Panobinostat Combined with High-Dose Gemcitabine/Busulfan/Melphalan with Autologous Stem Cell Transplant for Patients with Refractory/Relapsed Myeloma

Institution Study Number: **2014-0516**

Financial Support: Secura Bio, Inc.

Principal Investigator: Yago Nieto, MD, PhD
The University of Texas MD Anderson Cancer Center
Stem Cell Transplantation and Cellular Therapy Department
1515 Holcombe Blvd, Unit 0432
Houston, TX 77030
Telephone: 713.794.1752
Fax: 713.794.4902
ynieto@mdanderson.org

Collaborators: Borje Andersson, MD, PhD[1]
Qaiser Bashir, MD[1]
Roland L. Bassett, Jr., MS[2]
Richard E. Champlin, MD, PhD[1]
Robert Orlowski, MD, PhD[3]
Uday Popat, MD[1]
Muzaffar H. Qazilbash, MD[1]
Ben Valdez, PhD[1]

[1] The University of Texas MD Anderson Cancer Center, Stem Cell Transplantation and Cellular Therapy Department
[2] The University of Texas MD Anderson Cancer Center, Biostatistics Department
[3] The University of Texas MD Anderson Cancer Center, Lymphoma-Myeloma Department

Table of Contents

Protocol Body

1.0 Objectives

Primary endpoint:

1. To determine the progression-free survival (PFS) in patients with refractory or relapsed myeloma receiving panobinostat/gemcitabine/busulfan/melphalan (panobinostat/Gem/Bu/Mel) with autologous stem-cell transplant, either as a first or a salvage stem-cell transplant.

Secondary endpoints:

1. To evaluate the complete response (CR) rate.
2. To determine the overall survival (OS).
3. To determine the CR + very good partial remission (VGPR) rate.
4. To determine the overall response rate (ORR).
5. To determine minimal residual disease posttransplant, measured by multiparametric flow cytometry (MFC).
6. To describe the toxicity profile of panobinostat/Gem/Bu/Mel.
7. To analyze the predictive value of pretransplant levels in myeloma cells of XBP1, IRE1, XBP1u, XPB1s, XBP1u/XPBs ratio and Myc, by analyzing their correlation with CR, VGPR+CR and RR.
8. To study the prognostic effect of pretransplant levels in myeloma cells of XBP1, IRE1, XBP1u, XPB1s, XBP1u/XPBs ratio and Myc, by analyzing their correlation with PFS and OS.

2.0 Background

2.1. Current Status and Shortcomings of High-Dose Chemotherapy for Myeloma

High-dose chemotherapy (HDC) with autologous stem-cell transplant (ASCT) support results in significant benefit as part of first-line treatment of myeloma.[1, 2] However, most patients eventually experience tumor relapse after HDC. In addition, high-dose melphalan induces only 5-10% of CR with a median PFS of around 12 months in patients with primary refractory disease or in refractory relapse.[3-5] These data underscore the need to develop more active HDC regimens. While maintenance post-transplant treatment with lenalidomide or bortezomib improves PFS,[7-9] it is likely that ultimate success of maintenance strategies, i.e., long-term OS benefit, will still largely depend on the depth of response previously achieved by HDC. Thus, further exploration of novel preparative regimens for single transplantations is necessary with the short-term goal of improving CR rate.

Complete response is a major surrogate for long-term OS in myeloma. Achievement of a CR with HDC is a crucial step for long-lasting PFS and OS.[10, 11] This seems particularly critical in refractory or high-risk disease, whereas it may be less important in more smoldering tumors, who can still enjoy prolonged outcomes despite never achieving a CR.[12]

Multiparametric flow cytometry (MFC) of bone marrow exam to define immunophenotypic CR has gained acceptance in myeloma. This technique presents a sensitivity of 10^{-4} to 10^{-5}, superior to that of immunofluorescence or immunohistochemistry, and broader applicability than PCR.[13] Minimal residual disease (MRD) status by MFC at day 100 post-transplant has been shown to be a major prognostic factor after front-line HDC.[14]

2.2. Gemcitabine/Busulfan/Melphalan

As with most other tumors in which HDC plays a role, it is conceivable that an active drug combination will prove to be more effective than the current standard of single-agent melphalan. We have developed a combination of infusional gemcitabine, busulfan and melphalan (Gem/Bu/Mel), following these principles:

1. Synergy between gemcitabine and alkylators, based on inhibition of DNA damage repair.[15]
2. Gemcitabine infusions at FDR of 10 mg/m2/min avoid saturation of its intracellular metabolic activation, which results in improved antitumor activity and increased myelotoxicity compared to shorter infusions.[16] The increased myelotoxicity of FDR infusions is overcome by stem-cell support.
3. Minimal overlapping dose-limiting toxicity of the three agents at high doses.
4. Optimization of intravenous busulfan therapy by therapeutic drug monitoring.[17]

In our phase 1 trial of this combination (MDA 2006-0803) we saw early signals of high activity in 7 patients with refractory myeloma enrolled in the trial.[18] Five of them had primary refractory disease and 2 had refractory relapse, all pretreated with a median 4 prior regimens. Their disease status at transplant was progressive disease in 5 patients and stable disease or partial response in the remaining 2 patients. In this very poor prognosis small subgroup, 6 patients achieved a response, which met criteria for stringent CR in 3 of them. Three of these patients remain free of progression at more than 5 years.

These observations led us to test Gem/Bu/Mel in a phase 2 trial in refractory/relapsed myeloma (MDA 2010-0506).[19] The primary endpoint was the CR rate, targeting a 20% CR rate, which was deemed to be clinically relevant in this population where single agent high-dose melphalan is expected to induce 10% or less CRs. We enrolled 74 patients, median age 45 (22-68), who had received a median prior 4 lines of therapy (range, 2-13). Sixteen patients had myeloma unresponsive to all prior treatments; 32 patients had failed prior HDC; 27 patients had high-risk cytogenetics. Disease status at HDC was CR (N=9), PR (N=38) and no response (N=27, including tumor progression in 20). The CR rate was 24.6%, with 77.5% response rate. At median follow-up of 22 months (6-46), the PFS and OS rates are 45% and 69%, respectively. Among the 32 patients receiving Gem/Bu/Mel as a second salvage transplant, the median PFS was 21 months with 1-year PFS rate of 59%, seemingly superior to our previously published experience with salvage transplants.[17] There were 3 treatment-related deaths (1 pneumonia, 1 sudden cardiac arrest of undetermined etiology with normal postmortem exam findings, and 1 E coli neutropenic sepsis). The toxicity profile included mucositis (49% grade 2, 20% grade 3), dermatitis (20% grade 2, 7% grade 3), asymptomatic transaminase elevations (17% grade 2, 7% grade 3) and asymptomatic bilirubin elevations (3% grade2, 10% grade 3), with no cases of venoocclusive disease. There were no renal, cardiac, neurological or pulmonary toxicities.

2.3. Potentiation of Gem/Bu/Mel through Histone Deacetylase Inhibition

A major factor affecting the activity of alkylating agents is their access to DNA, which largely depends on the configuration of chromatin. Acetylation of lysine residues in the histones leads to charge neutralization, decreased binding to the DNA backbone, changes in the conformation of DNA and gene expression, and relaxation of chromatin. Histone acetyltransferases (HAT) and histone deacetylases (HDACs) add and remove acetyl groups, respectively. Addition of

acetyl groups by HATs or inhibition of HDACs results in the weakening of the bond between histones and DNA, increasing gene transcription and decondensing chromatin.

Histone deacetylase inhibitors (HDACi) induce relaxation of the chromatin, rendering the DNA more accessible to DNA-targeting agents such as alkylators and nucleoside analogues. To this end we combined the first-generation HDACi vorinostat with Gem/Bu/Mel. Our preclinical experiments showed marked synergy when vorinostat was added to GemBuMel, as determined by apoptosis or survival readouts in lymphoma B-cell and T-cell (J45) lines, which were resistant to those agents when exposed to them separately.[18]

Fig.1. Antitumor activity of vorinostat (SAHA) in concurrent exposure with gemcitabine/busulfan/melphalan in a chemotherapy-resistant T-cell line (J45).
Fig. 1-A: Apoptosis (% cells in subG1) assay. Fig. 1-B: Cell survival assay.

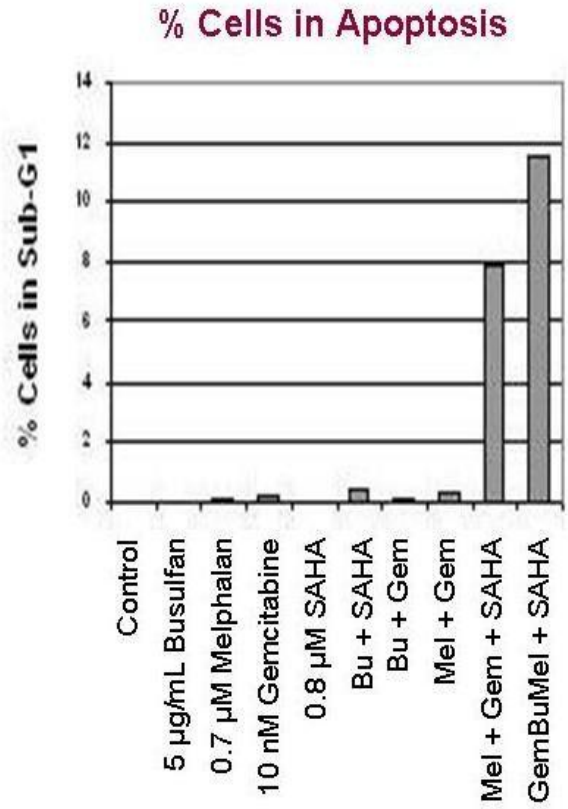


Fig. 1-A

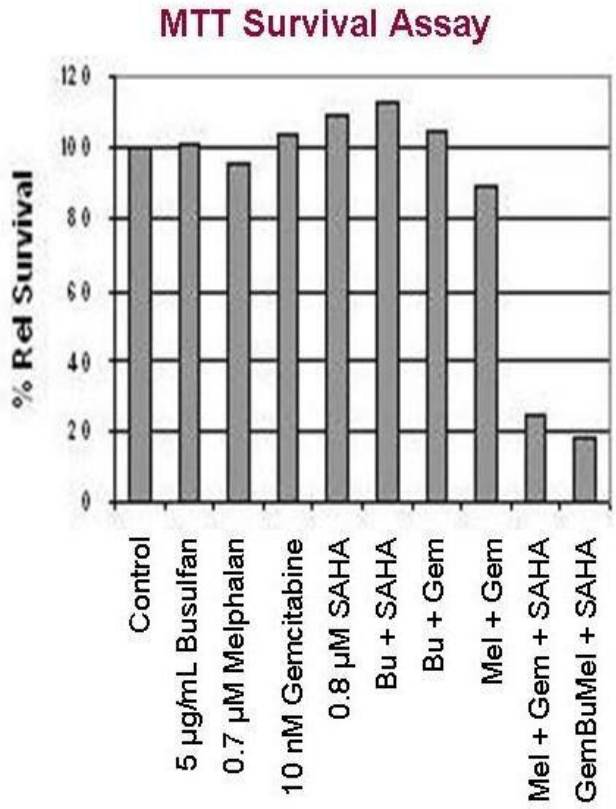
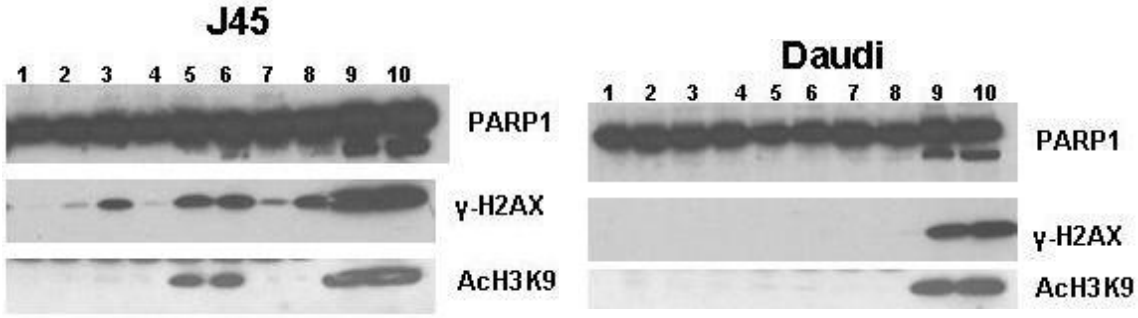


Fig. 3-B

In these experiments lymphoma cells exposed to vorinostat/gemcitabine/busulfan/melphalan experienced increased cleavage of PARP1 and increase in gamma-H2AX, reflecting increased DNA damage (Fig. 2)

Fig. 2. Western blots showing cleavage of PARP1, increase of gamma-H2AX and acetylated Histone 3. Lane1: control cells. Lanes 2-8: cells treated with SAHA or chemotherapy. Lane 9: SAHA + gemcitabine/melphalan. Lane 10: SAHA + gemcitabine/busulfan/melphalan.



These observations led to our clinical trial 2011-0407, evaluating a short schedule of vorinostat concurrent with GemBuMel with autologous stem cell support.[19] We combined GemBuMel at full doses with escalated doses of vorinostat from 200 mg daily to the maximally planned dose of 1,000 mg daily with good tolerance and no dose-limiting toxicities. There was no QT prolongation after treatment. The toxicity profile of vorinostat/Gem/Bu/Mel was comparable to that of Gem/Bu/Mel alone. The regimen was highly active across all lymphoma histologies.

2.4. Use of HDACi in Myeloma.

Clinical trials have shown the safety and increased activity of combinations of HDACi with other agents.[20-22] Bortezomib/vorinostat resulted in a small prolongation of PFS compared to bortezomib alone (7.6 vs. 6.8 months, P=0.01) in patients with relapsed/refractory myeloma.[23] A larger benefit was observed with the use of panobinostat, which is substantially more potent than vorinostat. In a phase 2 trial in patients with relapsed and bortezomib-refractory MM, the combination of panobinostat with bortezomib and dexamethasone was able to recapture responses in 35% of patients.[24]. In a subsequent phase III randomized trial the combination of panobinostat/bortezomib/dexamethasone was compared to bortezomib/dexamethasone in relapsed/refractory disease.[25] The addition of panobinostat resulted in a significant improvement in median PFS of 12.0 months vs. 8.1 months (hazard ratio 0.63, P< 0.0001), CR/near CR rate (27.6% vs. 15.7%, respectively; p = 0.00006), duration of response, time to response and median time to progression (12.7 vs. 8.5 months). The addition of panobinostat was associated with an increased frequency of thrombocytopenia (grade 3/4 in 67% vs. 31% of patients). Other grade 3/4 adverse events occurring more frequently in the panobinostat arm included lymphopenia (53% vs. 40%), neutropenia (34% vs. 11%), diarrhea (25% vs. 8%), and asthenia/fatigue (24% vs. 12%). However, these adverse events led to discontinuation in fewer than 5% of patients in the panobinostat arm.

On 02/23/2015 the FDA granted approval for panobinostat for patients with relapsed or refractor myeloma treated with at least two prior standard therapies, including bortezomib and an immunomodulatory agent. This is precisely the target population of this transplant study.

2.5. STUDY RATIONALE/PURPOSE

We wish to develop an effective high-dose regimen for refractory myeloma, building on our prior experience with SAHA/Gem/Bu/Mel, substituting panobinostat for SAHA. Panobinostat is a more effective drug for myeloma than vorinostat. Its toxicity profile suggests, as with vorinostat, the feasibility of its combination with Gem/Bu/Mel.

We hypothesize that epigenetic modulation of Gem/Bu/Mel with panobinostat is feasible and will increase the activity of the regimen. To facilitate the addition of panobinostat we will decrease the dose of gemcitabine in Gem/Bu/Mel compared to the regimen we tested in the phase 2 trial.

We will study the prognostic and predictive effect of study markers of unfolded protein response (UPR) in patients enrolled in this trial. As highly secretory immunoglobulin-producing cells, myeloma cells require an increased capacity to handle unfolded proteins within the endoplasmic reticulum (ER) under conditions of stress. The UPR includes transmembrane ER proteins, such as IRE1, which has RNase activity and removes an intron from the XBP1 mRNA. The spliced XBP1 protein (XPB1s) is a potent transcription factor that controls genes involved in ER membrane biosynthesis, protein import, chaperoning and ER-associated degradation of unfolded proteins. Myeloma cells are prone to ER stress and have a highly active UPR.

We will study panobinostat/GemBuMel in two separate cohorts of patients receiving a first or a salvage stem-cell transplant.

3.0 Patient Eligibility

3.1 Inclusion:

1. Age 18 to 65 years.
2. Refractory or relapsed myeloma, defined as one or more of the following:
    - 2.1. Treated with first-line therapy including at least 2 cycles of lenalidomide, bortezomib or thalidomide, and one or more of the following:
        - 2.1.1. Less than PR to first-line therapy.
        - 2.1.2. Relapse after 1st line therapy.
    - 2.2. High-risk cytogenetics, defined by del(13q) by conventional cytogenetics, or by del(17p), t(4;14), t(14;16), t(14;20) or 1q+ by FISH.
    - 2.3. Relapse after a prior ASCT.
    - 2.4. Plasma cell leukemia.
    - 2.5. Soft tissue plasmacytoma.
3. Adequate renal function, as defined by serum creatinine </=1.8 mg/dL and/or estimated serum creatinine clearance >/=50 ml/min.
4. Adequate hepatic function, as defined by SGOT and/or SGPT </=3 x upper limit of normal; serum bilirubin and alkaline phosphatase </=2 x upper limit of normal, unless proven to be due to disease involvement.

5. Adequate pulmonary function with FEV1, FVC and DLCO >/=50% of expected corrected for hemoglobin and/or volume.
6. Adequate cardiac function with left ventricular ejection fraction >/=40%. No uncontrolled arrhythmias or symptomatic cardiac disease.
7. Clinically euthyroid. Note: Patients are permitted to receive thyroid hormone supplements to treat underlying hypothyroidism.
8. Zubrod performance status < 2.
9. Negative Beta-HCG test in a woman of child-bearing potential, defined as not post-menopausal for 12 months or no previous surgical sterilization.
10. Availability of >/= 2.5 million CD34+ cells/kg previously apheresed.
11. Ability to provide written informed consent.

3.2. Exclusion criteria:

1. Prior whole brain irradiation.
2. Having received radiation therapy to head and neck (excluding eyes), and internal organs of chest, abdomen or pelvis in the month prior to enrollment.
3. Active hepatitis B, either active carrier (HBsAg +) or viremic (HBV DNA >/=10,000 copies/mL, or >/= 2,000 IU/mL).
4. Evidence of either cirrhosis or stage 3-4 liver fibrosis in patients with chronic hepatitis C or positive hepatitis C serology.
5. Active infection requiring parenteral antibiotics.
6. Known positivity for human immunodeficiency virus (HIV).
7. Autologous stem-cell transplant in the previous six months.
8. Needing valproic acid for any medical condition during the study or within 5 days prior to first panobinostat treatment.
9. Impairment of GI function or GI disease that may significantly alter the absorption of panobinostat.
10. Other concurrent severe and/or uncontrolled medical conditions (e.g., uncontrolled diabetes or active or uncontrolled infection) including abnormal laboratory values, that could cause unacceptable safety risks or compromise compliance with the protocol.
11. Impaired cardiac function or clinically significant cardiac diseases, including any one of the following:
    - 11.1. History or presence of sustained ventricular tachyarrhythmia. (Patients with a history of atrial arrhythmia are eligible but should be discussed with Secura Bio, Inc. (Secura Bio) prior to enrollment).
    - 11.2 Any history of ventricular fibrillation or torsade de pointes.
    - 11.3. Bradycardia defined as HR< 50 bpm. Patients with pacemakers are eligible if HR >/= 50 bpm.
    - 11.4. Screening ECG with a QTc > 470 msec.
    - 11.5. Right bundle branch block + left anterior hemiblock (bifascicular block).
    - 11.6. Myocardial infarction or unstable angina </= 12 months prior to starting study drug.
    - 11.7. Other clinically significant heart disease (e.g., CHF NY Heart Association class III or IV , uncontrolled hypertension, history of labile hypertension, or history of poor compliance with an antihypertensive regimen).
12. Have undergone major surgery </= 4 weeks prior to starting study drug or who have not recovered from side effects of such therapy.
13. Prior malignancy with in the last 5 years (except for basal or squamous cell carcinoma, or *in situ* cancer of the cervix).

14. Any significant history of non-compliance to medical regimens or unwilling or unable to comply with the instructions given to him/her by the study staff.
15. Received targeted agents within 2 weeks or within 5 half-lives of the agent and active metabolites (whichever is longer) and who have not recovered from side effects of those therapies.
16. Having received immunotherapy or chemotherapy within 2 weeks; or radiation therapy to > 30% of marrow-bearing bone within ≤ 2 weeks prior to starting study treatment; or who have not yet recovered from side effects of such therapies.
17. Grade >/= 3 nonhematological toxicity from prior therapy that has not resolved to </= grade 1.

4.0 Pretreatment evaluation

4.1. Within 30 days of study enrollment: Complete history and physical examination Assessment of performance status
Bone survey (within 6 months of study entry unless clinically indicated)
SPEP, UPEP, serum and urine immunofixation, serum free kappa and lambda light chain assay Beta-2 microglobulin
Chest X-ray
Echocardiogram or MUGA scan EKG
Pulmonary function tests TSH and free T4

4.2. Within 14 days of study enrollment:
CBC with differential, electrolytes, BUN, creatinine, glucose, total protein, albumin, calcium, phosphorus, uric acid, total bilirubin, alkaline phosphatase, LDH, AST, ALT, magnesium, and serum HCG in all female patients of childbearing potential.

4.3 Once enrolled, if not obtained within 30 days of study enrollment date:
Bone marrow aspirate and biopsies for morphology, multiparametric flow cytometry, (CD19, CD20, CD28, CD38, CD56, CD117, CD138, cyKappa, cyLambda), cytogenetic and FISH studies.

5.0 Study Registration

Each patient will be evaluated and approved for enrollment by the primary attending physician and the Study Chairman (or his designee). The study research coordinator will register each patient on protocol in the institutional CORe system.

6.0 Treatment Plan

Treatment will not commence until resolution of prior toxicities to grade 1 or less. Acetaminophen (Tylenol) shall not be administered for 72 hr before and on the day of administration of Busulfan or Melphalan. Voriconazole, posaconazole, fluconazole, itraconazole and metronidazole will be avoided from 7 days before start of chemotherapy to day -1.

6.1. Outpatient Busulfan Test

Dose: Day

	Treatment
……	Outpatient Busulfan 32 mg/m2 IV Test Dose (PK Sampling)
-12	Palifermin 60 microgram/kg IV (outpatient), not starting on Mon/Tues/Wed
-11	Palifermin 60 microgram/kg IV (outpatient)
-10	Palifermin 60 microgram/kg IV (outpatient)
-9	Admit / Panobinostat 20 mg PO
-8	Panobinostat 20 mg PO / Gemcitabine 1,875 mg/m2 IV / Busulfan AUC 4,000 IV
-7	Panobinostat 20 mg PO / Busulfan AUC 4,000 IV
-6	Panobinostat 20 mg PO / Busulfan AUC 4,000 IV
-5	Panobinostat 20 mg PO / Busulfan AUC 4,000 IV
-4	Panobinostat 20 mg PO
-3	Panobinostat 20 mg PO / Gemcitabine 1875 mg/m2 IV / Melphalan 60 mg/m2 IV
-2	Panobinostat 20 mg PO / Melphalan 60 mg/m2 IV
-1	Rest
0	Stem Cell Transplant / Palifermin 60 microgram/kg IV
+1	Palifermin 60 microgram/kg IV
+2	Palifermin 60 microgram/kg IV

Table 1. Treatment plan with outpatient busulfan test dose.

Day	**-9**	**-8**	**-7**	**-6**	**-5**	**-4**	**-3**	**-2**	**-1**	**0**
Admission	X									
Panobinostat	X	X	X	X	X	X	X	X		
Gemcitabine		X					X			
Busulfan		X	X	X	X					
Melphalan							X	X		
Peripheral Blood Progenitor Cell										X

6.2. Inpatient Busulfan Test Dose:

Day	**Treatment**
-14	Palifermin 60 microgram/kg IV (outpatient). Do not start on Monday/Tuesday
-13	Palifermin 60 microgram/kg IV (outpatient)
-12	Palifermin 60 microgram/kg IV (outpatient)
-11	Admit
-10	Inpatient Busulfan 32 mg/m2 IV Test Dose (PK Sampling)
-9	Panobinostat 20 mg PO
-8	Panobinostat 20 mg PO / Gemcitabine 1875 mg/m2 IV / Busulfan AUC 4,000 IV PK Sampling)
-7	Panobinostat 20 mg PO / Busulfan AUC 4,000 IV
-6	Panobinostat 20 mg PO / Busulfan AUC 4,000 IV
-5	Panobinostat 20 mg PO / Busulfan AUC 4,000 IV
-4	Panobinostat 20 mg PO
-3	Panobinostat 20 mg PO / Gemcitabine 1875 mg/m2 IV / Melphalan 60 mg/m2 IV
-2	Panobinostat 20 mg PO / Melphalan 60 mg/m2 IV

-1 Rest
0 Stem Cell Transplant / Palifermin 60 microgram/kg IV
+1 Palifermin 60 microgram/kg IV
+2 Palifermin 60 microgram/kg IV

Table 2. Treatment plan with inpatient busulfan test dose.

Day	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0
Admission	X											
Panobinostat			X	X	X	X	X	X	X	X		
Gemcitabine				X					X			
Busulfan		Test dose		X	X	X	X					
Melphalan									X	X		
Peripheral Blood Progenitor Cell												X

Oral panobinostat will be supplied as 20-mg capsules. During the study, panobinostat will be administered orally as once daily dose of 20 mg. Each dose of panobinostat should be taken with an 8 oz. / 240 ml glass of water. Patients should be instructed to swallow the capsules whole and not chew them. Patients must avoid grapefruit or grapefruit juice and seville (sour) oranges during the entire study.

On days when panobinostat is to be administered with other drugs it will be administered within 1 hour before the next drug. Repeat a full dose if emesis occurs within 30 minutes and tablets/tablet fragments are found in the vomit. The time of administration will be in the early morning, and the patient may need to be woken up by the nurse. The nurse must stay and witness the patient taking the drug.

Gemcitabine will be administered as a loading dose of 75 mg/m2 followed by continuous infusion of the remaining dose at 10mg/m2/minute. It will be followed immediately by busulfan on Day -8 and melphalan on Day -3.

Busulfan test dose will be administered as an outpatient any day within 1 week of Day -12. If given as an inpatient, the test dose will be administered on Day -10. The busulfan test dose of 32 mg/m2 will be based on actual body weight to be administered over 60 minutes. Busulfan pharmacokinetics will be done with the test dose and repeated with the first therapeutic dose on day-8. The doses of days -6 and -5 will be subsequently adjusted to target an AUC of 4,000
microMol.min . In the event that PK adjusting was not possible a dose of busulfan of 100 mg/m2 will be administered on days -6 and -5.

Melphalan will be administered at 60 mg/m2 on Days -3 and -2.

6.3 Supportive Treatment

Patients will receive standard supportive treatment as outlined below.

1. Dexamethasone 8 mg IV BID from day -9 PM to day -2 PM. Omit any other dexamethasone for chemotherapy premedication.
2. Mucositis supportive care:

2.1. Patients will receive a total of 6 doses of palifermin 60 mcg/kg IV daily. Three doses administrated prior to start chemo (a minimum of 24 hours must elapse between the last dose and first therapeutic dose of chemo) and three doses after the last chemo starting on day 0. Doses can be capped to vial size.
2.2. Caphosol oral rinses 30 mL four times a day will be used from day -9 until discharge.
2.3. Oral glutamine, 15 g four times a day, swished, gargled and spit will be started on day -9 until discharge.
2.4 Pyridoxine 100 mg IV/PO TID from Day -1.

G-CSF, antiemetics, infection prophylaxis, and other supportive care as per departmental standards.

6.4 Post-Transplant Therapies

Post-transplant therapies will be left at the discretion of the primary physician.

7.0 Post-Treatment Evaluation

7.1. Toxicity Monitoring:

During the treatment administration and until day +100 all patients will be monitored for toxicity, specifically for grade 3 or greater side effects, according to CTCAE v4.0. While admitted in hospital, patients will be monitored on a regular basis. Once discharged patient will return to clinic once a week or as determined by the primary physician until day +30.

7.2. Disease restaging:

7.2.1 Around 1 month post-transplant, day 100 (+/- 15 days), 6 months (+/- 30 days), 1 year (+/- 30 days) and about every 3-6 months thereafter for at least 2 years:
Complete history and physical examination.
SPEP, UPEP, serum and urine immunofixation, serum free kappa and lambda light chain assay.
Serum albumin, LDH, and beta-2 microglobulin.

7.2.2 On day +100 (+/- 15 days) post-transplant:
Bone marrow aspirate and biopsies for morphology, multiparametric flow cytometry, (CD19, CD20, CD28, CD38, CD56, CD117, CD138, cyKappa, cyLambda), cytogenetic and FISH studies. Afterwards, once a year or earlier if clinically indicated.

7.2.3 Bone survey: Only once per year

8.0 Criteria for Response

We will use the International Myeloma Working Group (IMWG) uniform response criteria.[26] All response categories require no known evidence of progressive or new bone lesions.

Complete response (CR): All of the following:
1. Negative immunofixation in serum and urine.
2. </= 5% plasma cells in the bone marrow.
3. Disappearance of any soft tissue plasmacytomas.

Note: While healing of preexisting bone lesions is not required, no new lytic lesions should appear. Further compression fracture of previously known spine lesion will not be considered as progressive disease.

Stringent complete response (sCR): All of the following:
1. CR as defined above.
2. Normal free light chain ratio
3. Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence (defined by absence of abnormal ê/ë ratio of >4:1 or <1:2)

Very good partial response (VGPR): One or more of the following:
1. Serum and urine M protein detectable by immunofixation but not by electrophoresis
2. 90% or greater reduction in serum M protein plus urine M protein level <100 mg per 24 hours.

Partial response (PR): All of the following:
1. Reduction by > 50% in serum monoclonal protein.
2. Reduction of urinary monoclonal protein to < 200 mg/24 or >90%.

Progressive disease (PD): Any one or more of the following:
1. Increase of >/= 25% from baseline in:
    1.1. Serum M protein (absolute increase must be >= 0.5 g/dL).
    1.2. Urine M component (absolute increase must be >= 200 mg/24h).
    1.3. (Only in patients without measurable serum and urine M protein levels) Difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL).
    1.4. Bone marrow plasma percentage (absolute % must be >=10%).
2. Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
3. Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.65 mmol/L) that can be solely attributed to the myeloma.

Stable disease: Not meeting criteria for CR, VGPR, PR or PD.

Clinical relapse: One or more of the following direct indicators of increasing disease and/or end-organ dysfunction:
1. Development of new soft tissue plasmacytomas or bone lesions on skeletal survey, MRI or other imaging.
2. Increase in the size of existing plasmacytomas or bone lesions: 50% (and at least 1

cm) increase as measured by the sum of the products of the cross-diameters of the measurable lesion.
3. Hypercalcemia (> 11.5 mg/dL).
4. Decrease in hemoglobin of > 2 g/dL) or to < 10 g/dL.
5 Rise in serum creatinine by >/=2 mg/dL.
6. Hyperviscosity.
7. Bone pain without imaging confirmation is not adequate to meet these criteria in trials.

Biochemical relapse (in patients who do not have clinical relapse):
1. Doubling of the M-component in 2 consecutive measurements separated by </=2 months.
2. Incr in the absolute levels of serum M protein by >/= 1 g/dL.
3. Increase of urine M protein by >/= 500 mg/24 hours.
4. Increase of involved FLC level by >/= 20 mg/dL (plus an abnormal FLC ratio) in 2 consecutive measurements separated by </= 2 months.

9.0 Criteria for Removal from the Study

1. Patient's withdrawal of the informed consent.
2. Patient's inability or unwillingness to have follow-up visits and/or laboratory tests required by this protocol.
3. An unexpected toxicity that is deemed unacceptable by the study PI.
4. Disease progression or relapse.
5. After two years of treatment completion.

10.0 Determination of Body Surface Area

For patients whose actual body weight is ≤ 20% above ideal body weight (defined by the MD Anderson dosing calculator), the actual body weight is used to calculate the body surface area (BSA). The actual body weight will also be used to calculate the BSA for the busulfan test dose. For purposes of gemcitabine and melphalan dosing, patients whose actual body weight is >20% above ideal body weight, an "adjusted body weight" is calculated using the midpoint between the actual and ideal body weight, and defining that as the adjusted body weight. That adjusted body weight is then used to calculate an "adjusted body surface area" that is used for chemotherapy dosing calculation purposes.

11.0 Reporting Requirements

Patients will be monitored for toxicity until day +100 or until documentation of reversal of toxicities related to this treatment. The intensity of adverse events (AE) will be assessed according to the Common Terminology Criteria v4.0 (CTCAE). Adverse events and protocol deviations will be reported accordingly to MDACC policy and procedures. Collection of adverse events will reflect the onset and resolution date and maximum grade. Intermittent events should be labeled as such and followed until resolution. If a patient is taken off study while an event is still ongoing, this will be followed until resolution unless another therapy is initiated. Pre-existing medical conditions will be recorded only if an exacerbation occurs during the active treatment period. Co-morbid events will not be scored separately.

11.1 Adverse events (toxicities) known to be produced by the chemotherapy regimen:

Gastrointestinal: Diarrhea (FDA boxed warning), nausea and vomiting, oral mucositis
Hepatic: Self-limited elevations of liver function enzymes; veno-occlusive disease
Hypersensitivity: Acute hypersensitivity reactions characterized by urticaria, pruritus, edema, and in some patients, tachycardia, hypotension and bronchospasm (rare)
Pulmonary: Pulmonary fibrosis and interstitial
pneumonitis. Skin: Rash.
Endocrine abnormalities: Hypothyroidism.
Cardiac abnormalities: QTc prolongation, arrhythmias.

11.2. Adverse events (toxicities) known to be produced by other treatment components:

The following events are not considered to be significant in relationship with the study treatment, will not be considered adverse events and will not be collected in the study database.

Myelosuppression-related: neutropenia, anemia, thrombocytopenia, platelet and RBC transfusions.
Flu-like symptoms: low grade fever, headache, chills, cough, rhinitis, myalgia, fatigue, sweating and insomnia.
Mood alteration: depression, anxiety, and agitation
Readmissions (lasting <10 days)
Low blood pressure due to dehydration requiring fluid
replacement Fluid overload.
Fatigue.
Laboratory serum metabolic values not reflecting end-organ (hepatic, renal) function and or those considered associated to the original disease
Events that are identified to be related to the supportive treatment, e.g., steroids, palifermin, antibiotics.

11.3 Adverse Events Considered Serious (SAEs):

1. Graft failure/rejection
2. Prolonged hospitalization due to infections and/or organ failure requiring extensive supportive care (i.e. dialysis, mechanical ventilation)
3. Readmissions from any cause resulting in a prolonged hospitalization (>10 days).
4. Any expected or unexpected event resulting in an irreversible condition and/ or leading to death.

Serious adverse events (SAE) will be reported to the PI or his designate, who in turn will notify the IRB following institutional policy.

11.4. Secura Bioinstructions for rapid notification of serious adverse events:

This is an investigator-initiated study sponsored by Secura Bio. The principal investigator has the obligation to report all serious adverse events to Secura Bio. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 24 hours.

Any serious adverse event occurring after the patient has provided informed consent and

until 4 weeks after the patient has stopped study participation must be reported. This includes the period in which the study protocol interferes with the standard medical treatment given to a patient (e.g. treatment withdrawal during washout period, change in treatment to a fixed dose of concomitant medication).

Serious adverse events occurring more than 4 weeks after study discontinuation need only be reported if a relationship to the Novartis study drug (or therapy) is suspected.

11.5. Protocol amendments or changes in study conduct

Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be reviewed by Novartis and the investigator before implementation. Amendments significantly affecting the safety of subjects, the scope of the investigation or the scientific quality of the study require additional approval by the IRB at each study center. A copy of the written approval of the IRB must be provided to Novartis. Examples of amendments requiring such approval are:

1. Increases in drug dose or duration of exposure of subjects,
2. Significant changes in the study design (e.g. addition or deletion of a control group),
3. Increases in the number of invasive procedures,
4. Addition or deletions of a test procedure required for monitoring of safety.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Novartis in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons Novartis must be notified and the IRB at the center must be informed immediately.

12.0 Correlative Studies

These correlative studies will be optional for patients participating in this trial. We will measure by RT-PCR the pretransplant levels of the following markers of UPR in myeloma cells extracted from a bone marrow aspirate: XBP1, IRE1, XBP1u, XPB1s, and Myc. Myeloma cells will be purified as described and cryopreserved until analysis.[27]

1. We will study the prognostic effect of pretransplant levels in myeloma cells of XBP1, IRE1, XBP1u, XPB1s, XBP1u/XPBs ratio and Myc, by analyzing their correlation with PFS and OS.

2. We will determine the predictive value of pretransplant levels in myeloma cells of XBP1, IRE1, XBP1u, XPB1s, XBP1u/XPBs ratio and Myc, by analyzing their correlation with CR, VGPR+CR and RR.

Correlative studies will be conducted in the laboratory of Ben Valdez, Ph.D. at MD Anderson.

13.0 Statistical Considerations

Overview:

This is a Phase II clinical trial examining the effect of panobinostat + Gemcitabine/Busulfan/ Melphalan (Gem/Bu/Mel) with hematopoietic cell support in patients with refractory or relapsed myeloma. There will be two parallel cohorts: 1) patients with refractory disease receiving their first transplant, and 2) patients receiving a second salvage transplant. We expect to enroll 40 patients in each cohort and a total of 80 patients in the study. The primary objective in each cohort is to assess whether progression-free survival (PFS) can be improved over historical patients treated with Gem/Bu/Mel. Secondary objectives include assessing overall survival, response rates, toxicity, and various biomarkers. Study endpoints will only be assessed among patients who have received the study treatment.

Primary Endpoint

Progression-free survival.

Secondary Endpoints

1. Complete response (CR) rate
2. Overall survival (OS)
3. CR + very good partial remission (VGPR) rate
4. Response rate (RR)
5. Minimal residual disease post-transplant measured by multiparametric flow cytometry
6. To describe the toxicity profile
7. To analyze the predictive value of pretransplant levels in myeloma cells of XBP1, IRE1, XBP1u, XPB1s, XBP1u/XPBs ratio and Myc, by analyzing their correlation with CR, VGPR+CR and RR.
8. To study the prognostic effect of pretransplant levels in myeloma cells of XBP1, IRE1, XBP1u, XPB1s, XBP1u/XPBs ratio and Myc, by analyzing their correlation with PFS and OS.

Sample Size and Power

The 1-year PFS rate in cohort 1 (refractory, 1st transplant) associated with GemBuMel is 62%. With 40 patients in this cohort, assuming exponentially-distributed PFS times, 1.5 years of accrual followed by 2 years of follow-up, and a one-sided 5% Type I error rate, 40 patients provides more than 80% power to detect an increase in one-year PFS to 75% in this cohort.

In cohort 2 (2nd transplant), the historical 1-year PFS rate is 55%. Under the same assumptions, 40 patients will provide more than 80% power to detect an increase in 1-year PFS to 69%.

Patients lost to follow-up before 1 year will be censored at the time of their last follow-up.

Safety Monitoring Endpoints

To ensure patient safety in this trial, we will monitor the rate of treatment-related mortality (TRM). We target a maximum TRM rate of no more than 5%. The method of Thall et al will be employed to perform interim safety monitoring.[28].

During the treatment administration and until day +100 all patients will be monitored for toxicity, specifically for grade 3 or greater side effects, according to CTCAE v4.0. Response will be assessed by day +100 using the International Myeloma Working Group (IMWG) uniform response criteria.

Safety Monitoring Rule

To monitor the treatment-related mortality (TRM) rate, a binary outcome, there are two possible elementary outcomes. They are 1 = [treatment-related death], 2 = [alive or death due to other causes]. We denote the probability vector with the experimental treatment by qE. We assume a Beta (0.1, 1.9) prior on qE, which corresponds to a mean TRM rate of 5%. Because we expect the TRM rate not to differ between the two cohorts of patients, this monitoring rule will be applied overall rather than by cohort.

The following decision criteria will be applied after a minimum of 2 patients has been evaluated, up to the last patient. Targeting a 5% TRM rate as a trade-off, the trial will be stopped early if:

$$\Pr[qE(\text{TRM rate}) > 5\% \mid \text{data}] > 0.975$$

That is, if at any time during the trial we determine that we have greater than 97.5% posterior probability that the TRM rate is higher than 5%, we will stop enrollment into the trial. Stopping boundaries corresponding to this probability criterion are found in the following table.

TRM Monitoring Rule Stopping Boundaries

Total number of patients:	Stop if this many patients have TRM:
1	Never stop with this many patients
2-4	2-4
5-12	3-12
13-22	4-22
23-33	5-33
34-45	6-45
46-58	7-58
59-71	8-71
72-79	9-79
80	Always stop at 80 patients

This stopping rule was simulated using the program Multc Lean Desktop version 2.1.0, available from the MDACC Department of Biostatistics. This leads to the operating characteristics found in the table below.

Operating Characteristics for Monitoring Rule

True Pr (TRM)	Early Stopping Probability	Sample Size Quartiles		
		25th	50th	75th
0.025	0.008	80	80	80
0.05	0.075	80	80	80
0.075	0.269	70	80	80
0.10	0.542	29	69	80
0.125	0.773	18	40	74

Secondary Analyses

Summary statistics will be provided for continuous variables. Frequency tables will be used to summarize categorical variables. Response rates (CR; CR/VGPR; RR) will be reported along with corresponding 95% confidence intervals. Logistic regression will be used to model the association between response rates and prognostic factors. Overall survival (OS) and progression free survival (PFS) will be estimated by the Kaplan-Meier method. Comparison of time to event endpoints by subgroups will be made using the log-rank test. Cox proportional hazards regression will be employed for univariate and multivariate analysis on time-to-event outcomes. The treatment-related morality rate will be computed and presented with 95% confidence interval. Adverse events will be tabulated for all patients.

We will analyze the correlation with PS and OS of pretransplant levels in myeloma cells of XBP1, IRE1, XBP1u, XPB1s, XBP1u/XPBs ratio and Myc, using the log-rank test. We will analyze the correlation with CR, VGPR+CR and RR of pretransplant levels in myeloma cells of XBP1, IRE1, XBP1u, XPB1s, XBP1u/XPBs ratio and Myc, using Fisher's F test.

14.0 Background Drug Information

14.1. Panobinostat

Panobinostat is a HDACi belonging to a structurally novel cinnamic hydroxamic acid class of compounds. It is a potent class I/II pan-HDACi with anti-tumor activity in pre-clinical models and cancer patients. Deacetylases (DAC) target lysine groups on chromatin and transcription factors and various non-histone proteins such as p53, tubulin, HSP90 and Rb. Panobinostat is formulated as an oral capsule.

Clinical development of panobinostat focuses on the oral formulation. The clinical program for the i.v. formulation is completed with no further company-sponsored studies currently planned. As of 31 December 2013, 36 clinical studies, including clinical pharmacology, phase I and phase II trials, as well as two randomized phase III studies have either been completed or are ongoing. A total of 2428 patients were enrolled, 235 for i.v. and 2193 for oral, who received at least one dose of panobinostat either as a single agent or in combination with other agents.

Patients were treated with panobinostat either TIW QW (666 patients) or TIW QOW (96 patients) in single agent trials. These patients comprise the pooled safety population experiencing adverse (AE) events during study treatment. The most frequent non-hematologic AE included gastrointestinal events (diarrhea, nausea, vomiting), mostly of grade 1-2, in both groups. Blood and lymphatic system disorders were the second most often reported specific system organ class, with dose-related thrombocytopenia being the most frequent AE. Fatigue, mostly grade 1-2, was also common among patients treated for TIW QW and TIW QOW. Thyroid function, as monitored by the measurement of TSH and free T4, did not reveal overt hyper- or hypothyroidism, with fluctuations in TSH values being within normal limits.

Table 4 All grade adverse events regardless of causality in patients receiving oral panobinostat three-times-a-week every-week (TIW QW)

Primary system organ class Preferred term	**20 mg (N=309 N %**	**30 mg (N=81) N %**	**40 mg (N=163) N %**	**60 mg (N=113) N %**	**TOTAL (N=666) N %**
-Any primary system organ class					
-Total	307 (99.4)	81 (100.0)	163(100.0)	113(100.0)	664 (99.7)
Blood and lymphatic system disorders					
-Total	193 (62.5)	50 (61.7)	145 (89.0)	87 (77.0)	475 (71.3)
Anemia	63 (20.4)	32 (39.5)	65 (39.9)	35 (31.0)	195 (29.3)
Febrile neutropenia	9 (2.9)	0 (0.0)	7 (4.3)	33 (29.2)	49 (7.4)
Leukopenia	19 (6.1)	1(1.2)	18 (11.0)	4 (3.5)	42 (6.3)
Neutropenia	53 (17.2)	4 (4.9)	48 (29.4)	29 (25.7)	134 (20.1)
Thrombocytopenia	133 (43.0)	31(38.3)	137(84.0)	58 (51.3)	359 (53.9)
Endocrine disorders					
-Total	21 (6.8)	7 (8.6)	27 (16.6)	9 (8.0)	64 (9.6)
Hypothyroidism	15 (4.9)	3 (3.7)	21 (12.9)	4 (3.5)	43 (6.5)
Gastrointestinal disorders					
-Total	246 (79.6)	76 (93.8)	152 (93.3)	107(94.7)	581(87.2)
Abdominal pain	33 (10.7)	11 (13.6)	30 (18.4)	23 (20.4)	97 (14.6)
Abdominal pain upper	26 (8.4)	5 (6.2)	24 (14.7)	9(8.0)	64(9.6)
Constipation	46 (14.9)	15 (18.5)	32 (19.6)	24 (21.2)	117(17.6)
Diarrhea	158 (51.1)	46 (56.8)	117 (71.8)	85 (75.2)	406 (61.0)
Dry mouth	17 (5.5)	6 (7.4)	22 (13.5)	9 (8.0)	54 (8.1)
Nausea	142(46.0)	51(63.0)	112(68.7)	67(59.3)	372(55.9)
Vomiting	68(22.0)	33(40.7)	73(44.8)	47(41.6)	221(33.2)
General disorders and administration site conditions					
-Total	229(74.1)	70(86.4)	137(84.0)	98(86.7)	534(80.2)
Asthenia	52(16.8)	6(7.4)	29(17.8)	21(18.6)	108(16.2)
Chills	19(6.1)	4(4.9)	13(8.0)	17(15.0)	53(8.0)
Fatigue	126(40.8)	56(69.1)	85(52.1)	59(52.2)	326(48.9)
Edema peripheral	62(20.1)	21(25.9)	30(18.4)	24(21.2)	137(20.6)
Pyrexia	61(19.7)	18(22.2)	67(41.1)	47(41.6)	193(29.0)
Infections and infestations					

-Total	152(49.2)	40(49.4)	101(62.0)	76(67.3)	369(55.4)
Sepsis	6(1.9)	3(3.7)	4(2.5)	13(11.5)	26(3.9)
Upper respiratory tract infection	12(3.9)	5(6.2)	24(14.7)	4(3.5)	45(6.8)
Urinary tract infection	23(7.4)	11(13.6)	10(6.1)	7(6.2)	51(7.7)
Investigations					
-Total	143(46.3)	40(49.4)	71(43.6)	57(50.4)	311(46.7)
Blood creatinine increased	37(12.0)	7(8.6)	13(8.0)	13(11.5)	70(10.5)
Platelet count decreased	13(4.2)	14(17.3)	4(2.5)	7(6.2)	38(5.7)
Weight decreased	44(14.2)	12(14.8)	30(18.4)	22(19.5)	108(16.2)
Metabolism and nutrition disorders					
-Total	179(57.9)	56(69.1)	92(56.4)	83(73.5)	410(61.6)
Anorexia	45(14.6)	10(12.3)	16(9.8)	24(21.2)	95(14.3)
Decreased appetite	49(15.9)	30(37.0)	49(30.1)	31(27.4)	159(23.9)
Dehydration	12(3.9)	12(14.8)	13(8.0)	19(16.8)	56(8.4)
Hypocalcemia	22(7.1)	3(3.7)	8(4.9)	21(18.6)	54(8.1)
Hypokalemia	33(10.7)	11(13.6)	28(17.2)	35(31.0)	107(16.1)
Hypophosphatemia	25(8.1)	1(1.2)	9(5.5)	14(12.4)	49(7.4)
Musculoskeletal and connective tissue disorders					
-Total	114(36.9)	29(35.8)	90(55.2)	43(38.1)	276(41.4)
Back pain	35(11.3)	8(9.9)	30(18.4)	13(11.5)	86(12.9)
Muscle spasms	19(6.1)	6(7.4)	32(19.6)	2(1.8)	59(8.9)
Myalgia	16(5.2)	1(1.2)	17(10.4)	2(1.8)	36(5.4)
Nervous system disorders					
-Total	147(47.6)	36(44.4)	86(52.8)	52(46.0)	321(48.2)
Dizziness	42(13.6)	14(17.3)	15(9.2)	10(8.8)	81(12.2)
Dysgeusia	44(14.2)	13(16.0)	28(17.2)	22(19.5)	107(16.1)
Headache	49(15.9)	14(17.3)	34(20.9)	16(14.2)	113(17.0)
Psychiatric disorders					
-Total	65(21.0)	17(21.0)	43(26.4)	38(33.6)	163(24.5)
Anxiety	12(3.9)	3(3.7)	18(11.0)	9(8.0)	42(6.3)
Insomnia	20(6.5)	10(12.3)	14(8.6)	19(16.8)	63(9.5)
Respiratory, thoracic and mediastinal disorders					
-Total	117(37.9)	42(51.9)	97(59.5)	53(46.9)	309(46.4)
Cough	30(9.7)	11(13.6)	48(29.4)	19(16.8)	108(16.2)
Dyspnea	49(15.9)	28(34.6)	32(19.6)	20(17.7)	129(19.4)
Epistaxis	16(5.2)	3(3.7)	22(13.5)	20(17.7)	61(9.2)
Skin and subcutaneous tissue disorders					
-Total	147(47.6)	21(25.9)	73(44.8)	38(33.6)	279(41.9)
Pruritus	56(18.1)	3(3.7)	22(13.5)	3(2.7)	84(12.6)
Vascular disorders					
-Total	61(19.7)	17(21.0)	26(16.0)	33(29.2)	137(20.6)
Hypotension	18(5.8)	4(4.9)	10(6.1)	18(15.9)	50(7.5)
Includes only events occurring in ≥10% of patients					

A patient with multiple occurrences of an AE is counted only once in that AE category. A patient with multiple adverse events within a primary system organ class is counted only once in the total row. If an AE frequency matches the criteria in one dose category, the frequency of that event is shown for all doses. Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class alphabetically.					

As shown above, AEs regardless of causality for TIW QW dosing were reported in 664 patients, 99.7% of the safety population for this dosing schedule. The most commonly reported AEs across doses were gastrointestinal: diarrhea in 406 patients (61.0%) and nausea in 372 patients (55.9%). Thrombocytopenia was the third most frequent AE in 359 patients (53.9%) with the highest frequency in the 40 mg dose level (137 patients; 84%). Fatigue also was commonly seen across dose levels in 326 patients (48.9%) overall. Of note hypothyroidism was reported in 12.9% of patients treated at the dose level of 40 mg, mostly deriving from study [CLBH589E2214] in HL patients who are known to have an increased risk for hypothyroidism.

Table 5. Grade 3-4 adverse events regardless of causality in patients receiving oral panobinostat three-times-a-week every-week (TIW QW)

Primary system organ class	**20 mg**	**30 mg**	**40 mg**	**60 mg**	**Total**
Preferred term	**N=309**	**N=81**	**N=163**	**N=113**	**N=666**
	N (%)	**N (%)**	**N (%)**	**N (%)**	**N (%)**
-Any primary system organ class					
-Total	209(67.6)	70(86.4)	150(92.0)	105(92.9)	534(80.2)
Blood and lymphatic system disorders					
-Total	120(38.8)	26(32.1)	138(84.7)	84(74.3)	368(55.3)
Anemia	29(9.4)	8(9.9)	35(21.5)	31(27.4)	103(15.5)
Febrile neutropenia	9(2.9)	0(0.0)	6(3.7)	31(27.4)	46(6.9)
Leukocytosis	4(1.3)	2(2.5)	0(0.0)	3(2.7)	9(1.4)
Leukopenia	2(0.6)	0(0.0)	11(6.7)	4(3.5)	17(2.6)
Neutropenia	42(13.6)	4(4.9)	39(23.9)	26(23.0)	111(16.7)
Thrombocytopenia	66(21.4)	21(25.9)	129(79.1)	56(49.6)	272(40.8)
Gastrointestinal disorders					
-Total	24(7.8)	20(24.7)	24(14.7)	31(27.4)	99(14.9)
Abdominal pain	5(1.6)	3(3.7)	7(4.3)	2(1.8)	17(2.6)

Ascites	0(0.0)	4(4.9)	0(0.0)	0(0.0)	4(0.6)
Diarrhea	10(3.2)	6(7.4)	6(3.7)	18(15.9)	40(6.0)
Nausea	6(1.9)	6(7.4)	2(1.2)	7(6.2)	21(3.2)
Vomiting	4(1.3)	3(3.7)	4(2.5)	3(2.7)	14(2.1)
General disorders and administration site conditions					
-Total	35(11.3)	25(30.9)	38(23.3)	41(36.3)	139(20.9)
Asthenia	8(2.6)	2(2.5)	7(4.3)	10(8.8)	27(4.1)
Fatigue	13(4.2)	19(23.5)	26(16.0)	24(21.2)	82(12.3)
General physical health deterioration	6(1.9)	2(2.5)	0(0.0)	1(0.9)	9(1.4)
Pain	3(1.0)	0(0.0)	0(0.0)	3(2.7)	6(0.9)
Pyrexia	4(1.3)	1(1.2)	4(2.5)	2(1.8)	11(1.7)
Hepatobiliary disorders					
-Total	3(1.0)	3(3.7)	6(3.7)	3(2.7)	15(2.3)
Hyperbilirubinemia	2(0.6)	0(0.0)	4(2.5)	2(1.8)	8(1.2)
Infections and infestations					
-Total	37(12.0)	12(14.8)	27(16.6)	49(43.4)	125(18.8)
Bacterial infection	0(0.0)	0(0.0)	1(0.6)	5(4.4)	6(0.9)
Infection	1(0.3)	2(2.5)	1(0.6)	1(0.9)	5(0.8)
Pneumonia	7(2.3)	2(2.5)	6(3.7)	6 (5.3)	21(3.2)
Sepsis	5(1.6)	3(3.7)	4(2.5)	9(8.0)	21(3.2)
Septic shock	2(0.6)	1(1.2)	1(0.6)	3(2.7)	7(1.1)
Urinary tract infection	1(0.3)	3(3.7)	0(0.0)	3(2.7)	7(1.1)
Investigations					
-Total	39(12.6)	14(17.3)	22(13.5)	26(23.0)	101(15.2)
Alanine aminotransferase increased	1(0.3)	1(1.2)	4(2.5)	1(0.9)	7(1.1)
Aspartate aminotransferase increased	1(0.3)	0(0.0)	5(3.1)	1(0.9)	7(1.1)
Electrocardiogram qt prolonged	6(1.9)	1(1.2)	0(0.0)	4(3.5)	11(1.7)
Platelet count decreased	8(2.6)	7(8.6)	3(1.8)	6(5.3)	24(3.6)
Weight decreased	2(0.6)	1(1.2)	4(2.5)	1(0.9)	8(1.2)
Metabolism and nutrition disorders					
-Total	42(13.6)	16(19.8)	27(16.6)	38(33.6)	123(18.5)
Anorexia	3(1.0)	1(1.2)	2(1.2)	5(4.4)	11(1.7)
Decreased appetite	2(0.6)	0(0.0)	5(3.1)	3(2.7)	10(1.5)
Dehydration	2(0.6)	4(4.9)	2(1.2)	5(4.4)	13(2.0)
Failure to thrive	1(0.3)	2(2.5)	0(0.0)	0(0.0)	3(0.5)
Hyperglycemia	6(1.9)	1(1.2)	3(1.8)	5(4.4)	15(2.3)
Hypoalbuminemia	1(0.3)	2(2.5)	1(0.6)	0(0.0)	4(0.6)
Hypocalcemia	4(1.3)	0(0.0)	1(0.6)	5(4.4)	10(1.5)
Hypokalemia	10(3.2)	3(3.7)	9(5.5)	15(13.3)	37(5.6)
Hyponatremia	7(2.3)	3(3.7)	2(1.2)	2(1.8)	14(2.1)
Hypophosphatemia	7(2.3)	1(1.2)	5(3.1)	10(8.8)	23(3.5)
Musculoskeletal and connective tissue disorders					
-Total	18(5.8)	2(2.5)	12(7.4)	7(6.2)	39(5.9)
Back pain	5(1.6)	1(1.2)	4(2.5)	2(1.8)	12(1.8)
Nervous system disorders					
-Total	24(7.8)	4(4.9)	16(9.8)	14(12.4)	58(8.7)
Lethargy	1(0.3)	0(0.0)	5(3.1)	4(3.5)	10(1.5)
Respiratory, thoracic and mediastinal disorders					

-Total	17(5.5)	14(17.3)	18(11.0)	10(8.8)	59(8.9)
Dyspnea	10(3.2)	8(9.9)	8(4.9)	1(0.9)	27(4.1)
Hypoxia	0(0.0)	2(2.5)	2(1.2)	3(2.7)	7(1.1)
Pleural effusion	3(1.0)	2(2.5)	1(0.6)	0(0.0)	6(0.9)
Pulmonary embolism	1(0.3)	2(2.5)	3(1.8)	0(0.0)	6(0.9)
Skin and subcutaneous tissue disorders					
-Total	20(6.5)	1(1.2)	6(3.7)	4(3.5)	31(4.7)
Pruritus	9(2.9)	0(0.0)	3(1.8)	1(0.9)	13(2.0)
Vascular disorders					
-Total	8(2.6)	5(6.2)	9(5.5)	8(7.1)	30(4.5)
Hypertension	1(0.3)	2(2.5)	1(0.6)	1(0.9)	5(0.8)
Hypotension	3(1.0)	1(1.2)	4(2.5)	5(4.4)	13(2.0)
Includes only events occurring ≥ 2% of patients in any dose group. A patient with multiple occurrences of an AE is counted only once in that AE category. A patient with multiple adverse events within a primary system organ class is counted only once in the total row. Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class alphabetically. If an AE frequency matches the criteria in one dose category, the frequency of that event is shown for all doses.					

As shown above, grade 3-4 AEs regardless of causality were reported in 534 patients, 80.2% of the safety population for the QW schedule. The most commonly reported grade 3-4 AEs across doses were thrombocytopenia in 272 patients (40.8%), neutropenia in111 patients (16.7%), anemia in 103 patients (15.5%), fatigue in 82 patients (12.3%) and febrile neutropenia in 46 patients (6.9%). There were more grade 3-4 hematologic AEs at higher dose levels, with the highest incidences at 40 and 60 mg. The highest incidence of febrile neutropenia was seen at the dose level of 60 mg (27.4%) compared to the other dose levels where the incidence was $\leq$ 3.7%. This could be because this dose level was only tested in leukemia patients, in whom febrile neutropenia is a common AE. Grade 3-4 thrombocytopenia, grade 3-4 neutropenia and grade 3-4 anemia accounted for 75.7% (272/359), 82.8% (111/134) and 52.8% (103/195) of their respective all grade events.
Grade3-4 diarrhea, grade 3-4 vomiting and grade 3-4 nausea accounted for less than 10% of their respective all grade events. For the TIW QOW dosing schedule, AEs regardless of causality were reported in 96 patients, which is 100% of the safety population. The most commonly reported AEs (all grades) across doses were diarrhea in 65 patients (67.7%), nausea in 60 patients (62.5%), fatigue in 54 patients (56.3%), vomiting in 42 patients (43.8%), thrombocytopenia in 41 patients (42.7%), pyrexia in 35 patients (36.5%) and anorexia in 33 patients (34.4%).

In the TIWQOW schedule, Grade 3-4 AEs regardless of causality were reported in 81

patients, 84.4% of the safety population. The most commonly reported Grade 3-4 AEs across doses were thrombocytopenia in 35 patients (36.5%), neutropenia in 25 patients (26.0%), fatigue in
14 patients (14.6%), diarrhea in 11 patients (11.5%), anemia in 10 patients (10.4%), and febrile neutropenia in 8 patients each (8.3%).

Overall, the most frequent Grade 3-4 AEs regardless of causality for both schedules (TIWQW and TIWQOW) were ascribed to the same SOC, namely blood and lymphatic system disorders.

FDA boxed warning for Panobinostat:
a. Warning: Fatal and Serious Toxicities: Severe Diarrhea and Cardiac Toxicities
b. Severe diarrhea occurred in 25% of panobinostat treated patients.
c. Severe and fatal cardiac ischemic events, severe arrhythmias, and ECG changes have occurred in patients receiving panotbinostat. Arrhythmias may be exacerbated by electrolyte abnormalities

Human pharmacokinetics
After oral administration, panobinostat is rapidly absorbed with no observed lag phase. Maximum plasma concentrations were generally reached within 1 hour after oral dosing. The absolute bioavailability was 30% and the mean (SD) half-life of panobinostat was comparable following i.v. and oral dosing ~15.0 hours. Moderate drug accumulation was observed with oral three-times-a-week schedule but not with the weekly i.v. schedule (1.4-fold drug accumulation with oral three-times-a-week dosing), consistent with the terminal half-life of 15 hours and dosing interval.

In vitro experiments suggested that the hepatic oxidative metabolism of panobinostat is mediated primarily by cytochrome P450 (CYP3A4), and to a lesser extent by CYP2D6 and CYP2C19. In addition to monooxygenation, hydrolysis of the hydroxamic chain were also found to be mediated (at least in-part) by the CYPs.

Dose proportionality
A positive and linear dose-exposure relationship was found following single i.v. administration (1.2 to 20 mg/m2, Rs = 0.83; p<0.0001). After oral dosing with 15 mg to 80 mg of panobinostat, dose-proportionality analysis indicated that systemic exposure increased nearly
dose-proportionally at doses below 60 mg and there is less than proportional increase in AUC after 60 mg and 80 mg doses of panobinostat. It appears that absorption may become limiting at doses · 60 mg of panobinostat.

Food Effect
Influence of food on panobinostat PK was evaluated in patients with advanced cancer who received 20 mg panobinostat twice a week and were randomized to receive panobinostat under fasting, high fat, and normal breakfast conditions. The overall exposure and inter-patient variability (CV 59%) in 34 patients remained unchanged with or without food, whereas Cmax was transiently reduced by <45% and Tmax prolonged by food (i.e., both normal and high fat breakfast). Since food did not alter the overall extent of absorption, food is unlikely to significantly impact panobinostat systemic exposure in cancer patients. Therefore, panobinostat can be administered without regard to food.

Electrocardiographic experience and cardiac safety of with panobinostat.
Cardiac safety in patients with hematologic malignancies

As of 31 December 2013, cardiac safety data for 666 patients treated with oral panobinostat TIW QW are available. All patients underwent intensive pre- and post-dose ECG monitoring. The most common finding is a post-baseline QTc increase of >30 and ·60 msec in approximately 22%. No cases of torsades de pointes have been observed. A post-baseline increase of >60 msec was less frequent (27 patients, 4.1%). QTc prolongation translating into an absolute value of 450 to 480 msec and of > 480 - 500 msec was measured in 88 patients (13.4%) and in 17 patients (2.6%), respectively. Absolute QTc prolongation > 500 msec was uncommon (6 patients, 0.9%), mostly referred to 5 patients treated at 60 mg weekly dose level.

The maximum change of QTc from baseline does not coincide with the peak plasma concentration-time course of panobinostat suggesting a possible delayed effect.

Drug interactions
Panobinostat is a CYP3A substrate and inhibits CYP2D6. Panobinostat is a P-glycoprotein (P-gp) transporter system substrate.
a. Agents that May Increase panobinostat Blood Concentrations
b. CYP3A Inhibitors: Coadministration of panobinostat with a strong CYP3A inhibitor increased the Cmax and AUC of panobinostat by 62% and 73% respectively, compared to when panobinostat was given alone.
c. Reduce dose to 10 mg when coadministered with strong CYP3A inhibitors (e.g., boceprevir, clarithromycin, conivaptan, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, voriconazole). Instruct patients to avoid star fruit, pomegranate or pomegranate juice, and grapefruit or grapefruit juice because these foods are known to inhibit CYP3A enzymes.
d. Agents that May Decrease panobinostat Plasma Concentrations

e. CYP3A Inducers: Coadministration of panobinostat with strong CYP3A inducers was not evaluated in vitro or in a clinical trial however, a reduction in panobinostat exposure is likely. An approximately 70% decrease in the systemic exposure of panobinostat in the presence of strong inducers of CYP3A was observed in simulations using mechanistic models. Therefore, the concomitant use of strong CYP3A inducers should be avoided.
f. Agents whose Plasma Concentrations May be Increased by panobinostat
g. CYP2D6 Substrates:
Panobinostat increased the median Cmax and AUC of a sensitive substrate of CYP2D6 by approximately 80% and 60%, respectively; however this was highly variable. Avoid coadministrating
panobinostat with sensitive CYP2D6 substrates (i.e., atomoxetine, desipramine, dextromethorphan, metoprolol, nebivolol, perphenazine, tolterodine, and venlafaxine) or CYP2D6 substrates that have a narrow therapeutic index (i.e., thioridazine, pimozide). If concomitant use of CYP2D6 substrates is unavoidable, monitor patients frequently for adverse reactions.
h. Drugs that Prolong QT interval
i. Concomitant use of anti-arrhythmic medicines (including, but not limited to amiodarone, disopyramide, procainamide, quinidine and sotalol) and other drugs that are known to prolong the QT interval (including, but not limited to chloroquine, halofantrine, clarithromycin, methadone, moxifloxacin, bepridil and pimozide) is not

recommended. Anti-emetic drugs with known QT prolonging risk, such as dolasetron, ondansetron, and tropisetron can be used with frequent ECG monitoring.

Hepatic Impairment
a. The safety and efficacy of panobinostat in patients with hepatic impairment has not been evaluated.
b. In a pharmacokinetic trial, patients with mild (bilirubin ·1xULN and AST >1xULN, or bilirubin >1.0 to 1.5x ULN and any AST) or moderate (bilirubin >1.5x to 3.0x ULN, any AST) hepatic impairment (NCI-ODWG criteria) had increased AUC of panobinostat by 43% and 105%, respectively. Reduce the starting dose of panobinostat in patients with mild or moderate hepatic impairment. Avoid use in patients with severe hepatic impairment. Monitor patients with hepatic impairment frequently for adverse events.
Renal Impairment
d. Mild [creatinine clearance (CrCl) ·50 to <80 mL/min] to severe renal impairment (CrCl <30 mL/min) did not impact the plasma exposure of panobinostat. Panobinostat has not been studied in patients with end stage renal disease (ESRD) or patients on dialysis. The dialyzability of panobinostat is unknown.
Monitoring parameters:
a. Complete Blood Count (CBC): Obtain a CBC before initiating treatment. Verify that the baseline platelet count is at least 100 x 109/L and the baseline absolute neutrophil count (ANC) is at least 1.5 x 109/L. Monitor the CBC weekly (or more often as clinically indicated) during treatment.
b. ECG: Perform an ECG prior to the start of therapy and repeat periodically during treatment as clinically indicated. Verify that the QTcF is less than 450 msec prior to initiation of treatment with
panobinostat . If during treatment with panobinostat , the QTcF increases to ·480 msec, interrupt treatment. Correct any electrolyte abnormalities. If QT prolongation does not resolve, permanently discontinue treatment with panobinostat. During the clinical trial, ECGs were performed at baseline and prior to initiation of each cycle for the first 8 cycles.
c. Serum Electrolytes: Obtain electrolytes, including potassium and magnesium, at baseline and monitor during therapy. Correct abnormal electrolyte values before treatment. During the trial, monitoring was conducted prior to the start of each cycle, at Day 11 of cycles 1 to 8, and at the start of each cycle for cycles 9 to 16.

14.2. Gemcitabine

Synonyms: Gemcitabine hydrochloride, difluorodeoxycytidine, 2',2'-difluorodeoxycytidine, dFdC, LY 188011

Common Trade Name(S): Gemzar®

Classification: Antimetabolite, cytotoxic

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

Mechanism of Action:

Gemcitabine, a pyrimidine analog, is structurally similar to cytarabine, but has a wider spectrum of antitumor activity due to its different cellular pharmacology and mechanism of action.
Gemcitabine is metabolized intracellularly to two active metabolites, Gemcitabine

diphosphate (dFdCDP) and Gemcitabine triphosphate (dFdCTP). The cytotoxic effects of Gemcitabine are exerted through incorporation of dFdCTP into DNA with the assistance of dFdCDP, resulting in inhibition of DNA synthesis and induction of apoptosis. Gemcitabine is a radiation-sensitizing agent.5 It is cell-cycle phase specific (S and G1/S-phases).

Pharmacokinetics:

Interpatient variability	3- to 4-fold interpatient and intrapatient variability
Oral absorption	No information found
Distribution	Widely distributed into tissues; also present in ascitic fluid. Cross blood brain barrier: No information found volume of distribution: IV infusion < 70 min: 50 L/m^2; IV infusion 70-285 min: 370 L/m^2 plasma protein binding< 10%
Metabolism	Metabolized intracellularly by nucleoside kinases to active metabolites dFdCDP and dFdCTP; also metabolized intracellularly and extracellularly by cytidine deaminase to inactive metabolite difluorodeoxyuridine (dFdU) Active metabolites: dFdCDP, dFdCTP Inactive metabolites: dFdU
Excretion	Mainly renal excretion Urine 92-98% over one week (89% as dFdU, < 10% as Gemcitabine) after a single dose of 1000 mg/m2 given over 30 minutes. Terminal half-life: IV infusion < 70 min: 0.7-1.6 h IV infusion 70-285 min: 4.1-10.6 h Clearance: IV infusion < 70 min: 41-92 L/h/m^2 (male), 31-69 L/h/m^2 (female)
Gender	Decreased volume of distribution and clearance in women
Elderly	Decreased clearance and increased half-life with increasing age
Children	No information found
Ethnicity	No information found

Special Precautions:
Carcinogenicity: No information found.
Mutagenicity: Not mutagenic in Ames test but mutagenic in mammalian *in vitro* mutation test. Gemcitabine is lactogenic in mammalian *in vitro* and *in vivo* chromosome tests.
Fertility: Decreased spermatogenesis and fertility in male mice.
Pregnancy: FDA Pregnancy Category D. There is positive evidence of human fetal risk, but the

benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective). ***Breastfeeding*** is not recommended due to the potential secretion into breast milk.

Side Effects:

ORGAN SITE	SIDE EFFECT	ONSET
	Dose-limiting side effects are in ***bold, italics***	I = immediate (onset in hours to days); E = early (days to weeks); D = delayed (weeks to months); L = late (months to years)
Allergy/Immunology	allergic reaction (4%, severe 0.2%)	I
anemia (68%, severe 8%)		E
Leucopenia (62%, severe 9%)		E
neutropenia (63%, severe 25%) nadir 7-10 days, recovery within 7 days		E
Blood/Bone marrow Febrile Neutropenia	***thrombocytopenia*** (24%, severe 5%) nadir 7-10 days, recovery within 7 days	E
cardiac arrhythmia (2%, severe 0.2%)		E
Cardiovascular	edema/peripheral edema (28%, severe 3%)	ED
Coagulation	hemolytic uremic syndrome (0.3%)	D
asthenia (42%, severe 2%)		E
Constitutional symptoms	fever (37%, severe < 1%)	IE
extravasation hazard: none		
alopecia (14%)		D
Dermatology	skin rash (25%, severe < 1%)	IE
emetogenic potential: low moderate		
constipation (8%, severe < 1%)		E
diarrhea (12%, severe < 1%)		E
nausea and vomiting (64%, severe 18%)		I
Gastrointestinal	stomatitis (8%, severe < 1%)	E
Hemorrhage	hematuria (31%, severe < 1%)	E
elevated alkaline phosphatase (55%, severe 9%)		E
elevated AST (67%, severe 9%)		E
elevated ALT (68%, severe 10%)		E
Hepatic	elevated bilirubin (13%, severe 2%)	E
Infection	infection (9%, severe 1%)	E
decreased level of consciousness (9%, severe < 1%)		E
Neurology	peripheral neuropathy (3%)	ED
Pain	pain (16%, severe 1%)	ED
Pulmonary	dyspnea (8%, severe 1%)	IE
elevated BUN (16%, severe 0%)		E
elevated creatinine (7%, severe < 1%)		E

Renal/genitourinary	Proteinuria (36%, severe < 1%)	E
Syndromes	flu-like symptoms (19%, severe 1%)30	E

Hemolytic uremic syndrome has been infrequently reported and is characterized by microangiopathic hemolytic anemia, thrombocytopenia and renal failure. The syndrome can present either acutely with severe hemolysis, thrombocytopenia and rapidly progressive renal failure, or more insidiously with mild or no thrombocytopenia and slowly progressive renal failure. The etiology of hemolytic uremic syndrome is unknown. The onset of the syndrome has been reported to occur during and shortly after gemcitabine therapy. If not treated promptly, the syndrome may result in irreversible renal failure requiring dialysis. Therefore, patients with impaired renal function should be monitored closely while being treated with gemcitabine.

Elevated liver enzymes: Gemcitabine causes transient and reversible elevations of liver function enzymes in about two-thirds of patients. However, these increases are rarely of clinical significance and there is no evidence of increasing hepatic toxicity with either longer duration of Gemcitabine treatment or cumulative dose.

Fever/Flu-like symptoms: Fever of any severity was reported in 37% of patients. It is frequently associated with other flu-like symptoms such as headache, chills, cough, rhinitis, myalgia, fatigue, sweating and insomnia. These symptoms are usually mild and transient, and rarely dose-limiting. The use of acetaminophen may provide symptomatic relief.

Severe pulmonary toxicity: Acute dyspnea may sometimes occur with gemcitabine therapy, but is usually self-limiting. However, severe pulmonary toxicities such as pulmonary edema, interstitial pneumonitis and adult respiratory distress syndrome have rarely been reported. The symptoms are manifested as progressive dyspnea, tachypnea, hypoxemia and pulmonary infiltrates on chest radiograph that are sometimes accompanied by fever and cough. Pulmonary toxicities usually occur after several cycles of gemcitabine, but have also been seen as early as the first cycle. Risk factors for pulmonary toxicities include prior radiation to the mediastinum.

Because of its structural similarities to cytarabine, gemcitabine is thought to cause lung injury by the same mechanism by inducing pulmonary capillary leakage. Management of pulmonary toxicities consists of discontinuation of gemcitabine and early supportive care with bronchodilators, corticosteroids, diuretics, and/or oxygen. Although pulmonary toxicities may be reversible with treatment, fatal recurrence of severe pulmonary symptoms was reported in one patient upon rechallenge with gemcitabine.

Skin rash**:** Typically mild to moderate in severity, with macular or finely granular maculopapular pruritic eruption on the trunk and extremities. It is not dose-limiting and usually responds to topical corticosteroids If needed, antihistamines such as diphenhydramine can be used.

Drug Interactions

BCG: Immunosuppressants may diminish the therapeutic effect of BCG. Risk X: Avoid combination

Bleomycin: Gemcitabine may enhance the adverse/toxic effect of Bleomycin. The risk of pulmonary toxicity may be increased. Risk D: Consider therapy modification

Denosumab: May enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased. Risk C: Monitor therapy

Echinacea: May diminish the therapeutic effect of Immunosuppressants. Risk D: Consider therapy modification

Fluorouracil: Gemcitabine may increase the serum concentration of Fluorouracil. Risk

C: Monitor therapy
Fluorouracil (Systemic): Gemcitabine may increase the serum concentration of Fluorouracil (Systemic). Risk C: Monitor therapy
Fluorouracil (Topical): Gemcitabine may increase the serum concentration of Fluorouracil (Topical). Risk C: Monitor therapy
Leflunomide: Immunosuppressants may enhance the adverse/toxic effect of Leflunomide. Specifically, the risk for hematologic toxicity such as pancytopenia, agranulocytosis, and/or thrombocytopenia may be increased. Management: Consider not using a leflunomide loading dose in patients receiving other immunosuppressants. Patients receiving both leflunomide and another immunosuppressant should be monitored for bone marrow suppression at least monthly. Risk D: Consider therapy modification
Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. Risk X: Avoid combination
Pimecrolimus: May enhance the adverse/toxic effect of Immunosuppressants. Risk X: Avoid combination
Roflumilast: May enhance the immunosuppressive effect of Immunosuppressants. Risk X: Avoid combination
Sipuleucel-T: Immunosuppressants may diminish the therapeutic effect of Sipuleucel-T. Risk C: Monitor therapy
Tacrolimus (Topical): May enhance the adverse/toxic effect of Immunosuppressants. Risk X: Avoid combination
Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. Risk C: Monitor therapy
Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Risk C: Monitor therapy
Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinial infections may develop. Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants.
Risk X: Avoid combination
Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. Risk C: Monitor therapy

Ethanol/Nutrition/Herb Interactions
Ethanol: Avoid ethanol (due to GI irritation).

Monitoring Parameters
CBC with differential and platelet count (prior to each dose); hepatic and renal function (prior to initiation of therapy and periodically, thereafter); monitor electrolytes, including potassium, magnesium, and calcium (when in combination therapy with cisplatin)

Administration

Infuse over 30 minutes. Note: Prolongation of the infusion time > 60 minutes has been shown to increase toxicity (some unlabeled protocols may include infusion times > 30 minutes). Gemcitabine is being investigated in clinical trials for fixed dose rate (FDR) infusion administration at doses from 1000-2200 mg/m2 at a rate of 10 mg/m2/minute. Prolonged infusion times increase the accumulation of the active metabolite, gemcitabine triphosphate. Patients who receive gemcitabine FDR experience more grade 3/4

hematologic toxicity.

For intravesicular (bladder) instillation, gemcitabine was diluted in 50-100 mL normal saline; patients were instructed to retain in the bladder for 1 hour.

Dosage Forms

Powder for injection, lyophilized: 20 mg/mL (200-mg and 1000-mg vial)

Reconstitute 200 mg vial with 5 mL of NS without preservative and 1000 mg vial with 25 mL of NS without preservative to yield a Gemcitabine concentration of 38 mg/mL. Reconstitution of concentrations greater than 40 mg/mL may result in incomplete dissolution and should be avoided. Reconstituted solution is stable for 24 hours at room temperature and should not be days at room temperature and under refrigeration. However, the manufacturer recommends that the admixture be used within 24 hours since the solution does not contain preservatives.
Bacterial challenge: Gemcitabine 2.4 mg/mL diluted in NS did not exhibit a substantial antimicrobial effect on the growth of four organisms inoculated into the solution. Diluted solutions should be stored under refrigeration whenever possible and that the potential for microbiological growth should be considered when assigning expiration periods.
Compatibility**:** The following are ***compatible*** via Y-site injection: amifostine, bleomycin, carboplatin, carmustine, cisplatin, cyclophosphamide, cytarabine, dactinomycin, daunorubicin, dexamethasone, dexrazoxane, diphenhydramine, docetaxel, dopamine, doxorubicin, etoposide, fludarabine, fluorouracil, granisetron, heparin, hydrocortisone, hydromorphone, idarubicin, ifosfamide, leucovorin, lorazepam, mannitol, meperidine, mesna, metoclopramide, mitoxantrone, morphine, ondansetron, paclitaxel, plicamycin, potassium chloride, ranitidine, sodium bicarbonate, streptozocin, teniposide, thiotepa, topotecan, vinblastine, vincristine, vinorelbine.
Incompatibility: The following are ***incompatible*** via Y-site injection: furosemide, irinotecan, methotrexate, methylprednisolone, mitomycin, prochlorperazine.

14.3. Busulfan

Therapeutic Classification: Antineoplastic Alkylating agent

Pharmaceutical data: Busulfan injection is a sterile, pyrogen-free solution provided in a mixture of dimethylacetamide (DMA) and polyethyleneglycol 400 (PEG400). It is supplied in 10 ml single use ampoules at a concentration of six (6) mg busulfan per ml. Each ampoule contains 60 mg of busulfan in 3.3 ml of DMA and 6.7 ml of PEG400. When diluted in normal saline or D5W to a concentration of 0.5 mg/ml, the resulting solution must be administered within eight
(8) hours of preparation including the three (3) hour infusion of the drug.

Stability and storage: Ampoules should be stored refrigerated at 2-8oC (35-46°F). Stable at 4°C for at least twelve (12) months. Additional stability studies are in progress. DO NOT use beyond the expiration date. DO NOT use if the solution is cloudy or if particulates are present.

Break off the top of the ampoule and use a syringe needle to remove the calculated volume of busulfan from the primary container. Remove the needle, replace with a new

needle which has been fitted with a 5.0 micron nylon filter (provided with packaged drug) and transfer the contents of the syringe into the calculated amount of either normal saline or D5W making sure that the drug flows into and through the solution. Do not put the busulfan solution into a syringe or IV bag, which does not contain the normal saline or D5W. Mix by inverting the container numerous times to ensure a homogenous solution. Place an appropriate label on the container with an expiration time of eight (8) hours from the time of preparation with directions to store at room temperature. Do not use if solution contains visible particulates. Record the actual volume on the label.

Place a suitable (non-vented or universal) intravenous administration set (gravity flow) into the outflow port of the container of the infusion solution.

Route of Administration: It is to be noted, that a sufficient amount of diluted busulfan should be added to compensate for the amount needed to prime the IV tubing; when hanging the infusate, the tubing should be primed with the busulfan solution and connected as close to the patient as possible, i.e. by a 3-way connector at the level of the central venous catheter. After completed infusion, the tubing with remaining busulfan (approximately 12 mL) should be disconnected and discarded. All busulfan infusions should be performed by programmable, controlled-rate pump.

The busulfan will be given by slow intravenous infusion over three (3) hours into a central venous catheter.

CAUTION: DO NOT ADMINISTER AS AN INTRAVENOUS PUSH OR BOLUS.

An infusion pump will be used with the busulfan solutions as prepared above. A new infusion set must be used for administration of each dose. Prior to and following each infusion, flush the catheter line with normal saline or (approximately 5 ml). Start the three-hour infusion at the calculated flow rate.
DO NOT infuse concomitantly with another intravenous solution of unknown compatibility.

If a delay in administration occurs after the infusion solution is prepared, the properly identified container should be kept at room temperature (20-25oC), but administration must be completed within eight (8) hours of preparation including the three (3) hour drug infusion.

Side effects: Dose limiting toxicity is expected to be hematological when used without stem cell support. Other toxicities seen frequently following high-dose busulfan in preparative regimens for bone marrow transplantation include: VOD, nausea, vomiting, pulmonary fibrosis, seizures, rash, and an Addison's-like syndrome.

Mechanism of action: Interferes with DNA replication and transcription of RNA through DNA alkylation, and ultimately results in the disruption of nucleic acid function.

Animal Tumor Data: Busulfan has been shown to be active against a variety of animal neoplasm *in vivo*, including mouse sarcoma 180 and Ehrlich's mouse ascites tumor.

Animal Toxicology: Busulfan fed to rats in an amount equivalent to about 0.5 mg/kg of final body weight per day slowed weight gain and produced bone marrow depression, pancytopenia and cataracts after about 10 weeks. In rats, LD5O was found to be 34 mg/kg intraperitoneally. When the drug was administered on day 13, 14, or 15 of gestation at a dose of 10 mg/kg to

rats, the progeny were prematurely sterile.

Human Pharmacology: Limited pharmacology data are available for the parenteral formulation to be used in this study and is detailed in Attachment II, Preliminary Pharmacokinetic Evaluation of Busulfan in a Phase II human Trial. The pharmacokinetic data suggests that the plasma decay of the formulation fits a two-compartment model. The oral formulation is absorbed from the gastrointestinal tract, and measurable blood levels are obtained within one-half totwo
(0.5-2.0) hours after ingestion. Within three (3) minutes after IV administration in rats, 90% of the drug disappears from the blood; similar rapid decreases in blood concentrations have been reported in man. Busulfan is reported to be extensively metabolized; twelve (12) metabolites have been isolated, but most have not been identified. The drug is slowly excreted in the urine, chiefly as methanesulfonic acid. Ten to fifty percent (10-50%) of a dose is excreted as metabolites within twenty-four (24) hours.

Drug interactions:

Metabolism/Transport

Effects Substrate of

CYP3A4 (major) **Drug**

Interactions

Antifungal Agents (Azole Derivatives, Systemic): May decrease the metabolism of Busulfan. Risk C: Monitor therapy

BCG: Immunosuppressants may diminish the therapeutic effect of BCG. Risk X: Avoid combination

Conivaptan: May increase the serum concentration of CYP3A4 Substrates. Management: Upon completion/discontinuation of conivaptan, allow at least 7 days before initiating therapy with drugs that are CYP3A4 substrates. Risk D: Consider therapy modification

CYP3A4 Inducers (Strong): May increase the metabolism of CYP3A4 Substrates. Risk C: Monitor therapy

CYP3A4 Inhibitors (Moderate): May decrease the metabolism of CYP3A4 Substrates. Risk C: Monitor therapy

CYP3A4 Inhibitors (Strong): May decrease the metabolism of CYP3A4 Substrates. Risk D: Consider therapy modification

Dasatinib: May increase the serum concentration of CYP3A4 Substrates. Risk C: Monitor therapy

Deferasirox: May decrease the serum concentration of CYP3A4 Substrates. Risk C: Monitor therapy

Denosumab: May enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased. Risk C: Monitor therapy

Echinacea: May diminish the therapeutic effect of Immunosuppressants. Risk D: Consider therapy modification

Herbs (CYP3A4 Inducers): May increase the metabolism of CYP3A4 Substrates. Risk C: Monitor therapy

Leflunomide: Immunosuppressants may enhance the adverse/toxic effect of Leflunomide. Specifically, the risk for hematologic toxicity such as pancytopenia, agranulocytosis, and/or thrombocytopenia may be increased. Management: Consider not using a leflunomide loading dose in patients receiving other immunosuppressants. Patients receiving both leflunomide and another immunosuppressant should be monitored for bone marrow suppression at least monthly. Risk D: Consider therapy modification

MetroNIDAZOLE: May increase the serum concentration of Busulfan. Risk D: Consider therapy modification

MetroNIDAZOLE (Systemic): May increase the serum concentration of Busulfan. Risk D: Consider therapy modification

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. Risk X: Avoid combination

Pimecrolimus: May enhance the adverse/toxic effect of Immunosuppressants. Risk X: Avoid combination

Roflumilast: May enhance the immunosuppressive effect of Immunosuppressants. Risk X: Avoid combination

Sipuleucel-T: Immunosuppressants may diminish the therapeutic effect of Sipuleucel-T. Risk C: Monitor therapy

Tacrolimus (Topical): May enhance the adverse/toxic effect of Immunosuppressants. Risk X: Avoid combination

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. Risk C: Monitor therapy

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Risk C: Monitor therapy

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinial infections may develop. Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants.
Risk X: Avoid combination

Vitamin K Antagonists (eg, warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. Risk C: Monitor therapy

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol due to GI irritation.

Food: No clear or firm data on the effect of food on busulfan

bioavailability. Herb/Nutraceutical: Avoid St John's wort (may decrease

busulfan levels). Please add:

Monitoring Parameters

CBC with differential and platelet count, liver function tests (evaluate transaminases, alkaline phosphatase, and bilirubin daily for at least 28 days post transplant)

Administration

Intravenous busulfan should be administered as a 2-hour via central line.

Premedicate with prophylactic anticonvulsant therapy (e.g., phenytoin or Keppra) prior to high-dose busulfan treatment.

14.4. Melphalan

Melphalan is an alkylating agent of the bischloroethylamine type. As a result, its cytotoxicity appears to be related to the extent of its interstrand cross-linking with DNA, probably by binding at the N position of guanine. Like other bifunctional alkylating agents, it is active against both
resting and rapidly dividing tumor cells.[7]

Formulation: Melphalan for injection is supplied as a sterile, nonpyrogenic, freeze-dried powder. Each single-use vial contains melphalan hydrochloride equivalent to 50 mg melphalan and 20 mg povidone.

Preparation: Melphalan for injection must be reconstituted by rapidly injecting 10 mL of the supplied diluent directly into the vial of lyophilized powder using a sterile needle and syringe. This provides a 5 mg/mL solution of melphalan. Immediately dilute the dose to be administered in 0.9% Sodium Chloride Injection, USP, to a concentration not greater than 0.45 mg/mL. Administer the diluted product over a minimum of 15 minutes. Complete the administration within 60 minutes of reconstitution.

Storage and stability: Melphalan for injection vials should be stored at controlled room temperature 15° to 30° C (59° to 86° F) and protected from light. The time between reconstitution/dilution and administration of melphalan should be kept to a minimum because reconstituted and diluted solutions of melphalan are unstable. Over as short a time as 30 minutes, a citrate derivative of melphalan has been detected in reconstituted

material from the reaction of melphalan with the diluent. Upon further dilution with saline, nearly 1% label strength of melphalan hydrolizes every 10 minutes. A precipitate forms if the reconstituted solution is stored at 5°C. Do not refrigerate the reconstituted product.

Adverse events associated with melphalan: The following information on adverse reactions is based on data from both oral and IV administration of melphalan as a single agent, using several different dose schedules for treatment of a wide variety of malignancies. Please refer to the Adverse Reactions and Warnings sections of the product package insert.

Hematologic: The most common side effect is bone marrow suppression. White blood cell count and platelet count nadirs usually occur 2 to 3 weeks after treatment, with recovery in 4 to 5 weeks after treatment. Irreversible bone marrow failure has been reported.

Gastrointestinal: Gastrointestinal disturbances such as nausea and vomiting, diarrhea, and oral ulceration occur infrequently. Hepatic toxicity, including veno-occlusive disease, has been reported.

Drug Interactions

BCG: Immunosuppressants may diminish the therapeutic effect of BCG. Risk X: Avoid combination

Cardiac Glycosides: Antineoplastic Agents may decrease the absorption of Cardiac Glycosides. This may only affect digoxin tablets. Exceptions: Digitoxin. Risk C: Monitor therapy

Carmustine: Melphalan may enhance the adverse/toxic effect of Carmustine. Specifically, melphalan may sensitize patients to carmustine lung toxicity. Risk C: Monitor therapy

CycloSPORINE: Melphalan may enhance the nephrotoxic effect of CycloSPORINE. Risk C: Monitor therapy

CycloSPORINE (Systemic): Melphalan may enhance the nephrotoxic effect of CycloSPORINE (Systemic). Risk C: Monitor therapy

Denosumab: May enhance the adverse/toxic effect of Immunosuppressants. Specifically, the risk for serious infections may be increased. Risk C: Monitor therapy

Echinacea: May diminish the therapeutic effect of Immunosuppressants. Risk D: Consider therapy modification

Leflunomide: Immunosuppressants may enhance the adverse/toxic effect of Leflunomide. Specifically, the risk for hematologic toxicity such as pancytopenia, agranulocytosis, and/or thrombocytopenia may be increased. Management: Consider not using a leflunomide loading dose in patients receiving other immunosuppressants. Patients receiving both leflunomide and another immunosuppressant should be monitored for bone marrow suppression at least monthly. Risk D: Consider therapy modification

Nalidixic Acid: May enhance the adverse/toxic effect of Melphalan. Necrotic enterocolitis

has been reported in pediatric patients. Risk X: Avoid combination

Natalizumab: Immunosuppressants may enhance the adverse/toxic effect of Natalizumab. Specifically, the risk of concurrent infection may be increased. Risk X: Avoid combination

Pimecrolimus: May enhance the adverse/toxic effect of Immunosuppressants. Risk X: Avoid combination

Roflumilast: May enhance the immunosuppressive effect of Immunosuppressants. Risk X: Avoid combination

Sipuleucel-T: Immunosuppressants may diminish the therapeutic effect of Sipuleucel-T. Risk C: Monitor therapy

Tacrolimus (Topical): May enhance the adverse/toxic effect of Immunosuppressants. Risk X: Avoid combination

Trastuzumab: May enhance the neutropenic effect of Immunosuppressants. Risk C: Monitor therapy

Vaccines (Inactivated): Immunosuppressants may diminish the therapeutic effect of Vaccines (Inactivated). Risk C: Monitor therapy

Vaccines (Live): Immunosuppressants may enhance the adverse/toxic effect of Vaccines (Live). Vaccinial infections may develop. Immunosuppressants may diminish the therapeutic effect of Vaccines (Live). Management: Avoid use of live organism vaccines with immunosuppressants; live-attenuated vaccines should not be given for at least 3 months after immunosuppressants.
Risk X: Avoid combination

Vitamin K Antagonists (e.g., warfarin): Antineoplastic Agents may enhance the anticoagulant effect of Vitamin K Antagonists. Antineoplastic Agents may diminish the anticoagulant effect of Vitamin K Antagonists. Risk C: Monitor therapy

Ethanol/Nutrition/Herb Interactions

Ethanol: Avoid ethanol (due to GI

irritation). Food: Food interferes with

oral absorption.

Pharmacodynamics/Kinetics

Note: Pharmacokinetics listed are for FDA-approved

doses. Absorption: Oral: Variable and incomplete

Distribution: Vd: 0.5-0.6 L/kg throughout total body water; low penetration into

CSF Protein binding: 60% to 90%; primarily to albumin, 20% to a1-acid

glycoprotein

Metabolism: Hepatic; chemical hydrolysis to monohydroxymelphalan and dihydroxymelphalan

Bioavailability: Unpredictable; 61% ± 26%, decreasing with repeated doses

Half-life elimination: Terminal: I.V.: 75 minutes; Oral: 1-2

hours Time to peak, serum: ~1-2 hours

Excretion: Oral: Feces (20% to 50%); urine (~10% as unchanged drug)

Hypersensitivity: Acute hypersensitivity reactions including anaphylaxis were reported in 2.4% of 425 patients receiving melphalan for myeloma. These reactions were characterized by urticaria, pruritus, edema, and in some patients, tachycardia, hypotension and bronchospasm.
These patients appeared to respond to antihistamine and corticosteroid therapy. If a hypersensitivity reaction occurs, IV or oral melphalan should not be readministered since hypersensitivity reactions have also been reported with oral melphalan.

Carcinogenesis: Secondary malignancies, including acute nonlymphocytic leukemia, myeloproliferative syndrome, and carcinoma, have been reported in patients with cancer treated with alkylating agents (including melphalan).

Other: Other reported adverse reactions include skin hypersensitivity, skin ulceration at injection site, skin necrosis rarely requiring skin grafting, vasculitis, alopecia, hemolytic anemia, pulmonary fibrosis and interstitial pneumonitis.

Monitoring Parameters
CBC with differential and platelet count, serum electrolytes, serum uric acid
Administration
Oral: Administer on an empty stomach (1 hour prior to or 2 hours after meals)
Parenteral: Due to limited stability, complete administration of I.V. dose should occur within 60 minutes of reconstitution
I.V.: Infuse over 15-30 minutes. Extravasation may cause local tissue damage; administration by slow injection into a fast running I.V. solution into an injection port or via a central line is recommended; do not administer by direct injection into a peripheral vein.
BMT only: Saline-based hydration preceding (2-4 hours), during, and following (6-12 hours) administration reduces risk of drug precipitation in renal tubules. Hydrolysis causes loss of 1% melphalan injection per 10 minutes.

15.0 References

1. Attal M, Harousseau JL, Stoppa AM, et al. A prospective randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. N Engl J Med 1996; 335: 91–7.

2. Child JA, Morgan GJ, Davies FE, et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med 2003; 348: 1875–83.

3. Vesole DH, Crowley JJ, Catchatourian R, et al. High-dose melphalan with autotransplantation for refractory multiple myeloma; Results of a Southwest Oncology Group phase II trial. J Clin Oncol 1999; 17: 2173-9.

4. Shimoni A, Smith TL, Aleman A, et al. Thiotepa, busulfan, cyclophosphamide (TBC)and autologous hematopoietic transplantation: an intensive regimen for the treatment of multiple myeloma. Bone Marrow Transplant 2001: 27: 821-8.

5. Agnastopoulos A, Aleman A, Ayers G, et al. Comparison of high-dose melphalan with a more intensive regimen of thiotepa, busulfan, and cyclophosphamide for patients with multiple myeloma. Cancer 2004; 100: 2607-12.

6. McCarthy PL, Owzar K, Hofmeister CC, et al. Lenalidomide after stem-cell transplantation for multiple myeloma. N Engl J Med 2012;366(19):1770-81.

7. Attal M, Lauwers-Cances V, Marit G, et al. Lenalidomide maintenance after stem-cell transplantation for multiple myeloma. N Engl J Med. 2012 May 10;366(19):1782-91.

8. Sonneveld P, Schmidt-Wolf IG, van der Holt B, et al. Bortezomib induction and maintenance treatment in patients with newly diagnosed multiple myeloma: results of the randomized phase III HOVON-65/ GMMG-HD4 trial. J Clin Oncol 2012;30(24):2946-55.

9. Lahuerta JJ, Mateos MV, Martínez-López J, et al. Influence of pre- and post-transplantation responses on outcome of patients with multiple myeloma: sequential improvement of response and achievement of complete response are associated with longer survival. J Clin Oncol 2008;26:5775–82.

10. Van de Velde HJK, Liu X, Chen G, et al. Complete response correlates with long-term survival and progression-free survival in high-dose therapy in multiple myeloma. Haematologica. 2007; 92:1399–406.

11. Barlogie B, Tricot G. Complete response in myeloma: a Trojan horse? Blood 2006;108:2134.

12. Harousseau J-L, Attal M, Avet-Loiseau H. The role of complete response in multiple myeloma. Blood 2009;114:3139-46.

13. Rawstron AC, Orfao A, Beksac M, et al. Report of the European Myeloma Network on multiparametric flow cytometry in multiple myeloma and related disorders.

Haematologica 2008;93:431-8.

14. Paiva B, Vidriales M-B, Cerveró J, et al. Multiparameter flow cytometric remission is the most relevant prognostic factor for multiple myeloma patients who undergo autologous stem cell transplantation. Blood 2008;112:4017-23.

15. Plunkett W, Huang P, Searcy CE, Gandhi V. Gemcitabine: preclinical pharmacology and mechanisms of action. Semin Oncol 1996;23(5 Suppl 10):3-15.

16. Gandhi V, Plunkett W, Du M, Ayres M, Estey EH. Prolonged infusion of gemcitabine: Clinical and pharmacodynamic studies during a phase I trial in relapsed acute myelogenous leukemia. J Clin Oncol 2002;20:665-73.

17. Kebriaei P, Madden T, Kazerooni R, et al. Intravenous busulfan plus melphalan is a highly effective, well-tolerated preparative regimen for autologous stem cell transplantation in patients with advanced lymphoid malignancies. Biol Blood Marrow Transplant 2011;17:412-20.

18. Nieto Y, Thall P, Valdez B, et al. High-dose infusional gemcitabine combined with busulfan and melphalan with autologous stem-cell transplantation in patients with refractory lymphoid malignancies. Biol Blood Marrow Transplant 2012;18:1677-86.

19. Nieto Y, Shah N, Popat U, et al. High-Dose Gemcitabine Combined With Busulfan and Melphalan (Gem/Bu/Mel) With Autologous Stem-Cell Transplant (ASCT) In Refractory and Relapsed Myeloma. Blood 2013 122:3346.

20. Valdez BC, Nieto Y, Murray D, et al. Epigenetic modifiers the synergistic cytotoxicity of combined nucleoside analog-DNA alkylating agents in lymphoma cell lines. Exp Hematol. 2012;40:800-810.

21. Nieto Y, Thall PF, Valdez BC, et al. Vorinostat (SAHA) Combined With High-Dose Gemcitabine/Busulfan/Melphalan (SAHA/Gem/Bu/Mel) With Autologous Stem-Cell Transplant (ASCT) In Patients With Refractory Lymphomas. Blood 2013 122:2095.

22. Badros A, Burger AM, Philip S, et al. Phase I study of vorinostat in combination with bortezomib for relapsed and refractory multiple myeloma. Clin Cancer Res 2009;15(5250-7).

23. Richardson P, Mitsiades C, Colson K, et al. Phase I trial of oral vorinostat (suberoylaniilide hydroxamic acid, SAHA) in patients with advanced multiple myeloma. Leuk Lymphoma 2008;49:502-7.

24. Weber DM, Graef T, Hussein M, et al. Phase I trial of vorinostat combined with bortezomib for the treatment of relapsing and/or refractory multiple myeloma. Clin Lymphoma Myeloma Leuk 2012;12:319-24.

25. Dimopoulos MA, Jagannath S, Yoon S-S, et al. Vantage 088: Vorinostat in combination with bortezomib in patients with relapsed/refractory multiple myeloma: Results of a global, randomized phase 3 trial. Lancet Oncol. 2013 Oct;14(11):1129-40.

26. Richardson PG1, Schlossman RL, Alsina M, et al. PANORAMA 2: panobinostat in combination with bortezomib and dexamethasone in patients with relapsed and bortezomib-refractory myeloma. Blood. 2013;122(14):2331-7.

27. Richardson PG, Hungria V, Yoon S-S, et al. Panorama 1: A randomized, double-blind, phase 3 study of panobinostat or placebo plus bortezomib and dexamethasone in relapsed or relapsed and refractory multiple myeloma. J Clin Oncol 32:5s, 2014 (suppl; abstr 8510).

28. Durie BGM, Harousseau J-L, San Miguel J, et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467-73.

29. Ling SCW, Lau EKK, Al-SHAbeeb A, et al. Response of myeloma to the proteasome inhibitor bortezomib is correlated with the unfolded protein response regulator XBP-1. Haematologica 2012:97;64-72.