THE UNIVERSITY OF TEXAS
MD Anderson Cancer Center

Protocol Page

Lenalidomide combined with Vorinostat/Gemcitabine/Busulfan/Melphalan with Autologous Stem-Cell Transplantation in Diffuse Large B-Cell Lymphoma of the ABC Subtype
2015-0558

Core Protocol Information

Short Title	Lenalidomide/Vorinostat/Gem/Bu/Mel + AutoSCT in DLBCL ABC Subtype
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Full Title:	Lenalidomide combined with Vorinostat/Gemcitabine/Busulfan/Melphalan with Autologous Stem-Cell Transplantation in Diffuse Large B-Cell Lymphoma of the ABC Subtype
Public Description:	The goal of this clinical research study is to find the highest tolerable dose of lenalidomide that can be given in combination with vorinostat, gemcitabine, busulfan, and melphalan, with a stem cell transplant, and with or without rituximab. Researchers also want to learn about the safety and effectiveness of this combination.
Protocol Type:	Standard Protocol
Protocol Phase:	Phase I/Phase II
Version Status:	Terminated 04/09/2019
Version:	09
Submitted by:	Peggy S. LeCompte--6/6/2018 10:32:09 AM
OPR Action:	Accepted by: Inar Y. Graur -- 6/6/2018 3:54:01 PM

Which Committee will review this protocol?

◉ The Clinical Research Committee - (CRC)

Protocol Body

1.0 Objectives

1.1 Primary Objectives:

- 1.1.1 Establish the maximum tolerated dose (MTD) of lenalidomide combined with vorinostat/gemcitabine/busulfan/melphalan with autologous stem-cell transplant ASCT)
- 1.1.2 Determine 2-year event-free survival (EFS)

1.2 Secondary Objectives:

- 1.2.1 Assess 2-year overall survival (OS)
- 1.2.2 Determine complete remission (CR) rate
- 1.2.3 Determine overall remission rate (ORR)
- 1.2.4 Describe the toxicity profile
- 1.2.5 Evaluate IRF4, SPIB, STAT1, p-STAT1, CARD11, I-kappa-Kinase-beta and p-I-kappa-Kinase-beta in PBMNC pre- and post-treatment (at baseline and on day -1)

2.0 Background

More active high-dose chemotherapy (HDC) regimens are needed for patients with refractory lymphoid tumors receiving an ASCT. To this end we have developed new regimens through a series of sequential trials following two overarching principles: Nucleoside analogue-induced inhibition of repair of alkylator-induced DNA damage, and epigenetic modulation of HDC. Such regimens have included busulfan/melphalan, gemcitabine/busulfan/melphalan and vorinostat/gemcitabine/busulfan/melphalan.

2.1 Busulfan/Melphalan (BuMel)

DNA-targeting alkylating agents form the backbone of most hematopoietic cell transplantation regimens based on their log-linear increases in tumor killing with increasing dose. The cytotoxic principle is believed to be DNA damage produced by direct linking to individual bases and cross-linking of the complementary DNA strands.

We developed a high-dose regimen of pharmacokinetically dose-adjusted intravenous busulfan combined with melphalan (BuMel, protocol 2004-0190), which was well tolerated with minimal hepatic toxicity (1 case of mild venoocclusive disease among 102 patients enrolled),[1] in contrast to earlier versions of this regimen. Thus, we considered BuMel a safe alkylator-based platform for our subsequent studies.

2.2 Gemcitabine/Busulfan/Melphalan (GemBuMel)

Critical factors modulating alkylating agent activity are the extent of DNA damage and repair. Thus, combined use of alkylating agents and drugs known to inhibit DNA repair, such as the nucleoside analogue gemcitabine, produces additive or synergistic effects. To exploit their synergy, we combined high-dose gemcitabine with BuMel (GemBuMel) (protocol 2006-0803), based on the following principles: [2]

1. Individual activity of the three drugs against lymphoid tumors.
2. Synergy between gemcitabine and the alkylating agents, based on inhibition of DNA

damage repair.

3. Improved antitumor activity of gemcitabine when administered at a prolonged fixed dose (FDR) compared to shorter infusions. Gemcitabine is activated by intracellular phosphorylation by deoxycitidine kinase (dCK), a rate-limited process. Previous studies had shown that an extracellular gemcitabine concentration below 20 micromolar resulted in optimal gemcitabine incorporation into DNA, and that higher concentrations saturated dCK. A FDR of 10 mg/m2/min avoids saturation of dCK and increases the antitumor activity and myelotoxicity of gemcitabine. The latter result is easily overcome in the transplant setting with stem-cell support.
4. Minimal overlapping extramedullary toxicity of the three agents.
5. Optimization of busulfan therapy by therapeutic drug monitoring.

In this dose- and schedule-finding trial we administered gemcitabine as a loading dose of 75 mg/m2 (calculated to reach a steady state concentration of 15 micromolar), followed by a continuous infusion at 10 mg/m2/min. The length of infusion of gemcitabine was escalated in successive cohorts. We enrolled 133 patients with refractory lymphoid tumors receiving an autologous transplant, including 80 with Hodgkin's lymphoma (HL) and 46 with non-Hodgkin's lymphoma (NHL). The optimal schedule was determined to be two doses of gemcitabine, one before each of the first doses of busulfan and melphalan. The optimal length of infusion of gemcitabine, following its loading dose, was established at 4.5 hours.

Table 1. GemBuMel schedule

Day	-8	-7	-6	-5	-4	-3	-2	-1	0
Gemcitabine 75 mg/m2 followed by 4.5-hr CI at 10 mg/m2/min	X					X			
Busulfan (target AUC: 4,000 microM.min/day)	X	X	X	X					
Melphalan 60 mg/m2/day						X	X		
PBPC infusion									X

Toxicity Profile of GemBuMel

At its MTD GemBuMel caused reversible mucositis (60% grade 2, 13% grade 3), skin toxicity (13% grade 2) and self-limited elevation of the transaminases (21% grade 2, 7% grade 3), with no grade 4 or 5 toxicities.

Antitumor Activity of GemBuMel

GemBuMel was highly active in all lymphoid diagnoses. The EFS and OS rates of patients with refractory HL were 61% and 94%, respectively, at current median follow-up of 24 (range, 3-50) months. These results compared favorably with those observed in two separate contemporaneous cohorts of refractory HL patients treated at our department since January 2005 with BEAM (N=79) or BuMel (N=38).[3]

All of these patients met eligibility criteria for 2006-0803 but either received BEAM off protocol

or were enrolled in the phase II trial of BuMel (2004-0190). The GemBuMel cohort had significantly worse prognostic features than the BEAM or BuMel groups, specifically a higher prevalence of PET-positive disease at the time of HDC, extranodal disease at the time of relapse and a higher number of prior relapses. In spite of its worse prognostic features, the GemBuMel group had significantly better EFS and OS than the BEAM or BuMel groups (Fig. 1).

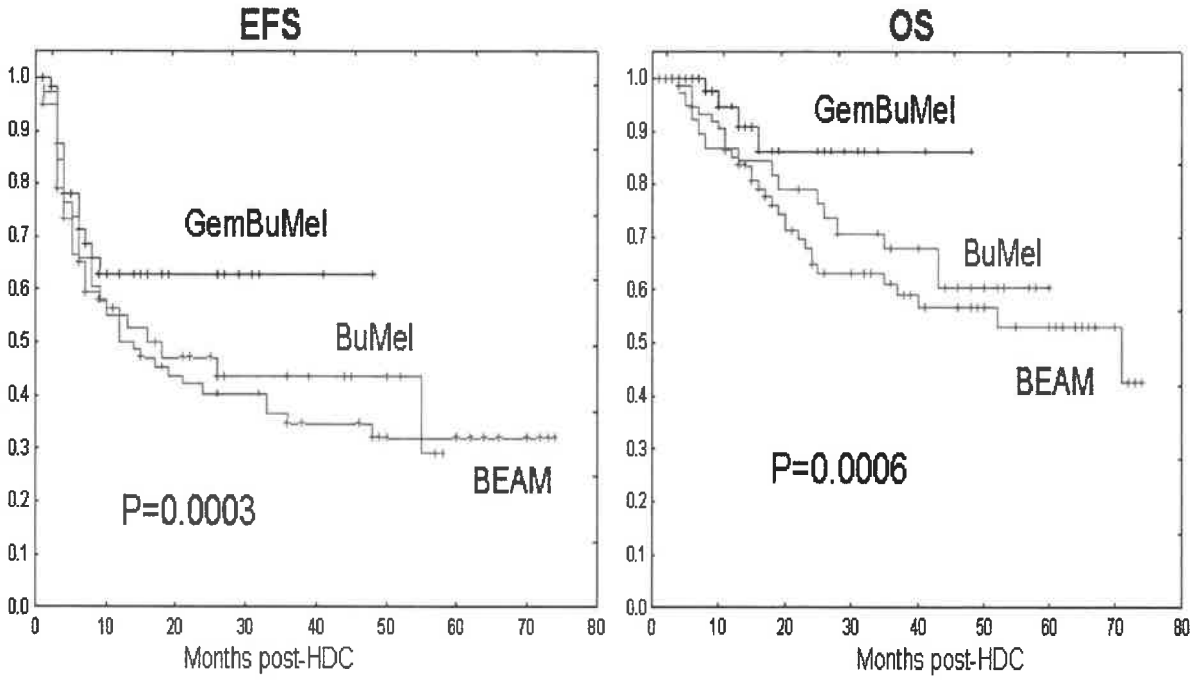


Fig 1. Comparison of GemBuMel, BEAM and BuMel in all patients with refractory HD treated since 1/2005.

2.3 Vorinostat/GemBuMel

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 (HATs) 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.

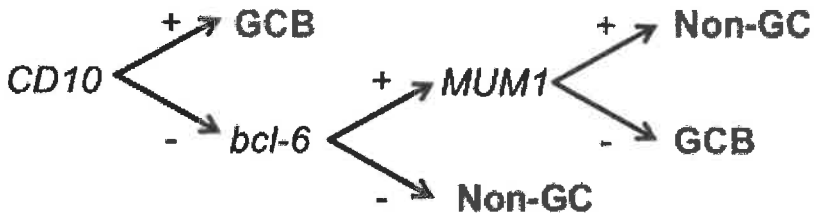
Vorinostat is an inhibitor of all classes of HDACs, inducing cell cycle arrest, differentiation and apoptosis. The duration of vorinostat-induced histone hyperacetylation is directly proportional to its dose. Vorinostat induces relaxation and decondensation of the chromatin, rendering the DNA more accessible to DNA-targeting agents such as alkylators and nucleoside analogues. Preclinical experiments by our collaborators Valdez and Andersson have shown striking synergy, determined by apoptosis or survival readouts, when vorinostat was added to GemBuMel (all drugs present at clinically achievable levels), in lymphoma B-cell (Daudi) and T-cell (J45) lines, which were resistant to those agents when exposed to them separately. The

optimal schedule of the combination of SAHA with GemBuMel was determined to be simultaneous SAHA/GemBuMel exposure, superior to sequential SAHA -> GemBuMel or GemBuMel -> SAHA. Lymphoma cells exposed to SAHA/gemcitabine/busulfan/melphalan experienced increased cleavage of PARP1 and increase in gamma-H2AX, reflecting increased DNA damage response.[4]

These observations led to clinical trial 2011-0407 to evaluate a short schedule of vorinostat combined with GemBuMel with autologous stem cell support. We gradually escalated the dose of vorinostat from 200 to 1,000 mg daily, with no regimen-related deaths and a toxicity profile comparable to that previously observed with GemBuMel alone. We did not see significant prolongations of QT from before to after treatment. We enrolled 78 patients (52 DLBCL, 20 HL, 6 T-NHL).[5] At median follow-up of 25 (16-41) months, the EFS and OS rates are 61.5% and 73% (DLBCL) and 45% and 80% (HL).

2.4 Treatment of DLBCL According to their Cell of Origin (COO) Subtype

Genomewide molecular profiling has revealed new subtypes of lymphoma that originate from lymphocytes that differ in developmental stage and that use distinct oncogenic programs, yet are indistinguishable under the microscope: Germinal-center B-cell-like (GCB) and activated B-cell-like (ABC) subtypes.[6] Until recently, COO classification of DLBCL had little influence on clinical practice. However, COO classifications have become more clinically relevant for two important reasons: (1) The development of new real-time COO assessment methods, including immunohistochemistry (IHC) and Nanostring technology, and (2) the identification of novel agents with subtype-specific activity, particularly against ABC DLBCL. The Hans algorithm is the most widely IHC method to establish COO.



Patients with ABC DLBCL have significantly worse outcome when treated with R-CHOP in first line.[7] Whether patients with relapsed ABC DLBCL have worse prognosis after HDC than those with relapsed GCB DLBCL is an unsettled issue. Several small single-center retrospective analyses have not detected COO differences in outcome after HDC, which suggests that HDC may overcome the poor prognostic features of the ABC subtype.[8, 9] In contrast, the prospective randomized trial CORAL showed worse outcomes after DHAP and BEAM (but not after RICE and BEAM) for the ABC subtype as compared to the GCB subtype.[10]

ABC lymphomas depend heavily on the antiapoptotic NFkB pathway, which is constitutively active in this subtype. NFkB is activated by three molecules: CARD11, BCL10 and MALT1 (CBM complex).[6] In approximately 10% of patients, CARD11 acquires activating mutations. NFkB can also be chronically activated by alterations that take place upstream of CBM, at the B-cell receptor level. About 20% of ABC lymphomas have activating mutations of the signaling subunits of the BCR, CD79A and CD79B. Furthermore, inactivation of A20, a negative regulator of NFkB signaling, occurs in ABC, but not GCB, lymphomas.

Therefore, NFkB is an attractive target in the treatment of ABC lymphomas. Lenalidomide has shown significant single-agent activity in relapsed ABC, but not GCB, DLBCL.[11] Its response rate in relapsed ABC DLBCL is 55%, vs. only 9% in GCB DLBCL. Further, the combination of lenalidomide-Rituximab-CHOP has been shown to overcome the adverse prognosis of ABC with outcomes comparable to those of R-CHOP in GCB tumors. [12] The mechanism of action of lenalidomide on ABC DLBCL is thought to be through binding to cereblon, which decreases NFkB and the transcription factor IRF4.[13]

Combinations of lenalidomide with alkylators and with vorinostat are synergistic.[14] Shah and Qazilbash from our group have shown that lenalidomide can be safely combined, at doses up to 100 mg/day x 7 days, with high-dose melphalan in patients with relapsed myeloma, with resulting marked antitumor activity.[15] The toxicity of lenalidomide/melphalan was not substantially different from that seen after melphalan alone.

Therefore, lenalidomide can be of benefit to patients with ABC DLBCL receiving HDC. We hypothesize that the combination of lenalidomide with vorinostat/GemBuMel is safe and active in patients with this DLBCL subtype.

3.0 Patient Eligibility

Inclusion criteria:

1. Age 15-65
2. Patients with ABC (determined by immunohistochemistry using the Hans algorithm) DLBCL with primary refractory disease, relapse <12 months after initial therapy, secondary IPI >1, less than partial response to salvage treatment or exposure to >3 salvage regimens
3. Adequate renal function, as defined by an estimated serum creatinine clearance >/= 50 ml/min (MDRD method) and/or serum creatinine </= 1.8 mg/dL
4. Adequate hepatic function (SGOT and/or SGPT </= 3 x ULN; bilirubin and ALP </= 2 x ULN
5. Adequate pulmonary function with FEV1, FVC and DLCO (corrected for Hgb) >/= 50%
6. Adequate cardiac function with left ventricular ejection fraction >/= 40%. No uncontrolled arrhythmias or symptomatic cardiac disease
7. ECOG performance status <2
8. Negative Beta HCG in woman with child-bearing potential
9. All study participants must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of the REMS® program.
10. Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program.

Exclusion criteria:

1. Grade >/= 3 non-hematologic toxicity from previous therapy that has not resolved to </= G1
2. Prior whole brain irradiation
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. HIV infection, unless receiving effective antiretroviral therapy with undetectable viral load and normal CD4 counts
7. Radiation therapy in the month prior to enrollment
8. History of arterial thromboembolic events in the past 3 months and of venous

thromboembolic events in the past month
9. History of hypersensitivity of lenalidomide or thalidomide

4.0 Pretreatment evaluation

4.1 The studies listed below will be done within 30 days prior to starting treatment, only if not already done within this time period:

Lab work:
Serum HCG in all female patients of childbearing potential, CBC with differential, SGPT, SGOT, calcium, glucose, uric acid, magnesium, serum bilirubin, BUN and creatinine, serum protein, albumin, alkaline phosphatase, electrolytes, PT and PTT, complete urinalysis, blood typing and infectious disease panel.
Chest X ray.
Pulmonary function tests with DLCO.
EKG.
Echocardiogram or MUGA.
PET/CT.

4.2 The following will be performed before admission if clinically indicated:
Brain MRI.
Bone marrow biopsy and aspirate with cytogenetic studies.

4.3 Pharmacodynamic studies (optional for patients participating in this trial):
We will determine IRF4, SPIB, STAT1, p-STAT1, CARD11, I-kappa-K-beta and p-I-kappa-K-beta in PBMNC pre- and post-treatment (at baseline and on day -1). The blood samples will be analyzed in the laboratory of Drs. Valdez and Andersson.

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. All protocol participants will be registered in the institutional CORe system.

6.0 Treatment Plan

6.1 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.

Table 2.A. Lenalidomide-Vorinostat-GemBuMel schedule (Inpatient Busulfan Test Dose)

Day	-13	-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2
Palifermin per standard of care	X	X	X											X	X	X
Admission			X													
Busulfan test dose				X												
Lenalidomide 50-100 mg PO daily					X	X	X	X	X	X	X	X				
Vorinostat					X	X	X	X	X	X	X	X				
Gemcitabine						X					X					
Busulfan						X	X	X	X							
Melphalan											X	X				
Rituximab					X											
PBPC infusion														X		

Table 2.B. Lenalidomide-Vorinostat-GemBuMel schedule (Outpatient Busulfan Test Dose)

Day		-12	-11	-10	-9	-8	-7	-6	-5	-4	-3	-2	-1	0	1	2
Palifermin per standard of care		X	X	X										X	X	X
Admission				X												
Lenalidomide 50-100 mg PO daily					X	X	X	X	X	X	X	X				
Vorinostat					X	X	X	X	X	X	X	X				
Gemcitabine						X					X					
Busulfan test dose	X															
Busulfan						X	X	X	X							
Melphalan											X	X				
Rituximab					X											
PBPC infusion														X		

Chemotherapy agents' doses and administration.
Chemotherapy agents used in the proposed treatment plans will be dosed and administered as outlined below.

Vorinostat and lenalidomide will be administered orally at the same time within 1 hour before the daily dose of chemotherapy. Repeat a full dose if emesis occurs within 30 minutes and tablets/tablet fragments are found in the vomit. If given inpatient, nurse should stay and witness the patient taking the drugs.

Gemcitabine will be administered as a loading dose of 75 mg/m^2 followed by prolonged infusion of 4.5 hours on days -8 and -3. It will be followed immediately by busulfan on day -8 and melphalan on day -3.

Busulfan pharmacokinetic-guided treatment (PK-guided). The Busulfan test dose can be administered either as an outpatient (preferable) before admission, or as an inpatient on day -10. The "test dose" of 32 mg/m^2 will be based on actual body weight to be administrated over 60 minutes. Busulfan pharmacokinetics will be performed with the test dose and the first dose

on day -8. The doses of days -6 and -5 will be subsequently adjusted to target an AUC of 4,000 microMol.min^{-1}.

In the event that PK adjusting were 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.

Patients with CD20+ tumors will receive rituximab 375 mg/m^2 on day -9 in the AM as an inpatient.

6.2 Supportive Treatment

Patients will receive standard supportive treatment as outlined below.

1. Dexamethasone 8 mg IV BID from day -8 AM to day -2 PM. Omit any other dexamethasone for chemotherapy premedication.
2. G-CSF per departmental standard of care.
3. Mucositis supportive care:
   - 3.1. Palifermin per departmental standard of care with 3 doses to be administered prior to starting chemotherapy and 3 doses starting on day 0. Doses can be capped at vial size.
   - 3.2. Caphosol oral rinses 30 mL four times a day will be used from day -8.
   - 3.3. Oral glutamine, 15 g four times a day, swished, gargled and swallowed will be started on day -8
4. Pyridoxine 100 mg IV/PO TID from day -1.
5. Enoxaparin 40 mg SQ daily from admission until platelet count drops below 50,000/mm3.

Other supportive treatment such as antiemetics or infection prophylaxis, as per departmental standard of care.

6.3 Dose Escalation of Lenalidomide

Dose escalation will proceed as shown on Table 3 (levels 1a-3a). If level 1a is too toxic, the dose of gemcitabine will be de-escalated to 2,475 and lenalidomide will be escalated as shown (levels 1b-3b).

Table 3. Dose Escalation

Level	Lenalidomide (mg/day)	Vorinostat (mg/day)	Gemcitabine (mg/m2/day)	Busulfan (mg/m2/d or AUC/day)	Melphalan (mg/m2/d)
1a	50	1000	2775	100 or 4,000	60
2a	75	1000	2775	100 or 4,000	60
3a	100	1000	2775	100 or 4,000	60
1b	50	1000	2475	100 or 4,000	60
2b	75	1000	2475	100 or 4,000	60
3b	100	1000	2475	100 or 4,000	60

6.4 Recommendations for Post-Transplant Radiotherapy

Involved field radiotherapy, starting 4-6 weeks after transplant, should be considered for patients who have engrafted neutrophils and platelets and who presented bulky (>5 cm) PET+ lesions at HDC (recommended) or have persistent PET+ lesions at day +30 post-SCT (strongly recommended). It should also be considered for PET+ lesions measuring <5 cm at HDC, particularly if previously bulky at the time of relapse or progression. In all cases feasibility of radiotherapy will be assessed based on prior radiation exposure and possibility to treat all relevant sites of disease.

7.0 Post-treatment evaluation

During the treatment administration and until day +100 all patients will be monitored for toxicity, which will be evaluated according to CTCAE v4.0. While admitted in hospital, patients will be monitored on a regular basis. Once discharged, patient will come once a week or as determined by the primary physician, until day +30. Treatment completion assessment will be performed around day +100.

Antitumor responses will be evaluated according to the Lugano Revised Criteria for Response Assessment.[16]

7.1 Treatment completion assessment. To be performed around day +100.

History, physical exam
Lab work: CBC, differential, platelets, SGPT, calcium, glucose, uric acid, magnesium, serum bilirubin, BUN and creatinine, serum protein, albumin, alkaline phosphatase, electrolytes, complete urinalysis.

Tumor response: PET/CT or CT of the chest, abdomen and pelvis, as medically indicated. Bone marrow aspiration and biopsy if medically indicated.

7.2 Off-Study Criteria: study duration will be the time from study registration until death, patient request, or day +100 after transplantation, whichever occurs first.

8.0 Determination of body surface area

For patients whose actual body weight is $\leq$ 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 and rituximab (CD20+ tumors). 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.

9.0 Determination of dose limiting toxicity (DLT)

9.1 Starting Dose and Dose Escalation

Patients will be enrolled as described in the statistical section. No more than 2 patients will be enrolled at any one time in a new dose level. Until the toxicities of at least 1 of those 2 patients are assessed and determined not to be DLT, no more patients will be enrolled at the new dose level. If, based on medical considerations, a third patient has to initiate treatment before that time, this third patient will be enrolled at the prior dose level.

9.2 Definition of DLT

Dose limiting toxicity will be defined as any grade 4 or 5 non-hematological, non-infectious toxicity attributable to Lenalidomide/Vorinostat/GemBuMel, as well as grade 3 mucositis and grade 3 skin toxicity lasting for more than 5 days at their peak severity. Consideration of DLT will exclude asymptomatic and self-limited elevation of the transaminases as well as laboratory serum metabolic values not reflecting end-organ function. The DLT assessment period will be 2 weeks.

10.0 Reporting Requirements

Patients will be followed up to day +100 after transplant 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.

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

Gastrointestinal: nausea and vomiting, diarrhea, oral mucositis
Hepatic: self-limited elevations of liver function enzymes; venoocclusive disease
Pulmonary: acute dyspnea, pulmonary fibrosis and interstitial pneumonitis.
Skin: rash.

10.2 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, would not be considered adverse events, and will not be collected in the study database.
Myelosuppression-related: neutropenia, anemia thrombocytopenia, platelets and RBCs 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.

10.3 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.

SAEs will be reported to the PI or his designate, who in turn will notify the IRB following institutional policy.

10.4 Pregnancies

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on lenalidomide, or within 28 days of the subject's last dose of lenalidomide, are considered immediately reportable events. Lenalidomide is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile or email using the Pregnancy Initial Report Form. The female subject may be referred to an obstetrician-gynecologist (not necessarily one with reproductive toxicity experience) or another appropriate healthcare profession for further evaluation.

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

10.5 Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking lenalidomide should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

10.6 Overdose

Overdose, as defined for this protocol, refers to lenalidomide dosing only. On a per dose basis, an overdose is defined as any dose that is higher than the protocol-specified dose of lenalidomide assigned to a given patient, regardless of any associated adverse events or sequelae.

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form.

10.7 Celgene Drug Safety Contact Information:

Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

10.8 Expedited Reporting by Investigator to Celgene

See Appendix B. - Celgene's Adverse Event Reporting/Drug Safety/Pharmacovigilance procedures.

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events of being related to lenalidomide based on the Investigator Brochure. In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (RV-CL-DLBCL-PI-006079) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

11.0 Statistical considerations

Phase 1 - Dose Escalation

The clinical trial will be a phase I design with an expansion phase. We will employ the Bayesian design method developed by Ji et al. to find the maximum tolerated dose (MTD) of the treatment combination of lenalidomide + vorinostat + gemcitabine + busulfan + melphalan + rituximab.[17] Three dose levels of lenalidomide will be considered (Table 4). The DLTs are defined in section 9.2 of the protocol. The targeted toxicity rate is 35%. We assume the prior distribution of the DLT rate δ is beta (1,1) and an equivalence interval of (0.30, 0.40). A maximum of 16 patients will be enrolled at the following dose levels:

Table 4. Treatment Doses to be Investigated

Level	Lenalidomide (mg/day)	Vorinostat (mg/day)	Gemcitabine (mg/m2/day)	Busulfan (mg/m2/d or AUC/day)	Melphalan (mg/m2/d)
1a	50	1000	2775	100 or 4,000	60
2a	75	1000	2775	100 or 4,000	60
3a	100	1000	2775	100 or 4,000	60
1b	50	1000	2475	100 or 4,000	60
2b	75	1000	2475	100 or 4,000	60
3b	100	1000	2475	100 or 4,000	60

We will begin by enrolling 2 patients at Dose Level 1a, and we will enroll patients in cohorts of size 2. Table 5 illustrates the trial monitoring chart to determine whether one should:

- Escalate to the next higher dose (E),
- Continue to enroll patients at the current dose (S),
- De-escalate to the next lower dose (D),
- Or determine that the current dose is unacceptable (DU)

This decision will be based on the number of patients treated at the current dose and the number of observed toxicities among those patients.

Table 5. Dose-Escalation Rules

Number of DLTs \ Number of Patients	2	4	6	8	10	12	14	16
0	E	E	E	E	E	E	E	E
1	S	S	E	E	E	E	E	E
2	DU	S	S	S	E	E	E	E
3		D	S	S	S	S	E	E
4		DU	D	S	S	S	S	S
5			DU	D	S	S	S	S
6			DU	DU	D	S	S	S
7				DU	DU	DU	S	S
8				DU	DU	DU	DU	S
9					DU	DU	DU	DU

E = Escalate to the next higher dose
S = Stay at the current dose
D = De-escalate to the next lower dose
U = The current dose is unacceptably toxic
MTD = 35%
Sample Size = 16
Epsilon1 = 0.05
Epsilon2 = 0.05

There are two exceptions to the above decisions:

1. If the current dose level is the lowest dose and the action is DU, then the dose of gemcitabine will be decreased and lenalidomide dose escalation will resume as described.

2. If the current dose level is the highest dose and the action is E, then treat future patients at the highest dose.

The MTD is defined as the highest dose for which the posterior probability of toxicity is closest to 35%, among all the tried doses i for which Pr (δ_i > 0.35 | data) < 0.95. Table 6 summarizes the operating characteristics of the proposed design for this trial for 4 scenarios defined by different toxicity rates for 4 doses. These operating characteristics are based on 2000 simulations of the trial.

Table 6. Operating Characteristics of Study Design

Dose	1b	1a	2a	3a	No Dose
Scenario 1					
True Toxicity Rate	0.025	0.05	0.15	0.25	
Selection Probability	0.002	0.029	0.154	0.816	0
Avg. # of Patients Treated	0.02	2.8	4.2	9.0	
Total Patients	16.0				
Overall Toxicity	0.187				
Scenario 2					
True Toxicity Rate	0.10	0.20	0.35	0.45	
Selection Probability	0.079	0.235	0.414	0.274	0
Avg. # of Patients Treated	0.6	6.1	6.0	3.3	
Total Patients	16.0				
Overall Toxicity	0.300				
Scenario 3					
True Toxicity Rate	0.35	0.45	0.55	0.65	
Selection Probability	0.59	0.202	0.112	0.017	0.081
Avg. # of Patients Treated	4.1	8.5	2.3	0.4	
Total Patients	15.4				
Overall Toxicity	0.443				
Scenario 4					
True Toxicity Rate	0.55	0.65	0.75	0.85	
Selection Probability	0.476	0.029	0.008	0.006	0.488
Avg. # of Patients Treated	6.6	5.7	0.5	0.0	
Total Patients	12.7				
Overall Toxicity	0.603				

Phase 2 - Expansion

Additional patients will be enrolled at the MTD dose level established in the Phase I design, up to a maximum combined accrual of 30 patients in both phases. Continuous monitoring of DLTs will be assessed for all patients in the expansion phase, beginning with the first five patients.

Assuming a prior beta distribution of (0.7, 1.3), the expansion phase will terminate if the Pr (δ_t > 0.35 | data) > 0.85, where δ_t is the DLT rate attributable to the treatment. The decision rule for terminating for toxicity is presented in Table 7 and the operating characteristics for this rule are presented in Table 8. The method used to produce the decision rule and operating characteristics was designed by Thall, Simon, and Estey.[18]

Table 7 Stopping Boundaries.

If there are these many DLTs or more	4	5	6	7	8	9	10
Stop if these many patients (or fewer) have been entered	7	9	11	14	16	18	19

Table 8 Operating Characteristics.

True % of DLTs	Pr (stopping early)	Median Sample Size (interquartile)
0.05	0.00	20 (20, 20)
0.20	0.04	20 (20, 20)
0.35	0.31	20 (11, 20)
0.50	0.74	7 (6, 20)
0.65	0.97	6 (5, 7)

Sample size and power

The primary objective of Phase 2 is to determine the efficacy as assessed by 2-year EFS. Assuming the 2-year EFS for standard treatment is 30% (historical control), the accrual rate is 1 year with a 2 year follow-up, a sample size of 20 patients treated at the MTD would achieve 81% power to detect a difference of 25% in EFS (55% for experimental treatment) using a one-sided significance level of 5% (SWOG statistical tools for one arm survival).

Data Analysis

Demographic and clinical characteristics will be summarized using descriptive statistics by dose level. The number of patients with DLTs will be reported at each dose level. OS will be computed from the date of ASCT to last known vital sign. Patients who are alive at the last follow-up date will be censored. EFS will be computed from the date of ASCT to date of disease progression or death. Patients who are alive and do not experience progression will be censored. EFS and OS will be estimated using the Kaplan-Meier method. CR rate and ORR will be tabulated and the proportion of patients experiencing response will be estimated with a corresponding 95% confidence interval. Patients who discontinue before the response assessment period will be considered non-responders. Additional analyses may be performed as appropriate.

12.0 Background Drug Information

12.1. Lenalidomide

Common trade named: Revlimid®

Class
Angiogenesis inhibitor
immunomodulating agents (IMiDs).
Antineoplastic agent
Tumor Necrosis factor (TNF) blocking agent

Dosage, adult (usual)
- **Myelodysplastic Syndromes:** The recommended starting dose is 10 mg daily orally. Dosing is continued or modified based upon clinical and laboratory findings.
- **Myeloma**: 25 mg once daily orally for 21 out of 28 days

Administration
Lenalidomide capsule are administrated orally with water. Patients should not break, chew or open the capsules

Monitoring
Platelet count, hemoglobin, WBC, and differential at start of therapy and prior to each subsequent course of therapy; serum creatinine, liver function tests, thyroid function tests; monitor for signs and symptoms of thromboembolism.

Women of childbearing age must have a pregnancy test within 10-14 days and 24 hours before lenalidomide, then 4 weeks after therapy discontinued.

Drug Dispensing Requirements
Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with the Celgene Corporation's Revlimid REMS® program. Per standard Revlimid REMS® program requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in, and must comply with, all requirements of the Revlimid REMS® program.

Further information about the Revlimid REMS® program is available at www.celgeneriskmanagement.com.

Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

Pregnancy Testing
Females must follow pregnancy testing requirements as outlined in the Revlimid REMS® program.

Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

For FCBP, pregnancy tests must occur within 10 - 14 days and again within 24 hours prior to prescribing lenalidomide. (prescriptions must be filled within 7 days) and at Day +30 (+/- 2days) post the last dose (D-2) of lenalidomide. (See Appendix G.: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).

Indications
- FDA labeled indications
- Low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities.
-Multiple myeloma in combination with dexamethasone is indicated for the treatment of multiple myeloma patients who have received at least one prior therapy.
- Non FDA labeled indications
- Metastatic malignant melanoma (investigational use): 10-25 mg once daily
- Myelofibrosis (investigational use): 5-10 mg once daily

Contraindications
- Hypersensitivity of lenalidomide products
- Previous resistance to the drug
- Pregnancy

Precautions
- No formal studies have been conducted in patients with renal impairment. this drug is known to be excreted by the kidney, and the risk of adverse reactions to this drug may be greater in patients with impaired renal function.
- Patients with Hepatic Disease: The pharmacokinetics of lenalidomide in patients with hepatic impairment have not been studied.
- Age: lenalidomide has been used in multiple myeloma (MM) clinical trials in patients up to 86 years of age.
- Check pregnancy test before administering lenalidomide
- Check CBC before administering lenalidomide
- Hypersensitivity reaction; do not re challenge
- Impairment of fertility
- Mutagenic, potentially
- Severe bone marrow depression
- Women of childbearing age should avoid becoming pregnant
- monitor for signs and symptoms of thromboembolism: prophylaxis

Adverse effects
>10%:
- Cardiovascular: Peripheral edema (8% to 21%) - Central nervous system: Fatigue (31% to 38%), pyrexia (21% to 23%), dizziness (20% to 21%), headache (20%)
- Dermatologic: Pruritus (42%), rash (16% to 36%), dry skin (14%)
- Endocrine & metabolic: Hyperglycemia (15%), hypokalemia (11%)
- Gastrointestinal: Diarrhea (29% to 49%), constipation (24% to 39%), nausea (22% to 24%), weight loss (18%), dyspepsia (14%), anorexia (10% to 14%), taste perversion (6% to 13%), abdominal pain (8% to 12%)
- Genitourinary: Urinary tract infection (11%)
- Hematologic: Thrombocytopenia (17% to 62%; grades 3/4:10% to 50%), neutropenia (28% to 59%; grades 3/4: 21% to 53%), anemia (12% to 24%: grades 3/4: 6% to 9%); myelosuppression is dose-dependent and reversible with treatment interruption and/or dose reduction
- Neuromuscular & skeletal: Muscle cramp (18% to 30%), arthralgia (10% to 22%), back pain (15% to 21%), tremor (20%), weakness (15%), paresthesia (12%), limb pain (11%)
- Ocular: Blurred vision (15%)

- Respiratory: Nasopharyngitis (23%), cough (20%), dyspnea (7% to 20%), pharyngitis (16%), epistaxis (15%), upper respiratory infection (14% to 15%), pneumonia (11% to 12%)

Pregnancy category - X
- Breast feeding: Infant risk cannot be ruled out

- How supplied: 5 mg, 10 mg, 15 mg and 25 mg capsules

12.2 Rituximab (Rituxan®)

Description: Rituximab is a monoclonal antibody targeted against CD20 primarily found on B lymphocytes. Rituximab causes cell lysis through complement mediated cytotoxicity and antibody-dependent cytotoxicity.

Preparation and stability: Dilute with NS or D5W to a final concentration of 1-4 mg/mL. Solution is stable at 2-8 degrees C for 24 hours and additional 24 hours at room temperature. Rituximab is supplied as 100 mg and 500 mg vials.

Administration: Administer according to institutional standards.

Adverse reactions: infusion reactions (fever, chills, hypotension), rarely anaphylaxis, acute respiratory distress syndrome, arrhythmias, lymphopenia, infection, hepatitis B reactivation, rarely progressive multifocal leukoencephalopathy, skin rash, tumor lysis syndrome, nausea/vomiting, arthralgias, myalgias, and severe mucocutaneous reactions (including Stevens-Johnson Syndrome and toxic epidermal necrolysis).

Storage: Diluted solutions of Rituximab should be stored refrigerated at 2-8 degrees C. Rituximab vials should be stored at 2-8 degrees C. and protected from direct sunlight. Do not freeze or shake.

See package insert for additional information.

12.3. Vorinostat (SAHA)

Therapeutic Category: Antineoplastic Agent, Histone Deacetylase Inhibitor
Adverse reactions:

>10%:

Cardiovascular: Peripheral edema (13%)

Central nervous system: Fatigue (52%), chills (16%), dizziness (15%), headache (12%), fever (11%)

Dermatologic: Alopecia (19%), pruritus (12%)

Endocrine & metabolic: Hyperglycemia (8% to 69%; grade 3: 5%), dehydration (1% to 16%)

Gastrointestinal: Diarrhea (52%), nausea (41%), taste alteration (28%), anorexia (24%), weight loss (21%), xerostomia (16%), constipation (15%), vomiting (15%), appetite decreased (14%)

Hematologic: Thrombocytopenia (26%; grades 3/4: 6%), anemia (14%; grades 3/4: 2%)

Neuromuscular & skeletal: Muscle spasm (20%)

Renal: Proteinuria (51%), creatinine increased (16% to 47%)

Respiratory: Cough (11%), upper respiratory infection (11%)

1% to 10%:

Cardiovascular: QTc prolongation (3% to 4%)

Dermatologic: Squamous cell carcinoma (4%)

Respiratory: Pulmonary embolism (5%)

≤1% (postmarketing, and/or case reports): Abdominal pain, angioneurotic edema, blurred vision, chest pain, cholecystitis, deafness, diverticulitis, dysphagia, DVT, enterococcal infection, exfoliative dermatitis, gastrointestinal bleeding, gastrointestinal hemorrhage, Guillain-Barré syndrome, hemoptysis, hypertension, hypokalemia, hyponatremia, infection, lethargy, leukopenia, MI, neutropenia, pneumonia, renal failure, sepsis, spinal cord injury, streptococcal bacteremia, stroke (ischemic), syncope, T-cell lymphoma, tumor hemorrhage, ureteric obstruction, ureteropelvic junction obstruction, urinary retention, vasculitis, weakness

Drug Interactions
Alfuzosin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. Risk C: Monitor therapy
Artemether: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. Risk X: Avoid combination
Chloroquine: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. Risk C: Monitor therapy
Ciprofloxacin: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. Risk C: Monitor therapy
Ciprofloxacin (Systemic): May enhance the QTc-prolonging effect of QTc-Prolonging Agents. Risk C: Monitor therapy
Divalproex: May enhance the thrombocytopenic effect of Vorinostat. This may increase the risk of gastrointestinal bleeding. Risk C: Monitor therapy
Dronedarone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Dronedarone. Risk X: Avoid combination
Gadobutrol: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. Risk D: Consider therapy modification
Lumefantrine: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. Risk X: Avoid combination
Nilotinib: May enhance the QTc-prolonging effect of QTc-Prolonging Agents. Risk X: Avoid combination
Pimozide: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Pimozide. Risk X: Avoid combination
QTc-Prolonging Agents: May enhance the adverse/toxic effect of other QTc-Prolonging Agents. Their effects can be additive, causing life-threatening ventricular arrhythmias. Risk D: Consider therapy modification
QuiNINE: QTc-Prolonging Agents may enhance the QTc-prolonging effect of QuiNINE. QuiNINE may enhance the QTc-prolonging effect of QTc-Prolonging Agents. Risk X: Avoid combination
Tetrabenazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Tetrabenazine. Risk X: Avoid combination
Thioridazine: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Thioridazine. Risk X: Avoid combination
Toremifene: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Toremifene.

The risk for potentially dangerous arrhythmias may be increased. Risk X: Avoid combination
Valproic Acid: May enhance the thrombocytopenic effect of Vorinostat. This may increase the risk of gastrointestinal bleeding. Risk C: Monitor therapy
Vandetanib: QTc-Prolonging Agents may enhance the arrhythmogenic effect of Vandetanib. Risk X: Avoid combination
Vitamin K Antagonists (e.g., warfarin): Vorinostat may enhance the anticoagulant effect of Vitamin K Antagonists. Risk C: Monitor therapy
Ziprasidone: QTc-Prolonging Agents may enhance the QTc-prolonging effect of Ziprasidone. The risk of a severe arrhythmia may be increased. Risk X: Avoid combination

Mechanism of Action

Inhibition of histone deacetylase enzymes, HDAC1, HDAC2, HDAC3, and HDAC6, which catalyze acetyl group removal from protein lysine residues (including histones and transcription factors). Inhibition of histone deacetylase results in accumulation of acetyl groups, leading to alterations in chromatin structure and transcription factor activation causing termination of cell growth leading to cell death.

Pharmacodynamics/Kinetics

There is not much difference in the extent and rate of absorption of vorinostat between fasted and fed state. The peak serum concentration is achieved at 2-4 hours with an estimated bioavailability of around 45%. It binds to plasma proteins by approximately 70%. Its major pathways of metabolism involve glucuronidation, mainly by the hepatic UGT2B17 and extrahepatic UGT1A8 enzymes,[18] and hydrolysis followed by b-oxidation to inactive metabolites. There is negligible biotransformation by cytochromes P450. Less than 1% of the dose is recovered as unchanged drug in urine. The mean terminal half-life was around 2 hours for both vorinostat and the *O*-glucuronide metabolite.
Protein binding: ~71%
Metabolism: Glucuronidated and hydrolyzed (followed by beta-oxidation) to inactive metabolites
Bioavailability: Fasting: ~43%
Half-life elimination: ~2 hours
Time to peak, plasma: With high-fat meal: ~4 hours (range: 2-10 hours)
Excretion: Urine: 52% (<1% as unchanged drug, ~52% as inactive metabolites)

Dosage

Oral: Adults: Cutaneous T-cell lymphoma: 400 mg once daily (continue until disease progression or unacceptable toxicity)
Dosage adjustment for intolerance: Reduce dose to 300 mg once daily; may further reduce to 300 mg daily for 5 consecutive days per week
In clinical trials, treatment was withheld for grade 4 anemia or thrombocytopenia or other grade 3 or 4 drug related toxicity, until resolved to ≤ grade 1. Therapy was reinitiated with dose modification.

Dietary Considerations

Take with food.

Monitoring Parameters

CBC with differential and serum chemistries, including calcium, magnesium, potassium, glucose and creatinine (baseline, then every 2 weeks for 2 months, then monthly), fluid status. Baseline and periodic ECGs were done in clinical trials.

Administration

Administer with food. Do not open, crush, or chew capsules. Maintain adequate hydration (·2 L/day fluids) during treatment.

Dosage Forms: 100 mg capsules

12.4. 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
Blood/Bone marrow Febrile Neutropenia	***anemia*** (68%, severe 8%)	E
	Leucopenia (62%, severe 9%)	E
	neutropenia (63%, severe 25%) nadir 7-10 days, recovery within 7 days	E
	thrombocytopenia (24%, severe 5%) nadir 7-10 days, recovery within 7 days	E
Cardiovascular	cardiac arrhythmia (2%, severe 0.2%)	E
	edema/peripheral edema (28%, severe 3%)	ED
Coagulation	hemolytic uremic syndrome (0.3%)	D
Constitutional symptoms	asthenia (42%, severe 2%)	E
	fever (37%, severe < 1%)	IE
Dermatology	*extravasation hazard:* none	
	alopecia (14%)	D
	skin rash (25%, severe < 1%)	IE
Gastrointestinal	*emetogenic potential:* low moderate	
	constipation (8%, severe < 1%)	E
	diarrhea (12%, severe < 1%)	E
	nausea and vomiting (64%, severe 18%)	I

	stomatitis (8%, severe < 1%)	E
Hemorrhage	hematuria (31%, severe < 1%)	E
Hepatic	elevated alkaline phosphatase (55%, severe 9%)	E
	elevated AST (67%, severe 9%)	E
	elevated ALT (68%, severe 10%)	E
	elevated bilirubin (13%, severe 2%)	E
Infection	infection (9%, severe 1%)	E
Neurology	decreased level of consciousness (9%, severe < 1%)	E
	peripheral neuropathy (3%)	ED
Pain	pain (16%, severe 1%)	ED
Pulmonary	dyspnea (8%, severe 1%)	IE
Renal/genitourinary	elevated BUN (16%, severe 0%)	E
	elevated creatinine (7%, severe < 1%)	E
	Proteinuria (36%, severe < 1%)	E
Syndromes	flu-like symptoms (19%, severe 1%)	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.

12.5. 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 to two (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).

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 3-hour via central line.

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

12.6. 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^7 position of guanine. Like other bifunctional alkylating agents, it is active against both resting and rapidly dividing tumor cells.

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.

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