CLINICAL STUDY PROTOCOL

Phase II Trial of the Combination of Decitabine, SQ Bortezomib and Pegylated Liposomal Doxorubicin (PLD or Doxil ® or LipoDox®) for the Treatment of Patients with Relapsed/Refractory Acute Myelogenous Leukemia (AML)

Protocol Number: UCDCC#230
Indication: Acute Myeloid/Myelogenous Leukemia
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Therapeutic Area: Oncology

Protocol History		
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This is an investigator-initiated study. The principal investigator, Joseph Tuscano MD, (who may also sometimes be referred to as the sponsor-investigator), is conducting the study and acting as the sponsor. Therefore, the legal/ethical obligations of the principal investigator include both those of a sponsor and those of an investigator.

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PROTOCOL SUMMARY

Title
Phase II Trial of the Combination of Decitabine, SQ Bortezomib and Pegylated Liposomal Doxorubicin (PLD or Doxil® or LipoDox®) for the Treatment of Patients with Relapsed/Refractory Acute Myelogenous Leukemia (AML)

Objectives
The primary objectives of this study are to:
- Assess response rate and progression free survival (PFS)

The secondary objectives of this study are to:
- Assess overall survival and toxicity

Patient Population
Patients with AML who have either relapsed or refractory disease as well as previously untreated patients with AML who are not candidates for standard induction therapy

Specific inclusion and exclusion criteria are detailed in Section 3.2.

Number of Patients
29. Fifteen subjects were enrolled prior to amendment 7, two subjects were enrolled per amendment 9 and up to 12 additional subjects will be enrolled per amendment 10 (detailed in Section 5.2).

Study Design and Methodology
Phase II, open label

Treatments Administered
Induction:
Decitabine 20mg/m^2 (IV) days 1-10
Bortezomib: 1.3mg/m^2 (SQ) days 5, 8, 12, and 15
PLD or Doxil® or LipoDox®: 40mg/m^2 (IV) day 12
Patients will receive a minimum of 1 cycle and a maximum of 4 cycles of induction. If there is no response or progression after two cycles of induction, they will be taken off the study.

Post-Induction:
Decitabine 20mg/m^2 (IV) days 1-5
Bortezomib: 1.3mg/m^2 (SQ) days 1 and 8
PLD or Doxil® or LipoDox®: 40mg/m^2 (IV) day 12
Patients will receive continued cycles of post-induction therapy until progression, intolerance, transplant or withdrawal of informed consent for a maximum of 12 cycles (induction cycles are counted towards this total).

Efficacy Data Collected
The following evaluations will be conducted to assess the efficacy of decitabine, subcutaneous bortezomib and PLD or Doxil® or LipoDox®:

- Peripheral blood counts
- Bone marrow biopsy (done at baseline, after each cycle of induction until complete response (CR) or CR with incomplete count recovery (CRi), and after every six cycles of post-induction therapy)

Safety Data Collected

The following evaluations will be conducted to assess the safety of decitabine, subcutaneous bortezomib and PLD or Doxil® or LipoDox®:

- There will be a safety lead-in with the first 6-9 subjects enrolled evaluated for DLTs during cycle 1.
- Assess for clinical adverse events every 4 weeks especially assessing for peripheral neuropathy, diarrhea, hypotension and tachycardia
- Comprehensive metabolic panel to assess the creatinine, bilirubin, AST and ALT levels. At least weekly during induction and every two weeks during post-induction therapy.

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LIST OF ABBREVIATIONS

Abbreviation	Definition
°C	degrees Celsius
μM	micromolar
20S	20S proteasome subunit
AE	adverse event
ANC	absolute neutrophil count
Bc1-2	B-cell lymphoma-2; a gene that inhibits apoptosis
BSA	body surface area
CAM	cell adhesion molecules
cm	centimeter
CR	complete response
CTCAE	(NCI) Common Terminology Criteria for Adverse Events
CTEP	Cancer Therapy Evaluation Program
CV	cardiovascular
dL	deciliter
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DOR	duration of response
EBMT	European Group for Blood and Marrow Transplant
E_{max}	maximum effect
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GI	gastrointestinal
GLP	Good Laboratory Practice
ht	height
IκB	I kappa B kinase; cytokine response kinase that activates transcription factor NF-kappa b at serine 32 and 36
ICAM-1	intercellular adhesion molecule 1
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IL-6	interleukin-6
IND	Investigational New Drug
IRB	institutional review board
IV	intravenous
IκBα	I kappa B alpha-associated protein kinase
kg	kilogram
Ki	inhibitory constant
lbs	pounds
m^2	square meters
MCL	mantle cell lymphoma

Abbreviation	Definition
mg	milligram
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
min	minute
mL	milliliter
MM	multiple myeloma
mm^3	cubic millimeters
mmol	millimole
MR	minor response
MTD	maximum tolerated dose
NCI	National Cancer Institute
nCR	near complete response
NF-κB	nuclear factor-κB
ng	nanogram
NHL	Non-Hodgkin's lymphoma
nM	nanomole
NYHA	New York Heart Association
ORR	Overall response rate
OS	overall survival
P21	p21(ras) farnesyl-protein transferase
P27	cyclin-dependent kinase inhibitor
P53	tumor suppressor protein with molecular weight of 53 kDa
PK	pharmacokinetics
PR	partial response
SAE	serious adverse event
TFI	treatment free interval
TNT	time to next therapy
TTP	time to progression
ULN	upper limit of normal
US	United States
US FDA	United States Food and Drug Administration
USP	United States Pharmacopeia
VCAM-1	vascular cell adhesion molecule 1
w/w	weight-to-weight ratio
wt	weight

1. INTRODUCTION AND STUDY RATIONALE

1.1 Overview of the Disease

Acute myeloid leukemia remains largely incurable despite advances that have been made in recent years into increasing the complete response (CR) rates. In elderly patients (over the age of 60), CR rates are lower, 40 to 50%, and long term disease-free and overall survival is less than 10%.[1] The therapeutic options for relapsed/refractory AML are significantly limited. Bortezomib has shown promising activity in patients with advanced hematologic malignancies, including those with leukemia and non-Hodgkin's lymphoma. Pre-clinical studies have shown that proteasome inhibition promotes apoptosis of tumor cells in part through stabilization of the negative regulator of nuclear factor kappa B (NF-κB). Several in-vitro studies have also shown bortezomib to induce apoptosis in human AML cells. In addition a recent phase I study that utilized bortezomib in combination with standard induction therapy patients with relapsed/refractory AML was shown to produce high response rates with minimal additional toxicity.[2] In this study there was no MTD established for bortezomib with the highest dose being 1.5mg/m^2 given on days 1, 4, 8 and 11. Anthracyclines, in part, exert anti-tumor activity by inducing an NF-κB driven, anti-apoptotic process. Laboratory evidence has suggested that activity of the transcription factor NF-κB promotes anthracycline resistance. This particular resistance can be overcome when a proteasome inhibitor is given in conjunction with the anthracycline. We showed that the combination of bortezomib 1.5mg/m^2 on days 1, 4, 8 and 11 with liposomal doxorubicin was well-tolerated with 13% of patients having grade 3 neurotoxicity.[52] The regimen showed modest activity in relapsed/refractory AML patients, with partial remissions in 20% of patients and blast count reductions in 79%.

The hypomethylating agents (HMA), including decitabine, have significant activity in AML and have been shown to work primarily through inhibition of DNA methyltrasnferase enzymes.[53-54] In addition, HMA have been shown to inhibit the NF-kB pathway including relocalization of NF-kB to the cytoplasm, likely as an off-target effect through IKK inhibition.[55-58] Recently, a 10-day dosing schedule of decitabine for AML has demonstrated significant activity, with CR rates of 40-64% in untreated older patients and 16% in relapsed/refractory patients.[59-61] The regimen is well-tolerated with febrile neutropenia, infections and myelosuppression most common. The 10-day decitabine regimen was combined with bortezomib in a phase I study in relapsed/refractory AML or untreated older patients.[62] The borezomib dose was escalated to 1.3mg/m^2 on days 5, 8, 12 and 15 without dose-limiting toxicities. Toxicities were similar to the 10-day decitabine studies, and grade 3 neurotoxicity related to bortezomib was seen in 3 of 19 patients (all three events were after induction). CR was achieved in 50% of untreated and 22% of relapsed/refractory patients.

These studies continued decitabine with or without bortezomib until disease progression or unacceptable toxicity.[53-54,59-62] Based on these studies, there are two ongoing clinical trials using the combination of 10-day decitabine and bortezomib with or without additional agents (NCT01420926 and NCT01861314). In NCT01420926, three of the bortezomib doses are being administered concurrently with the 10-days of decitabine (decitabine days 2-11 and bortezomib days 1, 4, 8 and 11).

Using the SC formulation of VELCADE® would provide patients with an easier schedule, reduced neurotoxicity due to decreased time in the infusion room and it would decrease overall cost of care.

1.2 VELCADE® (bortezomib) for Injection

1.2.1 Scientific Background

VELCADE® (bortezomib) for Injection is a small-molecule proteasome inhibitor developed by Millennium Pharmaceuticals, Inc., (Millennium) as a novel agent to treat human malignancies. VELCADE is currently approved by the United States Food and Drug Administration (US FDA) for the treatment of patients with multiple myeloma (MM). It is also indicated for the treatment of patients with mantle cell lymphoma (MCL) who have received at least 1 prior therapy. In the European Union (EU), VELCADE in combination with melphalan and prednisone is indicated for the treatment of patients with previously untreated MM who are not eligible for high-dose chemotherapy with bone marrow transplant. VELCADE is indicated as monotherapy for the treatment of progressive MM in patients who have received at least 1 prior therapy and who have already undergone or are unsuitable for bone marrow transplantation.

By inhibiting a single molecular target, the proteasome, VELCADE affects multiple signaling pathways. The antineoplastic effect of VELCADE likely involves several distinct mechanisms, including inhibition of cell growth and survival pathways, induction of apoptosis, and inhibition of expression of genes that control cellular adhesion, migration, and angiogenesis. Thus, the mechanisms by which VELCADE elicits its antitumor activity may vary among tumor types, and the extent to which each affected pathway is critical to the inhibition of tumor growth could also differ. VELCADE has a novel pattern of cytotoxicity in National Cancer Institute (NCI) in vitro and in vivo assays.[3] In addition, VELCADE has cytotoxic activity in a variety of xenograft tumor models, both as a single agent and in combination with chemotherapy and radiation.[4,5,6,7,8,9,10,11,12,13,14,15,16] Notably, VELCADE induces apoptosis in cells that over express bcl-2, a genetic trait that confers unregulated growth and resistance to conventional chemotherapeutics.[17]

The mechanisms of action leading up to apoptosis have been more clearly defined and include initiation of the unfolded protein response and direct/indirect effects on various molecular targets including cell cycle control proteins p27 and p21, cyclins, signal transduction molecules, transcription factors c-jun and HIF1-α, tumor suppressor protein p53, angiogenesis factors, and many others. VELCADE is thought to be efficacious in multiple myeloma via its inhibition of nuclear factor κB (NF-κB) activation, its attenuation of interleukin-6 (IL-6)-mediated cell growth, a direct apoptotic effect, and possibly anti-angiogenic and other effects.[18,19,20,21,22,23,24,25]

1.2.2 Nonclinical Pharmacology

Pharmacokinetic (PK) and pharmacodynamic studies were conducted in the rat and cynomolgus monkey. Upon intravenous (IV) bolus administration, VELCADE displays a rapid distribution phase ($t_{½}\alpha$ < 10 minutes) followed by a longer elimination phase ($t_{½}\beta$ 5-15 hours). VELCADE has a large volume of distribution (range 5-50 L/kg). The plasma PK profile is well described by a 2-compartment model.

The pharmacodynamic action of VELCADE is well established and can be measured through an ex vivo assay (20S proteasome activity).[26] This assay was used to determine the duration of drug effect in lieu of the PK data in the early preclinical toxicology studies as well as to set a guide for dose escalation in humans. Following dosing with VELCADE in the rat and cynomolgus monkey, proteasome inhibition in peripheral blood had a half-life less than 24 hours, with proteasome activity returning to pretreatment baseline within 24 hours in monkey and within 48 to 72 hours in rat after a single dose of VELCADE. Further, intermittent but high inhibition (> 70%) of proteasome activity was better tolerated than sustained inhibition. Thus, a twice-weekly clinical dosing regimen was chosen in order to allow return of proteasome activity towards baseline between dose administrations.

Subcutaneous administration

In monkeys, plasma bortezomib tmax generally occurred at 0.117 h following IV dosing and 0.117 to 0.25 h following SC dosing. After administration of 1.2 mg/m2, peak plasma concentration and AUC0-72h attained 124 ng/mL and 141 ng.h/mL following IV administration and 113 ng/mL and 211 ng.h/mL following SC administration on the last day of dosing, demonstrating a bioavailability close to 100%. Treatment with bortezomib induced an inhibition of the whole blood 20S proteasome activity reaching a maximal effect between 15 minutes and 1 hour after dosing. The profile of inhibition over time was comparable between cycles and similar after subcutaneous and intravenous injections.

1.2.3 Nonclinical Toxicity

Single-dose, IV toxicity studies were conducted with VELCADE in the mouse, rat, dog, and monkey to establish the single-dose maximum tolerated dose (MTD). The MTDs were 0.25 mg/kg (1.5 mg/m^2) and 0.067 mg/kg (0.8 mg/m^2) in the 2 most sensitive species, rat and monkey, respectively.

Repeat-dose, multicycle toxicity studies of 3 and 6 months in the rat and 9 months in the monkey, each with 8-week recovery periods, were conducted to characterize the chronic toxicity of VELCADE when administered by the clinical route and regimen of administration. The MTD in the 6-month rat study was 0.10 mg/kg (0.6 mg/m^2) and the key target organs were the gastrointestinal (GI) tract and hematopoietic and lymphoid systems. The MTD in the 9-month monkey study was 0.05 mg/kg (0.6 mg/m^2) and the key target organs were the GI tract, hematopoietic and lymphoid systems, peripheral nervous system, and kidney. Full or partial reversibility was observed for each of the toxicities described to date.

In general, the nature of the toxicity of VELCADE is similar across species, and target organs of toxicity in animals have been largely predictive of human toxicity. The toxicity of VELCADE in animals is characterized by a steep dose-response with mortality seen at dosages above the MTD. The cause of death at acutely lethal dosages is considered to be related to indirect cardiovascular (CV) effects of hypotension and vascular changes with secondary bradycardia and the cause of death in long-term studies has been attributed to GI or hematologic toxicity. The pharmacologic effects of VELCADE on the CV system have been extensively characterized and have demonstrated that indirect effects on CV function occur only at acutely lethal dosages and are abrogated by routine supportive care.

Subcutaneous administration

Repeat dose toxicity of VELCADE administered by subcutaneous and intravenous injection (up to 4 cycles of 11 days of VELCADE) was evaluated in cynomolgus monkeys. Each of cycles 1, 2 and 3 consisted of dosing on Days 1, 4, 8 and 11, followed by 1 week of recovery. VELCADE treatment at 1.2mg/m^2 IV or SC induced abnormal feces (soft, liquid and/or mucoid), emesis, reduced appetite and decreased activity. Local tolerance was very good for SC administration. There were no hematological changes associated with the administration of VELCADE SC or IV but slight decreases in total, protein and globulin values as well as microscopic changes in the peripheral nervous system, kidneys, bone marrow, and immune system of animals were seen. There were no clear differences in the incidence and severity of these findings between animals dosed subcutaneously and those treated intravenously. [25]

Additional detailed information regarding the nonclinical pharmacology and toxicology of VELCADE may be found in the most recent Investigator's Brochure.

1.2.4 Clinical Pharmacokinetics and Pharmacodynamics

The clinical pharmacology characterization of VELCADE has been determined from phase 1 studies in subjects with solid tumors and hematological malignancies, and confirmed in phase 2 studies in subjects with multiple myeloma.

VELCADE demonstrates multicompartmental pharmacokinetics. Following intravenous administration of 1.0 mg/m^2 and 1.3 mg/m^2 dose, the mean first-dose maximum observed plasma concentrations of VELCADE were 57 and 112 ng/mL, respectively, in 11 patients with MM and creatinine clearance values > 50 mL/min participating in a pharmacokinetics study. In subsequent doses, mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1.0-mg/m^2 dose and 89 to 120 ng/mL for the 1.3-mg/m^2 dose. The mean elimination half-life of VELCADE upon multiple dosing ranged from 40 to 193 hours. VELCADE is eliminated more rapidly following the first dose. Mean total body clearances were 102 and 112 L/h following the first dose for doses of 1.0 mg/m^2 and 1.3 mg/m^2, respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1.0 and 1.3 mg/m^2, respectively. Clinical experience has shown that the change in clearance does not result in overt toxicity from accumulation in this multidose regimen in humans.

In subjects with advanced malignancies, the maximum pharmacodynamic effect (inhibition of 20S activity) occurred within 1-hour postdose. At the therapeutic dose of 1.3 mg/m^2 in subjects with MM, the mean proteasome inhibition at 1 hour postdose was approximately 61%.

The time course of proteasome inhibition in subjects is characterized by maximum inhibition observed within the first hour after administration, followed by partial recovery of proteasome activity over the next 6 to 24 hours to within 50% of the pretreatment activity. On the Day 1, 4, 8, and 11 schedule, variable (10%–30%) levels of proteasome inhibition have been observed at the next scheduled dosing. In theory, this advantage allows cells to recover proteasome activity for normal cellular housekeeping functions between doses.

The relationship between VELCADE plasma concentrations and proteasome inhibition can be described by a maximum effect (E_{max}) model. The E_{max} curve is initially very steep, with small changes in plasma VELCADE concentration over the range of 0.5 to 2.0 ng/mL relating to large increases in the percent inhibition (0–60%). After that, a plateau occurs where marginal increases of proteasome inhibition are observed in spite of large changes in plasma VELCADE concentrations.

Subcutaneous administration

Following multiple 1.3 mg/m^2 doses, the mean (SD) maximum plasma bortezomib concentration (C_{max}) was approximately 10 times lower following SC administration (20.4 [8.9] ng/mL) compared with IV administration (223 [101] ng/mL), with a short Tmax of approximately one-half hour following VELCADE SC injection. However, AUC_{last} was equivalent for both routes of administration with a geometric mean ratio (SC to IV) of 0.992 and 90% CI of 80.18% to 122.80%; ie, within the standard 80 – 125% bioequivalence criteria.

The mean percent inhibition of proteasome activity (E_{max}) was comparable for the SC and IV groups (63.7% vs. 69.3%; respectively) following multiple 1.3 mg/m2 SC or IV doses of VELCADE. Mean AUE_{72} following SC injection was comparable to that of the IV injection and within the observed variability (CV = 36 - 55%).

The exploratory analyses showed that there were no apparent pharmacokinetic or pharmacodynamic differences related to the site of SC injection (abdomen versus thigh) taking into consideration the small sample size of the pharmacokinetic/pharmacodynamic part of the study.

Bortezomib was reconstituted to a concentration of 2.5 mg/mL for SC administration. In the randomized Phase 1 study CAN-1004, bortezomib was injected subcutaneously in a concentration of 1 mg/mL. The pharmacokinetic and pharmacodynamic parameters of the SC administration were comparable between the 2 studies (Table 1-1). Thus, the concentration of the SC injected solution does not appear to influence bortezomib pharmacokinetics or pharmacodynamics. The pharmacokinetic and pharmacodynamic parameters following IV administration in the current study were also comparable to those observed previously for IV administration.[27]

Table 1-1 Summary of Pharmacokinetic and Pharmacodynamic Parameters Following Subcutaneous Injections of VELCADE 1.3 mg/m^2 Using 2.5 mg/mL and 1.0 mg/mL Solutions

Parameter	2.5 mg/mL[a]	1.0 mg/mL[b]
C_{max} (ng/mL)[c]	20.4 (8.87)	22.5 (5.36)
T_{max} (h)[d]	0.5 (0.08-1.00)	0.5 (0.25-1.00)
AUC_{last} (ng.h/mL)[c]	155 (56.8)	195 (51.2)
AUE_{72} (%.h)[c]	1714 (617)	1619 (804)
E_{max} (%)[c]	63.7 (10.6)	57.0 (12.8)

AUC_{last}=area under the plasma concentration-time curve from time 0 to the time of last quantifiable time point; AUE_{72}=area under the percent inhibition-time curve from time 0 to 72 hours; E_{max}=observed maximum percent inhibition of 20S proteasome activity (ChT:T); h=hours; SD=standard deviation; T_{max}=time when C_{max} is observed

[a] 26866138-MMY-3021
[b] 26866138-CAN-1004
[c] Mean (SD)
[d] Median (range)

1.2.5 Clinical Experience

To date, more than 436,000 patients have been treated with VELCADE, including patients treated through Millennium-sponsored clinical trials, Investigator-Initiated Studies, the US NCI Cancer Therapy Evaluation Program (CTEP), and with commercially available drug. VELCADE has been commercially available since 13 May 2003.

The overall goal of the Millennium phase 1 program was to determine the MTD and dose-limiting toxicity (DLT) of VELCADE in a number of therapeutic settings involving subjects with various advanced malignancies. In a phase 1 trial in patients with refractory hematologic malignancies, the MTD for a twice weekly dosing for 4 weeks of a 42-day cycle was 1.04 mg/m^2/dose, with DLTs of thrombocytopenia, hyponatremia, hypokalemia, fatigue, and malaise.[28] The toxicity was greatest during the third and fourth weeks of therapy. In the 3-week schedule of VELCADE monotherapy (4 doses, given on Days 1, 4, 8, and 11 of a 21-day treatment cycle), the DLT occurred at 1.56 mg/m^2/dose (3 subjects with Grade 3 diarrhea and 1 with peripheral sensory neuropathy). Therefore, the MTD at this schedule was 1.3 mg/m^2/dose. In a 35-day treatment cycle with 4 weekly doses of VELCADE monotherapy, the MTD was 1.6 mg/m^2/dose and DLT included hypotension, tachycardia, diarrhea, and syncope.

In phase 1 clinical studies, antitumor activity was reported in subjects with Non-Hodgkin's Lymphoma (NHL), MM, Waldenström's Macroglobulinemia, squamous cell carcinoma of the nasopharynx, bronchoalveolar carcinoma of the lung, renal cell carcinoma, and prostate cancer.[29,30,31,32]

The safety and efficacy of VELCADE in subjects with MM were investigated in two phase 2 clinical studies, studies M34100-024 (subjects with first relapse)[33] and M34100-025 (subjects with second or greater relapse and refractory to their last prior therapy).[34] In M34100-025, 202 heavily pretreated subjects with refractory MM after at least 2 previous treatments received VELCADE, 1.3 mg/m^2 on Days 1, 4, 8, and 11 of a 21-day treatment cycle. The European Group for Blood and Marrow Transplant (EBMT) response criteria, as described by Blade[35] were utilized to determine disease response. Complete responses (CRs) were observed in 4% of subjects, with an additional 6% of patients meeting all criteria for CR but having a positive immunofixation test. Partial response (PR) or better was observed in 27% of subjects, and the overall response rate (CR, PR, and minor response [MR] combined) was 35%. Seventy percent of subjects experienced stable disease or better.

The phase 3 study (M34101-039)[36], also referred to as the APEX study, was designed to determine whether VELCADE provided benefit (time to progression [TTP], response rate, and survival) to patients with relapsed or refractory MM relative to treatment with high-dose dexamethasone. The study was also designed to determine the safety and tolerability of bortezomib relative to high-dose dexamethasone, and whether treatment with bortezomib was associated with superior clinical benefit and quality of life relative to high-dose dexamethasone. A total of 669 patients were enrolled and 663 patients received study drug (bortezomib: 331; dexamethasone: 332). Patients randomized to VELCADE received 1.3 mg/m^2 IV push twice weekly on Days 1, 4, 8, and 11 of a 3-week cycle for up to 8 treatment cycles as induction therapy, followed by 1.3-mg/m^2 VELCADE weekly on Days 1, 8, 15, and 22 of a 5-week cycle for 3 cycles as maintenance therapy. Patients randomized to dexamethasone received oral dexamethasone 40 mg once daily on Days 1 to 4, 9 to 12, and 17 to 20 of a 5-week cycle for up to 4 treatment cycles as induction therapy, followed by dexamethasone 40 mg once daily on Days 1 to 4 of a 4-week cycle for 5 cycles as maintenance therapy. The EBMT response criteria were utilized to determine disease response. There was a 78% increase in TTP for the bortezomib arm. Median TTP was 6.2 months for the VELCADE arm and 3.5 months for the dexamethasone arm ($p < 0.0001$). CR + PR was 38% with VELCADE versus 18% with dexamethasone ($p < 0.0001$). CR was 6% with bortezomib versus [illegible] with dexameth
CR) rate was 13% with bortezomib versus 2% with dexamethasone. In patients who had received only 1 prior line of treatment (bortezomib: 132; dexamethasone: 119), CR + PR was 45% with bortezomib vs 26% with dexamethasone ($p = 0.0035$). With a median 8.3 months of follow up, overall survival was significantly longer ($p = 0.0013$) for patients on the bortezomib arm versus patients on the dexamethasone arm. The probability of survival at 1 year was 80% for the VELCADE arm versus 66% for the dexamethasone arm which represented a 41% decreased relative risk of death in the first year with bortezomib

(p = 0.0005). In patients who had received only 1 prior line of treatment, the probability of survival at 1 year was 89% for the bortezomib arm versus 72% for the dexamethasone arm, which represented a 61% decreased relative risk of death in the first year with bortezomib (p = 0.0098). Updated response rates and survival data were reported for M34101-039.[37] The updated CR + PR rate was 43% with VELCADE. The CR + nCR rate was 16% with VELCADE. With a median 22 months of follow-up, overall survival was significantly longer for patients on the bortezomib arm versus patients on the dexamethasone arm. The median overall survival was 29.8 months (95% CI: 23.2, not estimable) for the VELCADE arm vs 23.7 months (95% CI: 18.7, 29.1) for the dexamethasone arm (hazard ratio = 0.77, p = 0.0272). The probability of survival at 1 year was 80% for the bortezomib arm versus 67% for the dexamethasone arm (p = 0.0002).

The safety and efficacy of VELCADE in relapsed or refractory mantle cell lymphoma (MCL) were investigated in an international, phase 2, multicenter study M34103-053, also referred to as the PINNACLE study.[38] The single-arm study was designed to evaluate the response rates, duration of response (DOR), TTP, overall survival (OS), and safety of bortezomib treatment in patients with relapsed or refractory mantle cell lymphoma. For 141 evaluable patients, the response rate was 31% (8% CR/unconfirmed CR [Cru]). Median time to response was 40 days (range 31-204 days). The median number of cycles administered across all patients was 4; in responding patients, the median number of cycles was 8. The median DOR by algorithm was 9.2 months and 13.5 months in patients with CR/CRu. Median TTP for both groups was 6.2 months. With a median follow-up of 13.4 months, overall survival had not been reached. The most commonly reported adverse events (AEs) were fatigue, peripheral neuropathy, and gastrointestinal events. A time-to-event update to the PINNACLE study[39] was reported after a median follow-up of 26.4 months. TTP was 6.7 months for all patients, 12.4 months in all responders. The median DOR was 9.2 months in all responders and had not been reached in patients achieving CR/Cru. Overall survival was 23.5 months in all patients and 36 months in patients with CR/Cru. Survival at 12 months was 69% overall and 91% in responding patients.

The phase 3 study (MMY 3002) known as the VISTA study, evaluated the safety and efficacy of the combination of VELCADE, melphalan, and prednisone in previously untreated multiple myeloma patients who were not candidates for stem cell transplant.[40] The study was designed to determine the benefit of adding VELCADE to MP (melphalan and prednisone) as assessed by TTP. Patients (682) were randomized to receive nine 6-week cycles of melphalan 9mg/m^2 and prednisone 60 mg/m^2 on Days 1 to 4, alone or in combination with VELCADE 1.3 mg/m^2 by IV bolus on Days 1, 4, 8, 11, 22, 25, 29, and 32 during Cycles 1 to 4, and on Days 1, 8, 22, and 29 during Cycles 5 to 9. Response was evaluated every 3 weeks using the EBMT criteria. At a preplanned interim analysis, the independent data monitoring committee recommended that the study be stopped since the

prespecified statistical boundary end point of TTP had been crossed. Response rates were 30% with 4% CR. The rates of partial response or better were 71% in the VELCADE (VMP) group compared to 34% in the MP group (p = 0.001). With follow-up of 16.3 months, the TTP for the VMP group was 24 months compared to 16.6 months in the MP group (p = 0.000001) and was associated with a 52% reduced time to progression. The median DOR was 19.9 months in the VMP group and 13.1 months in the MP group. Overall survival had not been reached in either group. Hematologic toxicity was similar in both groups. The incidence of peripheral sensory neuropathy and gastrointestinal symptoms was higher in the VMP group. The incidence of herpes zoster was 3% in patients in the VMP group who received antiviral prophylaxis. Fifteen percent of patients in the VMP group discontinued therapy due to AEs compared to 14% in the MP group.

The VISTA study update after extended follow-up of 25.9 months,[41] confirmed a survival benefit for the VMP group. Overall survival was not reached in either group: VMP group (75) deaths, 3 year OS 72%; MP group (111) deaths, 3 year OS 59% (p = 0.0032). Patients on VMP were less likely to start second-line therapy (VMP 38% vs MP 57% at the time of data cut-off) with a longer time to next therapy (TNT) and treatment free interval (TFI). Of the MP patients who received subsequent therapy, 43% went on to receive VELCADE.

Based on investigator-reported best responses to subsequent therapies, patients relapsing after therapy with a novel agent were not intrinsically more resistant than after receiving a traditional agent.

In the VISTA study, VMP was associated with prolonged TTP, TNT, TFI, and OS. Patients were successfully treated with subsequent IMiD-based therapy and retreated with bortezomib. After 36.7 months follow-up, OS continued to be superior for VMP. The OS for VMP had not yet been reached compared to MP (43.1 months).[42] In an updated analysis of overall survival based on 387 deaths (median follow-up 60.1 months), the median overall survival for VMP was 56.4 months and the MP was 43.1 months, with a hazard ration of 0.695 (95% CI: 0.57, 0.85).

SUBCUTANEOUS ADMINISTRATION

A randomized Phase 1 pilot study in 24 subjects with multiple myeloma demonstrated that both the IV and SC routes of VELCADE administration have similar systemic drug exposure and proteasome inhibition. Importantly, SC and IV administration of VELCADE appeared to result in similar efficacy profiles (ie, response rate) and similar safety profiles. The pilot study also provided preliminary evidence of good local tolerance for SC injection of VELCADE, when administered at 1 mg/mL concentration.

The data from the Phase 1 pilot study formed the basis of the design of a randomized, Phase 3 study that compared the efficacy and safety of subcutaneous versus intravenous bortezomib at the approved 1.3 mg/m^2 dose and twice per week schedule in patients with relapsed multiple myeloma [26]. 222 patients were randomly assigned in a 2:1 ratio to receive either subcutaneous (n=148) or intravenous (n=74) bortezomib. The response-evaluable population consisted of 145 patients in the subcutaneous group and 73 in the intravenous group. Patients received a median of eight cycles (range one to ten) in both groups.

The ORR (CR+PR) after 4 cycles of treatment, assessed by computer algorithm implementation of EBMT response criteria, was 42% in both the SC and IV treatment groups for the response-evaluable population. The ORR after 4 cycles in the IV arm was consistent with what was observed in historical single-agent VELCADE trials with relapsed multiple myeloma subjects. The stratified Mantel Haenszel estimate of the relative risk of achieving response for SC treatment group versus IV treatment group was 0.99 with 95% CI (0.71, 1.37). The 95% CI for ORR_SC - 0.6 ORR_IV was (6.1, 27.1), which excludes 0. Thus the study met the noninferiority objective (p-value for the noninferiority hypothesis was 0.00201). Results in the ITT population were similar; noninferiority of SC versus IV was also demonstrated.

The CR rate after 4 cycles of treatment was 6% in the SC treatment group and 8% in the IV treatment group; the nCR rate after 4 cycles of treatment was 6% in the SC treatment group and 5% in the IV treatment group; the very good partial response (VGPR) rate after 4 cycles of treatment was 4% in the SC treatment group and 3% in the IV treatment group. Therefore, 17% subjects in the SC treatment group and 16% subjects in the IV treatment group had obtained at least VGPR after the first 4 cycles.

The ORR (CR+PR) after 8 cycles of treatment was 52% in both the SC and IV treatment groups for the response-evaluable population. The stratified Mantel-Haenszel estimate of the common relative risk of achieving response for SC versus IV was 1.00 with 95% CI (0.77, 1.31). Twenty-five percent of subjects in the SC treatment group and 25% of subjects in the IV treatment group had obtained at least VGPR during the first 8 cycles.

The median TTP (Kaplan-Meier estimate) was 10.4 months in the SC treatment group and 9.4 months in the IV treatment group. The hazard ratio was 0.839 with 95% CI (0.564, 1.249), and the p=0.3866 (stratified log-rank test), indicating similar results between the SC and IV arm.

The median PFS (Kaplan-Meier estimate) was 10.2 months in the SC treatment group and 8.0 months in the IV treatment group. The hazard ratio was 0.824 with 95% CI (0.574,

1.183), and the p=0.2945 (stratified log-rank test), indicating comparable results between the SC and IV arm.

After a median follow-up of 11.8 months, the 1-year survival rate was 72.6% in the SC arm and 76.7% in the IV arm. The p-value for the difference in 1-year survival rate was 0.5037, indicating similar results between the SC and IV arm.

The median time to first response (Kaplan-Meier estimate) was 3.5 months for both the SC and IV treatment groups. The hazard ratio was 1.059 with 95% CI (0.716, 1. 567), and the p=0.7725 (stratified log-rank test), indicating similar results between the SC and IV arm. Among the responders, the median time to first response was 1.4 months (44 days) in the SC arm and 1.4 months (43 days) in the IV arm. Among the responders, the median duration of response (Kaplan-Meier estimate) was 9.7 months in the SC treatment group, compared with 8.7 months in the IV treatment group.

Overall, similar efficacy results were observed in the SC and IV treatment groups, and the study demonstrated that VELCADE SC administration is not inferior to VELCADE IV administration.[26]

1.2.6 Potential Risks of VELCADE

To date, more than 300,000 patients have been treated with VELCADE in both clinical trials investigating its use in hematological malignancies and solid tumors, and in patients who were treated with commercially available VELCADE.

Prescribing physicians and health care practitioners are referred to their locally approved product label for VELCADE regarding Indications and Usage, Contraindications, Warnings, and Precautions.

The known anticipated risks of VELCADE therapy are presented in Table 1-2 and Table 1-3. These risks are grouped according to the combined frequency observed in an integrated analysis of AEs in sponsored clinical studies of single-agent VELCADE dosed at 1.3 mg/m^2 twice weekly on a 21-day schedule, in patients with multiple myeloma and mantle cell lymphoma.

Table 1-2 Known Anticipated Risks of VELCADE by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term
Blood and Lymphatic System Disorders	
Most common	Thrombocytopenia*, anaemia*
Very common	Neutropenia*
Common	Lymphopenia, pancytopenia*, leukopenia*, febrile neutropenia
Cardiac Disorders	
Common	Tachycardia, atrial fibrillation, palpitations, cardiac failure congestive*
Uncommon	Cardiogenic shock*, atrial flutter, cardiac tamponade*±, bradycardia, atrioventricular block complete, arrhythmia, cardiac arrest*, cardiac failure, arrhythmia, pericardial effusion, pericarditis, pericardial disease±, cardiopulmonary failure±
Ear and Labyrinth Disorders	
Uncommon	Deafness, hearing impaired
Eye Disorders	
Common	Blurred vision, conjunctivitis, conjunctival haemorrhage
Gastrointestinal Disorders	
Most common	Constipation, diarrhoea*, nausea, vomiting*
Very common	abdominal pain (excluding oral and throat)
Common	Dyspepsia, pharyngolaryngeal pain, gastroesophageal reflux, abdominal distension, gastritis, stomatitis, mouth ulceration, dysphagia, gastrointestinal haemorrhage*, lower gastrointestinal haemorrhage*± rectal haemorrhage
Uncommon	Eructation, gastrointestinal pain, tongue ulceration, retching, upper gastrointestinal haemorrhage*, haematemesis*, oral mucosal petechiae, ileus paralytic*, ileus, odynophagia, enteritis, colitis, oesophagitis, enterocolitis, diarrhoea haemorrhagic, acute pancreatitis*, intestinal obstruction
General Disorders and Administration Site Conditions	
Most common	Fatigue, pyrexia
Very common	Chills, oedema peripheral, asthenia
Common	Neuralgia, lethargy, malaise, chest pain, mucosal inflammation*
Uncommon	Injection site pain, injection site irritation, injection site phlebitis, general physical health deterioration*, catheter-related complication

Table 1-2 Known Anticipated Risks of VELCADE by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term
Hepatobiliary Disorders	
Uncommon	Hyperbilirubinaemia, hepatitis*±
Immune System Disorders	
Uncommon	Drug hypersensitivity, angioedema
Infections and Infestations	
Very common	Upper respiratory tract infection, nasopharyngitis, pneumonia*, Herpes zoster*
Common	Lower respiratory tract infection*, sinusitis, pharyngitis, oral candidiasis, urinary tract infection*, sepsis∗, bactaeremia*, cellulitis∗, Herpes simplex, bronchitis, gastroenteritis*, infection
Uncommon	Septic shock*, catheter-related infection*, skin infection*, Herpes zoster disseminated*, lung infection∗, infusion site cellulitis, catheter site cellulitis, infusion site infection, urosepsis*, Aspergillosis*, tinea infection, Herpes zoster ophthalmic, Herpes simplex ophthalmic, meningoencephalitis herpetic±, varicella, empyema±, fungal oesophagitis±
Injury, Poisoning, and Procedural Complications	
Common	Fall
Uncommon	Subdural haematoma
Investigations	
Common	Weight decreased, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, blood alkaline phosphatase increased, liver function test abnormal, blood creatinine increased*
Uncommon	Gamma-glutamyltransferase (GGT) increased, oxygen saturation decreased*, blood albumin decreased, ejection fraction decreased*
Metabolism and Nutritional Disorders	
Very common	Decreased appetite, anorexia, dehydration*
Common	Hyperglycaemia, hypoglycaemia, hyponatraemia, hypokalaemia, hypercalcaemia*

Table 1-2 Known Anticipated Risks of VELCADE by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term
Musculoskeletal and Connective Tissue Disorders	
Very common	Bone pain, myalgia, arthralgia, back pain
Common	Muscular weakness
Uncommon	Limb discomfort
Neoplasms, Benign, Malignant, and Unspecified (including cysts and polyps)	
Uncommon	Tumour lysis syndrome*
Nervous System Disorders	
Most common	Peripheral neuropathy (including all preferred terms under the MedDRA High-level term Peripheral neuropathy NEC)
Very common	Paresthesia, dizziness excluding vertigo, headache
Common	Polyneuropathy, syncope, dysesthesia, dysgeusia, postherpetic neuralgia
Uncommon	Convulsion, loss of consciousness, ageusia, encephalopathy, paralysis*,autonomic neuropathy, reversible posterior leukoencephalopathy syndrome±, posterior reversible encephalopathy syndrome ϕ
Psychiatric Disorders	
Very common	Anxiety, insomnia
Common	Confusional state
Uncommon	Delirium
Renal and Urinary Disorders	
Common	Renal impairment*, renal failure*, haematuria
Uncommon	Micturition disorder
Respiratory, Thoracic, and Mediastinal Disorders	
Very common	Cough, dyspnoea
Common	Epistaxis, dyspnoea exertional, pleural effusion*, rhinorrhea, hypoxia*, pulmonary oedema*
Uncommon	Hemoptysis*, acute respiratory distress syndrome*, respiratory failure*, pneumonitis*, lung infiltration, pulmonary alveolar haemorrhage*, interstitial lung disease*, pulmonary hypertension*, pleurisy, pleuritic pain

Table 1-2 Known Anticipated Risks of VELCADE by MedDRA System Organ Class, Observed Incidence, and Preferred Term

System Organ Class Observed Incidence	Preferred Term
Skin and Subcutaneous Tissue Disorders	
Very common	Rash
Common	Rash pruritic, rash erythematous, urticaria, petechiae
Uncommon	Cutaneous vasculitis, leukocytoclastic vasculitis±
Vascular Disorders	
Common	Hypotension*, orthostatic hypotension
Uncommon	Cerebral haemorrhage*

Source: VELCADE® Investigator's Brochure Edition 17.

Most common = ≥ 30%, Very common = 10% to 29%, Common = 1% to 9%, Uncommon = < 1%.

* Fatal outcomes have been reported.

± Indicates a Preferred term not listed in the source table, however the event is deemed medically important and so is included.

ϕ Effective MedDRA update to version 14.0, the term 'reversible posterior leukoencephalopathy syndrome' updated to 'posterior reversible encephalopathy syndrome (PRES)'.

Table 1-3 Reports of Adverse Reactions From Postmarketing Experience

System Organ Class Preferred Term	Observed Incidence[a]
Blood and lymphatic system disorders	
Disseminated intravascular coagulation	Rare
Cardiac Disorders	
Atrioventricular block complete	Rare
Cardiac tamponade	Rare
Ear and labyrinth disorders	
Deafness bilateral	Rare
Eye Disorders	
Ophthalmic herpes	Rare
Optic neuropathy	Rare
Blindness	Rare
Gastrointestinal Disorders	
Acute pancreatitis	Rare
Ischemic colitis	Rare
Hepatobiliary disorders	
Hepatitis	Uncommon
Liver failure	Unknown
Infections and infestations	
Herpes meningoencephalitis	Rare
Septic shock	Rare
Progressive multifocal leukoencephalopathy	Very Rare
Immune System Disorders	
Angioedema	Rare
Nervous System Disorders	
Autonomic neuropathy	Rare
Dysautonomia	Unknown
Encephalopathy	Rare
Respiratory, thoracic and mediastinal disorders:	
Acute diffuse infiltrative pulmonary disease[b]	Rare
Acute respiratory distress syndrome (ARDS)	Rare
Interstitial pneumonia	Rare

Table 1-3 Reports of Adverse Reactions From Postmarketing Experience

System Organ Class Preferred Term	Observed Incidence[a]
Lung infiltration	Rare
Pneumonitis	Rare
Pulmonary hypertension	Rare
Skin and subcutaneous system disorders	
Acute febrile neutrophilic dermatosis	Unknown
Toxic epidermal necrolysis	Unknown

Source: VELCADE® Investigator's Brochure Edition 17.

a Incidence is assigned using the following convention: very common (≥ 1/10); common (≥ 1/100 and < 1/10); uncommon (≥ 1/1000 and < 1/100); rare (≥ 1/10,000 and < 1/1000); very rare (< 1/10,000, including isolated reports).

b Acute diffuse infiltrative pulmonary disease is a MedDRA Lower Level Term which corresponds to a Preferred Term of Interstitial lung disease.

Other medical events of interest that are considered not causally related to VELCADE include hepatic failure and QT prolongation. Fatal outcomes have been reported.

Women of childbearing potential should avoid becoming pregnant while being treated with VELCADE. Genotoxicity testing has shown that VELCADE is negative in the in vitro Ames assay and in the in vivo micronucleus assay, but it is a clastogen in the in vitro chromosomal aberration assay.

Additional details on the potential risks of VELCADE may be found in the current Investigator's Brochure.

SAFETY SUMMARY FOR SUBCUTANEOUS ADMINISTRATION

While the safety profile between the SC and IV treatment groups in general was comparable in most System Organ Classes (SOCs), a difference in incidence in certain safety parameters in favor of the SC treatment group was noted. One hundred and forty (95%) subjects in the SC treatment group and 73 (99%) subjects in the IV treatment group reported at least 1 treatment-emergent adverse event. In the SC treatment group, there was a lower incidence of Grade ≥3 adverse events as compared with the IV treatment group (57% vs. 70%, respectively); a lower incidence of adverse events leading to treatment discontinuations (22% in the SC treatment group and 27% in the IV treatment group); and a lower incidence of adverse events leading to dose modifications in the SC group: dose reduction (33% in the SC treatment group compared with 45% in the IV treatment group); dose withholding (30% in the SC treatment group compared with 39% in

the IV treatment group); or cycle delay (20% in the SC treatment group compared with 34% in the IV treatment group). Serious adverse events were similar between the 2 treatment groups (36% in the SC treatment group and 35% in the IV treatment group). Deaths during treatment (within 30 days of last dose) were 5% in the SC treatment group and 7% in the IV treatment group.

The SC treatment group reported a lower incidence in several adverse events associated with VELCADE toxicity. The incidence of peripheral neuropathy events (all Grades) was 38% in the SC treatment group and 53% in the IV treatment group; the incidence of Grade ≥2 peripheral neuropathy events was 24% in the SC treatment group and 41% in the IV treatment group; and the incidence of Grade ≥3 peripheral neuropathy event was 6% in the SC treatment group and 16% in the IV treatment group. There also appeared to be a trend towards lower incidence in gastrointestinal adverse events (37% for SC and 58% for IV, predominantly due to differences in Grade 1-2 abdominal pain, diarrhea, and dyspepsia); as well as a ≥5% difference in incidence of Grade 3 and 4 hematology laboratory results in the SC treatment group compared with the IV treatment group for white blood cells (8% in the SC treatment group compared with 18% in the IV treatment group), neutrophil count (22% in the SC treatment group compared with 28% in the IV treatment group) and platelets (18% in the SC treatment group compared with 23% in the IV treatment group).

Local tolerability of SC administration was acceptable. Nine (6%) subjects reported a local reaction to SC administration as an adverse event. Eighty-five (58%) subjects in the SC treatment group reported at least 1 local injection site reaction. The most common local injection site reaction was redness which was reported in 84 (57%) subjects. The majority of subjects with worst injection site reactions were assessed as mild (38%) or moderate (18%). Only 2 (1%) subjects were reported as having severe injection site reactions. All local site reactions resolved completely and rarely led to treatment modifications.

In conclusion, the SC administration of VELCADE has good local tolerance. The systemic safety profile for the SC administration of VELCADE was associated with a lower incidence of Grade ≥3 adverse events, and treatment modifications (discontinuations and dose reductions). In particular, there was a lower incidence of peripheral neuropathy NEC reported. [26]

1.3 **Pegylated liposomal doxorubicin (Doxil)**

1.3.1 **Scientific Background**

Doxorubicin HCl liposome injection is a cytotoxic anthracycline antibiotic isolated from *Streptomyces peucetius var. caesius*. The mechanism of action of doxorubicin HCl is thought to be related to its ability to bind to DNA and inhibit nucleic acid synthesis. Cell

structure studies have demonstrated rapid cell penetration and perinuclear chromatin binding, rapid inhibition of mitotic activity and nucleic acid synthesis, and induction of mutagenesis and chromosomal aberrations (Doxil® Product Information Booklet 2005). Greater than 90% of the drug (doxorubicin) is encapsulated in STEALTH® liposomes, microscopic vesicles composed of phospholipid bilayer that are capable of encapsulating active drugs. It is hypothesized that because of their small size (ca. 100 nm) and persistence in the circulation, the pegylated liposomes are able to penetrate the altered and often compromised vasculature of tumors. This hypothesis is supported by studies using colloidal gold-containing STEALTH® liposomes, which can be visualized microscopically. Evidence of penetration of STEALTH® liposomes from blood vessels and their entry and accumulation in tumors has been seen in mice with C-26 colon carcinoma tumors and in transgenic mice with Kaposi's sarcoma-like lesions. Once the STEALTH® liposomes distribute to the tissue compartment, the encapsulated doxorubicin HCl becomes available. The exact mechanism of release is not understood (Doxil® Product Information Booklet 2005).

Pegylated liposomal doxorubicin is a common treatment option, approved for patients with metastatic recurrent ovarian carcinoma who are refractory to paclitaxel and platinum-based chemotherapy. Although doxorubicin has been associated with poor response in recurrent ovarian cancer, pegylated liposomal doxorubicin has demonstrated efficacy in the treatment of recurrent/relapsed ovarian cancer in several clinical trials. Long-term follow up has shown that pegylated liposomal doxorubicin significantly prolongs survival compared with topotecan for patients with platinum sensitive recurrent ovarian carcinoma. Median overall survival was 107.9 weeks for platinum sensitive patients treated with pegylated liposomal doxorubicin compared to 70.1 weeks for those treated with topotecan[43]. For patients with platinum refractory disease, no statistically significant difference in survival was observed between the two groups. Median overall survival was 35.6 weeks for platinum refractory patients treated with pegylated liposomal doxorubicin compared to 41.3 weeks for those treated with topotecan.[44]

1.3.2 **Nonclinical Pharmacology**

Please see package insert (Appendix 8.8)

1.3.3 **Nonclinical Toxicity**

Please see package insert (Appendix 8.8)

1.3.4 Clinical Pharmacokinetics and Pharmacodynamics

According to the most recent label for pegylated liposomal doxorubicin (Doxil® Product Information Booklet 2005), linear pharmacokinetics were observed in 23 male Kaposi's after administration, with a relatively short first phase (approximately 5 hrs) and a prolonged second phase (approximately 55 hrs) that accounted for the majority of the area under the curve (AUC). At 50mg/m^2, the pharmacokinetics are reported to be nonlinear. At this dose the elimination halflife is expected to be longer and the clearance lower (compared to 20 mg/m^2). The exposure (AUC) is expected to be more than proportional at a 50 mg/m^2 dose when compared with the lower doses. In contrast to the pharmacokinetics of doxorubicin, which displays a large volume of distribution, ranging from 700 to 1100 L/m^2, the small steady state volume of distribution of pegylated liposomal doxorubicin shows that it is confined mostly to the vascular fluid volume. Plasma protein binding has not been determined for pegylated liposomal doxorubicin but is approximately 70% for doxorubicin. Doxorubicinol, the major metabolite of doxorubicin, was detected at very low levels (range: 0.8 to 26.2 ng/mL) in the plasma of patients who received 10 or 20 mg/m^2 pegylated liposomal doxorubicin. Plasma clearance was slow, with a mean clearance value of 0.041 L/h/m^2 at a dose of 20 mg/m^2. This is in contrast to doxorubicin, which displays a clearance value from 24 to 35L/h/m^2. Because of its slower clearance, the AUC of pegylated liposomal doxorubicin, primarily representing the circulating liposome-encapsulated doxorubicin, is approximately two to three times larger than the AUC for a similar dose of conventional doxorubicin HCl. Pharmacokinetics have not been separately evaluated in women, different ethnic groups or in individuals with renal or hepatic insufficiency. Drug-drug interactions between pegylated liposomal doxorubicin and other drugs, including antiviral agents, have not been evaluated.

1.3.5 Clinical Experience

Doxil has a number of clinical indications approved by the FDA. Its use in recurrent epithelial ovarian cancer patients who had failed platinum and taxane based therapy was established early on. A Phase II study that included the use of Doxil was performed in thirty-five consecutive patients with progressive ovarian cancer after either cisplatin or carboplatin and paclitaxel, or at least one platinum-based and one paclitaxel-based regimen.[45] Patients received intravenous (IV) liposomal doxorubicin 50 mg/m^2 every 3 weeks. Nine clinical responses (one complete response, eight partial responses) were observed (25.7%), The median progression-free survival was 5.7 months with an overall survival of 1.5 to 24+ months (median, 11 months). The most common toxicity that was associated with Doxil was the hand-foot syndrome (palmar-plantar erythrodysesthesia) seen in up to 20% of the patients in the above study. When the dose was decreased from 50mg/m^2 to 40mg/m^2, the anti-tumor effect was preserved with a significant improvement in the toxicity profile.

Doxil was then tested against Topotecan in a phase III trial in patients with relapsed or platinum refractory epithelial ovarian cancer. In this study, 474 patients with measurable and assessable disease were randomized to receive either PLD 50 mg/m^2 as a 1-hour infusion every 4 weeks or topotecan 1.5 mg/m^2/d for 5 consecutive days every 3 weeks.[46] The overall response rates for Doxil and Topotecan were 19.7% and 17.0%, respectively (P =.390). Median overall survival times were 60 weeks for PLD and 56.7 weeks for topotecan. For overall survival, Doxil was significantly superior to topotecan (P =.008), with a median of 108 weeks versus 71.1 weeks. Given the durability of responses as well as minimal toxicities associated with the drug, Doxil became an attractive treatment choice in relapsed or platinum refractory epithelial ovarian cancer.

The use of Doxil in metastatic breast cancer was established when non-inferiority of this drug to Doxorubicin was demonstrated. When two were compared in over 500 patients with metastatic breast cancer and normal cardiac function, the overall survival in the two groups were similar, but toxicities significantly lower in the Doxil group.[47] Overall survival was 21 and 22 months for Doxil and doxorubicin, respectively; HR=0.94; 95%CI 0.74-1.19. Alopecia (overall, 66% versus 20%; pronounced, 54% versus 7%), nausea (53% versus 37%), vomiting (31% versus 19%) and neutropenia (10% versus 4%) were more often associated with doxorubicin than Doxil. Palmar-plantar erythrodysesthesia (48% versus 2%), stomatitis (22% versus 15%) and mucositis (23% versus 13%) were more often associated with Doxil than doxorubicin.

Doxil is considered to be the accepted first-line therapy in AIDS-related Kaposi's sarcoma. Two Phase III trials compared single agent Doxil at a dose of 20mg/m^2 to a multi-agent chemotherapy regimen that included bleomycin and vincristine.[48],[49]Results noted a superior response rate in the patients in the Doxil group with fewer toxicities.

The combination of Doxil and Velcade has been studied in and is currently a FDA-approved treatment option for relapsed multiple myeloma. The DOXIL-MMY-3001 trial was a randomized phase III trial that studied either Velcade 1.3 mg/m^2 on days 1, 4, 8, and 11 of an every 21-days cycle, or the same bortezomib regimen with Doxil 30 mg/m^2 on day 4 in 646 patients.[50] Median time to progression improved from 6.5 months for bortezomib to 9.3 months with the Doxil + bortezomib combination (P = 0.000004; hazard ratio, 1.82 [monotherapy v combination therapy]; 95% CI, 1.41 to 2.35). The 15-month survival rate for doxil and bortezomib was 76% compared with 65% for bortezomib alone (P = 0.03). The complete plus partial response rate was 41% for bortezomib and 44% for Doxil + bortezomib, a difference that was not statistically significant. Median duration of response was increased from 7.0 to 10.2 months (P = 0.0008) with Doxil + bortezomib. Grade 3/4

adverse events though were more frequent in the combination group (80% v 64%). An increased incidence of grade 3/4 neutropenia, thrombocytopenia, asthenia, fatigue, diarrhea, and hand-foot syndrome was seen in the combination group. Notably, any grade hand-foot syndrome occurred in 16% of subjects with Doxil + bortezomib with 5% of subjects experiencing grade 3 and 0% grade 4. Grade 3/4 peripheral neuropathy was seen in 4% of subjects.

1.4 Decitabine

1.4.1 Scientific Background

Decitabine (5-aza-2'-deoxycitidine), an analogue of the natural nucleoside 2'-deoxycytidine, is a member of the hypomethylator or DNA methyltransferase inhibitor class. Decitabine is believed to exert its antineoplastic effects after phosphorylation and direct incorporation into DNA and inhibition of DNA methyltransferase, causing hypomethylation of DNA and cellular differentiation or apoptosis. Decitabine inhibits DNA methylation *in vitro,* which is achieved at concentrations that do not cause major suppression of DNA synthesis. Decitabine-induced hypomethylation in neoplastic cells may restore normal function to genes that are critical for the control of cellular differentiation and proliferation. In rapidly dividing cells, the cytotoxicity of decitabine may also be attributed to the formation of covalent adducts between DNA methyltransferase and decitabine incorporated into DNA. Non-proliferating cells are relatively insensitive to decitabine.

Decitabine is indicated for treatment of patients with myelodysplastic syndromes (MDS) including previously treated and untreated, *de novo* and secondary MDS of all French-American-British subtypes (refractory anemia, refractory anemia with ringed sideroblasts, refractory anemia with excess blasts, refractory anemia with excess blasts in transformation, and chronic myelomonocytic leukemia) and intermediate-1, intermediate-2, and high-risk International Prognostic Scoring System groups. Decitabine also has significant activity in AML as described in Section 1.1.[53-54,59-62] For more details, please refer to the Decitabine package insert (Appendix 8.10).

1.4.2 Nonclinical Pharmacology

Please refer to the Decitabine package insert (Appendix 8.10).

1.4.3 Nonclinical Toxicity

Please refer to the Decitabine package insert (Appendix 8.10).

Carcinogenicity studies with decitabine have not been conducted.

The mutagenic potential of decitabine was tested in several *in vitro* and *in vivo* systems. Decitabine increased mutation frequency in L5178Y mouse lymphoma cells, and mutations were produced in an Escherichia coli lac-I transgene in colonic DNA of decitabine treated mice. Decitabine caused chromosomal rearrangements in larvae of fruit flies.

The effect of decitabine on postnatal development and reproductive capacity was evaluated in mice administered a single 3 mg/m^2 IP injection (approximately 7% the recommended daily clinical dose) on day 10 of gestation. Body weights of males and females exposed in utero to decitabine were significantly reduced relative to controls at all postnatal time points. No consistent effect on fertility was seen when female mice exposed in utero were mated to untreated males. Untreated females mated to males exposed in utero showed decreased fertility at 3 and 5 months of age (36% and 0% pregnancy rate, respectively). In male mice given IP injections of 0.15, 0.3 or 0.45 mg/m^2 decitabine (approximately 0.3% to 1% the recommended clinical dose) 3 times a week for 7 weeks, decitabine did not affect survival, body weight gain or hematological measures (hemoglobin and WBC counts). Testes weights were reduced, abnormal histology was observed and significant decreases in sperm number were found at doses ≥0.3 mg/m^2. In females mated to males dosed with ≥0.3 mg/m2 decitabine, pregnancy rate was reduced and preimplantation loss was significantly increased.

1.4.4 Clinical Pharmacokinetics and Pharmacodynamics

Please refer to the Decitabine package insert (Appendix 8.10).

Decitabine has been shown to induce hypomethylation both *in vitro* and *in vivo.* However, there have been no studies of decitabine-induced hypomethylation and pharmacokinetic parameters.

Pharmacokinetic parameters were evaluated in patients. Eleven patients received 20 mg/m^2 infused over 1 hour intravenously (treatment Option 2). Fourteen patients received 15 mg/m^2 infused over 3 hours (treatment Option 1). Plasma concentration-time profiles after discontinuation of infusion showed a bi-exponential decline. The CL of decitabine was higher following treatment Option 2. Upon repeat doses there was no systemic accumulation of decitabine or any changes in PK parameters. Population PK analysis (N=35) showed that the cumulative AUC per cycle for treatment Option 2 was 2.3-fold lower than the cumulative AUC per cycle following treatment Option 1.

The exact route of elimination and metabolic fate of decitabine is not known in humans. One of the pathways of elimination of decitabine appears to be deamination by cytidine deaminase found principally in the liver but also in granulocytes, intestinal epithelium and whole blood.

1.4.5 Clinical Experience

Please refer to the Decitabine package insert (Appendix 8.10).

A randomized open-label, multicenter, controlled trial evaluated 170 adult patients with myelodysplastic syndromes (MDS) meeting French-American-British (FAB) classification criteria and International Prognostic Scoring System (IPSS) High-Risk, Intermediate-2 and Intermediate-1 prognostic scores. Eighty-nine patients were randomized to decitabine therapy plus supportive care (only 83 received decitabine), and 81 to Supportive Care (SC) alone. Patients with Acute Myeloid Leukemia (AML) were not intended to be included. Of the 170 patients included in the study, independent review (adjudicated diagnosis) found that 12 patients (9 in the decitabine arm and 3 in the SC arm) had the diagnosis of AML at baseline. Baseline demographics and other patient characteristics in the Intent-to-Treat (ITT) population were similar between the 2 groups.

Patients randomized to the decitabine arm received decitabine intravenously infused at a dose of 15 mg/m^2 over a 3-hour period, every 8 hours, for 3 consecutive days. This cycle was repeated every 6 weeks, depending on the patient's clinical response and toxicity. Supportive care consisted of blood and blood product transfusions, prophylactic antibiotics, and hematopoietic growth factors. The study endpoints were overall response rate (complete response + partial response) and time to AML or death. Responses were classified using the MDS International Working Group (IWG) criteria; patients were required to be RBC and platelet transfusion independent during the time of response.

The overall response rate (CR+PR) in the ITT population was 17% in decitabine-treated patients and 0% in the SC group ($p<0.001$). The overall response rate was 21% (12/56) in decitabine -treated patients considered evaluable for response (i.e., those patients with pathologically confirmed MDS at baseline who received at least 2 cycles of treatment). The median duration of response (range) for patients who responded to decitabine was 288 days (116-388) and median time to response (range) was 93 days (55-272). All but one of the decitabine -treated patients who responded did so by the fourth cycle. Benefit was seen in an additional 13% of decitabine -treated patients who had hematologic improvement, defined as a response less than PR lasting at least 8 weeks, compared to 7% of SC

patients. Decitabine treatment did not significantly delay the median time to AML or death versus supportive care. All patients with a CR or PR were RBC and platelet transfusion independent in the absence of growth factors. Responses occurred in patients with an adjudicated baseline diagnosis of AML.

Three open-label, single-arm, multicenter studies were conducted to evaluate the safety and efficacy of decitabine in MDS patients with any of the FAB subtypes. In one study conducted in North America, 99 patients with IPSS Intermediate-1, Intermediate-2, or high risk prognostic scores received decitabine by intravenous infusion at a dose of 20 mg/m2 IV over 1-hour daily, on days 1-5 of week 1 every 4 weeks (1 cycle). The results were consistent with the results of the controlled trial.

Several studies have evaluated the activity and safety of decitabine in AML, using a variety of dosing schedules. These studies are described in Section 1.1.[53-54,59-62] In the Cashen et al. and Kantarjian et al. studies, the overall response rate was 25% and 17.8% respective using a 5-day dosing schedule at 20mg/m^2 IV.[53-54] In the Blum et al., Bhatnagar et al. and Ritchie et al. studies, the overall response rate varied from 40-64% in the untreated setting and 16% in the relapsed/refractory setting.[59-62] Toxicities were similar in these studies and primarily included myelosuppresion, febrile neutropenia and infections, which are typical of this patient and disease population.

1.4.6 Potential Risks of Decitabine

For complete information on adverse reactions associated with Decitabine, please refer to the package insert section 6 and section 6 Tables 1 and 2 (Appendix 8.10).

Most Commonly Occurring Adverse Reactions: neutropenia, thrombocytopenia, anemia, fatigue, pyrexia, nausea, cough, petechiae, constipation, diarrhea, and hyperglycemia.

Adverse Reactions Most Frequently (≥1%) Resulting in Clinical Intervention in the Phase 3 Trials in the DECITABINE Arm:

- Discontinuation: thrombocytopenia, neutropenia, pneumonia, Mycobacterium avium complex infection, cardio-respiratory arrest, increased blood bilirubin, intracranial hemorrhage, abnormal liver function tests.
- Dose Delayed: neutropenia, pulmonary edema, atrial fibrillation, central line infection, febrile neutropenia.
- Dose Reduced: neutropenia, thrombocytopenia, anemia, lethargy, edema, tachycardia, depression, pharyngitis.

Discussion of Clinically Important Adverse Reactions

In the controlled trial using DECITABINE dosed at 15 mg/m2, administered by continuous intravenous infusion over 3 hours repeated every 8 hours for 3 days, the highest incidence of Grade 3 or Grade 4 adverse events in the DECITABINE arm were neutropenia (87%), thrombocytopenia (85%), febrile neutropenia (23%) and leukopenia (22%). Bone marrow suppression was the most frequent cause of dose reduction, delay and discontinuation. Six patients had fatal events associated with their underlying disease and myelosuppression (anemia, neutropenia, and thrombocytopenia) that were considered at least possibly related to drug treatment. Of the 83 DECITABINE-treated patients, 8 permanently discontinued therapy for adverse events; compared to 1 of 81 patients in the supportive care arm.

In the single-arm study (N=99) when DECITABINE was dosed at 20 mg/m2 intravenous, infused over one hour daily for 5 consecutive days, the highest incidence of Grade 3 or Grade 4 adverse events were neutropenia (37%), thrombocytopenia (24%) and anemia (22%). Seventy-eight percent of patients had dose delays, the median duration of this delay was 7 days and the largest percentage of delays was due to hematologic toxicities. Hematologic toxicities and infections were the most frequent causes of dose delays and discontinuation. Eight patients had fatal events due to infection and/or bleeding (seven of which occurred in the clinical setting of myelosuppression) that were considered at least possibly related to drug treatment. Nineteen of 99 patients permanently discontinued therapy for adverse events. No overall difference in safety was detected between patients >65 years of age and younger patients in these myelodysplasia trials. No significant gender differences in safety or efficacy were detected. Patients with renal or hepatic dysfunction were not studied. Insufficient numbers of non-white patients were available to draw conclusions in these clinical trials.

Serious Adverse Events that occurred in patients receiving DECITABINE regardless of causality, include:

• Blood and Lymphatic System Disorders: myelosuppression, splenomegaly.
• Cardiac Disorders: myocardial infarction, cardio-respiratory arrest, cardiomyopathy, atrial fibrillation, supraventricular tachycardia.
• Gastrointestinal Disorders: gingival pain, upper gastrointestinal hemorrhage.
• General Disorders and Administrative Site Conditions: chest pain, catheter site hemorrhage.
• Hepatobiliary Disorders: cholecystitis.
• Infections and Infestations: fungal infection, sepsis, bronchopulmonary aspergillosis, peridiverticular abscess, respiratory tract infection, pseudomonal lung infection, Mycobacterium avium complex infection.
• Injury, Poisoning and Procedural Complications: post procedural pain, post procedural

hemorrhage.
• Nervous System Disorders: intracranial hemorrhage.
• Psychiatric Disorders: mental status changes.
• Renal and Urinary Disorders: renal failure, urethral hemorrhage.
• Respiratory, Thoracic and Mediastinal Disorders: hemoptysis, lung infiltration, pulmonary embolism, respiratory arrest, pulmonary mass.
• Allergic Reaction: Hypersensitivity (anaphylactic reaction) to DECITABINE has been reported in a Phase 2 trial.

Post-marketing Experience
The following adverse reactions have been identified during postapproval use of DECITABINE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Cases of Sweet's Syndrome (acute febrile neutrophilic dermatosis) have been reported.

1.5 Study Rationale and Selection of Drug Doses

Acute myeloid leukemia remains largely incurable despite advances that have been made in recent years into increasing the complete response (CR) rates. In elderly patients (over the age of 60), CR rates are lower, 40 to 50%, and long term disease-free and overall survival is less than 10% (Dohner et al).[1] The therapeutic options for relapsed/refractory AML are significantly limited. Bortezomib has shown promising activity in patients with advanced hematologic malignancies, including those with leukemia and non-Hodgkin's lymphoma. Pre-clinical studies have shown that proteasome inhibition promotes apoptosis of tumor cells in part through stabilization of the negative regulator of nuclear factor kappa B (NF-κB). Several in-vitro studies have also shown bortezomib to induce apoptosis in human AML cells. In addition a recent phase I study that utilized bortezomib in combination with standard induction therapy patients with relapsed/refractory AML was shown to produce high response rates with minimal additional toxicity.[51] In this study there was no MTD established for bortezomib with the highest dose being 1.5mg/m^2 given on days 1,4, 8 and 11. Anthracyclines, in part, exert anti-tumor activity by inducing an NF-κB driven, anti-apoptotic process. Laboratory evidence has suggested that activity of the transcription factor NF-κB promotes anthracycline resistance. This particular resistance can be overcome when a proteosome inhibitor is given in conjunction with the anthracycline. Orlowski and colleagues performed a phase I study of bortezomib combined with pegylated liposomal doxorubicin (Doxil) in patients with advanced hematologic malignancies resulting in a number of patients (with MM, T-cell NHL, B-cell NHL) achieving significant responses. This was confirmed in a phase III trial in patients with relapsed Myeloma and the

combination of Velcade and Doxil is FDA approved for the treatment of relapsed myeloma. Given the available data suggesting efficacy of bortezomib in combination with doxil in patients with relapsed MM, chronic lymphocytic leukemia (CLL), and NHL as well as the known sensitivity of AML to anthracylines and *in vitro* data demonstrating the sensitivity of multiply resistant AML cells to bortezomib, we proposed the use of this combination in patients with relapsed/refractory AML or elderly patients that are not candidates for standard induction therapy.[52] We enrolled 15 patients who were evaluable. Toxicity was manageable with 13% of patients experiencing grade 3 neurotoxicity. Three partial responses were seen and there were reductions in blast counts in 79% of patients. The duration of response was short and the maximum number of completed cycles was two.

The hypomethylating agents (HMA), including decitabine, have significant activity in AML and have been shown to work primarily through inhibition of DNA methyltransferase enzymes and NF-κB.[53-58] Recently, a 10-day dosing schedule of decitabine (at 20mg/m^2 IV days 1-10 on a 28-day cycle) for AML has demonstrated significant activity, with CR rates of 40-64% in untreated older patients and 16% in relapsed/refractory patients.[59-61] The regimen is well-tolerated with febrile neutropenia, infections and myelosuppression most common. The 10-day decitabine regimen was combined with IV bortezomib in a phase I study in relapsed/refractory AML or untreated older patients.[62] The bortezomib dose was escalated to 1.3mg/m^2 on days 5, 8, 12 and 15 without dose-limiting toxicities. Toxicities were similar to the 10-day decitabine studies, and grade 3 neurotoxicity related to bortezomib was seen in 3 of 19 patients (all three events were after induction). CR was achieved in 50% of untreated and 22% of relapsed/refractory patients. These studies continued decitabine with or without bortezomib until disease progression or unacceptable toxicity.[53-54,59-62] Based on these studies, there is an ongoing clinical trial using the combination of 10-day decitabine and bortezomib (NCT01420926). In NCT01420926, three of the bortezomib doses are being administered concurrently with the 10-days of decitabine (decitabine days 2-11 and bortezomib days 1, 4, 8 and 11).

Given that we have shown the combination of SQ bortezomib and pegylated liposomal doxorubicin is safe and has activity in relapsed/refractory AML and the combination of decitabine and IV bortezomib is safe and has activity in relapsed/refractory AML, we propose testing the combination of decitabine, SQ bortezomib and pegylated liposomal doxorubicin in patients with relapsed/refractory AML or older untreated patients unfit for or who refuse induction chemotherapy. We will use dosing schema established as safe and effective from the prior studies, including the 10-day decitabine dosing and bortezomib at 1.3mg/m^2 and administration of post-induction therapy. One difference from the prior published regimen of 10-day decitabine and IV bortezomib is that we will give the bortezomib SQ, which is associated with decreased toxicity. Since the combination of all

three drugs is untested, however, we will assess for DLTs at our proposed starting dose levels using a 6-9 patient safety-lead in stage. Given that the first two subjects dosed on the dosing schedule per Amendment 9 both experienced DLTs of peripheral neuropathy, we have modified the dosing schedule in the current Amendment 10 and will start a new 6-9 patient safety lead-in stage. We will adjust the bortezomib dosing per the Blum et al regimen (62) during induction and move PLD later in the cycle to day 12. Our hypothesis is that there was synergistic toxicity between the three agents when given concurrently and this schedule will administer the PLD after completion of the decitabine and some of the bortezomib doses. The new dosing schedule is hypothesized to remain mechanistically relevant, given our hypothesis that NF-kB signaling can mediate anthracycline resistance and bortezomib inhibits NF-kB signaling. To lessen risk of neuropathy during post-induction courses, we are eliminating the day 15 and day 22 bortezomib doses and moving PLD later in the cycles to day 12.

2. STUDY OBJECTIVES

2.1 Primary Objectives

The primary objectives of this study are to:

- Assess response rate and progression free survival (PFS)

2.2 Secondary Objectives

The secondary objectives of this study are to:

- Assess overall survival and toxicity

3. INVESTIGATIONAL PLAN

This is an investigator-initiated study. The principal investigator, Joseph Tuscano, MD, otherwise known as the sponsor-investigator, is considered the study sponsor.

3.1 Overall Design and Plan of the Study

This is a Phase II, open label study of the combination of decitabine, bortezomib and pegylated liposomal doxorubicin for the treatment of patients with relapsed/refractory acute myeloid leukemia (AML) or untreated patients ineligible for standard induction therapy. A safety lead-in cohort will test the combination of decitabine, bortezomib and pegylated liposomal doxorubicin in the first 6-9 patients.

Treatment Regimen:
Induction:
Decitabine 20mg/m^2 (IV) days 1-10
Bortezomib: 1.3mg/m^2 (SQ) days 5, 8, 12, and 15
Pegylated liposomal doxorubicin: 40mg/m^2 (IV) day 12
Cycle repeats every 28 days

Patients will receive a minimum of 1 cycles and a maximum of 4 cycles of induction. If there is no response or progression after two cycles of induction, they will be taken off the study. Patients with persistent AML (>5% blasts) in the bone marrow will continue to receive induction cycles up to a maximum of 4 cycles. Patients achieving a blast count of less than 5% after any course of induction will proceed to the post-induction regimen. Dose reductions will be permitted as described in Section 3.3.3. Subsequent cycles of induction may be delayed at investigator discretion up to 14 days or to allow for resolution of non-hematologic toxicities to grade 2 or better. There are no hematologic parameters required for dosing during the induction phase, since subjects have active AML and blood count recovery is not expected. Please refer to the study calendar in Appendix 8.1 for further study treatment and assessment details.

Post-Induction:
Decitabine 20mg/m^2 (IV) days 1-5
Bortezomib: 1.3mg/m^2 (SQ) days 1 and 8
Pegylated liposomal doxorubicin: 40mg/m^2 (IV) day 12
Cycle repeats every 28 days

Patients will receive continued cycles of post-induction therapy until progression, intolerance, transplant, withdrawal of informed consent for a maximum of 12 cycles (induction cycles are counted towards this total). Dose reductions of decitabine, bortezomib and pegylated liposomal doxorubicin are permitted and summarized in Section 3.3.3. Additionally, pegylated liposomal doxorubicin will be discontinued once a patient reaches a lifetime cumulative doxorubicin dose of 550mg/m^2 (prior non-doxorubicin anthracycline dose will be included in this calculation, using published conversion factors). Following a 5-day course of decitabine, subjects without evidence of AML (defined as no minimal residual disease by flow cytometry, cytogenetics or molecular markers) but who had grade 4 neutropenia (<500/μL) of at least a 14-day duration will receive a dose reduction of decitabine to 4 days with the next cycle. A second dose reduction of decitabine to 3 days per cycle is permitted if grade 4 neutropenia of at least a 14-day duration occurs again. Patients with residual AML (defined as presence of minimal residual disease by flow cytometry, cytogenetics or molecular markers), however, will continue to receive 5 days of

decitabine per cycle. The first and subsequent cycles of post-induction therapy may be delayed at investigator discretion up to 14 days or to allow for resolution of non-hematologic toxicities to grade 2 or better and to allow neutrophils to recover to greater than 1000/μL and platelets to greater than 100,000/μL in patients with CR. For patients in CRi or with persistent AML, post-induction therapy may proceed without specific hematologic parameters. Use of hematologic growth factors is permitted for patients in CR/CRi. Please refer to the study calendar in Appendix 8.1 for further study treatment and assessment details.

Rules for the safety lead-in: the above intended induction dose of decitabine, bortezomib and pegylated liposomal doxorubicin will be tested in the first 6 patients. If 0-1 dose limiting toxicities (DLTs) are observed then the study will continue to accrue as per the Simon's two-stage design (refer to Section 5.2 – these safety lead-in patients will be included in the efficacy analysis). If 2 or more DLTs are observed in the first 6 patients, then 3 additional subjects will be assessed for DLTs. If 3 or more of the 9 subjects experience DLTs, enrollment will be halted and a different schedule or dose considered. The two subjects experiencing DLTs at the dosing schedule per Amendment 9 will not be included in this new safety lead-in cohort, but will be included in the response assessment as described in Section 5.2. For the safety lead-in, if patients do not experience a DLT during cycle 1 but miss more than 20% of the total planned treatment doses for the cycle, they will be replaced.

Definition of DLT: National Cancer Institute (NCI) Common Terminology Criteria for Adverse Effects (CTCAE) version 4.03 will be used. Toxicities will be considered related to the study drug unless there is a clear, well-documented, alternative explanation for the adverse effect.

DLT assessments will be based on treatment-related adverse events (AEs) in the first cycle (C1D1-C2D1 pre-dose). All patients who are not evaluable for toxicity will be replaced. Subjects will receive cycle 1 therapy regardless of neutropenia, anemia, or thrombocytopenia. RBC and platelet transfusion support is allowed during this time. Filgrastim will not be permitted during cycle 1, unless indicated for the treatment of febrile neutropenia. Antimicrobial prophylaxis will also be allowed. Dose limiting toxicity (DLT) in a given patient is defined as:

Any Grade 5 toxicity related to study treatment.

Hematologic:
Due to the nature of this disease, hematologic AEs will not be considering DLTs; however,

prolonged pancytopenia in the presence of a hypocellular bone marrow (i.e. cellularity 5% or less without evidence of AML) that lasts greater or equal to two weeks after the end of cycle 1 will be considered dose-limiting myelosuppression.

Non-Hematologic:
Any Grade 3 or 4 non-hematologic event (per NCI CTCAE, v4.03) that is considered related to study treatment in the opinion of the investigator with the following **exceptions**:
- Grade 3 infection or febrile neutropenia is not a DLT, however an infection with life-threatening consequences or requiring urgent intervention (Grade 4) will be considered a DLT if it is determined to be study drug related (e.g. in a subject starting treatment with a normal neutrophil count).
Grade 3 fatigue will not be considered a DLT.
Grade 3 nausea, vomiting or diarrhea persisting greater than or equal to 7 days or Grade 4 nausea, vomiting or diarrhea despite maximal antiemetic/antidiarrheal therapy will be considered a DLT.
Grade 3 AST or ALT elevation persisting for less than or equal to 7 days will not be considered a DLT. Grade 4 AST or ALT elevation lasting for any duration of time will be considered a DLT.
Grade 3 rash persisting for less than or equal to 7 days with or without steroids, unless it is a serious form of rash such as Toxic Epidermal Necrolysis, Steven's Johnson Syndrome or other desquamating rash or associated with anaphylaxis, will not be considered a DLT.

3.2 Selection of Patients

The total number of patients to be enrolled in this study is 29. Fifteen subjects were enrolled prior to amendment 7, and up to 14 additional subjects will be enrolled per amendment 7 (detailed in Section 5.2).

3.2.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

- Voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.
- Female patients who:
    - Are postmenopausal for at least 1 year before the Screening visit, OR
    - Are surgically sterile OR

- If they are of childbearing potential, agree to practice 2 effective methods of contraception at the same time from the time of signing the informed consent through 30 days after the last dose of study treatment, OR agree to completely abstain from heterosexual intercourse.

- Male patients, even if surgically sterilized (ie, status postvasectomy), who: must agree to 1 of the following: practice effective barrier contraception during the entire study treatment period and through a minimum of 30 days after the last dose of study drug, or completely abstain from heterosexual intercourse.

- Adults (age 18 to 90) with acute myeloid leukemia (AML), excluding the M3 subtype (acute promyelocytic leukemia), that are not likely to respond to conventional therapy, including:

  - Relapsed or refractory AML after one to four prior induction regimens (not counting consolidation therapies while in CR, not counting autologous transplant while in CR, and not counting prior low-intensity or investigational therapy)

  - Newly diagnosed AML patient's age not fit for standard therapy

- Bone marrow and peripheral blood studies must be available for confirmation of diagnosis. Cytogenetics, flow cytometry, and molecular studies (such as Flt-3 status) will be obtained as per standard practice

- Performance status of 60% or greater by the Karnofsky scale

- A minimum of 2 weeks (or five half-lives) must have elapsed since the completion of prior anti-AML chemotherapy. Hydroxyurea for control of blasts is not counted as chemotherapy, and may be given prior to and during cycle 1 of induction to control the white blood cell count.

- Patients may have had autologous transplant. They must be at least 100 days post transplant, and have had recovery of their counts with ANC >1000 and platelets greater than 100K at some point post-transplant, and be without active cytomegalovirus (CMV) or fungal disease

- There are no minimum hematological parameter requirements prior to the first two cycles, as patients with AML and MDS are understood to have low ANC and platelet counts when the disease is active.

- Patients must have a serum bilirubin ≤1.5 mg/dl, SGOT and SGPT ≤3 times the institutional upper limits of normal (unless due to Gilbert's syndrome).

3.2.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

- There is no specific platelet and absolute neutrophil count that will exclude patients from this study given the natural history of AML.
- Patient has ≥ Grade 2 peripheral neuropathy
- Patient had myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure (see Appendix 8.4), uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to study entry, any ECG abnormality at screening must be documented by the investigator as not medically relevant. An LVEF must be > 50.
- Patient has hypersensitivity to VELCADE, boron, or mannitol.
- Female subject is pregnant or lactating. Confirmation that the subject is not pregnant must be established by a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test result obtained during screening. Pregnancy testing is not required for postmenopausal or surgically sterilized women.
- Female patients who are lactating or have a positive serum pregnancy test during the screening period, or a positive urine pregnancy test on Day 1 before first dose of study drug, if applicable.
- Serious medical or psychiatric illness likely to interfere with participation in this clinical study.
- Diagnosed or treated for another malignancy within 3 years of enrollment, with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in situ malignancy, or low-risk prostate cancer after curative therapy.
- Participation in clinical trials with other investigational agents not included in this trial, within 14 days of the start of this trial and throughout the duration of this trial.
- Radiation therapy within 3 weeks before randomization. Enrollment of subjects who require concurrent radiotherapy (which must be localized in its field size) should be deferred until the radiotherapy is completed and 3 weeks have elapsed since the last date of therapy.

- Patients with active/uncontrolled CNS leukemia

- Patients eligible, at the time of starting treatment, for curative therapeutic approaches (such as allogeneic transplant) are not eligible for the trial. However, patients who achieve CR or PR as a result of therapy on this trial may proceed to allogeneic transplant.

- Patients may not receive any other anti-cancer therapy (cytotoxic, biologic, radiation, or hormonal other than for replacement) while on this study other than hydroxyurea for control of counts.

- Human Immunodeficiency Virus (HIV)-positive.

3.3 Study Treatments

3.3.1 Clinical Trial Materials

VELCADE® (bortezomib) for Injection is a sterile lyophilized powder for reconstitution and is supplied in vials containing VELCADE and mannitol at a 1:10 ratio. For example, vials containing 3.5 mg of VELCADE contain 35 mg of mannitol.

Doxil (Pegylated liposomal doxorubicin) is a sterile, translucent, red liposomal dispersion provided in single use glass vials. Each vial contains 20 mg/ 10 ml of doxorubicin HCL or 50 mg/25ml of doxorubicin HCL at a concentration of 2mg/ml.

Lipodox is a drug with the same active ingredient, dosage, strength, and route of administration as Doxil, and Lipodox is manufactured in a facility that has been inspected by FDA and found to be in compliance with current good manufacturing practices. Lipodox has not been approved by FDA, and therefore, FDA cannot consider it a "generic" of Doxil. The agency has exercised enforcement discretion for the importation of Lipodox during the critical shortage of Doxil.

Decitabine for Injection contains decitabine (5-aza-2'-deoxycitidine), an analogue of the natural nucleoside 2'-deoxycytidine. Decitabine is a fine, white to almost white powder with the molecular formula of C8H12N4O4 and a molecular weight of 228.21. Its chemical name is 4-amino-1-(2-deoxy-β- D-erythro-pentofuranosyl)-1,3,5-triazin-2(1*H*)-one. Decitabine is slightly soluble in ethanol/water (50/50), methanol/water (50/50) and methanol; sparingly soluble in water and soluble in dimethylsulfoxide (DMSO). Decitabine for Injection is a white to almost white sterile lyophilized powder supplied in a clear colorless glass vial. Each 20 mL, single dose, glass vial contains 50 mg decitabine, 68 mg monobasic potassium phosphate (potassium dihydrogen phosphate) and 11.6 mg sodium hydroxide. Please refer

to the package insert for decitabine (Appendix 8.10) for details.

The commercial supply of Doxil and decitabine will be used for this study.

3.3.2 Preparation, Handling, Storage, and Destruction of Drugs

VELCADE

Vials containing lyophilized VELCADE® (bortezomib) for Injection should be stored according to the label requirements. For the United States, store at USP Controlled Room Temperature which is 25ºC (77ºF); for Europe, do not store above 30ºC (86ºF); excursions permitted from 15 to 30ºC (59-86ºF). To date, stability data indicate that the lyophilized drug product is stable for at least 18 months when stored under the recommended conditions. Stability studies are ongoing, and Millennium Pharmaceuticals, Inc. will notify the investigator should this information be revised during the conduct of the study.

VELCADE is cytotoxic. As with all cytotoxic drugs, caution is required when preparing and handling VELCADE solutions. Cytotoxic drugs should only be handled by staff specially trained in the safe handling of such preparations. The use of gloves and other appropriate protective clothing is recommended. In case of skin contact, wash the affected area immediately and thoroughly with soap and water for at least 15 minutes. If product contacts eye, immediately flush eye thoroughly with water for at least 15 minutes. Always contact a physician after any form of body contact. All materials that have been used for preparation should be disposed of according to standard practices. A log must be kept of all disposed materials.

Prior to reconstitution the vials should remain in the cartons to protect them from light. Dissolution is completed in approximately 10 seconds. The reconstituted solution is clear and colorless, with a final pH of 5 to 6. Reconstituted VELCADE should be administered promptly and in no case more than 8 hours after reconstitution.

Drug Administration and Dosage Schedule

VELCADE Administration

Velcade will be administered at 1.3mg/m^2 SQ on days 5, 8, 12 and 15 of a 4 week cycle during induction courses and at 1.3mg/m^2 SQ on days 1, and 8 of a 4 week cycle during post-induction courses.

Drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s). Patients may be treated on an outpatient basis, if possible.

The drug will be prepared under the supervision of a pharmacist, or appropriately qualified and trained personnel. The amount (in mg) of drug to be administered will be determined based on body surface area. Body surface area is to be calculated based on body weight using a standard nomogram or calculation (see Appendix 8.3). The dose should be calculated on Day 1 of each cycle; the dose administered should remain the same throughout each cycle but should be recalculated at the start of the next cycle. If a patient experiences a >10% change in weight within a cycle, as determined by an unscheduled weight assessment, then the patient's dose should be recalculated at that time based on clinical judgment.

There must be at least 72 hours between each dose of VELCADE.

Intravenous and subcutaneous route of administration have different reconstituted concentration. Caution should be used when calculating the volume to be administered.

Reconstitution[1;2]: Different volumes of diluent were used to reconstitute the product for the different routes of administration. The reconstituted concentration of bortezomib for SC administration (2.5 mg/mL) was greater than the reconstituted concentration of bortezomib for IV administration (1.0 mg/mL). See Table 3-1 below.

Table 3-1. Reconstitution and Final Concentration of Bortezomib (3.5 mg Vial)

	IV	SC
Volume of diluent (normal [0.9%] saline)	3.5 mL	1.4 mL
Final bortezomib concentration	1 mg/mL	2.5 mg/mL

SUBCUTANEOUS ADMINISTRATION:

Drug is available in sterile, single use vials containing 3.5 mg of VELCADE. Each vial of VELCADE for Injection should be reconstituted under a laminar flow biological cabinet (hood) within eight hours before dosing with **1.4 mL** of normal (0.9%) saline, Sodium Chloride Injection USP, so that the reconstituted solution contains VELCADE at a concentration of **2.5 mg/mL** for subcutaneous administration.

Subcutaneous Administration Precautions:

- The drug quantity contained in one vial (3.5 mg) may exceed the usual dose required. Caution should be used in calculating the dose to prevent overdose.

- When administered subcutaneously, sites for each injection (thigh or abdomen) should be rotated.

- New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, erythematous, or indurated.

- If local injection site reactions occur following VELCADE administration subcutaneously, a less concentrated VELCADE solution (1 mg/mL instead of 2.5 mg/mL) may be administered subcutaneously. **Alternatively, the IV route of administration should be considered.**

- In clinical trials of VELCADE IV, local skin irritation was reported in 5% of patients, but extravasation of VELCADE was not associated with tissue damage. In a clinical trial of subcutaneous VELCADE, a local reaction was reported in 6% of patients as an adverse event, mostly redness.

VELCADE Destruction

Investigational VELCADE (expired or end of study) should be destroyed on site according to the institution's standard operating procedure. Be sure to document removal and destruction on drug accountability logs.

Doxil or LipoDox

Handling instructions for the preparation of Doxil or LipoDox (pegylated liposomal doxorubicin) solution for intravenous administration

Pegylated liposomal doxorubicin is a sterile, translucent, red liposomal dispersion provided in single use glass vials. Each vial contains 20 mg/ 10 ml of doxorubicin HCL or 50 mg/25ml of doxorubicin HCL at a concentration of 2mg/ml.

Caution should be exercised in the handling and preparation of pegylated liposomal doxorubicin:

- Use of gloves is required.
- If pegylated liposomal doxorubicin comes into contact with skin or mucosa, immediately wash thoroughly with soap and water.
- Pegylated liposomal doxorubicin should be considered an irritant and precautions should be taken to avoid extravasation. With intravenous administration, extravasation may occur with or without an accompanying stinging or burning sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of

extravasation have occurred, the infusion should be immediately terminated and restarted in another vein.
- Pegylated liposomal doxorubicin must not be given by the intramuscular or subcutaneous route.
- Refrigerate at 2°-8°C. Avoid freezing.
- Pegylated liposomal doxorubicin should be handled and disposed of in a manner consistent with other anticancer drugs.

Doxil or Lipodox Administration

The appropriate dose of pegylated liposomal doxorubicin, up to 90 mg, must be diluted in 250 mL of 5% Dextrose Injection, USP prior to administration. Doses exceeding 90 mg should be diluted in 500 ml of 5% Dextrose Injection, USP prior to administration. Aseptic technique must be strictly observed since no preservative or bacteriostatic agent is present in pegylated liposomal doxorubicin. The diluted preparation must be refrigerated at 2°C to 8°C (36°F to 46°F) and administered within 24 hours.

- Do not use with in-line filters.
- Do not mix with other drugs.
- Do not mix with any diluent other than 5% Dextrose Injection.
- Do not use any bacteriostatic agent, such as benzyl alcohol.

Pegylated liposomal doxorubicin is not a clear solution but a translucent, red liposomal dispersion.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if a precipitate or foreign matter is present.

Rapid flushing of the infusion line should be avoided.

Doxil or LipoDox Dosage and Administration

Pegylated liposomal doxorubicin will be administered once every four weeks as a single intravenous infusion at a dose of 40 mg/m^2 (day 12 of each cycle), at an initial rate of 1 mg/min to minimize the risk of infusion reactions. If no infusion-related AEs are observed, the rate of infusion can be increased to complete administration of the drug over one hour.
Body surface area (BSA) calculation will be based on actual body weight. Dose adjustments should be made for any change in body weight >10% occurring throughout the study. Patients seen to be benefiting from treatment with pegylated liposomal doxorubicin may continue to receive treatment once every three weeks until satisfactory response (CR, PR, SD), progression of disease, unacceptable toxicity, or death occurs or defined in the protocol. At all times, the investigator may discontinue the subject from the study at his or

her discretion for any reason. To manage adverse events such as hand-foot syndrome (HFS), stomatitis, or hematologic toxicity, the dose may be delayed or reduced.

Injection Site Effects

Pegylated liposomal doxorubicin is not a vesicant, but should be considered an irritant and precautions should be taken to avoid extravasation. With intravenous administration of pegylated liposomal doxorubicin, extravasation may occur with or without an accompanying stinging or burning sensation, even if blood returns well on aspiration of the infusion needle. If any signs or symptoms of extravasation have occurred, the infusion should be immediately terminated and restarted in another vein. The application of ice over the site of extravasation for approximately 30 minutes may be helpful in alleviating the local reaction. Pegylated liposomal doxorubicin must not be given by the intramuscular or subcutaneous route.

Infusion reactions

Serious and sometimes life-threatening or fatal allergic/anaphylactoid-like infusion reactions have been reported with pegylated liposomal doxorubicin. Medications to treat such reactions, as well as emergency equipment, should be available for immediate use. These reactions were characterized by one or more of the following symptoms: flushing, shortness of breath, facial swelling, headache, chills, chest pain, back pain, tightness in the chest and throat, fever, tachycardia, pruritus, rash, cyanosis, syncope, bronchospasm, asthma, apnea, and hypotension. In most patients, these reactions resolve over the course of several hours to a day once the infusion is terminated. In some patients, the reaction resolved when the rate of infusion was slowed. The majority of infusion-related events occur during the first infusion. Similar reactions have not been reported with conventional doxorubicin and they presumably represent a reaction to the pegylated liposomal doxorubicin liposomes or one of its surface components. The initial rate of infusion should be 1 mg/min to help minimize the risk of infusion reactions.

Storage and Stability

Refrigerate unopened vials of pegylated liposomal doxorubicin at 2°C to 8°C (36°F to 46°F). Avoid freezing. Prolonged freezing may adversely affect liposomal drug products; however, short-term freezing (less than 1 month) does not appear to have a deleterious effect on pegylated liposomal doxorubicin.

Decitabine

Please refer to the decitabine package insert (Appendix 8.10) for details regarding preparation, handling, storage and destruction of decitabine.

DECITABINE for Injection is supplied as a sterile, lyophilized white to almost white powder,

in a single-dose vial, packaged in cartons of 1 vial. Each vial contains 50 mg of decitabine.

DECITABINE is a cytotoxic drug and caution should be exercised when handling and preparing DECITABINE. Procedures for proper handling and disposal of antineoplastic drugs should be applied. Several guidances on this subject have been published. DECITABINE should be aseptically reconstituted with 10 mL of Sterile Water for Injection (USP); upon reconstitution, each mL contains approximately 5.0 mg of decitabine at pH 6.7-7.3. Immediately after reconstitution, the solution should be further diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection to a final drug concentration of 0.1‑1.0 mg/mL. Unless used within 15 minutes of reconstitution, the diluted solution must be prepared using cold (2˚C ‑ 8˚C) infusion fluids and stored at 2˚C ‑ 8˚C (36˚F ‑ 46˚F) for up to a maximum of 4 hours until administration. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Do not use if there is evidence of particulate matter or discoloration.

NDC 62856-600-01, 50 mg single-dose vial individually packaged in a carton. Store vials at 25°C (77°F); excursions permitted to 15-30°C (59-86°F).

Decitabine will be administered at 20mg/m^2 IV on days 1-10 of a 28-day cycle during induction cycles and at 20mg/m^2 IV on days 1-5 of a 28-day cycle during post-induction therapy cycles (as described in Section 3.1).

3.3.3 Dose Modifications and Delays

SQ Velcade Dose Modification and Delay

Before each drug dose, the patient will be evaluated for possible toxicities that may have occurred after the previous dose(s). Toxicities are to be assessed according to the NCI Common Toxicity Criteria for Adverse Events (CTCAE), Version 4.0

All previously established or new toxicities observed any time and that are related to VELCADE are to be managed as described in Table 3-2 Neuropathic pain and peripheral sensory neuropathy are to be managed separately as described in Table 3-3.

Table 3-2 Toxicity Management

Toxicity	Grade	Action
Nonhematological toxicity	3	Hold Velcade therapy
Hematological Toxicity	Any	None

For grade 3 nonhematologic toxicities related to VELCADE, VELCADE is to be held until the toxicity returns to Grade 1 or better.

Once VELCADE is reduced for any toxicity, the dose may not be re-escalated.

If after VELCADE has been held, the VELCADE-related toxicity does not resolve to Grade 1 or better, then VELCADE must be discontinued. Per investigator discretion, the patient may continue on protocol therapy without VELCADE.

If the toxicity resolves, as described above, VELCADE may be restarted at the same schedule the patient was on prior to holding therapy, and the dose must be reduced by approximately 25% as follows:

- If the patient was receiving 1.3 mg/m^2, reduce the dose to 1 mg/m^2.
- If the patient was receiving 1 mg/m^2, reduce the dose to 0.7 mg/m^2.

If the patient was receiving 0.7 mg/m^2, discontinue drug unless patient is responding, in which case, this should be discussed with the principal investigator.

Patients who experience SQ VELCADE-related neuropathic pain or peripheral sensory neuropathy are to be managed as presented in Table 3-3. Once the **dose is reduced for peripheral neuropathy, the dose may not be re-escalated.**

Table 3-3 Management of Patients With VELCADE-Related Neuropathic Pain and/or Peripheral Sensory or Motor Neuropathy

Severity of Peripheral Neuropathy Signs and Symptoms [a]	Modification of Dose and Regimen
Grade 1 (asymptomatic; loss of deep tendon reflexes or paresthesias) without pain or loss of function	No action
Grade 1 with pain or Grade 2 (moderate symptoms; limiting instrumental Activities or Daily Living [ADL])[b])	Reduce VELCADE to 1.0 mg/m^2
Grade 2 with pain or Grade 3 (severe symptoms; limiting self care ADL[c])	Withhold VELCADE therapy until toxicity resolves to grade 1. When toxicity resolves reinitiate with a reduced dose of VELCADE at 0.7 mg/m^2. If toxicity does not resolve, discontinue VELCADE. [d]
Grade 4 (life-threatening consequence; urgent intervention indicated)	Discontinue VELCADE[d]

Source: VELCADE USPI issued January 2012.
Abbreviations: ADL = activities of daily living
a Grading based on NCI Common Terminology Criteria for Adverse Events (CTCAE) v4.0.
b Instrumental ADL: refers to preparing meals, shopping for groceries or clothes, using telephone, managing money, etc
c Self care ADL: refers to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden
d Per investigator discretion, the patient may continue on protocol therapy without VELCADE.

Patients with mild hepatic impairment (bilirubin ≤ 1.5 × ULN) do not require a starting dose adjustment. Please note that patients with bilirubin levels > 1.5 ULN are excluded from enrollment in this protocol (unless due to Gilbert's Syndrome). If a patient develops moderate or severe hepatic impairment with bilirubin ≥ Grade 2 (> 1.5 -3.0 × ULN) while on study, the investigator should hold VELCADE until the toxicity returns to < Grade 2. Restarting VELCADE at the next lower dosed level could be considered at the Investigator's discretion and following exclusion of VELCADE-induced liver impairment and careful consideration of liver disease due to other causes.

Doxil or LipoDox Dose Modification and Delay

Patients treated with pegylated liposomal doxorubicin (PLD) should be carefully monitored for toxicity. Following the first appearance of a Grade 2 or higher adverse event related to PLD, the PLD dosing should be adjusted or delayed as described in Table 3-4. Once the dose has been reduced, it should not be increased at a later time (Doxil® Product Information Booklet 2012).

In general, most adverse events are manageable with dose reductions or delays. Management of more specific toxicities (e.g. such as HFS, hematologic toxicities, and stomatitis, which may be managed by dose delays and adjustments) are outlined in the relevant sections of the protocol. Pegylated liposomal doxorubicin exhibits nonlinear pharmacokinetics at 40 mg/m^2; therefore, dose adjustments may result in a non-proportional greater change in plasma concentration and exposure to the drug.

Table 3-4 Pegylated liposomal doxorubicin dose adjustment guideline for PLD-related toxicities

Toxicity	CTC Grade	Actions
Hand Foot Syndrome	Grade 1 (mild erythema, swelling, or desquamation not interfering with daily activities)	Re-dose, unless patient has experienced previous Grade 3 or 4 toxicity. If so, delay up to 2 weeks and decrease dose by 25%. Return to original dose interval.
	Grade 2 (erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or ulcerations less than 2cm in diameter.)	Delay dosing for up to 2 weeks or until resolved to Grade 0-1. If after 2 weeks there is no resolution, pegylated liposomal doxorubicin should bediscontinued. If resolved to Grade 0-1 within 2 weeks, and there was no prior Grade 3-4 HFS, continue treatment at previous dose and return to original dose interval. If patient experienced previous Grade 3-4 toxicity, continue treatment with a 25% dose reduction and return to original dose interval.
	Grade 3 (blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing)	Delay dosing up to 2 weeks or until resolved to Grade 0-1. Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, pegylated liposomal doxorubicin should be discontinued.
	Grade 4 (diffuse or local process causing infectious complications, or a bed ridden state or hospitalization)	Delay dosing up to 2 weeks or until resolved to Grade 0-1. Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, pegylated liposomal doxorubicin should be discontinued.
Hematologic toxicity (ANC, Platelets)	**Any Grade**	**None**
Stomatitis	Grade 1 (painless ulcers, erythema, or mild soreness)	Redose unless patient has experienced previous Grade 3 or 4 toxicity. If so, delay up to 2 weeks and decrease dose by 25%. Return to original dose interval
	Grade 2 (painful erythema, edema, or ulcers, but can eat)	Delay dosing up to 2 weeks or until resolved to Grade 0-1. If after 2 weeks there is no resolution, pegylated liposomal doxorubicin should be discontinued. If resolved to Grade 0-1 within 2 weeks, and there was no prior Grade 3-4 stomatitis, continue treatment at previous dose and return to original dose interval. If patient experienced previous Grade 3-4 toxicity, continue treatment with a 25% dose reduction and return to original dose interval.

	Grade 3 (painful erythema, edema, or ulcers, and cannot eat)	Delay dosing up to 2 weeks or until resolved to Grade 0-1. Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, pegylated liposomal doxorubicin should be discontinued.
	Grade 4 (requires parenteral support)	Delay dosing up to 2 weeks or until resolved to Grade 0-1. Decrease dose by 25% and return to pegylated liposomal doxorubicin original dose interval. If after 2 weeks there is no resolution, pegylated liposomal doxorubicin should be discontinued.
Diarrhea	Grade 2	Hold dose until recovery to Grade 0 then continue at current dose level. If grade 2 toxicity persists for more than 14 days beyond the date of the next intended dose, decrease the next scheduled
	Grade 3	Hold dose until recovery to Grade 0 then continue at current dose level. If grade 3 toxicity lasts longer than 3 days despite maximal medical attention to diarrhea decrease the next scheduled dose by 25% after resolution to Grade 0. If toxicity recurs and lasts longer than 3 days despite maximal medical attention to diarrhea, decrease original dose by 50% after resolution to Grade 0. If toxicity recurs again then discontinue treatment.
	Grade 4	Hold dose until recovery to Grade 0. In the event toxicity lasts >24 hours despite maximal medical attention discontinue treatment. If grade 4 toxicity lasts <24 hours reduce dose by 25% at next cycle. If toxicity recurs discontinue treatment.

Patients with febrile neutropenia

Patients developing febrile neutropenia during the course of study must be managed as per local institutional guidelines and is an expected event in patients with AML. For patients who develop febrile neutropenia, Doxil should either be held (if febrile neutropenia occurs before the scheduled dose), or dose reduced by 25% for the next cycle (if febrile neutropenia occurs after Doxil administration).

Table 3-5 Dose adjustment of pegylated liposomal doxorubicin in hepatically impaired patients

Serum Bilirubin (x ULN)	Dose Adjustment
1.2 – 3.0 mg/dL	Decrease dose by 25%
>3 mg/dL	Decrease dose by 50%

AST/ALT (x ULN)	Dose Adjustment
>3-5 times ULN	Decrease dose by 25%
>5 times ULN	Decrease dose by 50%

Cardiac toxicity

Cardiac function should be carefully monitored in patients treated with pegylated liposomal doxorubicin. (Doxil® Product Information Booklet 2005) The use of pegylated liposomal doxorubicin injection may lead to cardiac toxicity. Acute left ventricular failure can occur, particularly in patients who have received total dosage exceeding the currently recommended limit of 550 mg/m^2. Lower doses (400 mg/m^2) appear to cause heart failure in patients who have received prior radiotherapy to the mediastinal area or are receiving concomitant therapy with other potentially cardiotoxic agents such as cyclophosphamide. Pegylated liposomal doxorubicin should be administered to patients with a history of cardiovascular disease only when the potential benefit outweighs the risk, and cardiac function should be carefully monitored. All patients who enroll in the study are required to have a MUGA scan or a 2-D echocardiogram performed at screening (within 30 days prior to start of study medication), every two cycles starting with Cycle 7 (e.g., pre-Cycle 7, 9, 11, and End of Study Treatment. The LVEF value at screening must be >=50%. All MUGA/2-D echocardiograms must be recorded on video and maintained at the site. During treatment with pegylated liposomal doxorubicin, when a patient has reached a total (lifetime cumulative) anthracycline dose of 300 mg/m^2, follow-up MUGA scans or 2-D echocardiograms are to be performed every two cycles (and this schedule will replace the schedule of assessments every two cycles after Cycle 6 listed above for applicable patients). Additional evaluations may be performed throughout the trial as clinically indicated for patients receiving pegylated liposomal doxorubicin to monitor cardiac toxicity. If left ventricular ejection fraction declines to less than 45% or a decrease by an absolute value of 20% from the baseline value is noted, treatment with pegylated liposomal doxorubicin is to be temporarily suspended or discontinued and restarted at investigator discretion.[43] For subjects in CR continuing on post-induction therapy per protocol, pegylated liposomal doxorubicin should be discontinued once the total lifetime doxorubicin (or equivalent) dose of 550 mg/m^2 is reached or a maximum of 12 cycles. These subjects may continue on protocol therapy without pegylated liposomal doxorubicin at investigator discretion.

Other toxicities

If a patient in the pegylated liposomal doxorubicin arm experiences any other Grade 3 or 4 non-hematologic toxicity related to PLD, PLD should be held until the toxicity resolves to < Grade 2 and subsequent doses of Doxil should be dose reduced by 25%. If the ≥ Grade 3 toxicity recurs, PLD must be discontinued. These subjects may continue on protocol therapy without pegylated liposomal doxorubicin at investigator discretion.

Decitabine Dose Modification and Delay

Induction:

Grade 3 non-hematologic toxicities from cycle 1 should resolve to grade 2 or better before starting subsequent induction cycles of decitabine. Subsequent cycles of induction may be delayed at investigator discretion up to 14 days or to allow for resolution of non-hematologic toxicities to grade 2 or better. There are no hematologic parameters for administration of induction cycles of decitabine, since subjects have active AML and blood count recovery is not expected

Post-Induction:

Grade 3 non-hematologic toxicities from prior cycles should resolve to grade 2 or better before starting subsequent post-induction cycles of decitabine.

Following a 5-day course of decitabine, subjects without evidence of AML (defined as no minimal residual disease by flow cytometry, cytogenetics or molecular markers), but who had grade 4 neutropenia (<500/μL) of at least a 14-day duration will receive a dose reduction of decitabine to 4 days with the next cycle. A second dose reduction of decitabine to 3 days per cycle is permitted if grade 4 neutropenia of at least a 14-day duration occurs again. Patients with residual AML (defined as presence of minimal residual disease by flow cytometry, cytogenetics or molecular markers), however, will continue to receive 5 days of decitabine per cycle. Subsequent cycles of post-induction may be delayed at investigator discretion up to 14 days or to allow for resolution of non-hematologic toxicities to grade 2 or better and to allow neutrophils to recover to greater than 1000/μL and platelets to greater than 100,000/μL in patients with CR. There are no hematologic parameters for administration of post-induction cycles of decitabine in patients with persistent AML or in CRi.

3.3.4 Treatment Assignment

N/A

3.3.5 Blinding, Packaging, and Labeling

VELCADE will be supplied in vials as open-label stock. Both the box label and vial label will fulfill all requirements specified by governing regulations.

3.3.6 Concomitant Treatment

Investigators should consider using antiviral prophylaxis in subjects being treated with VELCADE.

Standard supportive care includes the use of, growth factors, packed red blood cells (PRBC) and platelets, admission for intravenous fluids and antimicrobial therapy as per the discretion of the treating physician. Hydroxyurea is permitted during cycle 1 of induction to control the white blood cell count.

3.3.7 Prohibited Concurrent Therapy

- Participation in clinical trials with other investigational agents, not included in this trial, within 14 days of the start of this trial and throughout the duration of this trial.

3.3.8 Treatment Compliance

All drugs will be administered to eligible patients under the supervision of the investigator or identified subinvestigator(s). The pharmacist will maintain records of drug receipt (if applicable), drug preparation, and dispensing, including the applicable lot numbers, patients' height, body weight, and body surface area (see Appendix 8.3), total drug administered in milliliters and milligrams, and date and time of administration. Any discrepancy between the calculated dose and dose administered and the reason for the discrepancy must be recorded in the source documents.

3.3.9 Precautions and Restrictions

It is not known what effects VELCADE has on human pregnancy or development of the embryo or fetus. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Non-sterilized female patients of reproductive age and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

Female patients must meet 1 of the following:

- Postmenopausal for at least 1 year before the screening visit, or
- Surgically sterile, or
- If they are of childbearing potential, agree to practice 2 effective methods of contraception from the time of signing the informed consent form through 30 days after the last dose of SQ VELCADE, or agree to completely abstain from heterosexual intercourse.

It is strongly recommended that at least 1 of these 2 methods be highly effective (see examples below).

Highly effective methods	Other effective methods (barrier methods)
Intra-uterine devices (IUD)	Latex condom
Hormonal contraceptives (birth control pills/oral contraceptives, injectable contraceptives, contraceptive patches, or contraceptive implants)	Diaphragm with spermicide Cervical cap Sponge

If one of the highly effective methods cannot be used, using 2 effective methods at the same time is recommended.

Male patients, even if surgically sterilized (ie, status postvasectomy) must agree to 1 of the following:

- Practice effective barrier contraception during the entire study treatment period and through a minimum of 30 days after the last dose of study drug, or completely abstain from heterosexual intercourse.

3.4 Duration of Treatment and Patient Participation

Patients will receive a minimum of 1 cycles and a maximum of 4 cycles of induction. If there is no response or if they have a DLT, they will be taken off the study. Patients will receive continued cycles of post-induction therapy until progression, intolerance, transplant, withdrawal of informed consent or a total of 12 cycles (including induction cycles) are administered.

3.5 Termination of Treatment and/or Study Participation

Patients must be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw, and in some cases is required to withdraw, patients from the study for any of the following reasons:

- Intercurrent illness
- Occurrence of an unacceptable adverse event
- A significant treatment cycle delay or SQ VELCADE interruption, at the investigator's discretion.
- Protocol violations

- Noncompliance
- Administrative reasons
- Failure to return for follow-up
- General or specific changes in the patient's condition unacceptable for further treatment in the judgment of the investigator
- Progressive disease at any time

At the time of withdrawal, all study procedures outlined for the End of Study visit should be completed. The primary reason for a patient's withdrawal from the study is to be recorded in the source documents.

3.6 Efficacy

3.6.1 Efficacy Measurements

All patients who are registered will be accounted for in the report of the results. To be evaluable for toxicity, a patient must receive at least one cycle of treatment and or have experienced a DLT in the first cycle. All patients who receive the first cycle of treatment will be included in the analysis of progression free and overall survival. Treatment efficacy will be determined by complete blood counts and bone marrow biopsy after each cycle of induction.

Definitions

Response and progression will be evaluated in this study using the Revised Recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia.

Measurable disease

Not applicable

Response Criteria- leukemia

The following categories from the Revised Recommendations of the International Working Group will be used: Morphologic leukemia-free state: Less than 5% blasts in an aspirate sample with marrow spicules and with a count of at least 200 nucleated cells. There are no Auer rods or persistence of

extramedullary disease. (The presence of a unique phenotype by flow cytometry identical to what was found in the pre-treatment specimen is viewed as persistence of leukemia [minimal residual disease]) Morphologic complete remission (CR): The patient achieves the morphologic leukemia-free state and has an absolute neutrophil count of > 1000/uL and platelet count ≥ 100,000/uL. The patient is independent of blood transfusions. No duration of response is required to fulfill these criteria. Cytogenetic complete remission (CRc): Patients who achieve a morphologic CR along with reversion to a normal karyotype by cytogenetic analysis. For patients who have unique markers by routine cytogenetics or by FISH upon enrollment, these markers will be followed on subsequent bone marrow examinations using the same technique(s) to evaluate for CRc. Molecular complete remission (CRm): Patients who achieve a morphologic CR with no residual disease by molecular or flow cytometric detection methods. For patients with unique multi-dimensional flow cytometry markers at the time of enrollment, these will be repeated on subsequent bone marrow studies to evaluate for CRm. Morphologic CR with incomplete blood count recovery (CRi): Patient fulfill the criteria for morphologic CR except for residual neutropenia (<1000/uL) and/or thrombocytopenia (<100,000/uL).

Partial Remission (PR): This requires the same hematologic values for a CR but with a decrease of at least 50% in the percentage of blasts to a post-treatment value of 5% to 25% in the bone marrow aspirate. (If the pre-treatment blast percentage was 50-100%, this must decrease to a value between 5-25%. If the pre-treatment blast percentage was 20-49%, this must decrease by at least half to a value greater than 5%). A value ≤ 5% is also considered a PR if Auer rods are present.

Treatment Failure:

Resistant disease: Patient does not achieve CR, CRi or PR upon repeat bone marrow examination after 2-4 cycles of induction therapy, persistent AML in blood or bone marrow.

Aplasia: Patient dies, death occurs while cytopenic with aplastic bone marrow.

Indeterminate cause: Patient dies with no blasts in peripheral blood but no bone marrow examination; Patient does not complete the first course of therapy.

Morphologic relapse: reappearance of blasts post-CR in peripheral blood or bone marrow.

Molecular or cytogenetic relapse: Reappearance of the molecular or cytogenetic abnormality

Duration of overall response-leukemia: The duration of overall response is measured from the time measurement. Criteria are met for CR or PR (whichever is first recorded) until the first date that treatment failure is objectively documented.

3.6.2 Safety Measurements

In addition to the requirements for adverse event reporting as outlined in section 6.0, this protocol is also subject to the UC Davis Cancer Center's (UCDCC) Data and Safety Monitoring Plan. The UCDCC is committed to pursuing high-quality patient-oriented clinical research and has established mechanisms to ensure both scientific rigor and patient safety in the conduct of clinical research studies. The UCDCC relies on a multi-tiered committee system that reviews and monitors all cancer clinical trials and ensures the safety of its participants, in compliance with institutional and federal requirements on adverse event (AE) reporting, verification of data accuracy, and adherence to protocol eligibility requirements, treatment guidelines, and related matters. The Scientific Review Committee (SRC) assumes overall oversight of cancer studies, with assistance and input from two independent, but interacting, committees: the Quality Assurance Committee and the Data Safety Monitoring Committee. A multi-level review system strengthens the ability of the UCDCC to fulfill its mission in conducting high quality clinical cancer research.

As per University of California Davis Cancer Center (UCDCC) Clinical Trials Support Unit (CTSU) SOP AM 506: Protocol Specific Meetings, the principal investigator (PI), clinical research coordinator (CRC), and the clinical research nurse meet at least monthly for ongoing study information, to discuss patient data and adverse events and to determine if dose escalation is warranted, when applicable.

According to the UCDCC Data and Safety Monitoring Plan (DSMP), any new serious adverse events related to the drugs being used on this trial are reviewed monthly by the UCDCC Data and Safety Monitoring Committee (DSMC) and any applicable changes to the study are recommended to the PI, if necessary.

The UCDCC Scientific Review Committee (SRC) determines if a UCDCC Data and Safety Monitoring Board (DSMB) is required. If required, the DSMC will appoint a DSMB. The

DSMB is responsible for reviewing study accrual logs, adverse event information and dose escalation meeting minutes (where applicable) to ensure subject safety and compliance with protocol defined guidelines.

4. ADVERSE EVENTS

All serious adverse events (SAEs) (regardless of expectedness, causality, and whether commercial or investigational VELCADE is used) must be reported to Millennium Pharmacovigilance (or designee). See Section 4.3 for the reporting of SAEs.

The sponsor-investigator is responsible to meet all regulations and requirements applicable to the sponsor-investigator.

4.1 Definitions

4.1.1 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

For this protocol an abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

Adverse Drug Reaction

An adverse drug reaction (ADR) is a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. This includes adverse reactions which arise from: use of a medicinal product within the terms of the marketing authorization; use outside the terms of the marketing authorization, including overdose, misuse, abuse and medication errors; and occupational exposure*.

* This corresponds to the exposure to a medicinal product for human use as a result of one's occupation, such as nurses who may handle products routinely in their occupational setting.

4.1.2 Serious Adverse Event Definition

Serious adverse event (SAE) means any untoward medical occurrence that at any dose:

- Results in death.
- Is life-threatening (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of an existing hospitalization (see clarification below on planned hospitalizations in Section 4.2).
- Results in persistent or significant disability or incapacity. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a congenital anomaly/birth defect.
- Is a medically important event. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient, require medical or surgical intervention to prevent one of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent.
    - Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
    - With respect to the suspected transmission via a medicinal product of an infectious agent; any organism, virus, or infectious particle (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), whether pathogenic or non-pathogenic, is considered an infectious agent.

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term severe is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance

(such as a Grade 3 headache). This is NOT the same as serious, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

4.2 Procedures for Reporting Serious Adverse Events (SAEs)

Adverse events (AEs) may be spontaneously identified by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. AEs which are serious must be reported to Millennium Pharmacovigilance (or designee) from first dose of VELCADE up to and including 30 days after administration of the last dose of VELCADE. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

Adverse Events which are serious must be reported to Millennium Pharmacovigilance (or designee) from the first dose of bortezomib up to and including 30 days after administration of the last dose of bortezomib. Any SAE that occurs at any time after completion of VELCADE treatment or after the designated follow-up period that the investigator and/or sponsor-investigator considers to be related to any study drug must be reported to the Millennium Pharmacovigilance (or designee). Planned hospital admissions or surgical procedures for an illness or disease that existed *before the patient was enrolled in the trial* are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Since this is an investigator-initiated study, the principal investigator Joseph Tuscano, MD, also referred to as the sponsor-investigator, is responsible for reporting serious adverse events (SAEs) to any regulatory agency and to the sponsor- investigator's EC or IRB. Regardless of expectedness or causality, all SAEs must also be reported in English to Millennium Pharmacovigilance or designee. Fatal and Life Threatening SAEs within 24 hours of the sponsor-investigator's observation or awareness of the event.

All other serious (non-fatal/non-life threatening) events within 5 calendar days of the sponsor-investigator's observation or awareness of the event.

See below for contact information for the reporting of SAEs to Millennium Pharmacovigilance.

The sponsor-investigator must fax the SAE Form per timelines above. A sample of an SAE Form will be provided.

The SAE report must include at minimum:

- Event term(s)
- Serious criteria
- Intensity of the event(s): Sponsor-investigator's or sub-investigator's determination. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version specified in the protocol, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.
- Causality of the event(s) and): Sponsor-investigator's or sub-investigator's determination of the relationship of the event(s) to study drug administration.

Follow-up information on the SAE may be requested by Millennium (or designee).

Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version used at your institution, as a guideline, whenever possible. The criteria are available online at http://ctep.cancer.gov/reporting/ctc.html.

In the event that this is a multisite study, the sponsor-investigator is responsible to ensure that the SAE reports are sent to Millennium Pharmacovigilance (or designee) from all sites participating in the study. Sub-investigators must report all SAEs to the sponsor-investigator so that the sponsor-investigator can meet his/her foregoing reporting obligations to the required regulatory agencies and to Millennium Pharmacovigilance, unless otherwise agreed between the sponsor-investigator and sub-investigator(s).

Relationship to all study drugs for each SAE will be determined by the investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

US and Canada
Toll-Free Fax Number: 1-800-963-6290
Email: TakedaOncoCases@cognizant.com

Suggested Reporting Form:

- US FDA MedWatch 3500A: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm
- Any other form deemed appropriate by the sponsor-investigator

All serious, unlabeled, (unexpected) adverse events will be reported to the FDA as required by 21 CFR 312.32 on the FDA MedWatch 3500a form. (Investigational New Drug) https://www.accessdata.fda.gov/scripts/medwatch/.

Reporting to the Institutional Review Board

Both serious and non-serious adverse events will be reported in accordance with UCD IRB Administration and UCD Cancer Center Clinical Trial Support Unit (CTSU) policies. The UC Davis IRB can be reached at (916) 703-9151.

4.3 Procedures for Reporting Drug Exposure during Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and permanently discontinue study drug(s). The sponsor-investigator must fax a completed Pregnancy Form (Appendix 8.10) or other approved equivalent form to the Millennium Pharmacovigilance or designee immediately (see Section 4.2). The pregnancy must be followed for the final pregnancy outcome (eg, delivery, still birth, miscarriage) and Millennium Pharmacovigilance will request this information from the sponsor-investigator.

If a female partner of a male patient becomes pregnant during the male patient's participation in this study, the sponsor-investigator must also immediately fax a completed Pregnancy Form (Appendix 8.10) to the Millennium Pharmacovigilance or designee (see Section 4.2). Every effort should be made to follow the pregnancy for the final pregnancy outcome.

5. STATISTICAL CONSIDERATIONS

5.1 Study Design and Overview of Primary and Secondary Endpoints

This is an open label, Phase II study in patients with relapse/refractory AML or previously untreated patients that are not candidates for standard induction therapy. The primary endpoints are overall response rate and PFS. The secondary endpoints are overall survival and toxicity. There will be a safety lead-in to assess dose-limiting toxicities (DLTs) in the first 6-9 subjects described in Section 3.1.

5.2 Sample Size Estimation/Accrual Rate

Up to 14 patients will be treated with decitabine, SQ VELCADE and doxil at dose levels previously established to be safe (including the two patients treated per the dosing schedule in Amendment 9). Fifteen patients have been treated to date through prior versions of this protocol with SQ bortezomib and peylated liposomal doxorubicin. Objective response (CR + CRi + PR) will be monitored using Simon's minimax 2-stage design. This study design is optimal in the sense that it minimizes the expected sample size among competing designs. The OR rate in relapsed/refractory AML patients treated with a 10-day decitabine regimen is estimated to be approximately 16%. A 30% increase in the objective response rate with the addition of VELCADE and Doxil to 46% would justify evaluation of this regimen in larger, more definitive trials. We assume a one-sided type I error rate of 5% and desire at least 80% power to conclude that this regimen elicits an objective response rate significantly greater than 16% if the true response rate of this regimen is 46% or higher. Under these assumptions, if 2 or fewer OR's are observed in the first 9 patients (which includes the two patients treated per the dosing schedule in Amendment 9), the principal investigator may conclude that regimen is insufficiently active to warrant further study. Otherwise, accrual will continue to a total of 14 patients. If 5 or more OR's are observed in 14 patients, this regimen will be deemed sufficiently active to warrant further study.

The sample size determination and rules for the safety lead-in portion are described in detail in Section 3.1.

5.3 Randomization and Stratification Factors

N/A

5.4 Evaluation of Efficacy

Primary analyses of outcome variables will use the intent-to-treat dataset, defined as all eligible patients enrolled in the study. Secondary analyses will be restricted to patients receiving at least one study drug. The primary endpoint (objective response) will be summarized with frequency tables and 95% confidence intervals, and compared to stopping rules at the planned interim analysis and at final analysis. Continuous variables (e.g., age, hematology values, molecular studies/cytogenetics/Fluorescent in situ hybridization (FISH)) will be summarized using the mean (s.d.) or median (range). Frequency tables will be used to summarize categorical variables. Logistic regression will be used to assess the impact of patient characteristics (e.g., cytogenetics) on the objective response rate. The distribution of time-to-event endpoints (e.g., CR, PFS, overall survival) will be estimated using the method of Kaplan and Meier. Comparison of time-to-event endpoints by important subgroups of patients (based on known prognostic factors, e.g cytogenetics) will be made using the

logrank test. Cox (proportional hazards) regression will be used to evaluate multivariable predictive models of time-to-event outcomes.

5.5 Evaluation of Safety

Toxicity information recorded will include the type, severity, time of onset, time of resolution, and the probable association with the study regimen. Tables will be constructed to summarize the observed incidence by severity and type of toxicity.

Data from all subjects who receive any study drug will be included in the safety analyses. The severity of the toxicities will be graded according to the NCI CTCAE v4.0 whenever possible. Unacceptable toxicity experienced in patients will be monitored according to guidelines for monitoring toxicity in pilot/phase II trials using sequential probability ratio test based criteria. The guidelines will be used to raise a flag if the number of patients who experience unacceptable toxicity is excessive is greater than 20%. Toxicity information recorded will include the type, severity, time of onset, time of resolution, and the probable association with the study regimen. Tables will be constructed to summarize the observed incidence by severity and type of toxicity. Baseline information (e.g. the extent of prior therapy, extent of disease) and demographic information will be presented, as well, to describe the patients treated in this Phase II study.

6. ADMINISTRATIVE REQUIREMENTS

6.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonization (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study, and retained according to the appropriate regulations. This is the responsibility of the sponsor-investigator.

6.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki. The Institutional Review Board (IRB)/Independent Ethics Committee (IEC) will review all appropriate study documentation in order to safeguard the rights, safety, and well-being of the patients. The study will only be conducted at sites where IRB/IEC

approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator. Millennium requests that the protocol and informed consent documents be reviewed by Millennium prior to IRB/IEC submission.

Minorities and Gender Statement

Recruitment is open to all minorities and both genders. Although distributions may vary by disease type, our recruitment procedures have been developed to enroll patients who are representative of the respective target population.

6.3 Patient Information and Informed Consent

The principles of informed consent are described by Federal Regulatory Guidelines (Federal Register Vol. 46, No. 17, January 27, 1981, part 50) and the Office for Protection from Research Risk Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR46). They must be followed to comply with FDA regulations for the conduct and monitoring of clinical investigations.

All patients will have signed an informed consent for participation in research activities in accordance with all institutional, NCI and Federal regulations, and will have been given a copy of the Experimental Subject's Bill of Rights.

Once signed, informed consent has been obtained and all pretreatment evaluations have been performed, patients will be entered on study according to UCD Clinical Trials Support Unit (CTSU) policy. To register a patient, the research nurse or data manager must complete the Eligibility Checklist and the Patient Registration Form. A patient accession number will then be assigned. Administration of study administration may not be initiated until the patient is registered.

6.4 Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

6.5 Patient Confidentiality

In order to maintain patient privacy, all data capture records, drug accountability records, study reports, and communications will identify the patient by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) from Millennium or its designees and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

The original data collection forms will be stored in secure cabinets in the UCD Clinical Trials Support Unit.

6.6 Protocol Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Changes to the protocol will require approval from Millennium and written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. The investigator will submit all protocol modifications to Millennium and the regulatory authority(ies) in accordance with the governing regulations.

Any departures from the protocol must be fully documented in the source documents.

Deviations in eligibility criteria are not allowed with the following exceptions: If the treating physician feels it is appropriate to request a deviation from the eligibility criteria, they must contact the PI to obtain approval. If approved, the protocol PI must immediately submit an amendment to the protocol if the deviation is likely to occur again. In addition, the treating physician must request a waiver of eligibility according to current IRB policies. All protocol deviations will be reported in accordance with UCD IRB Administration and UCD Cancer Center CTSU policies

6.7 On-site Audits

Regulatory authorities, the IEC/IRB, and/or Millennium may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

Quality assurance audits of select patients and source documents may be conducted by the UC Davis Cancer Center Quality Assurance Committee as outlined in the UC Davis Cancer Center Data and Safety Monitoring plan.

Quality control will be maintained by the CTSU Quality Assurance team according to CTSU policy.

6.8 Drug Accountability

Accountability for the drug at all study sites (including all subsites, if applicable) is the responsibility of the sponsor-investigator. The sponsor-investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site (if applicable), inventory at the site (if applicable), use by each patient, and return to Millennium or disposal of the drug will be maintained by the site and/or subsites. Accountability records will include drug receipt/destruction dates, quantities, lot numbers, expiration dates (if applicable), and corresponding registered patient numbers.

All material containing VELCADE will be treated and disposed of as hazardous waste in accordance with governing regulations.

6.9 Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact Millennium (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium quality representative.

A medication error is a preventable event that involves an identifiable patient and that leads to inappropriate medication use, which may result in patient harm. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a patient do not. Individuals who identify a potential medication error situation should immediately contact Millennium (see below) and report the event.

For Product Complaints or Medication Errors,
1-866-VELCADE (1-866-835-2233)
E-mail: medical@mlnm.com
FAX: 1-800-881-6092
Hours: Mon-Fri, 9 a.m. – 7 p.m. ET

Product complaints and medication errors in and of themselves are not AEs. If a product complaint or medication error results in an SAE, an SAE form should be completed and sent to Millennium Pharmacovigilance (refer to Section 4.2).

6.10 Premature Closure of the Study

This study may be prematurely terminated, if in the opinion of the sponsor-investigator or Millennium, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the sponsor-investigator or Millennium by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend, or discontinue the development of the drug

6.11 Record Retention

The sponsor-investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

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8. APPENDICES

8.1 Study Calendar/Toxicity and Events

		INDUCTION: Each cycle except as indicated (Absent allowed delays, cycles repeat every 28 days up to 4 cycles.)*													Post-Induction: Each cycle except as indicated (Absent allowed delays, cycles repeat every 28 days up to 12 cycles.)*						
	Pre-Study (≤14 days)	**D1**	**D2**	**D3**	**D4**	**D5**	**D6**	**D7**	**D8**	**D9**	**D10**	**D12**	**D15**	**Prior to next cycle[j]**	**D1-5**	**D8**	**D12**	**D22**	**Prior to next cycle[j]**	**Off Study**	**F/U until Relapse**
Doxil/LipoDox (Do)												Do					Do				
Bortezomib (B)						B			B			B	B		B (D1)	B					
Decitabine		D	D	D	D	D	D	D	D	D	D				D (D1-5)						
Informed consent	X																				
Demographics	X																				
Medical history	X																				
Physical exam	X	X[a]											X[a]	X	X[a]				X	X	X
Vital signs	X	X											X	X	X				X	X	X
Height	X																				
Weight	X	X											X	X	X				X	X	X
Performance status	X	X[a]											X[a]	X	X[a]				X	X	X
CBC w/diff	X	X[a]				X			X			X	X	X	X[a]				X	X	X
Serum chemistry[b]	X	X[a,c]				X[c]			X[c]			X[c]	X[c]	X	X[a,c]				X[c]	X	X
EKG[d]	X													X[d]					X[d]	X	
MUGA or ECHO[e]	X													X[e]					X[e]	X	
Adverse event evaluation	X	X----------X												X	X----------X						
Neurologic evaluation[f]	X													X					X	X	X
Bone Marrow Biopsy[g]	X													X[g]					X[g]	X[g]	X
B-HCG[h]	X																				
Prophylaxis[i]		X[i]												X[i]	X[i]				X[i]		

* Variations of ± 3 days of the scheduled visit are permitted.

a. Pre-treatment/pre-cycle studies need to be repeated in week 1 **only** if the patient's condition is deteriorating.

b. Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium.

c. Induction cycles only; chemistries weekly in addition to day 5, 12 and 15. For post-induction cycles, chemistries should be done prior to each new course and every two weeks, unless monitoring for prior AE resolution.

d. EKG to be done at baseline, after each induction cycle, after every 3 cycles of post-induction therapy, at the end of study, and as clinically indicated.

e. MUGA or ECHO to be done at screening (within 30 days prior to start of study medication), every two cycles starting with Cycle 7 [e.g. pre-Cycle 7, 9, 11 (note: induction and post-induction cycles are added together to determine cycle number)], and End of Study Treatment, and as clinically indicated. During treatment with pegylated liposomal doxorubicin, when a patient has reached a total (lifetime cumulative) anthracycline dose of 300 mg/m^2, follow-up MUGA scans or 2-D echocardiograms are to be performed every two cycles (and this schedule will replace the schedule of assessments every two cycles after Cycle 6 listed above for applicable patients).

f. Includes a motor exam, reflex exam, sensory exam and administration of the Neurotoxicity Assessment Tool.

g. Bone Marrow Bx/Aspirate done at baseline, after each induction cycle until CR, then every after every 6 cycles of post-induction therapy or with signs of relapse or as clinically indicated. Send for morphology (pathology), flow cytometry, cytogenetics. Also send for molecular studies if indicated.

h. Serum pregnancy test (women of childbearing potential).

i. Acyclovir prophylaxis will begin before cycle #1 and continue throughout treatment and for 6 months after completion

j. Repeats every 28 days, or up to every 42 days if awaiting resolution of Grade 3 or 4 AE's

k. Pegylated liposomal doxorubicin should be discontinued once a patient reaches a lifetime cumulative dose of 550mg/m2 doxorubicin (prior non-doxorubicin included in this value using published conversion factors). The patient may continue on post-induction therapy with decitabine and bortezomib.

8.2 Karnofsky Performance Status Scale

The following table presents the Karnofsky performance status scale.

Points	Description
100	Normal, no complaints, no evidence of disease
90	Able to carry on normal activity
80	Normal activity with effort; some signs or symptoms of disease
70	Cares for self; unable to carry on normal activity or to do active work
60	Requires occasional assistance but is able to care for most of his/her needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization indicated. Death not imminent
20	Very sick; hospitalization necessary; active support treatment necessary
10	Moribund; fatal processes progressing rapidly
0	Dead

Sources: Mor V, Laliberte L, Morris JN, Wiemann M. The Karnofsky Performance Status Scale: an examination of its reliability and validity in a research setting. *Cancer* 1984;53:2002-2007.

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8.3 Body Surface Area

Body surface area (BSA) should be calculated using a standard nomogram that yields the following results in meters squared (m^2):

$$\text{BSA} = \sqrt{\frac{Ht(inches) \times Wt(lbs)}{3131}}$$

or

$$\text{BSA} = \sqrt{\frac{Ht(cm) \times Wt(kg)}{3600}}$$

8.4 New York Heart Association Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease.

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

8.5 Common Terminology Criteria for Adverse Events

http://ctep.cancer.gov/reporting/ctc.html

8.6 RTOG/EORTC Late Radiation Morbidity Scoring Scheme

http://www.rtog.org/members/protocols/0211/app3.html

RTOG/EORTC Late Radiation Morbidity Scoring Scheme
Use for toxicity occurring greater than 90 days after radiation therapy.

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Bladder-Late RT Morbidity Scoring	No change from baseline	Slight epithelial atrophy/minor telangiectasia (microscopic hematuria)	Moderate frequency / generalized telangiectasia / intermittent macroscopic hematuria	Severe frequency and dysuria/severe generalized telangiectasia (often with petechiae); frequent hematuria; reduction in bladder capacity (<150 cc)	Necrosis/contracted bladder (capacity <100 cc) / severe hemorrhagic cystitis
Bone- Late RT Morbidity Scoring	No change from baseline	Asymptomatic; no growth retardation; reduced bone density	Moderate pain or tenderness; growth retardation; irregular bone sclerosis	Severe pain or tenderness; complete arrest of bone growth; dense bone sclerosis	Necrosis/ spontaneous fracture
Brain- Late RT Morbidity Scoring	No change from baseline	Mild headache; slight lethargy	Moderate headache; great lethargy	Severe headaches; severe CNS dysfunction (partial loss of power or dyskinesia)	Seizures or paralysis; coma
Esophagus-Late RT Morbidity Scoring	No change from baseline	Mild fibrosis; slight difficulty in swallowing solids; no pain on swallowing	Unable to take solid food normally; swallowing semi-solid food; dilatation may be indicated	Severe fibrosis; able to swallow only liquids; may have pain on swallowing; dilation required	Necrosis / perforation; fistula

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Heart- Late RT Morbidity Scoring	No change from baseline	Asymptomatic or mild symptoms; transient T wave inversion and ST changes; sinus tachycardia >110 (at rest)	Moderate angina on effort; mild pericarditis; normal heart size; persistent abnormal T wave and ST changes; low QRS	Severe angina; pericardial effusion; constrictive pericarditis; moderate heart failure; cardiac enlargement; EKG abnormalities	Tamponade / severe heart failure/severe constrictive pericarditis
Joint- Late RT Morbidity Scoring	No change from baseline	Mild joint stiffness; slight limitation of movement	Moderate stiffness; intermittent or moderate joint pain; moderate limitation of movement	Severe joint stiffness; pain with severe limitation of movement	Necrosis / complete fixation
Kidney- Late RT Morbidity Scoring	No change from baseline	Transient albuminuria; no hypertension; mild impairment of renal function; urea 25-35 mg%; creatinine 1.5-2.0 mg%; creatinine clearance >75%	Persistent moderate albuminuria (2+); mild hypertension; no related anemia; moderate impairment of renal function; urea >36–60 mg%; creatinine clearance >50-74%	Severe albuminuria; severe hypertension; persistent anemia (<10 g%); severe renal failure; urea >60 mg%; creatinine >4 mg%; creatinine clearance <50%	Malignant hypertension; uremic coma / urea >100%
Larynx- Late RT Morbidity Scoring	No change from baseline	Hoarseness; slight arytenoid edema	Moderate arytenoid edema; chondritis	Severe edema; severe chondritis	Necrosis

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Liver- Late RT Morbidity Scoring	No change from baseline	Mild lassitude; nausea; dyspepsia; slightly abnormal liver function	Moderate symptoms; some abnormal liver function tests; serum albumin normal	Disabling hepatic insufficiency; liver function tests grossly abnormal; low albumin; edema or ascites	Necrosis / hepatic coma or en-cephalopathy
Lung- Late RT Morbidity Scoring	No change from baseline	Asymptomatic or mild symptoms (dry cough); slight radiographic appearances	Moderate symptomatic fibrosis or pneumonitis (severe cough); low grade fever; patchy radiographic appearances	Severe symptomatic fibrosis or pneumonitis; dense radiographic changes	Severe respiratory insufficiency / continuous O_2 / assisted ventilation
Mucous membrane- Late RT Morbidity Scoring	No change from baseline	Slight atrophy and dryness	Moderate atrophy and telangiectasia; little mucus	Marked atrophy with complete dryness; severe telangiectasia	Ulceration
Salivary glands- Late RT Morbidity Scoring	No change from baseline	Slight dryness of mouth; good response on stimulation	Moderate dryness of mouth; poor response on stimulation	Complete dryness of mouth; no response on stimulation	Fibrosis
Skin- Late RT Morbidity Scoring	No change from baseline	Slight atrophy; pigmentation change; some hair loss	Patchy atrophy; moderate telangiectasia; total hair loss	Marked atrophy; gross telangiectasia	Ulceration

	Grade				
Toxicity	**0**	**1**	**2**	**3**	**4**
Small/Large intestine- Late RT Morbidity Scoring	No change from baseline	Mild diarrhea; mild cramping; bowel movement 5 x daily slight rectal discharge or bleeding	Moderate diarrhea and colic; bowel movement >5 x daily; excessive rectal mucus or intermittent bleeding	Obstruction or bleeding, requiring surgery	Necrosis / perforation fistula
Spinal cord- Late RT Morbidity Scoring	No change from baseline	Mild Lhermitte's syndrome	Severe Lhermitte's syndrome	Objective neurological findings at or below cord level treatment	Mono-, para-, quadriplegia
Subcutaneous tissue- Late RT Morbidity Scoring	No change from baseline	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; slight field contracture; <10% linear reduction	Severe induration and loss of subcutaneous tissue; field contracture >10% linear measurement	Necrosis
Eye- Late RT Morbidity Scoring	No change from baseline	Asymptomatic cataract; minor corneal ulceration or keratitis	Symptomatic cataract; moderate corneal ulceration; minor retinopathy or glaucoma	Severe keratitis; severe retinopathy or detachment; severe glaucoma	Panophthal-mitis; blindness
Radiation- Other (Specify, _____)	None	Mild	Moderate	Severe	Life-threatening or disabling

Neurotoxicity Assessment Tool

NEUROTOXICITY ASSESSMENT TOOL

Patient Name _____ Visit Date _____

Instructions for Patients[1,2]

By circling one (1) number per line, please indicate how true each statement has been for you **during the past 7 days.**

	Not at all	A little bit	Somewhat	Quite a bit	Very much
I have numbness or tingling in my hands	0	1	2	3	4
I have numbness or tingling in my feet	0	1	2	3	4
I feel discomfort in my hands	0	1	2	3	4
I feel discomfort in my feet	0	1	2	3	4
I have joint pain or muscle cramps	0	1	2	3	4
I feel weak all over	0	1	2	3	4
I have trouble hearing	0	1	2	3	4
I get a ringing or buzzing in my ears	0	1	2	3	4
I have trouble buttoning buttons	0	1	2	3	4
I have trouble feeling the shape of small objects when they are in my hand	0	1	2	3	4
I have trouble walking	0	1	2	3	4

Instructions for Health Care Professionals

This assessment tool is provided to help you evaluate peripheral neuropathy in patients receiving chemotherapy. Health care professionals may find discussion of patient responses helpful in determining the grade of neuropathy as defined by the NCI Common Toxicity Criteria listed below; there is no direct correlation between assessment scores and toxicity grades.

NCI Common Toxicity Criteria for Peripheral Neuropathy and Neuropathic Pain[3]

Peripheral Sensory Neuropathy (NCI CTC Grade)

1 Normal
2 Loss of deep tendon reflexes or paresthesia but not interfering with function
3 Objective sensory loss or paresthesia, interfering with function, but not with ADLs (Activities of Daily Living)
4 Sensory loss or paresthesia interfering with ADLs
5 Permanent sensory loss that interferes with function

Neuropathic Pain (NCI CTC Grade)

0 None
1 Mild pain not interfering with function
2 Moderate pain: pain or analgesics interfering with function, but not ADLs
3 Severe pain: pain or analgesics severely interfering with ADLs
4 Disabling

References: 1. Cella DF, Tulsky DS, Gray G, Sarafian B, Lloyd S, Linn E, et al. The functional assessment of cancer therapy (FACT) scale: development and validation of the general measure. *J Clin Oncol* 1993;11(3):570-79. **2.** Calhoun EA, Fishman A, Roland PY, Lurain JR, Change C-H, Cella D. Validity and selective sensitivity of the FACT/GOG-Ntx. Abstract 1751. 36th Annual Meeting of the American Society of Clinical Oncology, May 2000, New Orleans, LA. **3.** National Cancer institute Cancer Therapy Evaluation Program Common Toxicity Criteria, Version 2.0, June 1999.

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8.7 Package Insert for Doxil

http://www.doxil.com/assets/DOXIL_PI_Booklet.pdf

8.8 Package Insert for LipoDox

http://www.caraco.com/Lipodox/Lipodox-50%20injection-outsert.pdf

8.9 Package Insert for Decitabine

http://otsuka-us.com/products/Documents/DACOGEN.PI.pdf

8.11 Data Submission Schedule

Electronic versions of the eligibility checklist and case report forms will be sent to participating sites upon request.

All data will be collected using UC Davis data collection forms. Copies of the completed forms will be submitted to UC Davis data coordinating center for data entry and storage in a secure location. The original data collection forms will reside at the originating institution in secure location.

- SUBMIT WITHIN 24 HOURS OF REGISTRATION:
  Patient Registration Form

- SUBMIT WITHIN 14 DAYS OF REGISTRATION:
  In-House Pre-Study Evaluation Form (IH-102)

- SUBMIT WITHIN 7 DAYS OF SCREENING FAILURE:
  Patient Screen Failure Form (IH-103)

- SUBMIT WITH 14 DAYS OF CYCLE COMPLETION:
  In-House Adverse Event/Drug Relationship Form

- SUBMIT WITHIN 14 DAYS OF END OF EACH TREATMENT CYCLE:
  In-House Treatment Cycle Form (IH-201)

- SUBMIT WITHIN 14 DAYS OF EACH RESPONSE ASSESSMENT:
  Tumor Measurement Log

- SUBMIT WITHIN 14 DAYS OF OFF TREATMENT:
  End of Treatment/Expiration Form (IH-301)

- SUBMIT WITHIN 14 DAYS OF KNOWLEDGE OF DEATH IF PATIENT IS STILL ON STUDY OR 30–DAYS IF OFF STUDY:
  End of Treatment/Expiration Form (IH-301)

- SUBMIT WITHIN 2 DAYS OF KNOWLEDGE OF PROTOCOL DEVIATION:
  Clinical Trials Support Unit: Notice of Protocol Deviation

- SUBMIT WITHIN 14 DAYS OF EACH REQUIRED FOLLOW-UP ENCOUNTER:
  Follow-Up Form (IH-302)

- ALL SERIOUS ADVERSE EVENTS MUST BE REPORTED AS OUTLINED IN THE PROTOCOL

8.12 Pregnancy Form

MILLENNIUM
THE TAKEDA ONCOLOGY COMPANY

Pregnancy Form v03Nov2008 (IIS)

Report Type: ❒ Initial ❒ Follow-up | Date of Report: ___/___/_____ (DD MM Yr)

REPORTER INFORMATION: (Please forward if an alternative physician is more appropriate)

Reporter name: _____ Title: _____

Address: _____ Telephone No.: _____ Fax No. _____

City, State/Province: _____ Postal Code: _____ Country: _____

FATHER'S INFORMATION ❒ Father Unknown

Initials: _____ Date of Birth: ___/___/_____ (DD MM Yr) or Age: _____years

Participating in an MPI clinical study? ❒ No ❒ Yes
If no, what company product was taken: _____
If yes, please provide: Study drug: _____ Protocol No: _____
Center No: _____ Patient No: _____

Medical / Familial / Social History
(i.e. Include chronic illnesses: specify, familial birth defects/genetic/chromosomal disorders; habitual exposure: specify, alcohol/tobacco; drug exposure: specify, substance abuse and medication use. Please include drug treatment prior to or around the time of conception and/or during pregnancy)

_____
_____

Race: _____
Occupation: _____
Number of children: _____

MOTHER'S INFORMATION:

Initials: _____ Date of Birth: ___/___/_____ or Age: _____years
DD MM Yr

Participating in an MPI clinical study? ❒ No ❒ Yes
If no, what company product was taken: _____
If yes, please provide: Study drug: _____ Protocol No: _____
Center No: _____ Patient No: _____

Race: _____
Occupation: _____

Medical / Familial / Social History
(i.e. Include alcohol/tobacco and substance abuse; complications of past pregnancy, labor/delivery, fetus/baby; illnesses during this pregnancy; assisted conception: specify; other disorders including familial birth defects/genetic/chromosomal disorders; method of diagnosis consanguinity, etc.)

_____
_____
_____

Number of previous pregnancies: Full term ____ Pre-term _____

Outcomes of previous pregnancies:
(Please indicate number of occurrences)

- Spontaneous abortion: _____
- Therapeutic abortion: _____
- Elective abortion: _____
- Other: _____
- Normal live birth: _____
- Children born with defects: _____
- Stillbirth: _____
- Outcome unknown: _____

MOTHER'S DRUG EXPOSURE INFORMATION

Please include medical prescriptions, vaccinations, medical devices, OTC products, pregnancy supplements (such as folic acid, multivitamins)

Product Name	Dosage	Route administered to patient	Date of first use (DD/MM/Yr)	Date of end treatment (DD/MM/Yr)	Indication	Contraindicated to pregnancy
			(__/__/____)	(__/__/____)		❒Yes ❒No ❒Unk
			(__/__/____)	(__/__/____)		❒Yes ❒No ❒Unk
			(__/__/____)	(__/__/____)		❒Yes ❒No ❒Unk
			(__/__/____)	(__/__/____)		❒Yes ❒No ❒Unk

CURRENT PREGNANCY INFORMATION

Period at exposure: _____ weeks Trimester (1) (2) (3)
Date of last menstrual period: ____/____/_____ ❒ Unknown
DD MM Yr

Pregnancy Status

❒ Pregnancy Ongoing
Estimated date of delivery: ___/___/_____
DD MM Yr
❒ Live Birth
❒ Stillbirth
❒ Early Termination
- ❒ Spontaneous abortion*
- ❒ Therapeutic abortion*
- ❒ Elective abortion*
- ❒ Other*:_____

If box is checked, please note reason in "Additional Details" section below

Fetal/Neonatal Status

❒ Normal
❒ Birth defect (structural/chromosomal disorder)*
❒ Other (non-structural, premature birth, intrauterine death/stillbirth)*

If box is checked, please note details in "Additional details" section below

Additional Details:

Is there evidence of a defect from a prenatal test? ❒Yes ❒No

If yes, indicate which test(s) showed evidence of birth defect:

❒Ultrasound ❒Amniocentesis ❒Maternal Serum-Alpha-Fetoprotein

❒Chorionic Villi Sampling ❒Human Chorionic Gonadotropin ❒Other:_____

Please specify details of defect(s), disorder(s), and/or other anomaly(ies): _____

_____

What are the defect(s) attributed to:_____

Infant Information:

Gestational weeks at birth or at termination: _____weeks

Date of birth or termination: ___/___/_____
DD MM Yr

If multiple births (e.g. twins), indicate number: _____
(Please complete separate form for each child)

Birth Order (1, 2, 3, etc.) _____

Breast-fed: ❒Yes ❒ No ❒ Unk

Method of delivery: ❒ Normal vaginal ❒ Caesarean section
❒ Other: _____

Sex: ❒ Male ❒ Female ❒ Unk

Length: _____ ❒ cm ❒ in

Weight: _____ ❒ g ❒ lbs

Head circumference: _____ ❒ cm ❒ in

Apgar score (0-10) at 1 minute: ____ ❒ Unk

Apgar score (0-10) at 5 minute: ____ ❒ Unk

Resuscitation required: ❒ Yes ❒ No ❒ Unk

Admission to intensive care required:
❒ Yes ❒ No ❒ Unk

Additional Notes:

_____

_____

_____

Please attach RELEVANT LABORATORY TESTS AND PROCEDURES (e.g. results of ultrasounds, amniocentesis, chorionic villi sampling, or miscellaneous testing as applicable). In the case of an abnormal evolution or outcome, please send copies of results of all relevant laboratory testing and procedures, including pathology results of products of conception and or autopsy reports if applicable. Please submit any additional relevant information on a separate sheet.

Investigator signature: _____ Date: ___/___/_____
DD MM Yr

Investigator Name: _____