/mm³, total bilirubin \leq 1.5 ULN (with exception of Gilbert's disease), AST/ALT \leq 2.5 ULN, creatinine \leq 1.5 mg/dL or creatinine clearance \geq 50 ml/min, potassium and magnesium within normal limits.
8. Male patients agree to use an adequate method of contraception for the duration of the study.
9. Patient is available for periodic blood sampling, study related assessments, and management at the treating institution for the duration of the study.

6.2 Subject Exclusion Criteria

1. Patient who has had chemotherapy, radiotherapy, or biological therapy [including growth factors], within 30 days (42 days for nitrosoureas or mitomycin C) prior to initial dosing with study drug(s) or who has not recovered from adverse events due to agents administered more than 30 days earlier. Patients on a stable dose of steroids for at least 4 weeks prior to onset of study therapy may be included.
2. Patient is currently participating or has participated in a study with an investigational compound or device within 30 days of initial dosing with study drug(s).
3. Patient had prior treatment with an HDAC inhibitor (e.g., romidespin (Depsipeptide), NSC-630176, MS 275, LAQ-824, belinostat (PXD-101), LBH589, MGCD0103, CRA024781, etc). Patients who have received compounds with HDAC inhibitor-like activity, such as valproic acid, as anti-tumor therapy should not enroll in this study. Patients who have received such compounds for other indications, e.g. valproic acid for epilepsy, may enroll after a 30-day washout period.
4. Patients with active CNS lymphoma and/or lymphomatous meningitis are excluded. However, patients with a history of CNS lymphoma and/or lymphomatous meningitis who have been stable without evidence of CNS and/or leptomeningeal recurrence would be eligible. They must be off steroids or on a stable dose of steroids.
5. Patient with a primary central nervous system lymphoma.
6. Patient has known hypersensitivity to the components of study drug or its analogs.
7. Patient has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
8. Patient is, at the time of signing informed consent, a regular user (including "recreational use") of any illicit drugs, substance abuse or had a recent history (within the last year) of drug or alcohol abuse.



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9. Patient is expecting to father children within the projected duration of the study.
10. Patient has uncontrolled intercurrent illness or circumstances that could limit compliance with the study, including, but not limited to the following: active infection, acute or chronic graft versus host disease, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric conditions.
11. Patient has a history or current evidence of any condition, therapy, or lab abnormality that might confound the results of the study, interfere with the patient's participation for the full duration of the study or is not in the best interest of the patient to participate.
12. Patient has a history of a gastrointestinal surgery or other procedures that might, in the opinion of the investigator, interfere with the absorption or swallowing of the study drugs.
13. Patient with a "currently active" second malignancy, other than non-melanoma skin cancer and carcinoma in situ of the cervix, should not be enrolled. Patients are not considered to have a "currently active" malignancy if they have completed therapy for a prior malignancy, are disease free from prior malignancies for >5 years or are considered by their physician to be at less than 30% risk of relapse.
14. Patient is HIV +.
15. Patient has active hepatitis B or C.

7.0 RECRUITMENT PLAN

The trial will require 59 patients to meet study endpoints. 5 patients will be enrolled at Weill Cornell Medical College and 54 at Memorial Sloan-Kettering Cancer Center (MSKCC). With the targeted monthly accrual of 1-2 patients, this study will require about 3 years to complete accrual.

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or the research team at Memorial Sloan-Kettering Cancer Center (MSKCC) or Weill Cornell Medical College. If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.



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8.0 PRETREATMENT EVALUATION (APPENDIX 1)

1. History and physical exam including tumor measurements at the time of each visit (days 1 and 8 of every 28 day cycle).
2. CT scan of chest, abdomen and pelvis with oral and IV contrast unless there are allergic contraindications to IV contrast. CT scan with oral contrast only will then be permitted. Study should be performed within 6 weeks prior to study entry
3. PET scan. Study should be performed within 6 weeks prior to study entry
4. Bone marrow biopsy (unilateral permitted).
5. CBC, WBC differential count, platelet count, creatinine, BUN, AST/ALT, calcium, electrolytes, uric acid, LDH, total bilirubin, alkaline phosphatase within 7 days prior to study entry, HIV I/II antibodies, Hep B surface antigen profile, Hep B core AB profile, Hep B surface antibody, Hep C antibody profile
6. Urinalysis within 7 days prior to study entry.
7. FACT-Lym questionnaire within 7 days prior to study entry.
8. Electrocardiogram (EKG) within 7 days prior to study entry.
9. Serum pregnancy test (β -hCG) within 72 hours prior to receiving the first dose of vorinostat

9.0 TREATMENT/INTERVENTION PLAN

Rituximab 375 mg/m² intravenously day 1. Cyclophosphamide 600 mg/m² intravenously days 1 and 8, etoposide 70 mg/m² day 1 intravenously, then 140 mg/m² days 2 and 3 orally, vorinostat orally days 1-10 (see below), prednisone 60 mg/m² days 1-10. The regimen will be repeated every 4 weeks for 6 cycles unless there is disease progression or intolerance of the regimen due to toxicity.

Phase I:

The starting dose of vorinostat will be 300 mg orally days 1-10. All other agents will be held constant at the above doses. Three patients will be enrolled at this dose. If 0/3 experience DLT then the dose will be increased to 400 mg orally days 1-10. If 1/3 patient experiences a DLT then 3 more patients will be added at the 300 mg dose. If ≥ 2 patients experience DLT at 300 mg, the trial will be discontinued because of excessive toxicity. If ≤ 1 out of 6 patients experience a DLT at 300 mg then we will escalate to 400 mg and follow the same scheme. If 2 or more experience a DLT at 400 mg and only 3 patients were treated at 300 mg, then we will de-escalate to 300 mg and 3 additional patients will be added. If ≤ 1 out of 6 patients experience a DLT at 400 mg, then 400 mg will be the MTD for the Phase II part of the study. DLT is defined as any grade 3 or 4 non-hematological toxicity or grade 4 thrombocytopenia seen in the first cycle of treatment.

Phase II:

Chemotherapy will be administered in the doses and schedule above with the MTD for vorinostat that is determined in the Phase I portion of the trial.



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Growth factor support will start on day 11 (+/- 2 days) with either peg-filgrastim or filgrastim for at least 5 days. On day 1 of each cycle, drugs will be held for at least 1 week if absolute neutrophil count <1000 /mm, platelet count < 50000/mm or for any other non-hematological grade 3 or 4 toxicity. On day 8 of each cycle, vorinostat will be discontinued and the cyclophosphamide dose held for 1 week if absolute neutrophil count <1000 /mm, platelet count < 50000/mm or for any other non-hematological grade 3 or 4 toxicity. The subsequent cycle will begin 3 weeks after the second cyclophosphamide dose. In the phase II portion, the following dose modifications will be permitted if patients require admission for fever and with or without documented infection in the previous cycle of chemotherapy: reduction of cyclophosphamide dose by 25% on days 1 and 8 and omission of oral etoposide in subsequent cycles. If delays greater than 1 week are required, the Principal Investigator should be notified.

FACT-Lym will be administered at baseline and on first day of each treatment cycle and at all followup visits in first year of followup. The Patient Global Rating of Change will be administered at all assessments other than baseline, anchoring patient ratings to the previous visit in that first year.

Adverse experiences will be graded and recorded throughout the study according to NCI-CTCAE, version 3.0. Toxicities will be characterized in terms including duration, intensity, and time to onset.

9.1 Concomitant and Prohibited Medications/Treatments

The major pathway(s) for metabolism of vorinostat involves glucuronidation and hydrolysis followed by β -oxidation. Therefore, it is anticipated that vorinostat will not be subject to drug-drug interactions when co-administered with drugs that are known to be CYP enzyme inhibitors. Formal drug-drug interaction studies have not been performed with vorinostat. All concomitant medications received within 14 days before the first dose of study medication and 30 days after the last dose of study medication must be recorded in the source document and on the case report form.

The concomitant use of other medications/therapies is allowed unless specifically prohibited in the protocol. Patients should be stabilized prior to study entry on all medications.

- Prolongation of prothrombin time (PT) and International Normalized Ratio (INR) have been observed in patients receiving vorinostat concomitantly with coumarin-derivative anticoagulants. Physicians should carefully monitor PT and INR in patients concurrently administered vorinostat and coumarin derivatives.
- Patients may not receive chemotherapy, radiotherapy, biological therapy or investigational anticancer therapy during the study. Patients who require these therapies should be considered to have progressive disease and be withdrawn from the study.



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- Vorinostat should not be administered concomitantly with other HDAC inhibitors (e.g., valproic acid) as class-specific adverse reactions may be additive.

9.2 Diet

Vorinostat should be taken approximately 30 minutes after a meal whenever possible.

Altered taste and decreased food and liquid intake are associated with vorinostat administration. These toxicities can be actively managed with fluid management and nutritional consult.

During the period of vorinostat administration, patients should consume at least 2 liters of fluid orally, daily, to prevent dehydration. Patient may require electrolyte replacement. If patients are experiencing dysgeusia, popsicles or Gatorade may be successful in maintaining oral intake. Early use of anti-emetics should be encouraged.

9.3 Supportive Care Guidelines

Supportive treatment may include anti-emetics, antidiarrheal medications, anti-pyretics, anti-histamines, analgesics, antibiotics, and others, such as blood products. Patients who experience indigestion or gastroesophageal reflux symptoms on vorinostat may be treated with Proton Pump Inhibitors (PPIs) as well as H2 blockers as clinically indicated.

Growth factor support will start on day 11 with either peg-filgrastim or filgrastim for at least 5 days. On day 1 or 8 of each cycle, drugs will be held for at least 1 week if absolute neutrophil count <1000 /mm, platelet count < 50000/mm or for any grade 3 or 4 toxicity.

Patients will be permitted to receive appropriate supportive care measures as deemed necessary by the treating physician including but not limited to the items outlined below:

- **Diarrhea:** Diarrhea should be treated promptly with appropriate supportive care, including loperamide. Loperamide should not be taken prophylactically. Patients should be instructed to begin taking loperamide at the first sign of: 1) poorly formed or loose stool, 2) occurrence of more bowel movements than usual in one day or 3) unusually high volume of stool. Loperamide should be taken in the following manner: 4 mg at first onset of diarrhea, then 2 mg after each unformed stool. The daily dose of loperamide should not exceed 16 mg/day. Loperamide should be deferred if blood or mucus is present in the stool or if diarrhea is accompanied by fever. In this setting, appropriate diagnostic microbiologic specimens should be obtained to exclude an infectious etiology. Patients should also be advised to drink liberal quantities of clear fluids as detailed in Section [3.2.X] to help prevent dehydration.



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- **Nausea/vomiting:** Nausea and vomiting should be treated aggressively, and strong consideration should be given to the administration of prophylactic antiemetic therapy according to standard institutional practice. In particular, the use of antiemetics including 5HT3 antagonists and/or a prepatent plus dexamethasone is encouraged. Patients should be strongly encouraged to maintain liberal oral fluid intake (as detailed in Section [3.2.X]) during therapy, especially during the initial 14 days of each treatment cycle.
- **Anemia:** Treatment with vorinostat can cause dose-related anemia. If appropriate, the dose of vorinostat may be modified or therapy discontinued. (see Section 9 for dose modification guidelines). Transfusions [*and/or erythropoietin if not AML/MDS*] may be utilized as clinically indicated for the treatment of anemia, but should be clearly noted as concurrent medications.
- **Thrombocytopenia:** Treatment with vorinostat can cause dose-related thrombocytopenia. If platelet counts are reduced during treatment with vorinostat, the vorinostat dose may be modified or therapy discontinued. Transfusion of platelets may be used if clinically indicated.
- **Neutropenia:** Prophylactic use of colony-stimulating factors including G-CSF, pegylated G-CSF or GM-CSF should not be utilized during the first cycle of therapy. These factors may be utilized if clinically indicated in subsequent cycles as outlined in the guidelines for dose modification (see Section 9).
- **Hyperglycemia** has been observed in patients receiving vorinostat. Serum glucose should be monitored. Adjustment of diet and/or anti-hyperglycemic therapy may be necessary.
- **Hypokalemia or hypomagnesemia** should be corrected prior to administration of vorinostat, and consideration should be given to monitoring potassium and magnesium in symptomatic patients (e.g. patients with nausea, vomiting, diarrhea, fluid imbalance or cardiac symptoms.)
- **Pulmonary embolism and deep vein thrombosis** have been reported. Investigators should be alert to the signs and symptoms of these events. Physicians should be alert to the signs and symptoms of these events, particularly in patients with a prior history of thromboembolic events. If a pulmonary embolism is documented, subsequent vorinostat doses should not be administered, and the Principal Investigator should be notified.
- **QTc prolongation** has been observed. Baseline and periodic ECGs should be performed during treatment. Vorinostat should be administered with particular caution in patients with congenital long QT syndrome and patients taking anti-arrhythmic medicines or other medicinal products that lead to QT prolongation. If significant new QTc prolongation is



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observed, subsequent vorinostat doses should not be administered, and the Principal Investigator should be notified.

For information regarding vorinostat use, please refer to the vorinostat label.

10.0 EVALUATION DURING TREATMENT/INTERVENTION (APPENDIX 1)

1. History and physical examination including tumor measurements every 4 weeks.
2. Toxicity and FACT-Lym assessment every 4 weeks. Adverse experiences will be evaluated according to criteria outlined in the NCI Common Terminology Criteria for Adverse Events (CTCAE), version 3.0.
3. CBC and platelet count on days 1 and 8 of every 28-day cycle.
4. Creatinine, BUN, AST/ALT, calcium, electrolytes, uric acid, LDH, total bilirubin, alkaline phosphatase on day 1 of every 28-day cycle.
5. CT scan of chest abdomen and pelvis at the end of cycle 4 and cycle 6.
6. PET scan at the end of cycle 6.
7. End of Cycle 6 (+/- 1 week): History and physical examination including tumor measurements, Toxicity, FACT-Lym assessment, Global rating of Change assessment, CBC, Creatinine, BUN, AST/ALT, calcium, electrolytes, uric acid, LDH, total bilirubin, alkaline phosphatase. Bone marrow biopsy (if bone marrow involved prior to treatment) at completion of treatment..
8. FACT-Lym will be administered at baseline, on first day of each treatment cycle and at all followup visits in first year of follow up. The Global rating of Change will be administered at all first year visits other than baseline, and each rating will be anchored to the previous assessment.
9. Patients will be followed for five years after completing treatment or until relapse. Followup visits will include CBC, chemistry studies including serum LDH, and CT scans of the chest, abdomen and pelvis. FACT-Lym will be administered during followup visits during the first year. Starting from the End of Cycle 6 visit, the frequency of visits will be every 3 months (year 1), every 4 months (years 2 and 3) and every 6 months (years 5). Annual telephone calls will be made to patients who are not continuing in followup with the treating physician after 5 years to check on their health status.

11.0 TOXICITIES/SIDE EFFECTS

Toxicity will be described according the NCI Common Toxicity Criteria (Version 3.0). Doses of vorinostat will be either 300 mg or 400 mg daily according to a dose escalation/de-escalation scheme described in Section 9.0. Dose and schedule adjustments for the other agents will also be made according to the scheme described in Section 9.0.

11.1 Vorinostat

Adverse experiences (Section 9.3) considered by the Investigators to be at least possibly related to vorinostat in $\geq 10\%$ of patients across all Merck & Co., Inc. sponsored vorinostat clinical studies include (in descending frequency): fatigue, nausea, diarrhea, anorexia, vomiting, blood

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creatinine increased, hyperglycemia, weight decreased, thrombocytopenia, dysgeusia, constipation, dehydration, hemoglobin decreased, platelet count decreased, anemia, hypocalcemia, alanine aminotransferase increased, white blood cell count decreased, dyspnea, hyponatremia, aspartate aminotransferase increased, hypokalemia, dry mouth, alopecia, and muscle spasms.

Pregnancy and Contraception

Vorinostat can cause fetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies of vorinostat in pregnant women.

Results of animal studies indicate that vorinostat crosses the placenta and is found in fetal plasma. Doses up to 50 and 150 mg/kg/day were tested in rats and rabbits, respectively (~0.5 times the human exposure based on AUC₀₋₂₄). Treatment-related developmental effects including decreased mean live fetal weights, incomplete ossifications of the skull, thoracic vertebra, sternbra, metacarpals and skeletal variations (cervical ribs, supernumerary ribs, vertebral count and sacral arch variations) in rats and rabbits at the highest doses of vorinostat tested. The no observed effect level (NOEL) for these effects was 15 and 50 mg/kg/day (<0.1 times the human exposure based on AUC) in rats and rabbits. If the drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with vorinostat. Female patients enrolled in this study should either be post menopausal, free from menses for > 2 years, surgically sterilized or willing to use 2 adequate barrier methods of contraception to prevent pregnancy or agree to abstain from heterosexual activity throughout the study, starting with visit 1. Female patients of childbearing potential must have a negative serum pregnancy test (β -hCG) within 72 hours prior to receiving the first dose of vorinostat. Male patients enrolled in this study should also agree to use an adequate method of contraception for the duration of the study. Patients should be advised to discuss adequate birth control options with their physician.

If a patient or their partner inadvertently becomes pregnant while on treatment with vorinostat, the patient will immediately be removed from the study. The site will contact the patient at least monthly and document the patient's status until the pregnancy has been completed or terminated. The outcome of the pregnancy will be reported to the SPONSOR without delay and within 24 hours if the outcome is a serious adverse experience (e.g., death, abortion, congenital anomaly, or other disabling or life-threatening complication to the mother or newborn). If a male patient's partner becomes pregnant on study the pregnancy must be reported to the SPONSOR. The study investigator will make every effort to obtain permission to follow the outcome of the pregnancy and report the condition of the fetus or newborn to the SPONSOR.

Should a patient become pregnant refer to Safety Section for reporting instructions.



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Use in nursing women

It is unknown whether vorinostat is excreted in human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from vorinostat, breast feeding must be discontinued for the duration of therapy with vorinostat and the concomitantly used chemotherapy, if applicable.

11.2 Cyclophosphamide

Bone marrow suppression with neutropenia and thrombocytopenia. Less commonly, cardiotoxicity, hemorrhagic cystitis, and secondary malignancies.

11.3 Etoposide

Myelosuppression, alopecia, nausea vomiting headache, fever, hypotension, anorexia, and allergic reactions

11.4 Rituximab

Fever, chills, rigors, nausea, vomiting, urticaria, fatigue, headache, dizziness, pruritus, Bronchospasm, dyspnea, angioedema, rhinitis, hypotension, flushing, pain at disease sites, leukopenia, thrombocytopenia, anemia, tumor lysis syndrome, progressive multifocal leukoencephalopathy (PML), activation of or worsening of hepatitis B

11.5 Prednisone

Nausea, vomiting, dyspepsia, appetite change, edema, headache, dizziness, mood swings, insomnia, hypokalemia, hypertension, hyperglycemia, Cushingoid features (log-term use), ecchymoses, acne, skin atrophy (long-term use), impaired skin healing (long-term use)



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12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Responses for primary and secondary endpoints will be determined according to the Revised Response Criteria for Malignant Lymphoma³⁴ as described in the Table.

Response Definitions for Clinical Trials				
<i>Response</i>	<i>Definition</i>	<i>Nodal Masses</i>	<i>Spleen, Liver</i>	<i>Bone Marrow</i>
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) Variability 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) Variability 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) Variability 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, [18F]fluorodeoxyglucose; PET, position emission tomography; CT, computed tomography; PR, partial remission; SPD, sum of the product of the diameters; SD, stable disease; PD, progressive disease.

Overall survival is defined as the period from the date of study entry to the date of death due to any cause. Progression-free survival is defined as the period from the date of study entry to the date of disease progression or death due to any cause.

To compare results with those in the older literature, a secondary assessment of responses will be made according to the older “Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin’s Lymphomas” as described in the table³⁵. These criteria did not include results of PET scanning.



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Response Criteria for Non-Hodgkin’s Lymphoma

Response Category	Physical Examination	Lymph Nodes	Lymph Node Masses	Bone marrow
CR	Normal	Normal	Normal	Normal
CRu	Normal	Normal	Normal	Indeterminate
	Normal	Normal	> 75% decrease	Normal or indeterminate
PR	Normal	Normal	Normal	Positive
	Normal	≥ 50% decrease	≥ 50% decrease	Irrelevant
	Decrease in liver/spleen	≥ 50% decrease	≥ 50% decrease	Irrelevant
Relapse/progression	Enlarging liver/spleen; new sites	New or increased	New of Increased	Reappearance

13.0 CRITERIA FOR REMOVAL FROM STUDY

If at anytime the patient develops progressive disease he/she will be taken off study and referred for alternative therapy.

If at anytime the patient develops unacceptable toxicity he/she will be removed from study.

If at anytime the patient is found to be ineligible for the protocol as designated in the section on Criteria for Patient/Subject Eligibility (i.e., a change in diagnosis), the patient will be removed from the study.

14.0 BIOSTATISTICS

This is a phase I/II, open-label, multicenter, single arm trial. The goals are to determine the optimal dose of vorinostat when given in combination to rituximab, cyclophosphamide, etoposide and prednisone for elderly patients with relapsed or refractory DLBCL who are not candidates for autologous stem cell transplantation. The primary efficacy endpoint is complete response rate. Secondary efficacy endpoints include overall response rate (CR+PR) and one - year progression free and overall survivals. Quality of life endpoints are described in Section 14.1. Criteria of response are defined in section 12.0. The maximum number of assessable patients entered into the phase I and phase II components is 53 as described below.



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Phase I:

The starting dose of vorinostat will be 300 mg orally days 1-10. All other agents will be as described in Section 4.1. Three patients will be enrolled at this dose. If 0/3 experience DLT then the dose will be increased to 400 mg orally days 1-10. If 1/3 patient experiences a DLT then 3 more patients will be added at the 300 mg dose. If ≥ 2 patients experience DLT at 300 mg, the trial will be discontinued because of excessive toxicity. If ≤ 1 out of 6 patients experience a DLT at 300 mg then we will escalate to 400 mg and follow the same scheme. If two or more experience a DLT at 400 mg and only three patients were treated at 300 mg, then we will de-escalate to 300 mg and 3 additional pts will be added. If ≤ 1 out of 6 patients experience a DLT at 400 mg, then 400 mg will be the MTD for the Phase II part of the study. DLT is defined as any grade 3 or 4 non-hematological toxicity or grade 4 thrombocytopenia as evaluated in the first cycle of treatment. The Phase I part of the study will accrue a maximum of 12. The six patients treated at the MTD will be included in the Phase II part of the study.

Phase II statistical design:

With type I and type II errors of 0.1, based on a Simon two-stage design, the sample size needed to show a clinically significant improvement in complete response rate (CR) from 35% to 55% is 47 patients. If at least 8 patients out of 20 patients respond at the first stage, then the study will accrue 27 more patients at the second stage. If 7 or less patients respond at the first stage then the study will stop and conclude that this regimen has a CR lower or equal that 35%. If at least 21 patients respond at the end of the trial then this study will conclude that this regimen is promising in this patient population.

For the secondary endpoint of progression-free survival (PFS) it will be assumed that 47 patients will be followed up for at least one year as for the primary endpoint.

The overall response rate (CR+PR) and its 90% confidence interval will be estimated via binomial proportions.

Frequency of toxicity will be tabulated according to the NCI common toxicity criteria.

Assuming accrual rate of 1-2 patients per month, this trial will take approximately 26-53 months to complete. We expect to complete accrual within 3 years

14.1 Quality of life as measured by the FACT-Lym instrument.

FACT-Lym, the Functional Assessment of Cancer Therapy-Lymphoma, a validated QOL tool to evaluate quality of life in lymphoma clinical research, adds to the 27-item FACT-G a list of 15 lymphoma-specific questions⁹ (www.facit.org).

FACT-Lym will be administered at baseline, on first day of each treatment cycle and at all follow-up visits in the first year of follow-up which will be every 3 months for the first year. The



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FACT-Lym questionnaire will be administered to patients registered on the phase I and phase II portions of the trial.

The following FACT-Lym endpoints will be evaluated: Physical Well-being scale (raw scores), Functional Well-being scale (raw scores), Social/family Well-being scale (raw scores), Emotional Well-being scale (raw scores), Lymphoma scale (raw scores), Total score composed of all five scales (raw scores), Trial Outcome Index (TOI) composed of the physical well-being scale, functional well-being scale and the lymphoma specific scales (raw scores). Scoring of the FACT-Lym (version 4) will be done in accordance with the FACT-Lym as described in the Functional Assessment of Chronic Illness Therapy (FACIT) manual³⁶. For each endpoint, summary raw scores will be summarized using means and medians at each assessment point along with standard deviations and interquartile ranges.

The aim is to evaluate whether FACT-Lym scores improve across time, especially among responding patients. A general class of models for the analysis of longitudinal data is that of mixed models³⁷. For this study, a mixed-effects longitudinal model to evaluate selected FACT-Lym endpoints over time will be implemented. Each patient will be scheduled to complete up to fourteen assessments: Week 0 (Baseline), 4, 8, 12, 16, 20, 24, and then every 3 months for the first year of followup. For each post-Baseline assessment, we will use the date of questionnaire completion to compute the amount of time in months from baseline. The time variable will be set to zero for all Baseline questionnaires. An unstructured covariance pattern will be used to account for the correlations within patients, unless an alternative covariance structure better fits the data. The unstructured covariance pattern provides maximum flexibility and allows the variance of the endpoint to be different at each visit, and the covariance of each pair of visits to be different. We will attempt to use an unstructured covariance pattern to account for the correlations within patients. The unstructured covariance pattern, when viable, provides maximum flexibility and allows the variance of the endpoint to be different at each visit, and the covariance of each pair of visits to be different. Due to small sample size and potentially missing data, it is anticipated that less flexible covariance structures may need to be investigated. The basic analytical model will include fixed effects (time) and random effects (patient, patient*time). A quadratic effect (time²) may be included to evaluate the possibility of nonlinear change over time. Piece wise linear regression models may also be used to separately model the changes during the first month and the changes during subsequent months. Patient age and gender will be added to the basic model to determine if these variables have any independent effect on the FACT-Lym scores. A likelihood ratio test will be used to assess the contributions of these variables. The model parameter estimates, standard errors and *p*-values will be summarized. (Table 1). The effect of baseline characteristics on QOL will be evaluated in exploratory analyses.

A potential problem in QOL studies is that missing data are often not missing at random, e.g., patients who experience increased toxicity, disease progression or death are more likely to miss one or more assessments. If the probability of missingness depends on the unobserved QOL scores, then missing data are considered non ignorable, or missing not at random³⁸ (MNAR ; Little & Rubin, 1987). Formally distinguishing between missing at random (MAR) and MNAR is not trivial and relies on assumptions that are themselves untestable^{38,39}. Therefore, a pattern-



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mixture model to assist in the analysis of potentially non ignorable missing data will be implemented⁴⁰. For this method, patients will be stratified into groups defined as “dropouts” and “completers”, the cut-off time mark of assessment completion will depend on the missingness pattern at each assessment. Mixed-effects repeated measures models will be created within each stratum and parameter estimates for each stratum will then be combined into a weighted average for the entire study population. Estimated means at each time point will be calculated using the parameter estimates and standard errors from the final models. The parameters estimates from the pattern-mixture model will be compared to those from the naïve mixed-effects model.

On the other hand, an exploratory method of analysis, a joint model of FACT-Lym scores and time-to-progression will be also fit. This model is based on an extension of the two-stage linear random effects model, where each subjects’ random intercept and slope are allowed to be associated with the underlying time to event^{41,42}. The joint distribution of the continuous responses and the time-to-event variable are then estimated via maximum likelihood using the EM algorithm. The parameters estimates from the joint model of longitudinal measures and time-to-progression will be also compared to those from the naïve mixed-effects model.

SAS v9.1 will be used for all analyses. As these health-related quality of life analyses are considered exploratory, there is no need to adjust the significance level for multiple comparisons.

Table 1 Parameter estimates from mixed-effects longitudinal model

QOL Parameter	PWB	EWB	SWB	FWB	FACT-Lym	TOTAL	TOI
Mean change per month (slope)							
Parameter estimate	xx.xxxx	xx.xxxx	xx.xxxx	xx.xxxx	xx.xxxx	xx.xxxx	xx.xxxx
Standard error	xx.xxxx	xx.xxxx	xx.xxxx	xx.xxxx	xx.xxxx	xx.xxxx	xx.xxxx
p-value to test slope differ from zero	0.xxx	0.xxx	0.xxx	0.xxx	0.xxx	0.xxx	0.xxx

Anchoring interpretation of change to a subjective global rating from the patient. As this is an uncontrolled Phase I/II study, with FACT-Lymphoma measures periodically on the phase II portion, interpretation of any detected change will be aided by also asking patients to provide an estimate of the degree to which they have changed (improved or worsened), if at all, since baseline. We will use a 7-point patient global rating of change, adapted from Jaeschke et al (1989), to classify patients into those who have improved, worsened or not changed. These three distinct groups will then be compared on the FACT-Lymphoma subscales to provide some interpretation as to the meaningfulness of the noted change in terms of FACT-Lymphoma scores. We will evaluate general linear models using each patient's change score. Changes in patient- and provider-rated performance status, as well as patient-rated perceptions of QOL change, will be used to form three independent groups (better, no change, worse). We will look for confirmation that the FACT-Lymphoma



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measures provide clinically meaningful estimates of change. No imputation of missing data will be done for patients who fail to participate after baseline evaluation; however, we will prospectively monitor the reasons for missing data (e.g., refusal, disease progression, death) and will compare characteristics of patients who do and do not participate in the longitudinal study.

Jaeschke, R., Singer, J. & Guyatt, G. Measurement of health status: Ascertaining the minimally clinically important difference. *Controlled Clinical Trials*, Vol. 10, pp. 407-415, 1989.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am - 5:30pm at (646) 735-8000. The PPR fax numbers are (646) 735-0008 and (646) 735-0003. Registrations can be phoned in or faxed. The completed signature page of the written consent/verbal script, and a completed Eligibility Checklist must be faxed to PPR.

15.1.1 For Participating Sites:

Central registration for this study will take place at Memorial Sloan Kettering Cancer Center (MSKCC).

To complete registration and enroll a participant from another institution, the study staff at that site must contact the designated research staff at MSKCC to notify him/her of the participant registration. The site staff then needs to fax registration/eligibility documents to the **Clinical Trials Office (Lymphoma Department) at MSKCC Fax: 646-227-2427**.

The following documents must be sent for each enrollment **within 24 hours** of the informed consent form being signed:

- The completed or partially completed MSKCC eligibility checklist
- The signed informed consent and signed HIPAA Authorization form (Research Authorization)



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- Supporting source documentation for eligibility questions (laboratory results, pathology report, radiology reports, MD notes, physical exam sheets, medical history, prior treatment records, and EKG report).

Upon receipt, the research staff at Memorial Sloan Kettering Cancer Center will conduct an interim review of all documents. If the eligibility checklist is not complete, the patient will be registered PENDING and the site is responsible for sending a completed form within 30 days of the consent.

If the eligibility checklist is complete, participant meets all criteria, all source documentation is received, the participating site IRB has granted approval for the protocol, and the site is in good standing with MSKCC, the MSKCC research staff will send the completed registration documents to the MSKCC Protocol Participant Registration (PPR) Office to be enrolled as stated in section 15.1. The participant will be registered.

Once eligibility has been established and the participant is registered, the participant will be assigned an MSKCC Clinical Research Database (CRDB) number (protocol participant number). This number is unique to the participant and must be written on all data and correspondence for the participant. This protocol participant number will be relayed back to study staff at the registering site via e-mail and will serve as the enrollment confirmation.

16.0 DATA MANAGEMENT ISSUES

A Research Study Assistant (RSA) will be assigned to the study. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordinate the activities of the protocol study team.

The data collected for this study will be entered into a secured database (Clinical Research Database, CRDB) at Memorial Sloan-Kettering Cancer Center.

16.0.1 Data and Source Documentation for Participating Sites

Data

Standardized Case Report Forms (CRFs), directions for use and sign off requirements have been generated for this study. Blank case report forms will be sent to the study staff at each participating site for use. The participating Site PI is responsible for ensuring these forms are completed accurately, legibly and in a timely manner.



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Source Documentation

Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into CRFs. Relevant source documentation to be submitted throughout the study includes:

- Baseline measures to assess pre-protocol disease status (ex. CT, PSA, bone marrow)
- Treatment records
- Grade 3-5 toxicities/adverse events not previously submitted with SAE Reports
- Response designation

16.0.2 Data and Source Documentation Submission for Participating Sites

Participating sites should fax or e-mail CRFs and source documentation to MSKCC to the contact provided below. Submissions should include a cover page listing all CRFs enclosed per participant.

FAX: [646-227-2427] to the attention of [Protocol: 08-045: (Brett Wegner)] OR EMAIL: WegnerB@mskcc.org

16.0.3 Data and Source Documentation Submission Timelines for Participating Sites

Data and source documentation to support data should be transmitted to MSKCC according to chart: **Data and Source Submission Requirements and Timelines for Therapeutic Studies**



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	Baseline	Cycle 1-6	Post- Tx- Follow- up visits	SAE	Off Study
SUBMISSION SCHEDULE					
Source Documentation	Within 24 hours (see section 15.1.1)	within 14 days of end of cycle		Within 3 days of event (see section 17.2.1); updates to be submitted as available	Within 14 days of visit
CRFs	Within 7 days of visit				
Required Forms					
Demographics Form	X				
Medical History Form	X				
Concomitant Medications Form	X	X	X		X
Physical Exam Form	X	X	X		X
Treatment Form		X	X		X
Laboratory Form	X	X	X		X
Lesion/EOD Form			X ¹		X
Adverse Event Form		X	X	X	X
Serious Adverse Event Form				X	
Off Study Form					X
(FACT-Lym) QOL	X	X	X		
Global Rating of Change Questionnaire		X	X		



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16.0.4 Data Review and Queries for Participating Site Data

Research staff at MSKCC will review data and source documentation as it is submitted. Data will be monitored against source documentation and discrepancies will be sent as queries to the participating sites. Queries will be sent by MSKCC Research staff twice a month.

Participating sites should respond to data queries within 14 days of receipt.

16.1 Quality Assurance

Registration reports will be generated to monitor patient's accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study and potential problems will be brought to the attention of the study team for discussion and action.

Random-Sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of once a year or more frequently if indicated.

16.1.1 Quality Assurance for Participating Sites

Each site participating in the accrual of participants to this protocol will be audited by the staff of the MSKCC study team for protocol and regulatory compliance, data verification and source documentation. Audits may be accomplished in one of two ways: (1) selected participant records can be audited on-site at participating sites or (2) source documents for selected participants will be sent to MSKCC for audit. Audits will usually be determined by participant accrual numbers and rate of accrual, but can also be prompted by reported SAEs or request of MSKCC PI.

Audits will be conducted at least once shortly after initiation of participant recruitment at a site, annually during the study (or more frequently if indicated), and at the end or closeout of the trial. The number of participants audited will be determined by available time and the complexity of the protocol.

The audit will include a review of source documentation to evaluate compliance for:

- Informed consent documents and procedures
- Adherence to eligibility criteria
- Protocol defined treatment
- Required baseline, on study and follow-up protocol testing
- IRB documents (submitted amendments, annual continuing review reports, SAEs)
- Required specimen submission



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- Case Report Form submissions to MSKCC: timelines and accuracy

A wrap-up session will be conducted at the participating site and preliminary findings will be discussed with the participating site PI and research team. The preliminary results will be sent to the MSKCC PI.

Each audit will be summarized and a final report will be sent to the PI at the audited participating site within 30 days of the audit. The report will include a summary of findings, participant by participant case review, specific recommendations on any performance and/or shortcomings and request for corrective action, when necessary. When corrective action is required, the participating site must reply within 45 days of receipt of audit report with their corrective action plan.

A copy of the audit report and corrective action plan (if applicable) submitted by the participating site must be sent to the MSKCC IRB/PB, CRQA and maintained in the department's protocol regulatory binder.

16.1.2 Response Review

Since therapeutic efficacy is a stated primary objective, all sites participant's responses are subject to review by MSKCC's Therapeutic Response Review Committee (TRRC). Radiology, additional lab reports and possibly bone marrow biopsies and/or aspirates will need to be obtained from the participating sites for MSKCC TRRC review and confirmation of response assessment. These materials must be sent to MSKCC promptly upon request.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at <http://cancertrials.nci.nih.gov/researchers/dsm/index.html>. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: <http://inside2/clinresearch/Documents/MSKCC Data and Safety Monitoring Plan.pdf>

There are several different mechanisms by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: *Data and Safety Monitoring Committee (DSMC)* for Phase I and II



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clinical trials, and the *Data and Safety Monitoring Board (DSMB)* for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) Will be addressed and the monitoring procedures will be established at the time of protocol activation

16.3 Regulatory Documentation

Prior to implementing this protocol at MSKCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSKCC Institutional Review Board/Privacy Board (IRB/PB). Prior to implementing this protocol at the participating sites, approval for the MSKCC IRB/PB approved protocol must be obtained from the participating site's IRB.

The following documents must be provided to MSKCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Participating site laboratory certifications and normals

Upon receipt of the required documents, MSKCC will formally contact the site and grant permission to proceed with enrollment.

16.3.1 Amendments

Each change to the protocol document must be organized and documented by MSKCC and first approved by the MSKCC IRB/PB. Upon receipt of MSKCC IRB/PB approval, MSKCC will immediately distribute all non expedited amendments to the participating sites, for submission to their local IRBs.

Participating sites must obtain approval for amendments from their IRB within 90 calendar days of MSKCC IRB/PB approval. If the amendment is the result of a safety issue or makes eligibility criteria more restrictive, sites will not be permitted to continuing enrolling new participants until the participating site IRB approval has been granted.



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The following documents must be provided to MSKCC for each amendment within the stated timelines:

- Participating Site IRB approval
- Participating Site IRB approved informed consent form and HIPAA authorization

16.3.2 Additional IRB Correspondence

Continuing Review Approval

The Continuing Review Approval letter from the participating site's IRB and the most current approved version of the informed consent form should be submitted to MSKCC within 7 days of expiration. Failure to submit the re-approval in the stated timeline will result in suspension of study activities.

Deviations and Violations

A protocol deviation on this study is defined as a request to treat a research participant who does not meet all the eligibility criteria, pretreatment evaluation, or who requires alteration in their study plan. If a deviation from this protocol is proposed for a potential or existing participant at MSKCC or a participating site, approval from the MSKCC IRB/PB is required prior to the action. Participating sites should contact the MSKCC PI who will in turn seek approval from the MSKCC IRB/PB.

A protocol violation is anything that occurs with a participant, which deviated from the protocol without prior approval from the MSKCC IRB/PB. For protocol violations that are identified after they occur, the participating site should report to MSKCC as soon as possible. The MSKCC PI will in turn report the violation to the MSKCC IRB/PB.

Participating sites should report deviations and violations to their institution's IRBs as soon as possible per that site's institutional guidelines. Approvals/acknowledgments from the participating site IRB for protocol deviations and violations should be submitted to MSKCC as received.

Other correspondence

Participating sites should submit other correspondence to their institution's IRB according to local guidelines, and submit copies of that correspondence to MSKCC.

16.3.3 Document maintenance

The MSKCC PI and the Participating Site PI will maintain adequate and accurate records to enable the implementation of the protocol to be fully documented and the data to be subsequently verified.



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The participating sites will ensure that all participating site IRB correspondence (IRB approval letters referencing protocol version date and amendment number, IRB approved protocol, appendices, informed consent forms, deviations, violations, and approval of continuing reviews) is maintained in the regulatory binder on site and sent to MSKCC.

A regulatory binder for each site will also be maintained at MSKCC; this binder may be paper or electronic.

After study closure, the participating site will maintain all source documents, study related documents and CRFs for 3 years

16.4 Noncompliance

If a participating site is noncompliant with the data and regulatory requirements set forth in section 16.0-16.3, accrual privileges may be suspended and/or contract payments maybe withheld (if applicable), until the outstanding issues have been resolved.

17.0 PROTECTION OF HUMAN SUBJECTS

Inclusion of Children in Research

This protocol/project does not include children because the number of children is limited and because the majority are already accessed by a nationwide pediatric cancer research network. This statement is based on exclusion 4b of the NIH Policy and Guidelines on the Inclusion of Children as Participants in Research Involving Human Subjects.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board (IRB/PB).

17.2 Serious Adverse Event (SAE) Reporting

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from CRDB:



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- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following
 - A explanation of how the AE was handled
 - A description of the subject's condition
 - Indication if the subject remains on the study
 - If an amendment will need to be made to the protocol and/or consent form.

The PI's signature and the date it was signed are required on the completed report.

17.3 Regulatory And Reporting Requirements

17.3.1 Recording Adverse Experiences

An adverse experience is defined as any unfavorable and unintended change in the structure, function, or chemistry of the body temporally associated with the use of the SPONSOR's product, whether or not considered related to the use of the product. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition which is temporally associated with the use of the SPONSOR's product, is also an adverse experience.

Changes resulting from normal growth and development which do not vary significantly in frequency or severity from expected levels are not to be considered adverse experiences.

Examples of this may include, but are not limited to, teething, typical crying in infants and children, and onset of menses or menopause occurring at a physiologically appropriate time.

Adverse experiences may occur in the course of the use of a Merck product in clinical studies or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse, and from withdrawal.

Adverse experiences may also occur in screened subjects/patients during any pre allocation baseline period as a result of a protocol-specified intervention including washout or discontinuation of usual therapy, diet, placebo treatment, or a procedure.



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17.3.2 Adverse Experiences*

PI and participating investigators need to provide Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215-993-1220) with copies of all serious and/or unexpected adverse experiences, within two working days. PI and participating investigators also agree to establish and maintain records and make reports to the FDA with copies, as described above, to Merck for the following Adverse Experiences: (1) all serious, unexpected, adverse events, (2) any significant increase in the frequency of serious expected adverse events, and (3) any significant increase in the frequency of therapeutic failures. Additionally, PI and participating investigators must report any pregnancy occurring in association with use of a Merck Product to Merck & Co., Inc. (Attn: Worldwide Product Safety; FAX 215-993-1220). For any serious thromboembolic Adverse Experiences, PI and participating investigators must fax, at the same time as the submission to Merck of the original report, the additional information set forth on the Zolanza Thromboembolic Event Questionnaire. In addition, if the PI or participating investigator becomes aware of any new information regarding any Adverse Experience, he/she must submit that new information to Worldwide Product Safety within two working days.

17.3.3 Determination of reporting requirements

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) the characteristics of the adverse event including the grade (severity), the relationship to the study therapy (attribution), and the prior experience (expectedness) of the adverse event; 3) the phase (1, 2, or 3) of the trial; and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event. An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND) (vorinostat, bevacizumab). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label. Commercial agents are those agents not provided under an IND but obtained instead from a commercial source (paclitaxel, trastuzumab).

When a study arm includes both investigational and commercial agents, the following rules apply:

Concurrent administration: When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.

Sequential administration: When a study includes an investigational agent(s) and a commercial agent(s) on the same study arm, but the commercial agent(s) is given for a period of time prior to starting the investigational agent(s), expedited reporting of adverse events which occur prior to starting the investigational agent(s) would follow the guidelines for commercial agents. Once therapy with the investigational agent(s) is initiated, all expedited reporting of adverse events should follow the investigational guidelines.



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17.3.4 Steps to determine if an adverse event is to be reported in an expedited manner:

Step 1: Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (<http://ctep.cancer.gov>). Additionally, if assistance is needed, the NCI has an Index to the CTCAE that provides help for classifying and locating terms. All appropriate treatment locations should have access to a copy of the CTCAE.

Step 2: Grade the event using the NCI CTCAE.

Step 3: Determine whether the adverse event is related to the protocol therapy (investigational or commercial). Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

Step 4: Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is NOT listed in the current NCI Agent-Specific Adverse Event List for the investigational agent.

Step 5: Review the Additional instructions, requirements, and exceptions for this protocol specific requirements for expedited reporting of specific adverse events that require special monitoring.

Step 6: Determine if the protocol treatment given prior to the adverse event included investigational agent(s), a commercial agent(s), or a combination of investigational and commercial agents.

NOTE: If the patient received at least one dose of investigational agent, follow the guidelines for investigation agents. If no investigational agent was administered, follow the guidelines for non-investigational agents.

17.4 Serious Adverse Event (SAE) Reporting for Participating Sites

Responsibility of Participating Sites

- Participating sites are responsible for reporting all SAEs to the MSKCC PI via fax or e-mail within 3 calendar days of learning of the event.
- Participating sites should notify the MSKCC PI of any grade 5 event immediately.
- Participating sites should use the SAE Report Template (*appendix 7*) to report SAEs to MSKCC



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SAE contact information for the Coordinating Center is listed below:

Brett Wegner:

- FAX: [646-227-2427] **to the attention of** [SAE - Protocol: 08-045: (Brett Wegner)]
- EMAIL: WegnerB@mskcc.org

David Straus, M.D. – Principal Investigator

- EMAIL: StrausD@mskcc.org

Responsibility of MSKCC

- The MSKCC Research Staff is responsible for submitting all SAEs to the MSKCC IRB/PB as specified in 17.2 and 17.3.2
- The MSKCC PI is responsible for informing all participating sites about unexpected SAEs within 30 days of receiving the stamped SAE from the MSKCC IRB/PB.
- Any report pertaining to a grade 5 event will be distributed to the participating sites as soon as possible.

17.5 Safety Reports

- MSKCC will distribute outside safety reports to the participating sites immediately upon receipt.
- MSKCC must submit safety reports to the MSKCC IRB/PB according to institutional guidelines.
- Participating sites must submit safety reports to their institution's IRBs within 30 days of receipt from MSKCC or per participating site guidelines.

18.0 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.



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3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

18.1 For Participating Sites

The investigators listed on the protocol cover page and their qualified designees at each participating site may obtain informed consent and care for the participants according to good clinical practice and protocol guidelines.

Signed copies of the informed consent should be distributed as follows: One copy will be given to the participant to be retained for their personal records. One copy will be maintained on file at the MSKCC. The third copy will be confidentially maintained by the participating institution.

A note will be placed in the medical record documenting that informed consent was obtained for this study, and that the participant acknowledges the risk of participation.

19.0 Reference(s)

1. Feugier P, Van Hoof A, Sebban C, et al. Long-term results of the R-CHOP study in the treatment of elderly patients with diffuse large B-cell lymphoma: a study by the Groupe d'Etude des Lymphomes de l'Adulte. *J Clin Oncol.* 2005;23:4117-4126.
2. Kewalramani T, Zelenetz AD, Nimer SD, et al. Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma. *Blood.* 2004;103:3684-3688.
3. Chao NJ, Rosenberg SA, Horning SJ. CEPP(B): an effective and well-tolerated regimen in poor-risk, aggressive non-Hodgkin's lymphoma. *Blood.* 1990;76:1293-1298.
4. Borchmann P, Herbrecht R, Wilhelm M, et al. Results of a phase II study of pixantrone in combination with cyclophosphamide, vincristine and prednisone in patients with relapsed aggressive non-Hodgkin's lymphoma. *Blood.* 2006;108:Abstract #529.



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5. Sirohi B, Cunningham D, Norman A, et al. Gemcitabine, cisplatin and methylprednisolone (GEM-P) with or without Rituximab in relapsed and refractory patients with diffuse large B cell lymphoma (DLBCL). *Hematology*. 2007;12:149-153.
6. Bereshchenko OR, Gu W, Dalla-Favera R. Acetylation inactivates the transcriptional repressor BCL6. *Nat Genet*. 2002;32:606-613.
7. O'Connor OA, Heaney ML, Schwartz L, et al. 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.
8. Marchion DC, Bicaku E, Turner JG, Daud AI, Sullivan DM, Munster PN. Synergistic interaction between histone deacetylase and topoisomerase II inhibitors is mediated through topoisomerase IIbeta. *Clin Cancer Res*. 2005;11:8467-8475.
9. Cella D, Webster K, Cashy J, et al. Development of a measure of health-related quality of life for non-Hodgkin's lymphoma clinical research: The Functional Assessment of Cancer Therapy-Lymphoma (FACT-LYM). *Blood*. 2005;106:Abstract #750.
10. Webster K, Odom L, Peterman A, Lent L, Cella D. The Functional Assessment of Chronic Disease (FACIT) measurement system: Validation of version 4 of the core questionnaire. *Quality of Life Research*. 1999;8:604.
11. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. *J Clin Oncol*. 1993;11:570-579.
12. Webster K, Cashy J, Cella D, et al. Measuring quality of life (QOL) in patients with non-Hodgkin's lymphoma (NHL): The Functional Assessment of cancer Therapy-Lymphoma (FACT-Lym). *Quality of Life Research* 2005;14:1650.
13. Johnstone RW. Histone-deacetylase inhibitors: novel drugs for the treatment of cancer. *Nat Rev Drug Discov*. 2002;1:287-299.
14. 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.
15. Grunstein M. Histone acetylation in chromatin structure and transcription. *Nature*. 1997;389:349-352.
16. Richon VM, Emiliani S, Verdin E, et al. A class of hybrid polar inducers of transformed cell differentiation inhibits histone deacetylases. *Proc Natl Acad Sci U S A*. 1998;95:3003-3007.
17. Secrist JP, Zhou X, Richon VM. HDAC inhibitors for the treatment of cancer. *Curr Opin Investig Drugs*. 2003;4:1422-1427.
18. Munster PN, Troso-Sandoval T, Rosen N, Rifkind R, Marks PA, Richon VM. The histone deacetylase inhibitor suberoylanilide hydroxamic acid induces differentiation of human breast cancer cells. *Cancer Res*. 2001;61:8492-8497.
19. He LZ, Tolentino T, Grayson P, et al. Histone deacetylase inhibitors induce remission in transgenic models of therapy-resistant acute promyelocytic leukemia. *J Clin Invest*. 2001;108:1321-1330.
20. Ruefli AA, Ausserlechner MJ, Bernhard D, et al. 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.



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IRB#: 08-045A(6)

21. Huang L, Pardee AB. Suberoylanilide hydroxamic acid as a potential therapeutic agent for human breast cancer treatment. *Mol Med.* 2000;6:849-866.
22. Butler LM, Agus DB, Scher HI, et al. Suberoylanilide hydroxamic acid, an inhibitor of histone deacetylase, suppresses the growth of prostate cancer cells in vitro and in vivo. *Cancer Res.* 2000;60:5165-5170.
23. Vrana JA, Decker RH, Johnson CR, et al. Induction of apoptosis in U937 human leukemia cells by suberoylanilide hydroxamic acid (SAHA) proceeds through pathways that are regulated by Bcl-2/Bcl-XL, c-Jun, and p21CIP1, but independent of p53. *Oncogene.* 1999;18:7016-7025.
24. Mitsiades N, Mitsiades CS, Richardson PG, et al. Molecular sequelae of histone deacetylase inhibition in human malignant B cells. *Blood.* 2003;101:4055-4062.
25. Lindemann RK, Gabrielli B, Johnstone RW. Histone-deacetylase inhibitors for the treatment of cancer. *Cell Cycle.* 2004;3:e77-e86.
26. Warrenner R, Beamish H, Burgess A, et al. Tumor cell-selective cytotoxicity by targeting cell cycle checkpoints. *Faseb J.* 2003;17:1550-1552.
27. Glaser KB, Li J, Pease LJ, et al. Differential protein acetylation induced by novel histone deacetylase inhibitors. *Biochem Biophys Res Commun.* 2004;325:683-690.
28. Bali P, Pranpat M, Swaby R, et al. Activity of suberoylanilide hydroxamic acid against human breast cancer cells with amplification of her-2. *Clin Cancer Res.* 2005;11:6382-6389.
29. Kelly WK, O'Connor OA, Krug LM, et al. Phase I study of an oral histone deacetylase inhibitor, suberoylanilide hydroxamic acid, in patients with advanced cancer. *J Clin Oncol.* 2005;23:3923-3931.
30. Olsen E, Kim YH, Kuzel T, et al. Vorinostat (suberoylanilide hydroxamic acid, SAHA) is clinically active in advanced cutaneous T-cell lymphoma (abs. 7500). *J Clin Oncol.* 2006;24 (2006 ASCO Annual Meeting Proceedings, Part 1, 18S).
31. Duvic M, Talpur R, Zhang C, et al. A phase II trial of oral suberoylanilide hydroxamic acid (SAHA) in advanced cutaneous T-cell lymphoma (CTCL) unresponsive to conventional therapy (abs. 6571) *J Clin Oncol* (2005 ASCO Annual Meeting Proceedings, 23 (Part 1, 16S). 2006.
32. Garcia-Manero G, Yang H, Sanchez-Gonzales B, et al. Final results of a phase I study of the histone deacetylase inhibitor vorinostat (suberoylanilide hydroxamic acid (SAHA) in patients with leukemia and myelodysplastic syndrome (Abs. 2801). *Blood.* 2005;106.
33. Richardson P, Schlossman RL, Mitsiades CS, et al. Phase I clinical trial of oral administration of the histone deacetylase (HDAC) inhibitor suberoylanilide hydroxamic acid (SAHA) in patients with relapsed/refractory multiple myeloma (abs. 1503) *Blood.* 2004;104:420a.
34. Cheson BD, Pfistner B, Juweid ME, et al. Revised response criteria for malignant lymphoma. *J Clin Oncol.* 2007;25:579-586.
35. Cheson BD, Horning SJ, Coiffier B, et al. Report of an international workshop to standardize response criteria for non-Hodgkin's lymphomas. NCI Sponsored International Working Group. *J Clin Oncol.* 1999;17:1244.
36. Cella D. Manual of the Functional Assessment of Chronic Illness Therapy (FACIT Scales)- Version 4. Evanston Northwestern Healthcare & Northwestern University. 1997.



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37. Brown H, Prescott R. Applied Mixed Models in Medicine. 1999;New York, John Wiley & Sons.
38. Troxel AB, Fairclough DL, Curran D, Hahn EA. Statistical analysis of quality of life with missing data in cancer clinical trials. Stat Med. 1998;17:653-666.
39. Curran D, Bacchi M, Schmitz SF, Molenberghs G, Sylvester RJ. Identifying the types of missingness in quality of life data from clinical trials. Stat Med. 1998;17:739-756.
40. Little R. Modeling the drop-out mechanism in repeated-measures studies. Journal of the American Statistical Association. 1995;90:1112-1121.
41. Schluchter MD. Methods for the analysis of informatively censored longitudinal data. Stat Med. 1992;11:1861-1870.
42. Schluchter MD, Greene T, Beck GJ. Analysis of change in the presence of informative censoring: application to a longitudinal clinical trial of progressive renal disease. Stat Med. 2001;20:989-1007.

20.0 APPENDICES

- Appendix 1: Schedule of Protocol Events
- Appendix 2: Thromboembolic Event Questionnaire
- Appendix 3: Functional Assessment of Cancer Therapy-Lymphoma (FACT-Lym)
- Appendix 4: Patient diary to document oral medications on study
- Appendix 5: Global Rating of Change Questionnaire
- Appendix 6: Efficacy of Vorinostat
- Appendix 7: Serious Adverse Event Report Form