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SWOG

A RANDOMIZED PHASE I/II STUDY OF OPTIMAL INDUCTION THERAPY OF BORTEZOMIB, DEXAMETHASONE AND LENALIDOMIDE WITH OR WITHOUT ELOTUZUMAB (NSC-764479) FOR NEWLY DIAGNOSED HIGH RISK MULTIPLE MYELOMA (HRMM)

NCT #01668719

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AGENTS:

IND-Exempt Agents:
Bortezomib (PS-341, Velcade®) (NSC-681239)
Dexamethasone (Decadron) (NSC-34521)
Lenalidomide (Revlimid®) (NSC-703813)

SWOG-Held IND Agents:
Elotuzumab (BMS-901608) (NSC-764479)
(IND-116277)

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NRG/NRG Oncology
SWOG/SWOG

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CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA19103 Fax: 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org For more information, call the CTSU Help Desk at 888-823-5923 or the Regulatory Help Desk at 866-651-CTSU.	Please refer to the patient enrollment section for instructions on using the OPEN system.	Online Data Submission: This protocol will use Medidata Rave® for electronic data submission. Access Rave® using your active CTEP-IAM userid and password at the following url: https://login.imedidata.com/selectlogin Other Tools and Reports: Institutions participating through the CTSU continue to have access to other tools and reports available on the SWOG Workbench. Access this by using your active CTEP-IAM userid and password at the following url: https://crawb.crab.org/TXWB/ctsulogon.aspx
The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Sites must use the current form version and adhere to the instructions and submission schedule outlined in the protocol. CTSU sites should follow procedures outlined in the protocol for Site registration, Patient Enrollment, Adverse Event Reporting, Data Submission (including ancillary studies), and Drug Procurement.		
For patient eligibility questions contact the SWOG Data Operations Center by phone or email: 206-652-2267 myelomaquestion@crab.org **For treatment or toxicity related questions** contact the Study PI of the Coordinating Group.		
For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail: 888-823-5923 ctsucontact@westat.com All calls and correspondence will be triaged to the appropriate CTSU representative.		
For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website: https://www.ctsu.org		
The CTSU Web site is located at https://www.ctsu.or		

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SCHEMA

Phase I portion (open to limited institutions, any risk classification)

Induction RVD + Elotuzumab at assigned dose level (see Section 7.2)
followed by Maintenance (reduced dose RVD/Elo)

↓

Temporary closure to assess Phase II dose

↓

Phase II portion (open to all SWOG institutions, high risk patients only)

Randomization

Induction Arm 1 (RVD x 8 cycles)	Induction Arm 2 (RVD/Elo x 8 cycles)
↓	↓
Maintenance Arm 1 (Reduced dose RVD)	Maintenance Arm 2 (Reduced dose RVD/Elo)

Progression

↓

Off Protocol Treatment

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* Patients will be enrolled into either the Phase I portion of the Phase II portion, not both.

1.0 OBJECTIVES

1.1 Phase I

a. To determine appropriate Phase II dose of elotuzumab to use in combination with lenalidomide, bortezomib and dexamethasone for patients with multiple myeloma.

1.2 Phase II

a. To assess whether incorporation of the novel agent elotuzumab into the treatment algorithm of high risk multiple myeloma (HRMM) will improve progression-free survival (PFS).

b. To estimate the frequency and severity of toxicities of this treatment strategy in this patient population.

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2.0 BACKGROUND

MM is a neoplasm of plasma cells that is characterized by osteolytic bone lesions and organ damage, such as hypercalcemia, anemia, and renal insufficiency. Despite major advances in therapy, MM is still considered an incurable malignancy. While the introduction of immunomodulatory agents (IMiDs) and proteasome inhibitors, and advances in high dose therapy (HDT) administration (chemotherapy requiring stem cell rescue) have made an impact on progression-free survival (PFS) and overall survival (OS) for MM patients in general, patients with high-risk disease still have a poor long-term prognosis. Therefore, it is imperative to identify those patients with high-risk disease and develop novel therapeutic regimens that will extend progression-free survival (PFS) and overall survival (OS) in this group. To date, no clinical investigations in MM have targeted this specific patient population.

The National Cancer Institute (NCI) Myeloma Steering Committee convened a session in March 2011, to reach a consensus on how best to risk-stratify multiple myeloma, and to develop therapies targeting high risk disease. A consensus was reached on the definition of high-risk MM, which includes patients with one or more of the following findings.

- ***MyPRS 70-gene Poor Risk Score:*** The University of Arkansas group has published extensively on the 70-gene risk model (now available commercially as MyPRS gene signature, Signal Genetics Inc.). MyPRS recognizes 13-15% of *de novo* myeloma as high risk, and has been validated in the Intergroupe Francophone du Myélome (IFM) and Mayo Clinic data sets. *(1,2,3)*

- ***FISH or cytogenetics for t(14;16), t(14;20), and del(17p):*** Translocation (14;20)(q32;q12), which results in aberrant expression of MAF-B, is associated with poor prognosis in MM. *(4,5,6)* Translocation (14;16)(q32.3;q23), resulting in C-MAF proto-oncogene dysregulation, is also recognized as a poor prognostic feature in MM. *(7)* The case of patients with del(17p) is less clear, but all of the recently published reports showed that del(17p) remains a strong poor prognostic factor. *(8,9)*

- ***Primary plasma cell leukemia (PPCL)****: Even though no large study specifically dedicated for this patient population exists in the literature due to its relatively rare occurrence (approximately 3% of all MM), most thought leaders and experts agree that, based on available data, PPCL patients are high-risk in nature.* (10,11,12)

- ***Elevated serum LDH (≥ 2 x ULN):*** Presenting in up to 11% of newly diagnosed patients, this has been recognized as a poor prognostic marker with an aggressive lymphoma-like

behavior, which frequently presents with extramedullary disease. *(13,14,15)* Elevated LDH has also been recognized to add profound prognostic value to the International Staging System (ISS) prognostic system. *(16)*

2.1 Choice of RVD regimen as the Control Arm

The 3-drug induction regimen combining bortezomib (V) with lenalidomide (R) and dexamethasone (D) is an extremely promising front-line induction therapy. *(17)* RVD has been investigated in a Phase I-II trial in which 66 patients were enrolled. All patients responded, including 67% who achieved very good partial remission (VGPR) or better, and 39% who achieved CR or near-CR (nCR). Moreover, the patients with poor cytogenetics responded in a similar fashion to the patients with standard risk or normal cytogenetics. With a median follow-up of 21 months, the estimated 18-month PFS and OS with or without transplant was 75% and 97%, respectively. During the American Society of Hematology (ASH) 2010 Annual Meeting, the IFM reported the primary results of a Phase II study investigating 3 RVD cycles before HDT followed by autologous stem cell transplantation (ASCT) and 2 RVD cycles for consolidation. All patients except one received the whole planned treatment. After induction and HDT, 91% of patients were responders, including 68% with VGPR or better, and 36% with CR + stringent CR (sCR). *(18)*

The availability of novel agents has renewed the concept of maintenance. Five randomized studies with thalidomide (T) have been completed, of which 4 showed a benefit in PFS and OS with thalidomide maintenance. The more favorable toxicity profile of R makes it an ideal agent for maintenance therapy. Two large randomized Phase III trials, one conducted by the IFM, the other by an intergroup effort led by the CALGB, were presented in recent American Society of Clinical Oncology (ASCO) and ASH annual meetings. *(19,20,21,22,23,24,25)* Lenalidomide was given orally after HDT/ASCT at low dose until disease progression. Results were similar in both studies, with an improvement of PFS of around 24 months in the placebo arm versus not reached in the lenalidomide arm. An increased incidence of second primary malignancies in the 7% range has been recently reported in the R maintenance studies, prompting efforts to define the optimal duration of maintenance therapy, but such an increase has not been seen in other settings when melphalan was not incorporated into the treatment regimen at some point. A number of Phase II/III studies are evaluating post-induction therapy and post-autologous stem cell transplant maintenance with either bortezomib alone, or in combination with thalidomide/dexamethasone or lenalidomide/dexamethasone. *(26,27,28,29,30)*

2.2 Why Choose Elotuzumab?

CS1 is a cell surface glycoprotein universally expressed at high levels on MM cells but with limited expression on normal cells. *(31)* The function of CS1 is not well characterized, but it appears to play a critical role in interactions between MM cells and the bone marrow stromal cells. Elotuzumab (Elo) is a fully humanized monoclonal antibody against CS1 that has shown significant in vitro activity against human MM cell lines, and in vivo activity in mice MM xenograft mode. *(32)* Elo has also been evaluated in Phase I/II trials in patients with relapsed/refractory MM. As monotherapy, Elo demonstrated acceptable toxicity in Phase I studies, but modest anti-tumor activity depicted by stable disease (SD) status in six of 19 patients. *(33)*

Clinical studies of Elo combined with either lenalidomide plus dexamethasone or with bortezomib are showing considerable promise. In a preliminary analysis of an ongoing Phase I study of Elo plus bortezomib, the overall response rate (PR or better) was 48% among 27 evaluable patients, and responses were achieved in several bortezomib-refractory patients. *(34)* In a preliminary analysis of an ongoing Phase Ib combination study with lenalidomide and dexamethasone (LD), the overall response rate (ORR) was

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82% for all treated patients (n = 28), 96% for lenalidomide-naive patients (n = 22), and 82% among patients who had been refractory to their most recent treatment (n = 11). *(35)* In a Phase II study of the Elo/LD combination, the ORR was 85% for evaluable patients (22/26), and the remaining four patients had SD, while 31% achieved either a CR or VGPR. *(36)* For all Elo studies, adverse events (AEs) were primarily infusion-related and appeared to be readily manageable using adequate premedication. From the limited data available, it appears Elo in combination with either lenalidomide or bortezomib has comparable response rates in poor cytogenetic RRMM patients compared with those with standard or normal cytogenetics.

Elo is therefore the first monoclonal antibody that mediates antibody-dependent cellular cytotoxicity and that, in combination with either bortezomib, or lenalidomide and dexamethasone, has demonstrated clinical efficacy in relapsed/refractory MM. Based on these encouraging results and its safety profile, this study will combine Elo with RVD as induction and in maintenance for newly diagnosed HRMM.

2.3 Rationale for Delayed HDT/ASCT

The 2-year PFS in HRMM is approximately 50% even with HDT/ASCT. Since this therapeutic option is associated with toxicity and morbidity, the current trial will have the option to employ this therapeutic option only for patients at the time of progression or relapse.

2.4 Inclusion of Certain HIV+ Patients

Since HIV-positive patients are immunocompromised and most are treated with already myelosuppressive antiretroviral regimens, they may not tolerate intensive chemotherapies. Therefore, patients with HIV infection will be excluded from this study if they do not meet the parameters that are felt will allow safe participation in this study. HIV infected patients with sufficient CD4 cell count, acceptable viral load and who are not receiving the myelosuppressive agents zidovudine or stavudine will be included in this study (see Section 5.3e).

2.5 Inclusion of Women and Minorities and Planned Enrollment Report

This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. The anticipated accrual in the ethnicity/race and sex categories is shown in the table below.

Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	5	9	14
Not Hispanic or Latino	47	61	108
Total Ethnic	52	70	122
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	1	2	3
Black or African American	8	10	18
Native Hawaiian or other Pacific Islander	0	1	1
White	43	57	100
Racial Category: Total of all Subjects	52	70	122

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3.0 DRUG INFORMATION

Investigator Brochures

For this study, bortezomib, dexamethasone and lenalidomide are commercially available; therefore, Investigator Brochures are not applicable to these drugs. Information about commercial drugs is publicly available in the package inserts.

For this study, elotuzumab is investigational and is being provided under an IND held by SWOG. For INDs filed by SWOG, the protocol serves as the Investigator Brochure for the performance of the protocol. In such instances submission of the protocol to the Institutional Review Board (IRB) should suffice for providing the IRB with information about the drug. However, in cases where the IRB insists on having the official Investigator Brochure from the company, further information may be requested by contacting the SWOG Operations Office at 210/614-8808.

For more information regarding Investigator's Brochures, please refer to SWOG Policy 15.

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3.1 Bortezomib (Velcade®)(NSC-681239)

a. PHARMACOLOGY

Mechanism of Action: Bortezomib is a reversible inhibitor of the chymotrypsin-like activity of the 26S proteasome in mammalian cells. The 26S proteasome is a large protein complex that degrades ubiquitinated proteins. The ubiquitin-proteasome pathway plays an essential role in regulating the intracellular concentration of specific proteins, thereby maintaining homeostasis within cells. Inhibition of the 26S proteasome prevents this targeted proteolysis, which can affect multiple signaling cascades within the cell. This disruption of normal homeostatic mechanisms can lead to cell death.

b. PHARMACOKINETICS

1. Absorption: Following intravenous administration of 1 - 1.3 mg/m^2 doses to patients with multiple myeloma, the mean maximum plasma concentrations of bortezomib (C_{max}) after the first dose ranged from 57 and 112 ng/mL. In subsequent doses, when administered twice weekly, the mean maximum observed plasma concentrations ranged from 67 to 106 ng/mL for the 1 mg/m^2 dose and 89 to 120 ng/mL for the 1.3 mg/m^2 dose. The mean elimination half-life of bortezomib upon multiple dosing ranged from 40 to 192 hours after the 1 mg/m^2 dose and 76 to 108 hours after the 1.3 mg/m^2 dose. The mean total body clearances was 102 and 112 L/h following the first dose for doses of 1 mg/m^2 and 1.3 mg/m^2, respectively, and ranged from 15 to 32 L/h following subsequent doses for doses of 1 and 1.3 mg/m^2, respectively. Following an intravenous bolus or subcutaneous injection of 1.3 mg/m^2 dose to patients with multiple myeloma, the total systemic exposure after repeat dose administration (AUC_{last}) was equivalent for subcutaneous and intravenous administration. The Cmax after subcutaneous administration (20.4 ng/mL) was lower than intravenous (223 ng/mL).

2. Distribution: The mean distribution volume of bortezomib ranged from 498 to 1884 L/m^2 following single- or repeat-dose administration of 1 mg/m^2 or 1.3 mg/m^2 to patients with multiple myeloma, suggesting bortezomib is widely distributed to peripheral tissues. Plasma protein binding averaged 83%.

3. Metabolism: Bortezomib is primarily oxidatively metabolized via cytochrome P450 enzymes 3A4, 2C19, and 1A2. Metabolism by CYP 2D6 and 2C9 is minor. The major metabolic pathway is deboronation to form 2 boronated metabolites that subsequently undergo hydroxylation to several metabolites. Deboronated bortezomib metabolites are inactive as 26S proteasome inhibitors. Data indicates that plasma levels of metabolites are low compared to parent drug.

4. Elimination: Elimination pathways have not been characterized in humans.

c. Adverse effects

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

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2084 patients.* Below is the CAEPR for bortezomib (Velcade).

Version 2.7, March 25, 2019[1]

Adverse Events with Possible Relationship to Bortezomib (Velcade) (CTCAE 5.0 Term) [n= 2084]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia		
CARDIAC DISORDERS		
		Heart failure
GASTROINTESTINAL DISORDERS		
	Abdominal pain	
Constipation		
Diarrhea		
	Dyspepsia	
	Gastrointestinal hemorrhage[2]	
		Gastrointestinal perforation[3]
	Ileus	
Nausea		
Vomiting		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills	
	Edema limbs	
Fatigue		
Fever		

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Adverse Events with Possible Relationship to Bortezomib (Velcade) (CTCAE 5.0 Term) [n= 2084]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
HEPATOBILIARY DISORDERS		
		Hepatic failure[4]
		Hepatobiliary disorders - Other (hepatitis)[4]
INFECTIONS AND INFESTATIONS		
Infection[5]		
INVESTIGATIONS		
		Alanine aminotransferase increased[4]
		Alkaline phosphatase increased[4]
		Aspartate aminotransferase increased[4]
		Blood bilirubin increased[4]
		GGT increased[4]
		INR increased[4]
		Investigations - Other (albumin)[4]
	Neutrophil count decreased	
Platelet count decreased		
	Weight loss	
METABOLISM AND NUTRITION DISORDERS		
Anorexia		
	Dehydration	
		Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Back pain	
	Bone pain	
	Muscle cramp	
	Myalgia	
	Pain in extremity	
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Headache	
		Leukoencephalopathy
	Neuralgia	
	Paresthesia	
Peripheral motor neuropathy		
Peripheral sensory neuropathy		

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Adverse Events with Possible Relationship to Bortezomib (Velcade) (CTCAE 5.0 Term) [n= 2084]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		Reversible posterior leukoencephalopathy syndrome
PSYCHIATRIC DISORDERS		
	Anxiety	
	Insomnia	
RENAL AND URINARY DISORDERS		
		Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
		Adult respiratory distress syndrome
	Cough	
	Dyspnea	
	Pharyngeal mucositis	
		Pulmonary hypertension
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Rash maculo-papular	
VASCULAR DISORDERS		
	Hypotension	

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[3] Gastrointestinal perforation includes Colonic perforation, Duodenal perforation, Esophageal perforation, Gastric perforation, Ileal perforation, Jejunal perforation, Rectal perforation, and Small intestinal perforation under the GASTROINTESTINAL DISORDERS SOC.

[4] Cases of acute liver failure have been reported in patients receiving multiple concomitant medications and with serious underlying medical conditions. Other reported hepatic reactions include hepatitis, increases in liver enzymes, and hyperbilirubinemia.

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

Adverse events reported on bortezomib (Velcade) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that bortezomib (Velcade) caused the adverse event:

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BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (hematocrit low, hematocrit); Blood and lymphatic system disorders - Other (lymphadenopathy); Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Febrile neutropenia; Hemolytic uremic syndrome; Leukocytosis
CARDIAC DISORDERS - Asystole; Atrial fibrillation; Atrial flutter; Atrioventricular block complete; Cardiac arrest; Cardiac disorders - Other (cardiac amyloidosis); Cardiac disorders - Other (cardiomegaly); Chest pain - cardiac; Left ventricular systolic dysfunction; Mobitz type I; Myocardial infarction; Palpitations; Pericardial effusion; Pericardial tamponade; Pericarditis; Right ventricular dysfunction; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia; Ventricular arrhythmia; Ventricular fibrillation; Ventricular tachycardia
EAR AND LABYRINTH DISORDERS - Hearing impaired; Tinnitus
ENDOCRINE DISORDERS - Hypothyroidism
EYE DISORDERS - Blurred vision; Dry eye; Extraocular muscle paresis; Eye disorders - Other (chalazion); Eye disorders - Other (choroidal effusion); Eye disorders - Other (conjunctival hemorrhage); Eye disorders - Other (retinal hemorrhage with bilateral vision impairment); Keratitis; Watering eyes
GASTROINTESTINAL DISORDERS - Abdominal distension; Ascites; Belching; Bloating; Colitis; Dry mouth; Duodenal ulcer; Dysphagia; Enterocolitis; Esophagitis; Flatulence; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (colonic wall thickening); Gastrointestinal disorders - Other (early satiety); Gastrointestinal disorders - Other (ileitis); Gastrointestinal disorders - Other (ischemic bowel); Gastrointestinal disorders - Other (mouth/tongue ulceration); Gastrointestinal disorders - Other (retching); Gastrointestinal pain; Gingival pain; Hemorrhoids; Mucositis oral; Oral pain; Pancreatitis; Small intestinal obstruction; Typhlitis
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Edema face; Flu like symptoms; Gait disturbance; General disorders and administration site conditions - Other (catheter related complication); General disorders and administration site conditions - Other (hepato-renal syndrome); Hypothermia; Injection site reaction; Malaise; Multi-organ failure; Non-cardiac chest pain; Pain; Sudden death NOS
HEPATOBILIARY DISORDERS - Portal vein thrombosis; Sinusoidal obstruction syndrome
IMMUNE SYSTEM DISORDERS - Allergic reaction; Anaphylaxis; Cytokine release syndrome
INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Fall; Fracture; Vascular access complication
INVESTIGATIONS - Activated partial thromboplastin time prolonged; CD4 lymphocytes decreased; CPK increased; Carbon monoxide diffusing capacity decreased; Cardiac troponin I increased; Cardiac troponin T increased; Cholesterol high; Creatinine increased; Ejection fraction decreased; Investigations - Other (BUN); Investigations - Other (low chloride); Lipase increased; Lymphocyte count decreased; Serum amylase increased; Weight gain; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia; Metabolism and nutrition disorders - Other (failure to thrive); Metabolism and nutrition disorders - Other (hypoproteinemia)

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MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Avascular necrosis; Buttock pain; Chest wall pain; Generalized muscle weakness; Joint range of motion decreased; Muscle weakness lower limb; Osteonecrosis of jaw
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Acoustic nerve disorder NOS; Akathisia; Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysesthesia; Dysgeusia; Dysphasia; Edema cerebral; Encephalopathy; Facial muscle weakness; Facial nerve disorder; Hypersomnia; Intracranial hemorrhage; Ischemia cerebrovascular; Lethargy; Memory impairment; Nervous system disorders - Other (autonomic neuropathy, autonomic dysfunction); Nervous system disorders - Other (cranial palsy); Nervous system disorders - Other (dysautonomia); Nervous system disorders - Other (L sided facial droop); Nervous system disorders - Other (paralysis); Nervous system disorders - Other (polyneuropathy); Nervous system disorders - Other (tongue paralysis); Presyncope; Seizure; Somnolence; Spinal cord compression; Stroke; Syncope; Tremor; Vasovagal reaction
PSYCHIATRIC DISORDERS - Agitation; Confusion; Delirium; Depression; Personality change; Psychosis
RENAL AND URINARY DISORDERS - Bladder spasm; Chronic kidney disease; Cystitis noninfective; Hematuria; Proteinuria; Renal and urinary disorders - Other (bilateral hydronephrosis); Renal and urinary disorders - Other (glomerular nephritis proliferative); Renal calculi; Urinary frequency; Urinary incontinence; Urinary retention; Urinary tract pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Allergic rhinitis; Aspiration; Atelectasis; Bronchopulmonary hemorrhage; Bronchospasm; Epistaxis; Hiccups; Hypoxia; Laryngeal edema; Mediastinal hemorrhage; Pharyngolaryngeal pain; Pleural effusion; Pleuritic pain; Pneumonitis; Postnasal drip; Pulmonary edema; Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (obstructive airways disease); Respiratory, thoracic and mediastinal disorders - Other (respiratory distress); Respiratory, thoracic and mediastinal disorders - Other (tachypnea); Tracheal mucositis; Tracheal stenosis; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Bullous dermatitis; Dry skin; Erythema multiforme; Erythroderma; Hyperhidrosis; Pain of skin; Palmar-plantar erythrodysesthesia syndrome; Pruritus; Purpura; Rash acneiform; Skin and subcutaneous tissue disorders - Other (angioedema); Skin and subcutaneous tissue disorders - Other (leukoclastic vasculitis); Skin and subcutaneous tissue disorders - Other (skin lesion NOS); Urticaria
VASCULAR DISORDERS - Capillary leak syndrome; Flushing; Hematoma; Hypertension; Thromboembolic event; Vascular disorders - Other (trach site); Vasculitis

Note: Bortezomib (Velcade) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

2. Pregnancy and Lactation: Pregnancy Category D. It is not known whether bortezomib is excreted in human milk.

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3. Drug Interactions: Closely monitor patients receiving bortezomib in combination with strong CYP3A4 inhibitors. Concomitant use of strong CYP3A4 inducers is not recommended. Due to potential drug interactions, a complete patient medication list should be screened prior to initiation of bortezomib.

d. DOSING & ADMINISTRATION

1. Dosing – See Treatment Plan

2. Bortezomib may be administered subcutaneously rotating injection sites or intravenously as a 3 to 5 second bolus intravenous injection. Bortezomib should not be administered by any other routes. Because each route of administration has a different reconstituted concentration, caution should be used when calculating the volume to be administered. For each 3.5 mg single-use vial of bortezomib reconstitute with the following volume of 0.9% sodium chloride based on the route of administration.

Route of administration	Bortezomib (mg/vial)	Diluent (0.9% Sodium Chloride)	Final Bortezomib concentration (mg/mL)
Intravenous	3.5 mg	3.5 mL	1 mg/mL
Subcutaneous	3.5 mg	1.4 mL	2.5 mg/mL

e. STORAGE & STABILITY

Please refer to the current FDA-approved package insert for storage, stability and special handling information.

f. HOW SUPPLIED

1. Bortezomib for injection is supplied in single-use 10 mL vials containing 3.5 mg of bortezomib as a white to off-white sterile lyophilized powder.

2. Bortezomib is commercially available and will not be supplied. Please refer to the current FDA-approved package insert for additional information.

3.2 Dexamethasone (Decadron) (NSC-34521)

a. DESCRIPTION

Dexamethasone (Decadron) is a synthetic adrenocortical steroid and is readily absorbed from the gastrointestinal tract. Chemically, dexamethasone is 9-fluoro-11b, 17, 21-trihydroxy-16a-methyl-pregna-1, 4-diene-3, 20-dione.

b. TOXICOLOGY

Human Toxicology: Possible adverse effects associated with the use of dexamethasone are: fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, exacerbation of infection (e.g., tuberculosis), exacerbation or symptoms of diabetes, psychosis, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, esophagitis, peptic ulcer, dermatologic disturbances,

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convulsions, vertigo and headache, endocrine abnormalities, ophthalmic changes, and metabolic changes. Some patients have experienced itching and other allergic, anaphylactic or other hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia and arthralgia. Phenytoin phenobarbital and ephedrine enhance metabolic clearance of corticosteroids.

Corticosteroids should be used cautiously in patients with hypothyroidism, cirrhosis, ocular herpes simplex, existing emotional instability or psychotic tendencies, nonspecific ulcerative colitis, diverticulitis, fresh intestinal anastomoses, peptic ulcer, renal insufficiency, hypertension, osteoporosis and myasthenia gravis. Immunization procedures (especially smallpox vaccination) should not be undertaken in patients on corticosteroids.

c. PHARMACOLOGY

Kinetics: Natural and synthetic glucocorticoids are readily and completely absorbed from the GI tract. Dexamethasone is insoluble in water. Glucocorticoids have salt-retaining properties, although dexamethasone nearly completely lacks this property. Dexamethasone may suppress the body's response to viral and bacterial infections. Equivalent doses are as follows:

Dexamethasone	Methyl-prednisolone and Triamcinolone	Prednisolone and Prednisone	Hydrocortisone	Cortisone
0.75 mg	4 mg	5 mg	20 mg	25 mg

Formulation: Dexamethasone is available in seven potencies (0.25 mg, 0.5 mg, 0.75 mg, 1.5 mg, 2 mg, 4 mg, and 6 mg) in tablet form.

Storage and Stability: Dexamethasone is to be stored at room temperature.

Administration: For this study, dexamethasone is administered orally and intravenously.

Supplier: Dexamethasone is commercially available and therefore is to be purchased by a third party. This drug will not be supplied by the NCI.

Please refer to the package insert for complete information.

3.3 Elotuzumab (BMS-901608) (NSC-764479) (IND-116277)

a. PHARMACOLOGY

Elotuzumab is an immunostimulatory humanized recombinant IgG1 monoclonal antibody that targets the SLAMF7 (Signaling Lymphocytic Activation Molecule Family member 7) protein. SLAMF7 is highly expressed on myeloma cells independent of cytogenetic abnormalities. SLAMF7 is also expressed on natural killer (NK) cells, plasma cells and at significantly lower levels on specific immune cell subsets, but is not detected on normal solid tissues or hematopoietic stem cells. Elotuzumab directly activates NK cells through the SLAMF7 pathway and Fc receptors. It also targets SLAMF7 on myeloma cells and facilitates the interaction with NK cells to mediate the killing of myeloma cells through antibody-dependent cellular cytotoxicity (ADCC).

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b. PHARMACOKINETICS

The pharmacokinetics (PK) of elotuzumab has been assessed in 3 clinical studies following various dose regimens. These regimens included multiple doses with a dose every other week (HuLuc63-1701), or a dose every 10 or 11 days (HuLuc63-1702) when administered with bortezomib. A weekly dose for 8 doses followed by every other week doses (HuLuc63-1703) when administered in combination with lenalidomide and dexamethasone was also assessed.

1. Absorption:

HuLuc63-1701: Following administration of the first dose, Cmax increased in a dose proportional manner across a dose range of 0.5 to 20 mg/kg. AUC however increased in a non-linear fashion with increasing dose. The elotuzumab serum trough concentration (C_{min}) appeared to stabilize after administration of the second dose when elotuzumab was administered IV every 2 weeks with doses ranging from 0.5-2mg/kg suggesting that steady-state was achieved. However, the trough serum concentration of elotuzumab continuously increased through administration of the fourth dose for the doses of 5 to 20 mg/kg, suggesting that steady-state was not achieved at higher doses (5 to 20 mg/kg) within the first treatment cycle. Following administration of the fourth dose, accumulation varied with dose such that the geometric mean accumulation ratio ranged from 0.8 to 2.5 across all treatments.

HuLuc63-1702: Elotuzumab serum concentrations peaked within 7 hours after the start of infusion for the majority of subjects. For both Cycle 1 and Cycle 4, the increase of C_{max} and AUC appeared to be more than dose-proportional from 2.5 to 10 mg/kg and dose-proportional from 10 to 20 mg/kg.

HuLuc63-1703: Preliminary PK analysis results are limited to C_{min} and C_{max} for the HuLuc63-1703 (elotuzumab/lenalidomide) study. Following administration of elotuzumab every 7 days for the first 2 cycles, and every 14 days for all subsequent cycles in combination with lenalidomide and dexamethasone (HuLuc63-1703), the steady-state C_{min} concentrations associated with the 10 and 20 mg/kg doses were above the anticipated therapeutic trough concentration of 70 mcg/mL

2. Distribution:

Elotuzumab volume of distribution was approximately 3 to 6 L (HuLuc63-1701) or ranged from 41 to 69 ml/kg (HuLuc63-1702)

3. Metabolism:

HuLuc63-1701: Geometric mean elotuzumab clearance (15.5 to 69.3 mL/h decreased and mean terminal half-life (2.1 to 7.8 days) increased with an increase in dose from 0.5 to 20 mg/kg suggesting a saturation of target-mediated clearance, resulting in greater than proportional increases in exposure compared to dose.

HuLuc63-1702: The mean clearance values were 0.54, 0.43, 0.20, and 0.23 ml.h/kg after a single dose of 2.5,5,10, and 20 mg/kg of elotuzumab, respectively.

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4. Elimination:

HuLuc63-1702: On Cycle 1 Day 1, the harmonic mean terminal phase elimination half-life observed was 4 to 8 days after single doses of 2.5-20mg/kg of elotuzumab, respectively.

c. ADVERSE EFFECTS

1.

Adverse Events with Possible Relationship to Elotuzumab		
Likely (>20%)	**Less Likely (4 - ≤20%)**	**Rare but Serious (≤3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Lymphopenia		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chest pain	
IMMUNE SYSTEM DISORDERS		
	Hypersensitivity	
INFECTIONS AND INFESTATIONS		
	Herpes zoster	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
	Infusion related reaction	
INVESTIGATIONS		
Weight decreased		
NERVOUS SYSTEM DISORDERS		
	Hypoesthesia	
PSYCHIATRIC DISRODERS		
	Mood changes	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
Cough		
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
	Night sweats	

Warnings and Precautions: Elotuzumab can cause infusion reactions. Infusion reactions were reported in ≤ 10 % of patients treated with elotuzumab and all were ≤ Grade 3. The majority (70 – 80%) of patients who experienced an infusion reactions had them during the first dose. The most common symptoms of an infusion reaction included fever, chills, and hypertension

2. Pregnancy and Lactation: It is not known whether elotuzumab can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Both men and women should use effective contraception while they or their partners receive elotuzumab. It is not known whether elotuzumab is excreted in human milk. Women receiving elotuzumab should discontinue nursing.

3. Drug Interactions: No studies on pharmacokinetic drug interactions have been performed. Due to potential drug interactions, a complete patient medication list, including elotuzumab, should be screened prior to initiation of and during treatment with elotuzumab. See Section 8.0 Toxicities to be Monitored and Dosage Modifications.

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d. DOSING & ADMINISTRATION

1. See Section 7.0 Treatment Plan

2. Elotuzumab should be administered through a sterile, non-pyrogenic, low protein binding in-line filter using automated infusion pump according to the rate table below. See Section 8.3d for patients who experience an infusion reaction.

Dose	Starting rate	Rate change	Maximum rate
1	0.5 mL/min	May increase by 0.5 mL/min every 30 minutes	2.0 mL/min
2*	1.0 mL/min		
3*	1.5 mL/min		
Subsequent*	2.0 mL/min	n/a	

* If previous infusion tolerated.

3. Patients should receive premedications with IV corticosteroids, H1 and H2 antihistamines and acetaminophen prior to each elotuzumab infusion.

e. HOW SUPPLIED

1. Elotuzumab will be supplied free of charge from Bristol-Myers Squibb (BMS) or distribution by Almac Clinical Services.

2. Elotuzumab for injection is supplied as a sterile, white to off-white, preservative-free, lyophilized cake in 400 mg vials.

f. STORAGE, PREPARATION & STABILITY

1. Elotuzumab should be stored under refrigeration at 2°C to 8°C and protected from direct sunlight. Do not freeze or shake.

2. Elotuzumab requires reconstitution with Sterile Water for Injection (SWFI) prior to IV administration. Add 17 mL SWFI to the 400 mg vial to give a concentration of 25 mg/mL. The maximum deliverable volume from the vial after reconstitution is 16 mL.

Elotuzumab is further diluted in either 0.9% sodium chloride (NS) or 5% dextrose injection (D5W) for final concentration of 1 mg/mL - 6 mg/mL. During drug preparation, vigorous mixing or shaking is to be avoided. Elotuzumab is compatible with polyvinyl chloride and polyolefin bags.

Elotuzumab is not formulated with a preservative. Once a dose is prepared, elotuzumab should be administered IV within 24 hours of reconstitution. If not used immediately, the infusion solution may be stored refrigerated between 2°C to 8°C (36°F to 46°F), and protected from light for up to 24 hours (a maximum of 8 hours of the total 24 hours can be at room temperature, 20°C to 25°C (68°F to 77°F), and room light). If the prepared dose is refrigerated, the drug solution should be equilibrated to room temperature and gently inverted to mix before administration. Do not use the accelerated warming method. After the specified storage time, the prepared solution should be discarded.

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3. No data are available indicating potential incompatibility of elotuzumab with other drugs. Other drug should not be added or infused simultaneously through the same IV line.

g. DRUG ORDERING & ACCOUNTABILITY

1. Drug Ordering

Drug Request Form to Almac Clinical Services at PaLogistics.ClinicalServices@Almacgroup.com. The form can be found on the protocol abstract page of the SWOG website (www.swog.org). ACS will ship drug for next day delivery for orders received before 12:00 p.m. E.S.T. Monday through Wednesday. Orders received after 12:00 p.m. E.S.T. Wednesday will be processed and shipped the next business morning. Orders received Thursday or Friday will be processed on Monday for next day (Tuesday) delivery. Emergency shipments may be requested but are subject to approval and shipment surcharge. Shipments will not be made on Fridays except in emergency requests.

2. Drug Handling and Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and disposal of all drugs received from the supplier using the NCI Drug Accountability Record Form (DARF) available at http://ctep.cancer.gov.

Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI DARF. If the trial is a placebo control trial – indicate that separate DARFs are needed for each patient to also include the placebo drug supply.

3. Drug return and/or disposition instruction

a. Drug Disposition: Unused drug supplies should NOT be returned. Unused vials left over when the study closes and expired or partially used vials should be destroyed on site per local institutional guidelines and documented accordingly on the DARF. Due to contamination and exposure issues, all destruction should occur in a timely manner.

b. Drug Expiration: If packaging does not have expiration date, it should be obtained from BMS by contacting Murielle Mueller at Murielle.Mueller@bms.com. If packaging has expiration date, indicate drug expiration date on the DARF under Manufacturer and Lot #.

4. Contact information

Questions about drug orders or shipping should be directed to the Almac Clinical Services at 215/660-8500.

3.4 Lenalidomide (Revlimid®) (NSC-703813)

a. PHARMACOLOGY

Mechanism of Action: Lenalidomide possesses immunomodulatory, antiangiogenic, and antineoplastic properties. Experiments have demonstrated that lenalidomide inhibits the growth of cells derived from patients with multiple

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myeloma and del (5q) myelodysplastic syndromes in vitro. Lenalidomide causes a delay in tumor growth in some *in vivo* nonclinical hematopoietic tumor models, including multiple myeloma. Lenalidomide inhibits the secretion of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), from peripheral blood mononuclear cells. Lenalidomide also inhibited the expression of cyclooxygenase-2 (COX-2) but not COX-1 *in vitro*.

b. PHARMACOKINETICS

1. Absorption: Lenalidomide is rapidly absorbed following oral administration. Following single and multiple doses of lenalidomide in patients with multiple myeloma or myelodysplastic syndrome the maximum plasma concentrations occurred between 0.5 and 6.0 hours post-dose. The single and multiple dose pharmacokinetic disposition of lenalidomide is linear with AUC and C_{max} values increasing proportionally with dose. Multiple dosing at the recommended dose-regimen does not result in drug accumulation. Systemic exposure (AUC) of lenalidomide in multiple myeloma and myelodysplastic syndrome patients with normal or mild renal function (CLcr ≥ 60 mL/min) is approximately 60% higher as compared to young healthy male subjects. Administration of a single 25 mg dose of lenalidomide with a high-fat meal in healthy subjects reduces the extent of absorption, with an approximate 20% decrease in AUC and 50% decrease in C_{max}. In the trials where the efficacy and safety were established for lenalidomide, the drug was administered without regard to food intake.

2. Distribution: In vitro (^{14}C)-lenalidomide binding to plasma proteins is approximately 30%.

3. Metabolism: Lenalidomide undergoes limited metabolism. Unchanged lenalidomide is the predominant circulating component in humans. Two identified metabolites are hydroxy-lenalidomide and N-acetyl-lenalidomide; each constitutes less than 5% of parent levels in circulation.

4. Elimination: Elimination is primarily renal. Following a single oral administration of [^{14}C]-lenalidomide (25 mg) to healthy subjects, approximately 90% and 4% of the radioactive dose is eliminated within ten days in urine and feces, respectively. Approximately 82% of the radioactive dose is excreted as lenalidomide in the urine within 24 hours. The renal clearance of lenalidomide exceeds the glomerular filtration rate. The mean half-life of lenalidomide is 3 hours in healthy subjects and 3 to 5 hours in patients with multiple myeloma or myelodysplastic syndrome.

c. ADVERSE EFFECTS

1. Contraindications: Lenalidomide is contraindicated in pregnant women and women capable of become pregnant and in patients who have demonstrated hypersensitivity to lenalidomide.

2. Warnings and Precautions:

a. Fetal Risk: Lenalidomide is a thalidomide analogue. Thalidomide is a known human teratogen that causes life-threatening human birth defects. An embryofetal development study in non-human primates indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during

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pregnancy, similar to birth defects observed in humans following exposure to thalidomide during pregnancy. If lenalidomide is used during pregnancy, it may cause birth defects or death to a developing baby. Females of childbearing potential must be advised to avoid pregnancy while on lenalidomide. Two effective contraceptive methods should be used during therapy, during dose interruptions and for at least 4 weeks after completing therapy. Male patients, even those who have had a vasectomy, must agree to use a condom during sexual contact with a pregnant woman or a woman who can become pregnant.

b. Reproductive Risk and Special Prescribing Requirements (Revlimid REMS™ Program): Because of this potential toxicity and to avoid fetal exposure, lenalidomide is only available under a special restricted distribution program called "Revlimid REMS™". Prescribers and pharmacists registered with the program can prescribe and dispense the product to patients who are registered and meet all the conditions of the Revlimid REMS™ program. Please consult the package insert or Celgene for full details on the Revlimid REMS™ Program.

c. Hematologic Toxicity: Lenalidomide *can cause significant neutropenia and thrombocytopenia.*

d. Venous and Arterial Thromboembolic Events: There is an increased risk of venous thromboembolism (VTE), predominantly deep vein thrombosis (DVT) and pulmonary embolism, in multiple myeloma patients treated with lenalidomide in combination with dexamethasone or other chemotherapy. The risk of VTE is lower in myelodysplastic syndrome and mantle cell lymphoma patients treated with lenalidomide monotherapy. There also is an increased risk of arterial thromboembolic events (predominantly myocardial infarction and cerebrovascular events), in patients treated with lenalidomide and dexamethasone, and to a lesser extent with melphalan and prednisone. As a consequence, patients with known risk factors for thromboembolism should be closely monitored. Action should be taken to minimize all modifiable risk factors (e.g., smoking, hypertension, and hyperlipidemia). Concomitant administration of erythropoietic agents or previous history of thromboembolic events also may increase thrombotic risk in these patients. Patients and physicians are advised to observe for signs and symptoms of thromboembolism. Prophylactic antithrombotic medicines should be recommended, especially in patients with additional thrombotic risk factors.

e. Allergic Reactions: Angioedema and serious dermatologic reactions syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported. These events can be fatal. Patients with a prior history of Grade 4 rash associated with thalidomide treatment should not receive lenalidomide. Lenalidomide interruption or discontinuation should be considered for Grade 2-3 skin rash. Lenalidomide must be discontinued for angioedema, Grade 4 rash, exfoliative or bullous rash, or if SJS or TEN is suspected and should not be resumed following discontinuation for these reactions. Lenalidomide capsules contain lactose and risk-benefit of treatment should be evaluated in patients with lactose intolerance.

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f. Tumor Lysis Syndrome: Fatal instances of tumor lysis syndrome have been reported during treatment with lenalidomide. The patients at risk of tumor lysis syndrome are those with high tumor burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

g. Tumor Flare Reaction: Tumor flare reaction has occurred during investigational use of lenalidomide for CLL and lymphoma, and is characterized by tender lymph node swelling, low grade fever, pain and rash. Treatment of CLL or lymphoma with lenalidomide outside of a well-monitored clinical trial is discouraged.

h. Hepatotoxicity: Cases of transient liver laboratory abnormalities (predominantly transaminases) were reported in patients treated with lenalidomide. Treatment with lenalidomide should be interrupted and restarted once the levels return to baseline. Successful re-challenge without recurrence of liver laboratory elevation was reported in some patients.

i. Second primary malignancies (SPM): Lenalidomide has demonstrated the potential to cause SPM in a small number of treated patients. All individuals treated with lenalidomide should be closely followed for the occurrence of SPM.

3. Refer to package insert or manufacturer website for the most complete and up to date information on contraindications, warnings and precautions, and adverse reactions

Comprehensive Adverse Events and Potential Risks list (CAEPR) for Lenalidomide (CC-5013, NSC 703813)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 4081 patients.* Below is the CAEPR for lenalidomide (CC-5013).

Version 2.6, December 24, 2015[1]

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 4.0 Term) [n= 4081]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
Anemia		
CARDIAC DISORDERS		
		Myocardial infarction[2]
ENDOCRINE DISORDERS		
	Hypothyroidism	
GASTROINTESTINAL DISORDERS		

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Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 4.0 Term) [n= 4081]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
Constipation		
Diarrhea		
	Nausea	
		Pancreatitis
	Vomiting	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
	Chills	
	Edema limbs	
Fatigue		
	Fever	
HEPATOBILIARY DISORDERS		
		Hepatic failure
IMMUNE SYSTEM DISORDERS		
		Anaphylaxis
		Immune system disorders - Other (graft vs. host disease)[3]
INFECTIONS AND INFESTATIONS		
	Infection[4]	
INVESTIGATIONS		
		Lipase increased
	Lymphocyte count decreased	
Neutrophil count decreased		
Platelet count decreased		
	Weight loss	
	White blood cell decreased	
METABOLISM AND NUTRITION DISORDERS		
	Anorexia	
		Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
	Arthralgia	
	Back pain	
	Musculoskeletal and connective tissue disorders - Other (muscle cramp/muscle spasm)	
	Myalgia	
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
		Leukemia secondary to oncology chemotherapy[5]
		Myelodysplastic syndrome[5]

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Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 4.0 Term) [n= 4081]		
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor flare) [6]
		Treatment related secondary malignancy[5]
NERVOUS SYSTEM DISORDERS		
	Dizziness	
	Headache	Stroke[2]
		Leukoencephalopathy
PSYCHIATRIC DISORDERS		
	Insomnia	
RENAL AND URINARY DISORDERS		
		Acute kidney injury
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		
	Cough	
	Dyspnea	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
		Erythema multiforme
	Hyperhidrosis	
	Pruritus	
	Rash maculo-papular	
	Skin and subcutaneous tissue disorders - Other (pyroderma gangrenosum)	
		Stevens-Johnson syndrome
		Toxic epidermal necrolysis
SURGICAL AND MEDICAL PROCEDURES		
		Surgical and medical procedures -Other (impaired stem cell mobilization)[7]
VASCULAR DISORDERS		
	Thromboembolic event[8]	

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Myocardial infarction and cerebiovascular accident (stroke) have been observed in multiple myeloma patients treated with lenalidomide and dexamethasone.

[3] Graft vs. host disease has been observed in subjects who have received lenalidomide in the setting of allo-transplantation.

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[4] Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.
[5] There has been an increased frequency of secondary malignancies (including AML/MDS) in multiple myeloma patients being treated with melphalan, prednisone, and lenalidomide post bone marrow transplant
[6] Serious tumor flare reactions have been observed in patients with Chronic Lymphocytic Leukemia (CLL) and lymphoma.
[7] A decrease in the number of stem cells (CD34 + cells) collected from patients treated with > 4 cycles of lenalidomide has been reported.
[8] Significantly increased risk of deep vein thrombosis (DVT), pulmonary embolism (PE) and arterial thrombosis has been observed in patients with multiple myeloma receiving lenalidomide with dexamethasone.
[9] Gastrointestinal hemorrhage includes: Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC
[10] Gastrointestinal obstruction includes: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Obstruction gastric, Rectal obstruction, and Small intestinal obstruction under the GASTROINTESTINAL DISORDERS SOC.
[11] Osteonecrosis of the jaw has been seen with increased frequency when lenalidomide is used in combination with bevacizumab, docetaxel (Taxotere®), prednisone, and zolendronic acid (Zometa®)

NOTE: While not observed in human subjects, lenalidomide, a thalidomide analogue, caused limb abnormalities in a developmental monkey study similar to birth defects caused by thalidomide in humans. If lenalidomide is used during pregnancy, it may cause birth defects or embryo-fetal death. Pregnancy must be excluded before start of treatment. Prevent pregnancy during treatment by the use of two reliable methods of contraception.

Adverse events reported on lenalidomide (CC-5013) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that lenalidomide (CC-5013) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (eosinophilia); Blood and lymphatic system disorders - Other (monocytosis); Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Febrile neutropenia; Hemolysis; Spleen disorder
CARDIAC DISORDERS - Acute coronary syndrome; Atrial fibrillation; Atrial flutter; Atrioventricular block first degree; Cardiac arrest; Cardiac disorders - Other (cardiovascular edema); Cardiac disorders - Other (ECG abnormalities); Chest pain - cardiac; Heart failure; Left ventricular systolic dysfunction; Palpitations; Pericarditis; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia; Ventricular tachycardia
EAR AND LABYRINTH DISORDERS - Tinnitus
ENDOCRINE DISORDERS - Cushingoid; Hyperthyroidism
EYE DISORDERS - Blurred vision; Conjunctivitis; Dry eye; Flashing lights; Retinopathy

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GASTROINTESTINAL DISORDERS - Abdominal distension; Abdominal pain; Anal mucositis; Ascites; Colonic perforation; Dry mouth; Dyspepsia; Dysphagia; Flatulence; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (Crohn's Disease aggravated); Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (pale feces); Gastrointestinal hemorrhage[9]; Gastrointestinal obstruction[10]; Ileus; Mucositis oral; Rectal mucositis; Small intestinal mucositis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - General disorders and administration site conditions - Other (edema NOS); Malaise; Multi-organ failure; Non-cardiac chest pain; Pain

HEPATOBILIARY DISORDERS - Cholecystitis

IMMUNE SYSTEM DISORDERS - Allergic reaction; Immune system disorders - Other (angioedema)

INFECTIONS AND INFESTATIONS - Infections and infestations - Other (Opportunistic infection associated with >=grade 2 lymphopenia)

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Fall; Fracture; Hip fracture; Vascular access complication

INVESTIGATIONS - Activated partial thromboplastin time prolonged; Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Cholesterol high; Creatinine increased; Electrocardiogram QT corrected interval prolonged; INR increased; Investigations - Other (hemochromatosis)

METABOLISM AND NUTRITION DISORDERS - Acidosis; Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Bone pain; Chest wall pain; Generalized muscle weakness; Joint effusion; Muscle weakness lower limb; Musculoskeletal and connective tissue disorders - Other (rhabdomyolysis); Neck pain; Osteonecrosis of jaw[11]; Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain

NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysgeusia; Dysphasia; Edema cerebral; Encephalopathy; Intracranial hemorrhage; Ischemia cerebrovascular; Memory impairment; Myelitis; Nervous system disorders - Other (hyporeflexia); Nervous system disorders - Other (spinal cord compression); Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Somnolence; Syncope; Transient ischemic attacks; Tremor

PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Psychosis

RENAL AND URINARY DISORDERS - Urinary frequency; Urinary incontinence; Urinary tract pain

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Reproductive system and breast disorders - Other (hypogonadism); Vaginal hemorrhage

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Atelectasis; Bronchopulmonary hemorrhage; Epistaxis; Hypoxia; Laryngeal mucositis; Pharyngeal mucositis; Pleural effusion; Pneumonitis; Pulmonary hypertension; Respiratory failure; Tracheal mucositis; Voice alteration

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SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Nail loss; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome); Urticaria
VASCULAR DISORDERS - Hot flashes; Hypertension; Hypotension; Phlebitis; Vascular disorders - Other (hemorrhage NOS)

Note: Lenalidomide (CC-5013) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

4. Pregnancy and Lactation: Pregnancy Category X. If pregnancy does occur during treatment, immediately discontinue the drug. Under these conditions, refer patient to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling. Any suspected fetal exposure to lenalidomide must be reported via CTEP-AERS as outlined in Section 16.0. It is not known whether lenalidomide is excreted in human milk. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from lenalidomide, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

5. Drug Interactions: Results from human in vitro metabolism studies and nonclinical studies show that lenalidomide is neither metabolized by nor inhibits or induces the cytochrome P450 pathway suggesting that lenalidomide is not likely to cause or be subject to P450-based metabolic drug interactions. *In vitro*, lenalidomide is a substrate of P-glycoprotein (P-gp).

   a. Digoxin: When digoxin was co-administered with multiple doses of lenalidomide (10 mg/day) the digoxin C_{max} and AUC0-∞ were increased by 14%. Periodic monitoring of digoxin plasma levels, in accordance with clinical judgment and based on standard clinical practice in patients receiving this medication, is recommended during administration of lenalidomide.

   b. Warfarin: Co-administration of multiple doses of 10 mg lenalidomide with single dose warfarin (25 mg) had no effect on the pharmacokinetics of total lenalidomide or R- and S-warfarin. Expected changes in laboratory assessments of PT and INR were observed after warfarin administration, but these changes were not affected by concomitant lenalidomide administration. It is not known whether there is an interaction between dexamethasone and warfarin. Close monitoring of PT and INR is recommended in multiple myeloma patients taking concomitant warfarin.

   c. Concomitant Therapies That May Increase the Risk of Thrombosis: Erythropoietic agents, or other agents that may increase the risk of thrombosis, such as estrogen containing therapies, should be used with caution in multiple myeloma patients receiving lenalidomide with dexamethasone.

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d. DOSING & ADMINISTRATION

1. Dosing – See Treatment Plan

2. Lenalidomide should be taken at about the same time each day, either with or without food. The capsules should not be opened, broken, or chewed. Lenalidomide should be swallowed whole with water. Refer to package insert for complete details on drug administration.

e. HOW SUPPLIED

1. Lenalidomide is available in 2.5 mg, 5 mg, 10 mg, 15 mg, 20 mg, and 25 mg capsules for oral administration.

2. 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 Revlimid REMS™ program of Celgene Corporation. All investigators who prescribe lenalidomide to participants on this study, and all study participants, must be registered in and must comply with all requirements of the Revlimid REMS™ program. Prescriptions must be filled within 7 days for females of childbearing potential and 14 days for all other risk categories. **Only enough lenalidomide for one treatment cycle will be supplied to the patient each cycle.**

3. Drug Ordering: The **S1211** Revlimid® (lenalidomide) Study Drug Shipment Request Form should be faxed to the number on the form to order lenalidomide. Lenalidomide should be shipped to the participating site. For additional information on Revlimid® (lenalidomide) or the REMS™ program, please visit www.revlimidrems.com.

4. Drug Handling and Accountability:

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and disposal of all drugs received from the supplier using the NCI Drug Accountability Record Form (DARF) available at http://ctep.cancer.gov.

Electronic logs are allowed as long as a print version of the log process is the exact same appearance as the current NCI DARF. If the trial is a placebo control trial – indicate that separate DARFs are needed for each patient to also include the placebo drug supply.

5. Drug Return and Disposition

All unused drug should be returned to the participating site for destruction. Unused drug supplies should not be returned to Celgene. Unused drug should be destroyed on site per local institutional guideline.

f. STORAGE, PREPARATION & STABILITY

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature].

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4.0 STAGING CRITERIA

4.1 Diagnostic Criteria

Multiple Myeloma* - normally all three are required, except for circumstances outlined in notes a-c.

Monoclonal plasma cells in the bone marrow ≥ 10% and/or presence of a biopsy-proven plasmacytomas. [a]

Monoclonal protein present in the serum and/or urine [b]

Myeloma-related organ dysfunction (1 or more from the CRAB list below) [c]

[C] Calcium elevation in the blood (serum calcium > 11.5 mg/L or corrected calcium > 2.75 mmol/L)
[R] Renal insufficiency (serum creatinine > 2 mg/dl)
[A] Anemia (hemoglobin < 10 g/dl or more than 2 g below the lower limit of institutional normal)
[B] Lytic bone lesions, severe osteopenia or pathologic fractures [a]

[a] If a solitary (biopsy-proven) plasmacytomas or osteoporosis alone (without fractures) are the sole defining criteria, then ≥ 30% plasma cells are required in the bone marrow.
[b] If no monoclonal protein is detected (non-secretory disease), then ≥ 30% monoclonal bone marrow plasma cells and/or a biopsy-proven plasmacytomas required.
[c] A variety of other types of end organ dysfunctions can occasionally occur and lead to a need for therapy. Such dysfunction is sufficient to support classification as myeloma if proven to be myeloma related.

Diagnostic criteria are based on (http://bloodjournal.hematology.org/content/117/18/4701.full).

*Note that non-secretory patients are not eligible for this study.

4.2 Chromosomal Status (if available)

Patients will be sub-classified based on results of conventional cytogenetics and FISH assays.

Conventional Cytogenetics:

a. Normal
b. Abnormal 13/hypodiploidy
c. Abnormal other

FISH

a. Chromosome 13 deletion
b. p53 locus on chromosome 17

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5.0 ELIGIBILITY CRITERIA

Each of the criteria in the following section must be met in order for a patient to be considered eligible for registration. Use the spaces provided to confirm a patient's eligibility. For each criterion requiring test results and dates, please record this information on the Onstudy Form and submit via MediData Rave® (see Section 14.0). Any potential eligibility issues should be addressed to the Data Operations Center in Seattle at 206/652-2267 prior to registration.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday 4 weeks later would be considered Day 28. This allows for efficient patient scheduling without exceeding the guidelines. **If Day 14, 28 or 56 falls on a weekend or holiday, the limit may be extended to the next working day.**

5.1 Disease Related Criteria

a. Patients must have newly diagnosed active MM as defined in Section 4.1. (See Sections 5.2a and 5.2b for prior therapy information.)

Except where otherwise indicated below that assessment is required within 14 days, all tests for establishing baseline disease status must be completed within 28 days prior to registration for patients with no prior therapy, or within 28 days prior to initiation of first Induction course for patients with prior therapy.

b. **For the Phase II portion only** patients must have high risk MM based on one or more of the following criteria at the time of initial diagnosis (prior to any chemotherapy):

1. Poor risk genomic signature according to the University of Arkansas 70-gene model (available clinically as MyPRS score, Signal Genetics, Inc.) **AND/OR**
2. Translocation (14;16), and/or translocation (14;20), and/or deletion (17p) by florescence in-situ hybridization (FISH) or cytogenetics **AND/OR**
3. Primary plasma cell leukemia (defined by either ≥ 2,000 plasma cells/mL of peripheral blood, or 20% on a manual differential count **AND/OR**
4. Serum lactate dehydrogenase (LDH) ≥ 2 x Institutional Upper Limit of Normal (IULN) **AND/OR**
5. 1q21 amplification by FISH analysis **AND/OR**
6. High risk by the SKY92 signature.

All tests for establishing high risk status must be completed within 28 days prior to registration for patients with no prior therapy, or within 28 days prior to initiation of first Induction course for patients with prior therapy.

c. Patients with non-secretory MM or known amyloidosis are not eligible.

d. Patients must have measurable disease as defined by Section 10.1a within 28 days prior to registration (or prior to initiation of first induction course for patients with prior therapy).

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5.2 Prior Therapy Criteria

a. Patients on the Phase I portion may not have received ANY prior chemotherapy. Patients on the Phase II portion may have received one prior cycle of any non-investigational chemotherapy. Prior chemotherapy must have been completed within 56 days prior to registration and all toxicities must have resolved to ≤ Grade 1. Patients on either portion may have received prior treatment with dexamethasone, providing total number of days of treatment was ≤ 14 days and total treatment dose was ≤ 360 mg.

b. Patients may have received prior radiotherapy for symptomatic localized bone lesions or impending spinal cord compression only. Radiotherapy must be completed at least 14 days prior to registration and all toxicities must have resolved to ≤ Grade 1.

5.3 Clinical/Laboratory Criteria

a. Patients must have adequate marrow function defined by the following within 14 days prior to registration:

1. ANC ≥ 1,000 cells/mm^3 without growth factor support

AND

2. Platelet count ≥ 70,000 cells/mm^3 for patients who have bone marrow plasmacytosis < 50%; or ≥ 50,000 cells/mm^3 for patients who have bone marrow plasmacytosis of ≥ 50%

b. Patient must have adequate hepatic function defined by the following within 14 days prior to registration:

1. Total bilirubin ≤ 1.5 x IULN

AND

2. SGOT/AST and SGPT/ALT ≤ 2.5 x IULN

c. Patients must have adequate renal function as evidenced by creatinine clearance (CrCL) ≥ 30 mL/min, measured by a 24-hour urine collection or estimated by the Cockcroft and Gault formula within 14 days prior to registration:

$$\text{CrCl} = \frac{(140 - \text{patient's age} \times \text{patient's weight in kilograms}) \times 0.85 \text{ (if female)}}{72 \times \text{patient's serum creatinine}}$$

d. Patients must not have active involvement of the central nervous system (CNS) with MM (by clinical evaluation). Patients with documentation of, or clinical signs or symptoms consistent with, CNS involvement of MM must have a lumbar puncture that is negative for CNS involvement of MM. The lumbar puncture must be completed within 14 days prior to registration. Patients with no previous history of documented CNS involvement and with no clinical signs or symptoms consistent with CNS involvement are not required to have completed a lumbar puncture prior to registration. Note that monitoring of CNS involvement and treatment with intrathecal therapy is recommended during protocol treatment.

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e. Patients who are known to be HIV+ are eligible providing they meet all of the following additional criteria within 28 days prior to registration:

1. CD4 cells ≥ 500/mm^3

2. Viral load of < 50 copies HIV mRNA/mm^3 if on cART or < 25,000 copies HIV mRNA if not on cART

3. No zidovudine or stavudine as part of cART

Patients who are HIV+ and do not meet all of these criteria are not eligible for this study.

f. Patients must have baseline skeletal survey (whole body x-ray) to document lytic lesions, osteopenia or compression fracture.

g. Patients must have Zubrod Performance Status ≤ 2 (see Section 10.6).

h. Patients must be ≥ 18 years of age.

i. Patients with known Hepatitis B or Hepatitis C infection may be eligible providing they have viral load < 800,000 IU/L within 28 days prior to registration.

j. Patients must not have POEMS syndrome (plasma cell dyscrasia with polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes).

k. Patients must not have clinically significant illness including uncontrolled, active infection requiring intravenous antibiotics, New York Heart Association (NYHA) Class III or Class IV heart failure (see Appendix 18.2), unstable angina pectoris, myocardial infarction within the past 6 months, uncontrolled ≥ Grade 3 cardiac arrhythmias, uncontrolled hypertension, or uncontrolled diabetes mellitus. Patients must have undergone an EKG within 28 days prior to registration.

Uncontrolled diabetes: An Hg A1C > 7% within 14 days prior to registration. The same criterion will be used in patients with confirmed diagnosis of diabetes mellitus who have been on a stable dietary or therapeutic regimen for this condition in the last three months.

Uncontrolled blood pressure and hypertension: SBP > 140 mm Hg or DBP > 90 mm Hg within 14 days prior to registration. Patients are permitted to be receiving multiple anti-hypertensive medications (unless otherwise indicated in the study). All blood pressure measurements within the 14 days prior to registration and on Day 1 of Cycle 1 must be SBP ≤ 140 and DBP ≤ 90. An exception can be made by a healthcare provider for a patient with a single blood pressure elevation who upon rechecking has a normal blood pressure.

- See ACCF/AHA.AMA-PCPI joint statement.

l. Patients must have history and physical examination within 28 days prior to registration.

m. Patients must not have any psychiatric illness that could potentially interfere with the completion of treatment according to this protocol.

n. Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days prior to registration. (Note: that pregnancy testing is also required within 24 hours prior

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to treatment on Cycle 1, Day 1.) Furthermore, they must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control: one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before starting lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP, even if they have had a successful vasectomy. A FCBP is a sexually mature woman 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). See Appendix 18.4: Elotuzumab Reproductive Warnings, for additional elotuzumab related pregnancy and contraception information, including instructions to investigators.

o. No other prior malignancy is allowed except for the following: adequately treated basal cell or squamous cell skin cancer, *in situ* cervical cancer, adequately treated Stage I or II cancer from which the patient is currently in complete remission, or any other cancer from which the patient has been disease free for five years.

5.4 Specimen Submission Criteria

a. Patients must be offered participation in banking of specimens for future research. With the patient's consent, specimens (serum and bone marrow biopsy core) must be submitted to the repository. Patient consent must be obtained before specimens are submitted. See Section 15.1 for further information, including specimen submission timepoints.

5.5 Regulatory Criteria

a. Patients must be registered to the mandatory Revlimid REMS™ program and must be willing and able to comply with the requirements of the Revlimid REMS™ program.

b. Patients or their legally authorized representative must be informed of the investigational nature of this study and must sign and give written informed consent in accordance with institutional and federal guidelines.

c. As a part of the OPEN registration process (see Section 13.4 for OPEN access instructions) the treating institution's identity is provided in order to ensure that the current (within 365 days) date of institutional review board approval for this study has been entered in the system.

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6.0 STRATIFICATION FACTORS

Patients in the Phase II portion of the study will be stratified as follows:

Primary plasma cell leukemia and/or high LDH (as defined in Section 5.1b) vs. everyone else.

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7.0 TREATMENT PLAN

For treatment or dose modification questions, please contact Dr. Saad Usmani at 248/225-5642, Dr. Sikander Ailawadhi at 904/953-7290, or Dr. Jatin Shah at 713/745-6130. For dosing principles or questions, please consult the SWOG Policy #38 "Dosing Principles for Patients on Clinical Trials" at http://swog.org (then click on "Policies and Manuals" under the "Visitors" menu and choose Policy 38).

7.1 General Treatment Instructions

a. This study will be conducted in two sequential parts. Patients will be enrolled into either the Phase I portion or the Phase II portion, but not both.

Phase I – In the Phase I portion of the study, patients will be treated with bortezomib, lenalidomide, dexamethasone and various dose levels of elotuzumab to determine the optimal dose to be used in this combination. Details are in Section 7.2.

Phase II – In the Phase II portion of the study, eligible patients will be randomized to either 8 cycles of RVD (bortezomib, lenalidomide, dexamethasone) or 8 cycles of RVD + elotuzumab at the dose determined during the Phase I portion (10 mg/kg).

b. Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10-14 days prior to registration and again within 24 hours prior to starting Cycle 1. Day 1 of lenalidomide (see Section 5.3n). In the event of pregnancy, lenalidomide must be discontinued immediately. **Patients may not remain on protocol treatment while pregnant.**

c. Elotuzumab requires pre-medication with H1 blocker (diphenhydramine, 25-50 mg PO or IV, or equivalent), H2 blocker (ranitidine, 50 mg IV, or equivalent) and acetaminophen (650-1,000 mg PO) administered 30-90 minutes prior to elotuzumab administration. Elotuzumab requires vital sign monitoring prior to, during and after administration as per Sections 9.1 and 9.2.

d. Stem cell mobilization is allowed (not required) after 2-4 cycles of therapy per local procedures. Protocol treatment may be interrupted for up to 4 weeks to allow for the collection. If the protocol treatment is interrupted for collection, treatment will resume with the next treatment cycle. This interruption should be noted on the **S1211** Treatment Form. Patients progressing in the absence of therapy during the interruption may resume protocol treatment at the discretion of the treating investigator.

e. Restaging will be performed every cycle using the serum and/or urine protein electrophoresis with immunofixation and serum free light chains to assess disease response. Bone marrow aspiration and biopsy will be performed after the baseline sampling, to confirm the achievement of a complete remission (CR), or as clinically indicated. Responses will be determined using International Myeloma Working Group (IMWG) Uniform Response Criteria. *(36-38)* The overall response rate will be calculated on an intent-to-treat basis, will include patients who have achieved at least a partial remission (PR), and will also incorporate those who are judged to be in a very good partial remission (VGPR), CR, and stringent CR (sCR). Patients will be eligible for the next treatment cycle (Induction or Maintenance) providing the restaging shows continued remission and toxicities have resolved per Section 8.0.

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f. The Maintenance Arm will be consistent with the Induction Arm the patient receives; i.e. patients receiving RVD Induction will receive RVD Maintenance and patients receiving RVD /Elo Induction will receive RVD/Elo Maintenance.

g. Patients on the Phase II portion that have received the allowable one cycle of chemotherapy prior to registration will begin protocol therapy on Cycle 2 and will receive a maximum of 7 Induction chemotherapy cycles on protocol (Cycles 2-8).

h. Patients should receive deep vein thrombosis (DVT) prophylaxis and varicella-zoster virus (VZV) prophylaxis (to include acyclovir) per local institutional standard.

i. Use of bisphosphonates is allowed per local institutional guidelines in accordance with National Comprehensive Cancer Network (NCCN) guidelines after stem-cell collection and during Maintenance.

7.2 Phase I Run-In – RVD/Elo x 8 cycles

Agent	Dose	Route	Days*
Bortezomib [1]	1.3 mg/m^2	SC (or IV)	1, 4, 8, 11
Lenalidomide [2]	25 mg	PO (once daily)	1-14
Dexamethasone [2,3]	20 mg	PO/IV	1, 2, 4, 5, 8, 9, 11, 12, (15)
Elotuzumab** (Cycles 1-2)	Assigned dose (10 mg/kg or 5 mg/kg)	IV	1, 8, 15
Elotuzumab** (Cycles 3-8)	Assigned dose (10 mg/kg or 5 mg/kg)	IV	1, 11

* 1 cycle = 21 days

** Elotuzumab dose will be assigned at the time of registration and communicated to the registering institution as part of the registration confirmation. Dose Level 1 = 10 mg/kg. Dose Level 2 = 5 mg/kg. Dosing will begin at Dose Level 1 and follow the rules outlined below. A third dose level may be explored if Dose Level 2 is not tolerated.

[1] IV bortezomib may be used only in instances of toxicity to SC administration. Bortezomib doses (whether SC or IV) should be given prior to elotuzumab doses on days when both drugs are given.

[2] Drug compliance for oral treatment will be recorded by patients in the Intake Calendar (see Appendix 18.3). Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each cycle. Calendar should be kept in the patient's clinic chart. Note that the Intake Calendar is provided only as a tool for tracking compliance. Sites may utilize other source documentation in place of the Intake Calendar at the discretion of the treatment physician.

[3] On days of elotuzumab infusion, dexamethasone will be administered intravenously at least 45 minutes before the start of elotuzumab infusion. On Days when elotuzumab is not administered, or if the elotuzumab dose is skipped or discontinued, dexamethasone may be administered orally or by IV at the discretion of the treating physician. Dexamethasone is given on Day 15 of Cycles 1 and 2 as pre-medication for elotuzumab. Dexamethasone is not given on Day 15 of Cycles 3-8.

NOTE: The Phase I portion of this study requires attendance on biweekly conference calls. See Section 15.2 for details.

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a. Dose Determination Rules

1. Dose Limiting Toxicity (DLT) is defined in Section 7.2b.

2. Only DLTs occurring in the first cycle will be used to guide dosing determination of elotuzumab for future patients.

3. Patients will be considered evaluable for DLT if they received one cycle of therapy or developed a DLT. If a patient does not develop a DLT but does not complete all doses during the first cycle due to any reason, the patient will be considered not evaluable for DLT and will be replaced.

4. The following dosing scheme will be used for dose determination:

- Evaluate 6 patients at Dose Level 1.
- If 1/6 or fewer patients have DLT at Dose Level 1 (DLT experienced in less than a third of patients), this will be the dose for the Phase II trial.
- If more than 1/6 patients have DLT at Dose Level 1, stop enrollment at this dose after the 2nd patient with DLT and enroll 6 patients at Dose Level 2. (Enroll 6 patients, evaluate for toxicity, enroll additional patients as required)
- If 1/6 or fewer patients have DLT at Dose Level 2 (DLT experienced in less than a third of patients), this will be the dose for the Phase II trial.
- Further testing will need to be discussed if necessary.

b. Definition of Dose-Limiting Toxicity

Toxicities will be graded according to the NCI Common Terminology Criteria for Adverse Events Version 4.0.

Dose-limiting toxicities (DLT) apply only during Cycle 1. The following events occurring in the first cycle of treatment are considered dose limiting.

1. Any Grade 3 or greater non-hematological toxicity will be a DLT, with the exception of: alopecia; inadequately treated nausea, vomiting or diarrhea; inadequately treated hyperglycemia; or hypersensitivity reaction. For a baseline abnormality prior to drug therapy, a worsening by at least 2 toxicity grades and of clinical significance will be considered a DLT.

2. Grade 3 nausea, vomiting or diarrhea will be a DLT if it occurs despite appropriate anti-emetic and anti-diarrheal therapy.

3. Grade 3 hyperglycemia will be a DLT if the patient is symptomatic or glucose level is > 300 mg/ml despite appropriate administration of insulin and/or oral diabetic agents.

4. Grade 4 neutropenia lasting more than 7 days or Grade 3 or 4 neutropenia associated with fever (≥ 38.5°C).

5. Grade 4 thrombocytopenia. Grade 3 thrombocytopenia lasting more than 7 days or associated with hemorrhage.

6. Delay of treatment with ANY agent for 14 days or more due to possibly, probably, or definitely treatment related toxicity during Cycle 1.

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c. Except when they conflict with Section 7.2, the guidelines included in Section 8.0 should be followed for patients on the Phase I portion of the study.

d. A patient on the Phase I portion of the study who develops a DLT while on Dose Level 1 should have treatment held until the toxicity resolves, and then may continue on treatment at Dose Level 2. A patient on the Phase I portion of the study who develops a DLT while on Dose Level 2 should have treatment stopped and will not receive further elotuzumab. Only DLTs occurring in the first cycle and at the patient's first Dose Level of treatment will be used to guide dose determination for the Phase II portion of the trial as per Section 7.2a.4.

7.3 Phase II Induction

a. Arm 1 – RVD x 8 cycles [1]

Agent	Dose	Route	Days*
Bortezomib [2]	1.3 mg/m^2	SC (or IV)	1, 4, 8, 11
Lenalidomide [3]	25 mg	PO (once daily)	1-14
Dexamethasone [3]	20 mg	PO/IV [4]	1, 2, 4, 5, 8, 9, 11, 12

* 1 cycle = 21 days

[1] Patients that received a cycle of chemotherapy prior to registration will begin protocol treatment with Cycle 2 and will receive a total of 7 cycles of protocol therapy (Cycles 2-8).

[2] IV bortezomib may be used only in instances of toxicity to SC administration.

[3] Drug compliance for oral treatment will be recorded by patients in the Intake Calendar (see Appendix 18.3). Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each cycle. Calendar should be kept in the patient's clinic chart. Note that the Intake Calendar is provided only as a tool for tracking compliance. Sites may utilize other source documentation in place of the Intake Calendar at the discretion of the treatment physician.

[4] PO or IV at discretion of the treating physician.

b. Arm 2 – RVD/Elo x 8 cycles [1]

Agent	Dose	Route	Days*
Bortezomib [2]	1.3 mg/m^2	SC (or IV)	1, 4, 8, 11
Lenalidomide [3]	25 mg	PO (once daily)	1-14
Dexamethasone [3]	20 mg	PO/IV [4]	1, 2, 4, 5, 8, 9, 11, 12, (15)
Elotuzumab** (Cycles 1-2)	10 mg/kg	IV	1, 8, 15
Elotuzumab** (Cycles 3-8)	10 mg/kg	IV	1, 11

* 1 cycle = 21 days

** Induction and Maintenance dosing of elotuzumab will be determined during the Phase I run-in (see Section 7.2). The first 10 patients enrolled will be monitored for toxicity during the first treatment cycle. If 4 or more patients (> 30%) experience a DLT (as defined in Section 7.2b) the study will be stopped for dose consideration.

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[1] Patients that received a cycle of chemotherapy prior to registration will begin protocol treatment with Cycle 2 and will receive a total of 7 cycles of protocol therapy (Cycles 2-8).
[2] IV bortezomib may be used only in instances of toxicity to SC administration. Bortezomib doses (whether SC or IV) should be given prior to elotuzumab doses on days when both drugs are given.
[3] Drug compliance for oral treatment will be recorded by patients in the Intake Calendar (see Appendix 18.3). Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each cycle. Calendar should be kept in the patient's clinic chart. Note that the Intake Calendar is provided only as a tool for tracking compliance. Sites may utilize other source documentation in place of the Intake Calendar at the discretion of the treatment physician.
[4] On days of elotuzumab infusion, dexamethasone will be administered intravenously at least 45 minutes before the start of elotuzumab infusion. On Days when elotuzumab is not administered, or if the elotuzumab dose is skipped or discontinued, dexamethasone may be administered orally or by IV at the discretion of the treating physician. Dexamethasone is given on Day 15 of Cycles 1 and 2 as pre-medication for elotuzumab. Dexamethasone is not given on Day 15 of Cycles 3-8.

7.4 Phase I and II - Maintenance (treat until progression)

a. Arm 1 – RVD (for patients on Phase II, Arm 1)

Agent	Dose	Route	Days*
Bortezomib [1]	1.0 mg/m^2	SC (or IV)	1, 8, 15
Lenalidomide [2]	15 mg	PO (once daily)	1-21
Dexamethasone [2]	12 mg	PO	1, 8, 15

*1 cycle = 28 days
[1] IV bortezomib may be used only in instances of toxicity to SC administration.
[2] Drug compliance for oral treatment will be recorded by patients in the Intake Calendar (see Appendix 18.3). Institutional CRAs will review and ascertain patient adherence with protocol therapy at the end of treatment for each cycle. Calendar should be kept in the patient's clinic chart. Note that the Intake Calendar is provided only as a tool for tracking compliance. Sites may utilize other source documentation in place of the Intake Calendar at the discretion of the treatment physician.

b. Arm 2 – RVD/Elo (for patients on Phase I and Phase II, Arm 2)

Agent	Dose	Route	Days*
Bortezomib [1]	1.0 mg/m^2	SC (or IV)	1, 8, 15
Lenalidomide [2]	15 mg	PO (once daily)	1-21
Dexamethasone [2, 3]	12 mg	PO/IV	1, 8, 15
Elotuzumab	10 mg/kg	IV	1, 15

*1 cycle = 28 days
** Induction and Maintenance dosing of elotuzumab will be determined during the Phase I run-in (see Section 7.2).
[1] IV bortezomib may be used only in instances of toxicity to SC administration.
[2] Drug compliance for oral treatment will be recorded by patients in the Intake Calendar (see Appendix 18.3). Institutional CRAs will review and ascertain

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patient adherence with protocol therapy at the end of treatment for each cycle. Calendar should be kept in the patient's clinic chart. Note that the Intake Calendar is provided only as a tool for tracking compliance. Sites may utilize other source documentation in place of the Intake Calendar at the discretion of the treatment physician.

[3] On days of elotuzumab infusion, dexamethasone will be administered intravenously at least 45 minutes before the start of elotuzumab infusion. On Days elotuzumab is not administered, or if the elotuzumab dose is skipped or discontinued, dexamethasone may be administered orally or by IV at the discretion of the treating physician.

[4] For patients on the Phase I portion, the appropriate dose may not be known when the patient begins Maintenance. If this is the case, the patient should continue the dose received during Induction.

7.5 Criteria for Removal from Protocol Treatment

a. Progression of disease or relapse (as defined in Section 10.1).

b. Unacceptable toxicity.

c. Treatment delay for any reason except stem cell collection during Induction > 8 weeks or during Maintenance > 6 weeks. See Section 7.1d for allowable delays due to stem cell collection.

d. The patients may withdraw from the study at any time for any reason.

7.6 Discontinuation of Treatment

All reasons for discontinuation of treatment must be documented in the Off Treatment Notice.

7.7 Follow-Up Period

All patients will be followed until death or 6 years after registration, whichever occurs first.

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8.0 TOXICITIES TO BE MONITORED AND DOSE MODIFICATIONS

8.1 NCI Common Terminology Criteria for Adverse Events

Effective with Revision #12, two different versions of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be used on this study.

a. Serious Adverse Event (SAE) reporting

The CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5.0 will be utilized **for SAE reporting only**. The CTCAE Version 5.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov) All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0.

b. Routine toxicity reporting

This study will utilize the CTCAE Version 4.0 for routine toxicity reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (https://ctep.cancer.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0.

8.2 General Considerations

c. Missed doses are to be omitted rather than made up.

d. If multiple toxicities are experienced, dose modifications will be based on the toxicity requiring the largest dose reduction.

e. Reductions are based on the dose given in the preceding cycle and are based on toxicities observed since the prior toxicity evaluation.

f. Once a dose is reduced, patients will continue at the new dose. No dose re-escalations are allowed.

NOTE: Patients who begin lenalidomide at a reduced dose due to renal insufficiency or other existing condition will be allowed to dose increase to the full starting dose. This must be captured on the Treatment Form.

g. If a study drug must be permanently discontinued the patient will be removed from protocol therapy.

8.3 Dose Reductions for Toxicity

See Section 8.3e for dose reduction instructions for bortezomib related neuropathy.

a. Bortezomib and Lenalidomide

At the discretion of the treating physician, dose reduction for each drug (bortezomib or lenalidomide) can be done separately based on best judgment of which drug it was that caused the toxicity.

Induction

Drug	Full Dose (Dose Level 0)	Level -1	Level -2	Level -3
Bortezomib	1.3 mg/m^2 (D 1, 4, 8, 11)	1.0 mg/m^2 (D 1, 4, 8, 11)	1.0 mg/m^2 (D1, 8)	0.7 mg/m^2 (D1, 8)
Lenalidomide	25 mg	15 mg	10 mg	

Maintenance

Drug	Full Dose (Dose Level 0)	Level -1	Level -2	Level -3
Bortezomib	1.0 mg/m^2 (D 1, 8, 15)	0.7 mg/m^2 (D 1, 8, 15)	0.7 mg/m^2 (D1, 15)	Discontinue
Lenalidomide	15 mg	10 mg	5 mg	

Before each dose of bortezomib, patients will be evaluated for possible toxicities that may have occurred with the previous dose(s). Previously established or new toxicities observed any time are to be managed as follows:

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Patients experiencing bortezomib and/or lenalidomide related ≥ Grade 3 non-hematologic or Grade 4 hematologic toxicity will have their dose held until toxicity has resolved to Grade 1 or better, and then will have their dose reduced one level from previous dose received.

If, after bortezomib and lenalidomide have been held, and the toxicity does not return to ≤ Grade 1 within 8 weeks during Induction or within 6 weeks during Maintenance, then the patient must be removed from protocol treatment.

b. Lenalidomide

Dose Reduction Guidelines

Toxicity	Dose Reduction
Grade 4 hematologic toxicity	Hold dose until toxicity resolves to ≤ Grade 1, then re-start dose at one dose level below previous dose administered
Renal insufficiency: GFR > 60 GFR 30-59 GFR < 30 (no dialysis)	 Administer to Dose Level 0 (full dose) Reduce to Dose Level -1 Reduce to Dose Level -2

c. Dexamethasone

In general, dose reduction of dexamethasone is not allowed. However, in the case of Grade 3 or 4 gastrointestinal bleeding or severe diabetes, dexamethasone must be discontinued. In that case, lenalidomide and bortezomib therapy will continue. For other Grade 3 or 4 toxicities with dexamethasone rather than discontinue the drug, dose may be reduced by up to 50% if side effects persist despite administration of supportive care per local institutional standards.

Maintenance dose reduction is permitted for dexamethasone with a first reduction of 4 mg followed by increments of 4 mg to maximize tolerance and compliance. Dose tapering over a week is also allowed to alleviate symptoms of steroid withdrawal. Also, the one day/week schedule is allowed in this setting if necessary with dose/day reductions as necessary (noted above) for Grade > 3 toxicities.

Exception: Dexamethasone must be given as pre-medication for elotuzumab. For patients receiving elotuzumab, dexamethasone (8 mg during Induction or 4 mg during Maintenance) IV must be given at least 45 minutes before the start of elotuzumab infusion, regardless of dexamethasone dose reduction.

d. Elotuzumab

Infusion reactions during the elotuzumab infusion: For a Grade ≥ 2 elotuzumab infusion-related reaction, the infusion must be interrupted. The subject should be treated as clinically indicated with one or more of the following medications or interventions: antiemetics, antihistamines, analgesics, corticosteroids, leukotriene inhibitors, oxygen inhalation, epinephrine, bronchodilators, or other supportive measures as indicated. Subjects with a Grade 4 elotuzumab infusion reaction must have elotuzumab permanently

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discontinued. These subjects should continue to receive bortezomib, lenalidomide and dexamethasone per protocol.

Once the elotuzumab infusion-related reaction has resolved to Grade ≤ 1, the infusion can be restarted at 0.5 mL/minute. If symptoms do not recur after 30 minutes, the infusion rate may be increased in a stepwise fashion (0.5 mL/minute every 30 minutes) to a maximum of 2 mL/minute or the rate at which the infusion reaction occurred, whichever is lower. Subjects who experience an infusion reaction require vital signs to be monitored every 30 minutes for 2 hours after the end of the elotuzumab infusion. If the elotuzumab infusion reaction recurs, the infusion must be stopped and not restarted on that day.

Appropriate therapy should be administered to address the subject's signs and symptoms. The infusion can be reattempted at the next protocol defined infusion time point at the investigator's discretion per local institutional standards.

Infusion reactions after the completion of elotuzumab infusion: Should a Grade ≥ 2 infusion reaction occur following completion of an elotuzumab infusion, the subject should be treated as clinically indicated with 1 or more of the following medications or interventions: diphenhydramine, acetaminophen, hydrocortisone, H2 inhibitor, leukotriene inhibitor, oxygen inhalation, epinephrine, bronchodilators, or other supportive measures as indicated.

Elotuzumab infusions on subsequent weeks after a prior Grade ≥ 2 infusion reaction: Subjects with prior Grade 2 or higher infusion reactions should have future infusions started at 0.5 mL/min and then escalated in a stepwise fashion (0.5 mL/minute every 30 minutes).

e. Bortezomib Dose Reduction for Neuropathy

Patients experiencing bortezomib related neuropathy should have their dose reduced as follows:

Severity of Peripheral Neuropathy Signs and Symptoms	Modification of Dose and Regimen
Grade 1	No action
Grade 1 with pain or Grade 2	Reduce to Dose Level -1
Grade 2 with pain or Grade 3	Withhold bortezomib therapy until toxicity resolves to ≤ Grade 1. When toxicity resolves, reinitiate at Dose Level -2 (and change treatment schedule to once per week for Induction, SC or once every two weeks for Maintenance, SC). In event of repeat toxicity, withhold bortezomib therapy until toxicity resolves to ≤ Grade 1, reinitiate at Dose Level -3 (and continue treatment schedule at once per week for Induction, SC or once every 2 weeks for Maintenance, SC.). Do not use IV for Dose Level -2 or -3 administration.
Grade 4	Discontinue bortezomib

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8.4 Clotting Events

Patients who experience a deep vein thrombosis (DVT), pulmonary embolus (PE), or other clotting event should have study drug temporarily held while full-dose anticoagulation such as enoxiparin 1 mg/kg twice daily or dose adjusted UFH is initiated. Investigators may choose to place patients on chronic warfarin (INR 2-3) at the same time as definitive anticoagulation is established, change from UFH to LMWH or continue LMWH as secondary prophylaxis. Once the patient is fully anticoagulated, s/he should resume the same dose of study drug s/he was receiving prior to the thrombotic event and stop the aspirin.

8.5 G-CSF

G-CSF use is allowed per local institutional guidelines.

8.6 Concomitant Medication

Any systemic, anti-myeloma therapy or steroids other than those prescribed by the protocol are prohibited while on protocol therapy. Guidelines for selection and use of other concomitant medications should be derived from the lenalidomide, bortezomib and dexamethasone prescribing information. Other than study medications, administration of any therapeutic or diagnostic investigational agent (for any indication) is prohibited while on study.

8.7 Dose Modification Contacts

For treatment or dose modification questions, please contact Dr. Saad Usmani at 248/225-5642, Dr. Sikander Ailawadhi at 904/953-7290, or Dr. Jatin Shah at 713/745-6130.

8.8 Adverse Event Reporting

Unexpected or fatal toxicities (including suspected reactions) must be reported to the Operations Office, to the Study Chair, to the IRB and the NCI. The procedure for reporting adverse reactions is outlined in Section 16.0.

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9.0 STUDY CALENDAR

9.1 Phase I

		INDUCTION										MAINTENANCE [12]					
REQUIRED STUDIES	Pre-Study	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Complete Response	1 Cycle				Prog	Follow Up [4]
		WK 1	Wk 2	Wk 3									Wk 1	Wk 2	Wk 3	Wk 4		
PHYSICAL																		
History and Physical Exam [16]	X	X			X	X	X	X	X	X	X		X					X
Weight and Performance Status	X																	
Toxicity Notation	X	X	X	X	X	X	X	X	X	X	X		X		X			
Intake Calendar				X	X	X	X	X	X	X	X					X		
Lenalidomide Education and Counseling [1]	X				X	X	X	X	X	X	X		X					
Risk Assessment [15]	X																	
LABORATORY STUDIES																		
CBC, Diff, Platelets	X			X	X	X	X	X	X	X	X		X		X			X
Bone Marrow Aspirate/Biopsy	X											X						
Serum β2 microglobulin	X																	
Albumin	X																	
CRP	X																	
Glucose	X																	
LDH	X																	
FISH [6]	X																	
Cytogenetics [6]	X																	
Electrolyte Panel (must include Ca+) [5]	X	X		X	X	X	X	X	X	X	X		X		X			

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		INDUCTION										MAINTENANCE [12]					
REQUIRED STUDIES	Pre-Study	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Complete Response	1 Cycle				Prog	Follow Up [4]
		WK 1	Wk 2	Wk 3									Wk 1	Wk 2	Wk 3	Wk 4		
Serum Creatinine [5]	X	X			X	X	X	X	X	X	X		X		X			
Total Bilirubin [5]	X	X			X	X	X	X	X	X	X		X		X			
SGOT/SGPT [5]	X	X			X	X	X	X	X	X	X		X		X			
Creatinine Clearance (measured or calculated) [5]	X	X			X	X	X	X	X	X	X		X		X			
CNS Clinical Evaluation	X																	
HIV/Hep B/HepC Test [11]	X																	
Pregnancy Test [2]	X	X	X	X	X	X	X	X	X	X	X		X					X
Vital Signs [17]		X	X	X	X	X	X	X	X	X	X		X		X			
X-RAYS AND SCANS																		
EKG [8]	X																	
Skeletal Survey [18]	X																	
RESPONSE ASSSSMENT [13]																		
Serum Protein Electrophoresis	X	X			X	X	X	X	X	X	X	X	X				X	
Serum Quantitative Immunoglobulins	X	X			X	X	X	X	X	X	X	X	X				X	
24 hour Urine for: Total protein	X	X			X	X	X	X	X	X	X	X	X				X	
Protein electrophoresis [7]	X	X			X	X	X	X	X	X	X	X	X				X	
Serum and Urine Immunofixation electrophoresis	X	X			X	X	X	X	X	X	X	X	X				X	
Serum Free Light Chains [14]		X			X	X	X	X	X	X	X	X	X				X	

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REQUIRED STUDIES	Pre-Study	INDUCTION									Complete Response	MAINTENANCE [12]				Prog	Follow Up [4]
		Cycle 1			Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	1 Cycle					
		WK 1	Wk 2	Wk 3								Wk 1	Wk 2	Wk 3	Wk 4		
SPECIMEN SUBMISSION																	
Serum/Biopsy for Banking [9]	X											X				X	
TREATMENT [3]																	
Bortezomib		X	X		X	X	X	X	X	X	X	X	X	X			
Dexamethasone		X	X		X	X	X	X	X	X	X	X	X	X			
Lenalidomide		X	X		X	X	X	X	X	X	X	X	X	X			
Elotuzumab [10]		X	X	X	X	X	X	X	X	X	X	X		X			

NOTE: Forms are found on the protocol abstract page on the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.

1 Lenalidomide counseling must be performed every 28 days (see Section 5.3n and Appendix 18.4).
2 Females of childbearing potential must have negative pregnancy test 10-14 days prior to registration and again within 24 hours prior to starting treatment on Cycle 1, Day 1. Pregnancy testing must be repeated weekly for the first 28 days, then every 28 days (or every 14 days for women with irregular menstrual periods), and again 28 days after the last dose of lenalidomide (or 14 and 28 days after for women with irregular periods). Pregnancy testing will also be performed for missed periods or irregular menstrual bleeding. (See Section 5.3n and 7.1b.).
3 See Section 7.0.
4 At minimum, follow-up exams will consist of physical exam and CBC, Diff, Plts. Additional exams may be performed as clinically indicated. Follow-up will be every 3 months after patient is off treatment for a total of 6 years from registration.
5 To be performed on Day 1 of each cycle (± 2 days) or more often if clinically indicated. For Arm 2 (RVD/Elo) only: To be performed on Day 11 (± 2 days) for Cycles 3-8.
6 Optional
7 Urine M-component must be quantified.
8 To be performed at baseline, then as clinically indicated.
9 With patient consent serum and bone marrow biopsy core will be submitted as outlined in Section 15.1.
10 Elotuzumab administration for Induction Cycles 1-2 will be on Days 1, 8 and 15 and Cycles 3-8 will be on Days 1 and 11 (see Section 7.3).
11 Tests required for patients known to be positive for HIV, HepB or HepC to determine viral load; optional for all others.
12 Repeat until progression.
13 Pre-study (within 14 days prior to registration), then on Day 1 (± 3 days) of Cycles 2-8, then on Day 1 (± 3 days) of each Maintenance Cycle until disease progression, then at least every 3 months (or more often if clinically indicated) during follow-up.
14 Free light chains to be used for response assessment once M-spike has returned to normal on 3 consecutive SPEP/UPEP.
15 See Section 5.1b.
16 To be performed on Day 1 (± 2 days) of each cycle.
17 Vital signs should include body temperature, respiratory rate, blood pressure and heart rate. For Cycles 1 and 2, vital should be taken prior to elotuzumab pre-medication administration, prior to elotuzumab administration, thirty minutes after the start of elotuzumab infusion, at the end of infusion, and 30 and 120 minutes after infusion. For subsequent cycles vitals should be taken 30 minutes after elotuzumab infusion. For Grade ≥ 2 infusion reaction, vitals should be monitored every 30 minutes until 2 hours after infusion, regardless of cycle.
18 Whole body x-ray.

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9.2 Phase II

		INDUCTION										MAINTENANCE [12]					
REQUIRED STUDIES	Pre-Study	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Complete Response	1 Cycle				Prog	Follow Up [4]
		WK 1	Wk 2	Wk 3									Wk 1	Wk 2	Wk 3	Wk 4		
PHYSICAL																		
History and Physical Exam [16]	X	X			X	X	X	X	X	X	X		X					X
Weight and Performance Status	X																	
Toxicity Notation	X			X	X	X	X	X	X	X	X		X		X			
Intake Calendar				X	X	X	X	X	X	X	X					X		
Lenalidomide Education and Counseling [1]	X				X	X	X	X	X	X	X		X					
Risk Assessment [15]	X																	
LABORATORY STUDIES																		
CBC, Diff, Platelets	X			X	X	X	X	X	X	X	X		X		X			X
Bone Marrow Aspirate/Biopsy	X											X						
Serum β2 microglobulin	X																	
Albumin	X																	
CRP	X																	
Glucose	X																	
LDH	X																	
FISH [6]	X																	
Cytogenetics [6]	X																	
Electrolyte Panel (must include Ca+) [5]	X	X		X	X	X	X	X	X	X	X		X		X			

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		INDUCTION										MAINTENANCE [12]					
REQUIRED STUDIES	Pre-Study	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Complete Response	1 Cycle				Prog	Follow Up [4]
		W 1	W 2	W 3									W 1	W 2	W 3	W 4		
Serum Creatinine [5]	X	X			X	X	X	X	X	X	X		X		X			
Total Bilirubin [5]	X	X			X	X	X	X	X	X	X		X		X			
SGOT/SGPT [5]	X	X			X	X	X	X	X	X	X		X		X			
Creatinine Clearance (measured or calculated) [5]	X	X			X	X	X	X	X	X	X		X		X			
CNS Clinical Evaluation	X																	
HIV/Hep B/HepC Test [11]	X																	
Pregnancy Test [2]	X	X	X	X	X	X	X	X	X	X	X		X					X
Vital Signs [17]		X	X	X	X	X	X	X	X	X	X		X		X			
X-RAYS AND SCANS																		
EKG [8]	X																	
Skeletal Survey [18]	X																	
RESPONSE ASSESSMENT [13]																		
Serum Protein Electrophoresis	X	X			X	X	X	X	X	X	X	X	X				X	
Serum Quantitative Immunoglobulins	X	X			X	X	X	X	X	X	X	X	X				X	
24 hour Urine for: Total protein	X	X			X	X	X	X	X	X	X	X	X				X	

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		INDUCTION										MAINTENANCE [12]					
REQUIRED STUDIES	Pre-Study	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Complete Response	1 Cycle				Prog	Follow Up [4]
		W 1	W 2	W 3									W 1	W 2	W 3	W 4		
Protein electrophoresis [7]	X	X			X	X	X	X	X	X	X	X	X				X	
Serum and Urine Immunofixation electrophoresis	X	X			X	X	X	X	X	X	X	X	X				X	
Serum Free Light Chains [14]		X			X	X	X	X	X	X	X	X	X				X	
SPECIMEN SUBMISSION																		
Serum/Biopsy for Banking [9]	X											X					X	
TREATMENT [3]																		
ARM 1																		
Bortezomib		X	X		X	X	X	X	X	X	X		X	X	X			
Dexamethasone		X	X		X	X	X	X	X	X	X		X	X	X			
Lenalidomide		X	X		X	X	X	X	X	X	X		X	X	X			
ARM 2																		
Bortezomib		X	X		X	X	X	X	X	X	X		X	X	X			
Dexamethasone		X	X		X	X	X	X	X	X	X		X	X	X			
Lenalidomide		X	X		X	X	X	X	X	X	X		X	X	X			
Elotuzumab [10]		X	X	X	X	X	X	X	X	X	X		X		X			

NOTE: Forms are found on the protocol abstract page on the SWOG website (www.swog.org). Forms submission guidelines are found in Section 14.0.
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Footnotes

1 Lenalidomide counseling must be performed every 28 days (see Section 5.3n and Appendix 18.4).
2 Females of childbearing potential must have negative pregnancy test 10-14 days prior to registration and again within 24 hours prior to starting treatment on Cycle 1, Day 1. Pregnancy testing must be repeated weekly for the first 28 days, then every 28 days (or every 14 days for women with irregular menstrual periods), and again 28 days after the last dose of lenalidomide (or 14 and 28 days after for women with irregular periods). Pregnancy testing will also be performed for missed periods or irregular menstrual bleeding. (See Section 5.3n and 7.1b.).
3 See Section 7.0. Patients that have received the allowable one cycle of chemotherapy prior to registration will receive a maximum of 7 cycles of Induction therapy.
4 At minimum, follow-up exams will consist of physical exam and CBC, Diff, Plts. Additional exams may be performed as clinically indicated. Follow-up will be every 3 months after patient is off treatment for a total of 6 years from registration.
5 To be performed on Day 1 of each cycle (± 2 days) or more often if clinically indicated. For Arm 2 (RVD/Elo) only: To be performed on Day 11 (± 2 days) for Cycles 3-8.
6 Optional
7 Urine M-component must be quantified.
8 To be performed at baseline, then as clinically indicated.
9 With patient consent serum and bone marrow biopsy core will be submitted as outlined in Section 15.1.
10 Elotuzumab administration for Induction Cycles 1-2 will be on Days 1, 8 and 15 and Cycles 3-8 will be on Days 1 and 11 (see Section 7.3).
11 Tests required for patients known to be positive for HIV, HepB or HepC to determine viral load; optional for all others.
12 Repeat until progression.
13 Pre-study (within 14 days prior to registration), then on Day 1 (± 3 days) of Cycles 2-8, then on Day 1 (± 3 days) of each Maintenance Cycle until disease progression, then at least every 3 months (or more often if clinically indicated) during follow-up.
14 Free light chains to be used for response assessment once M-spike has returned to normal on 3 consecutive SPEP/UPEP.
15 See Section 5.1b.
16 To be performed on Day 1 (± 2 days) of each cycle.
17 Vital signs should include body temperature, respiratory rate, blood pressure and heart rate. For Cycles 1 and 2, vital should be taken prior to elotuzumab pre-medication administration, prior to elotuzumab administration, thirty minutes after the start of elotuzumab infusion, at the end of infusion, and 30 and 120 minutes after infusion. For subsequent cycles vitals should be taken 30 minutes after elotuzumab infusion. For Grade ≥ 2 infusion reaction, vitals should be monitored every 30 minutes until 2 hours after infusion, regardless of cycle.
18 Whole body x-ray.

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10.0 CRITERIA FOR EVALUATION AND ENDPOINT ANALYSIS

10.1 Response Criteria

Multiple Myeloma:

For the purpose of establishing one set of criteria for both Phase II and Phase III multiple myeloma studies, the following definitions will be used. These definitions are based on the International Uniform Response Criteria for Multiple Myeloma.

a. **Measurable Disease**: Measurable, quantifiable protein criteria must be present. Acceptable protein criteria are:

- Serum M protein ≥ 1 g/dL (≥ 10 g/L), quantified by using densitometry on serum protein electrophoresis (SPEP).

  AND / OR

- Urine M protein [Bence-Jones Protein] ≥ 200 mg/24 hrs (≥ 0.2 g/24 hrs), quantified by 24-hour urine protein electrophoresis (UPEP, see Section 10.2.b).

  AND / OR

- Bone marrow plasma cells ≥ 30%

  OR

- Patients who have both serum M protein levels < 1 g/dL AND urine M protein levels < 200 mg/24 hrs at baseline may be followed by serum free light chain (FLC) assay if involved free light chain level ≥ 10 mg/dL (≥ 100mg/L).

b. **Objective Status:**

Stringent Complete Response (sCR):
- Meets all of the criteria for Complete Response (CR) ***and***
- Normal serum free light chain ratio ***and***
- Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence

Complete Response (CR):
- Disappearance of all evidence of serum and urine M proteins on immunofixation electrophoresis studies ***and***
- < 5% plasma cells in bone marrow ***and***
- Disappearance of any soft tissue plasmacytomas

Very Good Partial Response (VGPR):
- Meets all of the criteria for Partial Response (PR) ***and***
- Serum and urine M proteins detectable by immunofixation but not on electrophoresis ***or***
- ≥ 90% reduction in serum M protein and urine M protein < 100 g/24 hrs

Partial Response (PR):
- If the patient had soft tissue plasmacytomas present at baseline and they were assessed at this disease assessment: ≥ 50% reduction in size of soft tissue plasmacytomas (see Section 10.2.h) ***and***
- If the patient had ≥ 30% plasma cells in bone marrow at baseline and a bone marrow biopsy was done: ≥ 50% reduction in plasma cells ***and***

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- ≥ 50% reduction in serum M protein and reduction in urine M protein ≥ 90% or to < 200 mg/24hr ***or***
- If patient had serum M protein < 1 g/dL, urine M protein < 200 mg/24 hrs, and an involved serum free light chain level ≥ 10 mg/dL at baseline: ≥ 50% decrease in the difference between involved and uninvolved serum free light chain levels

Stable Disease (SD):

- Patient does not meet criteria for Stringent Complete Response, Complete Response, Very Good Partial Response, Partial Response, or Progression.

Progression (PD): **Any one or more of the following:**

- Serum M protein increase ≥ 25% from lowest response level (or an increase of ≥ 1 g/dL if serum M protein was ≥ 5 g/dL at baseline), with an absolute increase of ≥ 0.5 g/dL ***or***
- Urine M protein increase ≥ 25% from baseline (or lowest response level), with an absolute increase of ≥ 200 mg/24 hrs ***or***
- If patient had serum M protein < 1 g/dL, urine M protein < 200 mg/24 hrs, and an involved serum free light chain level ≥ 10 mg/dL at baseline: ≥ 25% increase in the difference between involved and uninvolved serum free light chain level, with an absolute increase of ≥ 10 mg/dL or
- Bone marrow plasma cell percentage increase ≥ 25% from baseline (or lowest response level), with the absolute plasma cell % ≥ 10% ***or***
- New bone lesions or soft tissue plasmacytomas, or definite increase in size of existing bone lesions or soft tissue plasmacytomas (see Section 10.2.h) ***or***
- Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to multiple myeloma

Relapse (REL): **Any one or more of the following:**

Direct indicators of increasing disease and/or end organ dysfunction (CRAB features): For progressive disease, serum M-component increases of ≥ 1 gm/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL. It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice

- Development of new soft tissue plasmacytomas or bone lesions
- Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥ 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion
- Hypercalcemia (> 11.5 mg/dL) [2.65 mmol/L] attributable to MM
- Decrease in hemoglobin of ≥ 2 g/dL [1.25 mmol/L] attributable to MM
- Rise in serum creatinine by ≥ 2 mg/dL [177 mol/L or more]

NOTE: If a disease assessment indicates that a patient is experiencing a Stringent Complete Response, Complete Response, Very Good Partial Response, Partial Response, or Progression, this should be confirmed by a second disease assessment (see Section 10.3), and this should be done prior to the institution of any new therapy. The second disease assessment may be done at any time.

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10.2 Notes

a. "M protein" may also be known by the following synonyms: M-spike, monoclonal protein, myeloma protein, monoclonal paraprotein, M-component.

b. Urine M protein measurement is estimated using 24-hour urine protein electrophoresis (UPEP) only. Random or 24 hour urine tests measuring kappa and lambda light chain levels are not reliable and are not recommended.

c. Patients with 'measurable disease' in both the serum and urine (serum M protein ≥ 1g/dL and urine M protein ≥ 200 mg/24h) at baseline need to be followed by both SPEP and UPEP for response assessment.

d. Except for assessment of Complete Response, patients with 'measurable disease' restricted to the serum (serum M protein ≥ 1 g/dL and urine M protein < 200 mg/24h) at baseline may be followed by SPEP only. Likewise, except for assessment of Complete Response, patients with 'measurable disease' restricted to the urine (serum M protein < 1 g/dL and urine M protein ≥ 200 mg/24h) at baseline may be followed by UPEP only.

e. Patients with serum M protein ≥ 1 g/dL and/or urine M protein ≥ 200 mg/24h at baseline will be assessed for response based on SPEP and/or UPEP results only. Except for assessment of Stringent Complete Response, serum free light chain (FLC) assay response requirements are only applicable to patients who had serum M protein < 1 g/dL, urine M protein < 200 mg/24 hrs, and an involved serum free light chain level ≥ 10 mg/dL at baseline. A normal serum free light chain ratio is required for all patients for a Stringent Complete Response.

f. To qualify for a Complete Response, both serum and urine immunofixation must be carried out and must be negative, regardless of the size of the baseline M protein in the serum or urine.

g. Skeletal survey (whole body x-ray) is not required for assessment of response unless clinically indicated, but is recommended once a year in clinical practice. Stringent Complete Response, Complete Response, Very Good Partial Response, Partial Response, and Stable Disease all require no known evidence of progressive or new bone lesions if radiographic studies were performed, but radiographic studies are not required to satisfy these response requirements.

h. The size of the soft tissue plasmacytomas is defined as the sum of the products of the cross-diameters of each plasmacytoma. The size of the bone lesions will be determined in a similar manner. A definite increase in the size is defined as a ≥ 50% increase (and at least 1 cm^2) of this sum.

10.3 Best Response

This is calculated from a sequence of Objective Status (see Section 10.1.b) evaluations.

Stringent Complete Response (sCR): An objective status of Stringent Complete Response on at least two sequential disease assessments. Only one bone marrow biopsy, done during one of these two disease assessments, is required to confirm the response.

Complete Response (CR): An objective status of Complete Response on at least two sequential disease assessments. Only one bone marrow biopsy, done during one of these two disease assessments, is required to confirm the response.

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Very Good Partial Response (VGPR): An objective status of Very Good Partial Response on at least two sequential disease assessments.

Partial Response (PR): An objective status of Partial Response on at least two sequential disease assessments.

Unconfirmed sCR (UsCR): One objective status of Stringent Complete Response (based on evidence from serum and urine studies and, if drawn, bone marrow biopsy) but the confirmation studies are either not done, or when done, do not meet the requirements necessary to confirm response. This must be documented before progression and at least three weeks after registration.

Unconfirmed CR (UCR): One objective status of Complete Response (based on evidence from serum and urine studies and, if drawn, bone marrow biopsy) but the confirmation studies are either not done, or when done, do not meet the requirements necessary to confirm response. This must be documented before progression and at least three weeks after registration.

Unconfirmed VGPR (UVGPR): One objective status of Very Good Partial Response, but the confirmation studies are either not done, or when done, do not meet the requirements necessary to confirm response. This must be documented before progression and at least three weeks after registration.

Unconfirmed PR (UPR): One objective status of Partial Response, but the confirmation studies are either not done, or when done, do not meet the requirements necessary to confirm response. This must be documented before progression and at least three weeks after registration.

Stable / No Response (STA): At least one objective status of Stable at least three weeks after registration, but not qualifying as any of the above. If radiographic studies were performed there should be no known progressive or new bone lesions.

Increasing Disease (INC): First objective status recorded (other than Unknowns or those before three weeks) of Progression, provided this occurs within eight weeks of registration.

Inadequate Assessment Response Unknown (NASS): Progression greater than eight weeks after registration and either all objective statuses prior to registration are unknown or the only known objective statuses occurred less than three weeks after registration.

10.4 Time to Death

From date of registration to date of death due to any cause. Patients last known to be alive are censored at date of last contact.

10.5 Progression-Free Survival

From date of registration to date of first documentation of progression or death due to any cause. Patients last known to be alive and progression-free are censored at date of last contact.

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10.6 Performance Status

Patients will be graded according to the Zubrod performance status scale.

POINT	DESCRIPTION
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of self-care but unable to carry out any work activities; up and about more than 50% of waking hours.
3.	Capable of limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

11.0 STATISTICAL CONSIDERATIONS

11.1 Phase I Run-In

There will be a small Phase I run-in to ensure safety of this treatment combination. Six patients (high or low risk) will initially be treated with bortezomib, lenalidomide, dexamethasone per protocol and elotuzumab at 10 mg/kg. If one or fewer patients experience a DLT this dose level of elotuzumab will be considered safe and the Phase II portion of the trial will be done using this dose level.

If two or more patients experience a DLT, this dose level will be deemed too toxic and an additional six patients will be treated at a lower dose level of elotuzumab as defined in Section 7.2a. If one or fewer patients experience a DLT this dose level of elotuzumab will be considered safe and the Phase II portion of the trial will be done using this dose level.

11.2 Phase II Trial

The main portion of the trial is a randomized Phase II study for patients diagnosed with high risk multiple myeloma as defined by the eligibility criteria in Section 5.0. There will be equal allocation to each of the two treatment arms: bortezomib, lenalidomide, dexamethasone (RVD) and bortezomib, lenalidomide, dexamethasone plus elotuzumab (RVD/Elo). This study is designed to assess efficacy and safety of this treatment combination. A dynamic balancing randomization algorithm will be utilized to ensure that the assignment of treatments is balanced across all the stratification factors. This procedure balances the marginal distribution of the stratification factors between these treatment regimens.

11.3 Primary Endpoint

The primary objective of this study is to compare progression-free survival (PFS) as defined in Section 10.5. The primary endpoint of progression-free survival was chosen as it is a better surrogate for overall survival than response rate in multiple myeloma.

All patients who have signed a consent form and have been randomized will be evaluable for PFS.

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11.4 Secondary Endpoints

Toxicity of this new treatment combination will be assessed.

Secondary efficacy endpoints include overall survival (OS) and response (PR or better) rate.

11.5 Sample Size and Power Justification for Primary Endpoint

The study will accrue 100 eligible patients (50 per arm). An additional 30 patients (15 per arm) will be accrued to account for ineligible patients and patients withdrawing consent. The median expected PFS in the control arm (RVD) is based on two University of Arkansas studies: UARK 2003-33 (TT3a) and UARK 2006-66 (TT3b). High risk patients on those studies were defined based on the GEP-70 risk score. Since no other risk factors were used to determine high risk in this setting and since the treatment approach used is very different from the treatment in this protocol, a randomized study is felt to be more appropriate in this setting. Median PFS in that patient group was 2.2 years. It is anticipated that approximately 20% of newly diagnosed myeloma patients are high risk as defined in this protocol. Thus, based on **S0777**, it is anticipated that this study will accrue approximately 25 high risk patients per year. Assumption of uniform accrual of 25 patients per year, four years of accrual and an additional 2 years of follow-up yields a study with 82% power and a one-sided significance level alpha of 0.1 to detect a hazard ratio of 1.75 between the two treatment arms or an increase in median progression-free survival from 2 years to 3.5 years in the RVD/Elo arm compared to the RVD arm. These calculations are based on the assumption of exponential distribution of progressions and a median PFS of 2 years in the control arm (RVD). Total time to study completion is approximately 6 years.

The study team realizes that this is an aggressive hazard ratio, but the goal was to design a study that would give results in a reasonable time frame and allow for flexibility as other promising agents for this patient population come along. Such agents could be investigated with appropriate amendments for this protocol or on a new protocol. If this hazard ratio is not achieved, but there is a promising trend for the primary and secondary objectives, this information will still be very helpful to inform a Phase III study and this trial will serve as a starting point to find better treatment options for this high risk patient population.

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11.6 Analysis of Primary Endpoint

Efficacy analysis will be performed on an intent to treat basis. A stratified log-rank test will be used to compare PFS in the two treatment arms. The analysis for the primary endpoint will be performed after the last patient has been followed for 2 years. Assuming exponential survival, uniform recruitment of 25 patients per year, an accrual period of 4 years and a follow-up period of 2 years, 64 progressions are expected to occur within 6 years. The number of progressions is based on the alternative hypothesis. In addition, the distribution of PFS in each arm will be estimated using the method of Kaplan-Meier by treatment group. Exploratory multivariate analyses will be performed to assess the treatment effect adjusting for key prognostic factors using the Cox proportional hazard regression model. The covariates that will be considered include baseline age, sex, LDH, albumin, β-2 microglobulin, creatinine, hemoglobin, platelet count and the actual risk category (GEP-70, FISH or CA, PCL, LDH).

11.7 Interim Analysis for Futility

An interim analysis for futility will be performed after approximately half the number of events have been observed. Based on the alternative hypothesis and the assumption that events are exponentially distributed, 32 progressions are expected to occur within 43

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months or 3 years and 7 months. At this time the alternative hypothesis of a hazard ratio between arms of 1.75 at a significance level of 0.008. The beta spent at this time point will be 0.059, thus only affecting the overall power of the study minimally. This translates into a probability of early termination under the null hypothesis of no effect of elotuzumab of 50% and a probability of 5.9% of early termination under the alternative hypothesis. The crossing boundaries are based on beta spending function of O'Brian Fleming Lan-DeMets. If the alternative hypothesis cannot be rejected the study will continue as planned, otherwise the rejection of the alternative hypothesis would lead to early termination and the conclusion that RVD/Elo is not better than RVD alone. The actual decision to terminate the study early will be made by the Data Safety Monitoring Committee, and will consider toxicity and other endpoints.

11.8 Safety Analysis

All eligible patients that have initiated treatment will be considered evaluable for toxicity analyses. The maximum Grade for each toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. With 50 patients per study arm, the probability of any particular toxicity can be estimated within ±15% (95% confidence interval). Any toxicity having a true occurrence rate of 5% or more within one of the treatment arms is likely to be observed in at least one patient (probability ≥ 92%).

There is no formal Data and Safety Monitoring Committee (DSMC) for the Phase I portion of this study. During the Phase I portion, toxicity and accrual monitoring are done routinely by the Study Chairs, Study Statisticians and the Disease Committee Chair. A conference call between the study team and participating investigators takes place every other week to discuss enrollment, patient progress, adverse events, DLTs, and dose escalation/de-escalation decisions. Formal toxicity reports are published Group-wide every 6 months. In addition, the Statistical Center, Adverse Event Coordinator at the Operations Office, SAE Physician Reviewer and Study Chair monitor toxicities on an ongoing basis.

A Data and Safety Monitoring Committee will oversee the conduct of the randomized Phase II portion of this trial. A majority of the voting members of the DSMC are from outside of SWOG, and at least one outside member is a patient advocate, and one is a statistician. The Group Statistician (or designee), two representatives from the Cancer Therapy Evaluation Program (CTEP) (one physician and one statistician) and one representative of the Division of Cancer Prevention (DCP) are non-voting members. The members of this Committee will receive confidential reports every 6 months from the SWOG Statistical Center, and will meet at the Group's bi-annual meetings or hold conference calls necessary. They will receive additional reports, if needed, for assessment of adverse events, or other study related matters. The Committee will be responsible for decisions regarding possible termination and/or early reporting of the study, and any major study amendments.

In addition to the above DSMC review, toxicity and accrual monitoring during the randomized Phase II portion will be done routinely by the Study Chair, Study Statistician and the Disease Committee Chair. Endpoint monitoring is done by the Study Statistician and Study Chair. Accrual reports are generated weekly, and formal toxicity reports are generated every 6 months. In addition, the Statistical Center, Adverse Event Coordinator at the Operations Office, SAE Physician Reviewer and Study Chair monitor toxicities on an ongoing basis.

11.9 Analysis of Secondary Endpoints

Secondary efficacy endpoints include response rate (PR or better) and overall survival. All efficacy analyses will be performed on an intent to treat basis. The response rate will be calculated based on the responses achieved as defined in Section 10.3. The number of patients who achieve a PR or better will be divided by the number of patients in the

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intent to treat population. Comparisons between arms will be made using Fisher's Exact Test.

Overall survival will be evaluated using a stratified long-rank test to compare the experimental arm to the control arm. In addition, the method of Kaplan-Meier will be used to estimate and display the distribution of the endpoints over time.

12.0 DISCIPLINE REVIEW

This study will not utilize discipline review.

13.0 REGISTRATION GUIDELINES

13.1 Registration Timing

Patients must be registered (and randomized if in the Phase II portion) prior to initiation of treatment (no more than seven working days prior to planned start of treatment).

13.2 Investigator/Site Registration

Prior to the recruitment of a patient for this study, investigators must be registered members of a Cooperative Group. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU Web site (http://ctep.cancer.gov/investigatorResources/investigator_registration.htm). Questions should be directed to the CTEP Investigator Registration Help Desk by e-mail at pmbregpend@ctep.nci.nih.gov.

Each investigator or group of investigators at a clinic site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials at https://www.ctsu.org.

Requirements for site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

Note: Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

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13.3 OPEN Registration Requirements

The individual registering the patient must have completed the appropriate SWOG Registration Worksheet. The completed form must be referred to during the registration but should not be submitted as part of the patient data.

Oncology Patient Enrollment Network (OPEN) will also ask additional questions that are not present on the SWOG Registration Worksheet. The individual registering the patient must be prepared to provide answers to the following questions:

a. Institution CTEP ID

b. Protocol Number

c. Registration Step

d. Treating Investigator

e. Cooperative Group Credit

f. Credit Investigator

g. Patient Initials

h. Patient's Date of Birth

i. Patient SSN (SSN is desired, but optional. Do not enter invalid numbers.)

j. Country of Residence

k. ZIP Code

l. Gender (select one):

- Female Gender
- Male Gender

m. Ethnicity (select one):
- Hispanic or Latino
- Not Hispanic or Latino
- Unknown

n. Method of Payment (select one):
- Private Insurance
- Medicare
- Medicare and Private Insurance
- Medicaid
- Medicaid and Medicare
- Military or Veterans Sponsored NOS
- Military Sponsored (Including Champus & Tricare)
- Veterans Sponsored
- Self Pay (No Insurance)
- No Means of Payment (No Insurance)
- Other
- Unknown

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o. Race (select all that apply):
- American Indian or Alaska Native
- Asian
- Black or African American
- Native Hawaiian or other Pacific Islander
- White
- Unknown

13.4 Registration Procedures

a. All site staff (SWOG and CTSU Sites) will use OPEN to enroll patients to this study. OPEN is a web-based application that is integrated with the CTSU Enterprise System for regulatory and roster data and, at the time of patient registration, initializes the patient in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org, or from the OPEN Patient Registration link on the SWOG CRA Workbench.

b. Prior to accessing OPEN site staff should verify the following:

a. All eligibility criteria have been met within the protocol stated time frames and the affirmation of eligibility on the Registration Worksheet has been signed by the registering investigator or another investigator designate. Site staff should refer to Section 5.0 to verify eligibility.
b. All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).
c. The study site listed as "approved" in the CTSU RSS.

c. Access requirements for OPEN:

- Site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account. This is the same account (user ID and password) used for the CTSU members' web site. Additional information about obtaining a CTEP-IAM account can be found at http://ctep.cancer.gov/branches/pmb/associate_registration.htm. Questions should be directed to the CTEP Associate Registration Help Desk by e-mail at ctepreghelp@ctep.nci.nih.gov.

- To perform registrations, the site user must have been assigned the 'Registrar' role on the SWOG or CTSU roster:

1. If you are a SWOG member, to perform registrations on SWOG protocols you must have an equivalent 'Registrar' role on the SWOG roster. Role assignments are handled through SWOG.

2. If you are not a SWOG member, to perform registrations on SWOG protocols you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

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d. Further instructional information is provided on the OPEN tab on the CTSU members' side of the CTSU website at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

13.5 Exceptions to SWOG registration policies will not be permitted.

a. Patients must meet all eligibility requirements.

b. Institutions must be identified as approved for registration.

c. Registrations may not be cancelled.

d. Late registrations (after initiation of treatment) will not be accepted.

14.0 DATA SUBMISSION SCHEDULE

14.1 Data Submission Requirement

Data must be submitted according to the protocol requirements for **ALL** patients registered, whether or not assigned treatment is administered, including patients deemed to be ineligible. Patients for whom documentation is inadequate to determine eligibility will generally be deemed ineligible.

14.2 Master Forms

Master forms can be found on the protocol abstract page on the SWOG website (www.swog.org) and (with the exception of the sample consent form and the Registration Worksheet) must be submitted on-line via the Web; see Section 14.3a for details.

14.3 Data Submission Procedures

a. SWOG institutions must submit data electronically via the Web using Medidata Rave® at the following url:

https://login.imedidata.com/selectlogin

1. If prompted, select the 'CTEP-IAM IdP' link.

2. Enter your valid and active CTEP-IAM userid and password. This is the same account used for the CTSU members' web site and OPEN.

b. You may also access Rave® via the SWOG CRA Workbench. Go to the SWOG web site (http://swog.org) and logon to the Members Area using your SWOG Roster ID Number and password. After you have logged on, click on *Workbenches*, then *CRA Workbench* to access the home page for the CRA Workbench and follow the link to Rave® provided in the left-hand navigation panel.

To access the CRA Workbench the following must be done (in order):

1. You are entered into the SWOG Roster and issued a SWOG Roster ID Number,

2. You are associated as an investigator or CRA/RN at the institution where the patient is being treated or followed,

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3. Your Web User Administrator has added you as a web user and has given you the appropriate system permissions to view data for that institution.

For assistance with points 1 and 2 call the Operations Office at 210/614-8808. For point 3, contact your local Web User Administrator (refer to the "Who is my Web User Administrator?" function on the swog.org Members logon page).

For difficulties with the CRA Workbench, please email technicalquestion@crab.org.

14.4 Data Submission Overview and Timepoints

a. WITHIN 7 DAYS OF REGISTRATION:

Submit the following:

Onstudy Form

Baseline Tumor Assessment Form for Multiple Myeloma

Radiology reports from all scans performed to assess disease at baseline

Baseline Abnormality Form (Phase I patients only)

See Section 15.0 for specimen submission requirements.

b. WITHIN 14 DAYS OF REGISTRATION:

Submit the Institutional Cytogenetics Report and FISH Analysis Report

c. FOR PHASE I PATIENTS ONLY AT THE END OF EACH WEEK OF INDUCTION TREATMENT DURING CYCLE 1:

Submit the **S1211** Adverse Event Form

d. AT THE END OF EACH CYCLE OF INDUCTION TREATMENT:

Submit the following:

S1211 Treatment Form

S1211 Adverse Event Form (Phase I patients during Cycles 2-8, Phase II patients during all cycles)

Follow-Up Tumor Assessment Form for Multiple Myeloma

See Section 15.0 for specimen submission requirements.

e. AT THE END OF EACH CYCLE OF MAINTENANCE TREATMENT:

Submit the following:

S1211 Treatment Form

S1211 Adverse Event Form

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f. EVERY 3 MONTHS DURING MAINTENANCE:

Submit the Follow-Up Tumor Assessment Form for Multiple Myeloma

g. WITHIN 14 DAYS OF PROGRESSION/RELAPSE:

Submit the Follow-Up Form (if the patient was off protocol treatment) documenting date, site and method for determining progression/relapse

See Section 15.0 for specimen submission requirements.

h. WITHIN 14 DAYS OF DISCONTINUATION OF TREATMENT:

Submit the Off Treatment Notice

i. WITHIN 14 DAYS OF KNOWLEDGE OF SECONDARY MALIGNANCY

Submit a copy of the Follow-Up Form

See Section 15.0 for specimen submission requirements.

j. EVERY 3 MONTHS AFTER OFF TREATMENT FOR 6 YEARS FROM INITIAL REGISTRATION OR UNTIL DEATH (WHICHEVER COMES FIRST)

Submit a copy of the Follow-Up Form

k. WITHIN 4 WEEKS OF KNOWLEDGE OF DEATH:

Submit the Notice of Death and a final Treatment Form and Adverse Event Form (if the patient was still on protocol treatment) or Follow-Up Form (if the patient was off protocol treatment) documenting death information.

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15.0 SPECIAL INSTRUCTIONS

15.1 Translational Medicine and Banking

Specimens for translational medicine and banking (submitted to the SWOG Specimen Repository – Solid Tissue, Myeloma and Lymphoma Division-Lab #201) (optional for patient):

a. With patient's consent specimens (**serum and bone marrow biopsy core**) must be submitted at the following times (see Sections 9.1 and 9.2):

1. Pretreatment (within 28 days prior to registration)

2. Complete Response

3. Relapse/Progression

4. At diagnosis of secondary malignancy

b. Specimen collection and submission instructions for the serum and bone marrow biopsy core specimens can be accessed on the SWOG Specimen Submission webpage (http://swog.org/Members/ClinicalTrials/Specimens/MyelSpecimens.asp).

c. Specimen collection kits are not being provided for this submission; sites will use institutional supplies.

15.2 Phase I Portion: Mandatory Conference Calls

A mandatory conference call will take place every other week. The call will update participants on the current status of the trial and will include representatives from the study team, investigators from all participating institutions and representatives from Bristol-Myers Squibb. At this time any serious toxicities encountered will be discussed and appropriate action taken. In between these regularly scheduled conference calls, investigators will be informed of important study decisions via e-mail.

Institutional participation on these calls requires the identification of an investigator contact and a CRA contact. Prior to registration of the first patient, each institution must provide the contact names, e-mail addresses, and phone numbers to the SWOG Operations Office. Institutions will be responsible for keeping this information up-to-date and must notify the study Protocol Coordinator (Cara Laubach, e-mail: claubach@swog.org or phone: 210/614-8808) of any changes. The investigator and the contact CRA will receive e-mail reminders with the conference call information.

16.0 ETHICAL AND REGULATORY CONSIDERATIONS

The following must be observed to comply with Food and Drug Administration regulations for the conduct and monitoring of clinical investigations; they also represent sound research practice:

Informed Consent

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

Institutional Review

This study must be approved by an appropriate institutional review committee as defined by Federal Regulatory Guidelines (Ref. Federal Register Vol. 46, No. 17, January 27, 1981, part 56) and the Office for Protection from Research Risks Reports: Protection of Human Subjects (Code of Federal Regulations 45 CFR 46).

Drug Accountability

An investigator is required to maintain adequate records of the disposition of investigational drugs according to procedures and requirements governing the use of investigational new drugs as described in the Code of Federal Regulations 21 CFR 312.

Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31 and October 31.

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Confidentiality

Please note that the information contained in this protocol is considered confidential and should not be used or shared beyond the purposes of completing protocol requirements until or unless additional permission is obtained.

16.1 Adverse Event Reporting Requirements

a. Purpose

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. The following guidelines prescribe expedited adverse event reporting for this protocol. Also see Appendix 18.1 for general and background information about expedited reporting.

b. Reporting method

This study requires that expedited adverse event reporting use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted to the SWOG Operations Office electronically via the CTEP-AERS Web-based application located at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

c. When to report an event in an expedited manner

Some adverse events require 24-hour notification (refer to Table 16.1) via CTEP-AERS. When Internet connectivity is disrupted, a 24-hour notification is to be made to SWOG by telephone at 210-614-8808, or by email at adr@swog.org. Once Internet connectivity is restored, a 24-hour notification that was made by phone or using adr@swog.org must be entered electronically into CTEP-AERS by the original submitter at the site.

When the adverse event requires expedited reporting, submit the report within the number of calendar days of learning of the event specified in Table 16.1 or 16.2, as applicable.

d. Other recipients of adverse event reports

The SWOG Operations Office will forward reports and documentation to the appropriate regulatory agencies and drug companies as required.

Adverse events determined to be reportable to the Institutional Review Board responsible for oversight of the patient must be reported according to local policy and procedures.

e. **Expedited reporting for investigational agents**

Expedited reporting is required if the patient has received at least one dose of the investigational agent(s) as part of the trial. Reporting requirements are provided in Table 16.1. The investigational agents used in Phase I and Arm 2 of Phase II

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of this study is elotuzumab. If there is any question about the reportability of an adverse event or if on-line CTEP-AERS cannot be used, please telephone or email the SAE Specialist at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.1
Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse events that Occur on Studies under an Non-CTEP IND within 30 Days of the Last Administration of the Investigational Agent/Intervention[1] Elotuzumab (Phase I and Arm 2 of Phase II)

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:
- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:
- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

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f. **Additional Instructions or Exceptions to CTEP-AERS Expedited Reporting Requirements for Phase 1 and Early Phase 2 Studies Utilizing an Agent under a non-CTEP-IND:**

1) **Group-specific instructions.**

Supporting Documentation Submission - Within **5 calendar days** submit the following to the SWOG Operations Office by fax to 210-614-0006 or mail to the address below:

- Printed copy of the first page of the CTEP-AERS report
- Copies of clinical source documentation of the event
- If applicable, and they have not yet been submitted to the SWOG Data Operations Center, copies of Off Treatment Notice and/or Notice of Death.

g. **Expedited reporting for commercial agents**

Commercial reporting requirements are provided in Table 16.2. The commercial agent(s) used in this study are bortezomib, dexamethasone and lenalidomide. If there is any question about the reportability of an adverse event, please telephone or email the SAE Program at the Operations Office, 210/614-8808 or adr@swog.org, before preparing the report.

Table 16.2: Expedited reporting requirements for adverse events experienced by patients on Arm 1 of the Phase II portion of this study who have received the commercial drug(s) listed in Section 16.1g above within 30 days of the last administration of the commercial agent(s).

Attribution	Grade 4		Grade 5[a]	
	Unexpected	Expected	Unexpected	Expected
Unrelated or Unlikely			**CTEP-AERS**	**CTEP-AERS**
Possible, Probable, Definite	**CTEP-AERS**		**CTEP-AERS**	**CTEP-AERS**

CTEP-AERS: Indicates an expedited report is to be submitted via CTEP-AERS within 10 calendar days of learning of the event[b].

[a] This includes all deaths within 30 days of the last dose of treatment with a commercial agent(s), regardless of attribution. Any death that occurs more than 30 days after the last dose of treatment with a commercial agent(s) and is attributed (possibly, probably, or definitely) to the agent(s) and is not due to cancer recurrence must be reported according to the instructions above.

[b] Submission of the on-line CTEP-AERS report plus any necessary amendments generally completes the reporting requirements. You may, however, be asked to submit supporting clinical data to the Operations Office in order to complete the evaluation of the event. If requested, the specified data should be sent within 5 calendar days by fax to 210-614-0006.

h. **Reporting Secondary Malignancy, including AML/ALL/MDS**

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

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

- Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

2. Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

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

For more information see:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

3. Supporting documentation should be submitted to CTEP in accordance with instructions provided by the CTEP-AERS system. A copy of the report and the following supporting documentation must also be submitted to SWOG Operations Office within 30 days:

- a copy of the pathology report confirming the AML/ALL /MDS diagnosis
- (if available) a copy of the cytogenetics report

SWOG
ATTN: SAE Program
4201 Medical Drive, Suite 250
San Antonio, Texas 78229

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the report must be submitted for the most recent trial.

i. **Reporting Pregnancy, Fetal Death, and Death Neonatal**

1. **Pregnancy** Study participants who become pregnant while on study; that pregnancy should be reported in an expedited manner via CTEP-AERS as **Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)"** under the **Pregnancy, puerperium and perinatal conditions** SOC.

Additionally, the pregnancy outcome for patients on study should be reported via CTEP-AERS at the time the outcome becomes known, accompanied by the same Pregnancy Report Form used for the initial report.

2. **Fetal Death** Fetal Death defined in CTCAE as "A disorder characterized by death in utero; failure of the product of conception to show evidence of respiration, heartbeat, or definite movement of a voluntary muscle after expulsion from the uterus, without possibility of resuscitation" should be reported expeditiously as **Grade 4 "pregnancy, puerperium and perinatal conditions – Other (pregnancy loss)" under the**

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Pregnancy, puerperium and perinatal conditions SOC.

3. **Death Neonatal** Neonatal death, defined in CTCAE as "A disorder characterized by cessation of life occurring during the first 28 days of life" that is felt by the investigator to be at least possibly due to the investigational agent/intervention should be reported expeditiously.

   A neonatal death should be reported expeditiously as **Grade 4 "General disorders and administration – Other (neonatal loss)"** under the **General disorders and administration** SOC.

*Fetal death and neonatal death should **NOT** be reported as a Grade 5 event. If reported as such, the CTEP-AERS interprets this as a death of the patient being treated.*

NOTE: When submitting CTEP-AERS reports for "Pregnancy, "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should also be completed and faxed with any additional medical information to 301-230-0159. The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

The Pregnancy Information Form is available at:
http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm

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18.0 APPENDIX

18.1 Determination of Expedited Adverse Event Reporting Requirements

18.2 New York Heart Association Classifications

18.3 Intake Calendar

18.4 ELOTUZUMAB REPRODUCTIVE WARNINGS

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18.1 Determination of Expedited Adverse Event Reporting Requirements

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Directions for routine reporting are provided in Section 14.0.) Additionally, certain adverse events must be reported in an expedited manner to allow for more timely monitoring of patient safety and care. Expedited adverse event reporting principles and general guidelines follow; specific guidelines for expedited adverse event reporting on this protocol are found in Section 16.1.

All serious adverse events determined to be reportable to the Institutional Review Board responsible for the oversight of the patient must be reported according to local policy and procedures. Documentation of this reporting should be maintained for possible inspection during quality assurance audits.

Steps to determine if an adverse event is to be reported in an expedited manner (*This includes all events that occur while on treatment or within 30 days of the last dose of protocol treatment.*)

Step 1: Determine whether the patient has received an investigational agent, commercial agent, or a combination of investigational and commercial agents.

An investigational agent is a protocol drug administered under an Investigational New Drug Submission (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.
When a study includes both investigational and commercial agents, the following rules apply.

- ***Concurrent administration*:** When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events would follow the guidelines for investigational agents.
- ***Sequential administration*:** When a study includes an investigational agent(s) and a commercial agent(s) on the same study arm with sequential administration all expedited reporting of adverse events should follow the guidelines for the type of agent being given. For example, if the patient begins the study on the investigational agent(s), then all expedited reporting of adverse events should follow guidelines for the investigational agent(s). Once the patient begins receiving the commercial agent(s) then all expedited reporting of adverse events should follow the guidelines for commercial agent(s).

Step 2: Identify the type of event using the NCI Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. A copy of the CTCAE can be downloaded from the CTEP home page (http://ctep.cancer.gov)**.** Additionally, if assistance is needed, the NCI has an Index to the CTCAE that provides help for classifying and locating terms.

Step 3: Grade the event using the NCI CTCAE version specified in the protocol for reporting serious adverse events.

Step 4: Determine if the adverse event is Expected or an Exception to Expedited Reporting.

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An adverse event is considered **unexpected,** for expedited reporting purposes only, when either the type of event or the severity of the event is **not** listed in one of the areas outlined above.

Step 5: Determine whether the adverse event involved hospitalization or a prolongation of hospitalization (≥ 24 hours).

Step 6: Additionally, for commercial drugs, determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite. Consult the appropriate table for expedited reporting criteria for commercial agent(s).

NOTE: Any event that occurs more than 30 days after the last dose of study agent and is attributed (possible, probable, or definite) to the study agent(s) must be reported according to the instructions above and as outlined in the appropriate table in Section 16.1.

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18.2 New York Heart Association Classifications

Class	Cardiac Symptoms	Limitations	Need for Additional Rest*	Physical Ability To Work**
I	None	None	None	Full Time
II	Only moderate	Slight	Usually only slight or occasional	Usually full time
III	Defined, with less than ordinary activity	Marked	Usually moderate	Usually part time
IV	May be present even at rest, & any activity increases discomfort	Extreme	Marked	Unable to work

* To control or relieve symptoms, as determined by the patient, rather than as advised by the physician.

** At accustomed occupation or usual tasks.

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18.3 Intake Calendar

SWOG Patient ID_____ Patient Initials (L, F, M) _____ **SWOG Study #**_____

Institution/Affiliate _____ Physician _____

Instructions for the participant:

This is a monthly calendar on which you are to record the number of tablets/pills/capsules you take each day. Be sure you have enough calendars to last until your next appointment. If you develop any side effects from the tablets/pills/capsules, mark this on the calendar on the day you note the effect. Bring your calendars with you each time you have an appointment.

If you have questions contact: _____ Telephone: _____

Your next appointment is: _____

Special instructions:

Month: **Year:**

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday

Patient Signature:_____

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18.4 Elotuzumab Reproductive Warnings

Females of child bearing potential (FCBP) must use an effective method of birth control during the course of the study, in a manner such that risk of failure is minimized.

Before study enrollment, FCBP must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. The subject must sign an informed consent form documenting this discussion.

All FCBP MUST have a negative pregnancy test within 72 hours before receiving elotuzumab. The minimum sensitivity of the pregnancy test must be 25 IU/L or equivalent units of HCG. If the pregnancy test is positive, the subject must not receive elotuzumab and must not be enrolled in the study. *(Note that for this study, compliance with the lenalidomide pregnancy testing satisfactorily completes this requirement.)*

In addition, all FCBP should be instructed to contact the investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, and the pregnancy will not be terminated, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety).

Protocol-required procedures for study discontinuation and follow-up must be performed on the subject unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated.

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Informed Consent Model for S1211

*NOTES FOR LOCAL INSTITUTION INFORMED CONSENT AUTHORS:

This model informed consent form has been reviewed by the DCTD/NCI and is the official consent document for this study. Local IRB changes to this document are allowed. (Institutions should attempt to use sections of this document that are in bold type in their entirety.) Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to the risks or alternatives sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language, justification and a copy of the IRB minutes must be forwarded to the SWOG Operations Office for approval before a patient may be registered to this study.

Please particularly note that the questions related to banking of specimens for future study are in bolded type and may not be changed in any way without prior approval from the SWOG Operations Office.

Readability Statistics:	
Flesch Reading Ease	62.5 (targeted above 55)
Flesch-Kincaid Grade Level	8.5 (targeted below 8.5)

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- Instructions and examples for informed consent authors are in *[italics]*.
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- The term "study doctor" has been used throughout the model because the local investigator for a cancer treatment trial is a physician. If this model is used for a trial in which the local investigator is not a physician, another appropriate term should be used instead of "study doctor".
- The dates of protocol updates in the header and in the text of the consent is for reference to this model only and should not be included in the informed consent form given to the prospective research participant.
- The local informed consent must state which parties may inspect the research records. This includes the NCI, the drug manufacturer for investigational studies, any companies or grantors that are providing study support (these will be listed in the protocol's model informed consent form) and SWOG.

  "SWOG" must be listed as one of the parties that may inspect the research records in all protocol consent forms for which patient registration is being credited to SWOG. This includes consent forms for studies where all patients are registered directly through the SWOG Data Operations Office, all intergroup studies for which the registration is being credited to SWOG (whether the registration is through the SWOG Data Operations Office or directly through the other group), as

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well as consent forms for studies where patients are registered via CTSU and the registration is credited to SWOG.

- When changes to the protocol require revision of the informed consent document, the IRB should have a system that identifies the revised consent document, in order to preclude continued use of the older version and to identify file copies. An appropriate method to identify the current version of the consent is for the IRB to stamp the final copy of the consent document with the approval date. The stamped consent document is then photocopied for use. Other systems of identifying the current version of the consent such as adding a version or approval date are allowed as long as it is possible to determine during an audit that the patient signed the most current version of the consent form.

*NOTES FOR LOCAL INVESTIGATORS:

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This model for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is titled: "Taking Part in Cancer Treatment Research Studies". This pamphlet may be ordered on the NCI Web site at *https://cissecure.nci.nih.gov/ncipubs* or call 1-800-4- CANCER (1-800-422-6237) to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for authors and investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

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S1211, "A Randomized Phase I/II Study of Optimal Induction Therapy of Bortezomib, Dexamethasone and Lenalidomide with or without Elotuzumab (NSC-764479) for Newly Diagnosed High Risk Multiple Myeloma (HRMM)"

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this study because you have multiple myeloma.

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Who is doing this study?

SWOG is sponsoring this trial. SWOG is an adult cancer clinical trials organization. SWOG is funded through the National Cancer Institute, and its network consists of about four thousand physicians at almost three hundred institutions throughout the United States. Your study doctor has met all requirements to be a member of SWOG and to perform National Cancer Institute-funded research through this Group.

Why is this study being done?

One of the standard treatments for your type of cancer is the combination of bortezomib, lenalidomide and dexamethasone (RVD). Elotuzumab is an experimental cancer drug. It is currently being tested in cancer patients. There are laboratory results that suggest that RVD might work better if elotuzumab is added.

This study will be conducted in two parts. Patients will take part in either Part I or Part II, not both. Since Part I has finished, all future patients will take part in Part II.

Patients in Part I can have any type of newly diagnosed myeloma. You will get the usual dose of RVD along with elotuzumab. If the elotuzumab causes bad side effects, the dose will be lowered as new patients take part in the study. This part of the study is being done to find the best dose of elotuzumab to use with RVD and to test the safety of giving all of these drugs together. Once the best dose is

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decided, this part of the study will end and the second part will start.

Patients in Part II of the study must have high risk myeloma. This means your myeloma is harder to treat. All patients in this part of the study will be treated with RVD. About half of the patients in this part will also get elotuzumab (at the dose decided in the first part of the study). This part of the study is being done to find out what effects, good and/or bad, adding elotuzumab to RVD has on you and your myeloma.

How many people will take part in the study?

About 138 people will take part in this study. About 8 people will be in Part I, and about 130 will be in Part II.

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What will happen if I take part in this research study?

Before you begin the study …

You will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

- Physical exam
- Blood tests (including tests to check the liver and kidneys)
- EKG (to check the heart)
- Bone marrow tests
- Urine tests
- Skeletal survey
- Pregnancy test (if you are a woman able to have a child)

Many of these tests will also be done again during the study. Women that can get pregnant will have a pregnancy test repeated weekly for the first month, then monthly during treatment, and again one month after finishing treatment. If your periods are irregular you will have a pregnancy test every 2 weeks and then 2 weeks and 1 month after finishing treatment.

One of the drugs on this study, lenalidomide, is being provided by the company Celgene through a program called “Revlimid REMS™” (REMS). To take part in this study, you will need to take part in REMS. REMS has some a list of conditions that you must agree to before taking part. You will also need to follow the program requirements during the study. The requirements are mostly in place to ensure that patients don’t become pregnant or father a baby while lenalidomide is still in your body. This is because lenalidomide is known to harm the baby’s

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development. This is discussed further below. Your doctor will discuss the REMS requirements with you, and more information is available online at www.revlimidrems.com.

During the study …

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will be treated in either Part I or Part II of the study. Your doctor will tell you which part you will be in.
Treatment has 2 steps, A) Induction and B) Maintenance. Induction is given to help get rid of your disease. Maintenance is given to help try to keep it from coming back.

A) Induction

Part I

Patients in Part I will get RVD and elotuzumab for induction. You will get up to 8 cycles of treatment. Each cycle has a total of 21 days, but you will not get drug on all of the days. You will get induction treatment as outlined in the table below:

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Drug	How Given	Days Given
Lenalidomide (**R**evlimid)	By mouth	1-14
Bortezomib (**V**elcade)	As a shot under your skin (or into the vein [IV] if your side effects won't allow the shot)	1, 4, 8, 11
Dexamethasone	By mouth or into your vein (IV)	1, 2, 4, 5, 8, 9, 11, 12 During Cycles 1 and 2, Day 15
Elotuzumab	Into your vein (IV)	1, 8, 15 for 2 cycles, then 1, 11 for the other 6 cycles

On days when you get elotuzumab, dexamethasone will be given into your vein at least 45 minutes before elotuzumab. On days you don't get elotuzumab, but you do get dexamethasone, or if you skip or miss a dose of elotuzumab, your doctor may give you dexamethasone by mouth instead.

Lenalidomide should be taken at about the same time every day. You can take it with or without food.

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Part II

Patients in Part II will be "randomized" to treatment in one of the study groups described below. Randomization means that you are put into a study group by chance. A computer program will place you in one of the study groups. Neither you nor your doctor can choose the group you will be in. You will have an equal chance of being put in each group. Your doctor will tell you which group you are put in.

The induction treatment for each Group will be given as follows:

Group 1
Patients in Group 1 will get induction treatment with RVD. You will get up to 8 cycles of induction treatment. Each cycle has a total of 21 days, but you will not get drug on all of the days. You will get induction treatment as outlined in the table below:

Drug	How Given	Days Given
Lenalidomide (**R**evlimid)	By mouth	1-14
Bortezomib (**V**elcade)	As a shot under your skin (or into the vein [IV] if your side effects won't allow the shot)	1, 4, 8, 11
Dexamethasone	By mouth or into your vein (IV)	1, 2, 4, 5, 8, 9, 11, 12

Lenalidomide should be taken at about the same time every day. You can take it with or without food.

Group 2
Patients in Group 2 will get the same induction treatment as Group 1, but will also get elotuzumab given into their vein by IV on Days 1, 8, and 15 for the first 2 cycles, and then on Days 1 and 11 for the other 6 cycles. Patients in this group will also get dexamethasone on Day 15 for the first 2 cycles.

For both Groups, your doctor may collect stem cells by drawing blood from you. These stem cells are collected so they can be used in the future to treat your myeloma after you are done with this study, if you need it. This is optional and is done for regular standard treatment even if you do not take part in a clinical trial. Your doctor will discuss it with you as part of your treatment options if he/she thinks it is appropriate for you.

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B) Maintenance

After you finish induction treatment, you will get maintenance treatment. The maintenance treatment will be given as follows:

You will get cycles of maintenance treatment with RVD until your disease gets worse, if that happens. Each cycle has a total of 28 days, but you will not get drug on all of the days. You will get maintenance treatment as outlined in the table below:

Drug	How Given	Days Given
Lenalidomide (**R**evlimid)	By mouth	1-21
Bortezomib (**V**elcade)	As a shot under your skin (or into your vein [IV] if your side effects won't allow the shot)	1, 8, 15
Dexamethasone	By mouth or into your vein (IV)	1, 8, 15

Lenalidomide should be taken at about the same time every day. You can take it with or without food.

The patients that got elotuzumab with their Induction will get the same RVD maintenance outlined above, but will also get elotuzumab given into their vein by IV on Days 1 and 15. If you skip or miss a dose of elotuzumab, your doctor may give you dexamethasone by mouth instead.

All patients will also get an Intake Calendar when you start treatment. This is used to help you and your doctor keep track of the drugs you are taking. It will be used to track how much drug you take and to make sure you are not getting sick because of the drugs. You will use the Intake Calendar until you have completed all study treatments.

We do not expect that you will need to be admitted to the hospital to get this treatment. Your doctor may admit you to the hospital for other disease-related reasons though, and if this happens you can get treated during your hospital stay.

How long will I be in the study?

After you are finished taking treatment on this study, the study doctor will ask you to visit the office for follow-up exams every 3 months until 6 years from when you start treatment. At these visits you will have a physical exam and urine blood tests, and possibly other tests if your doctor thinks you need them. Your doctor will then ask you to come in less often until your disease gets worse.

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Can I stop being in the study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the treatment can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest, if you do not follow the study rules, or if the study is stopped.

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What side effects or risks can I expect from being in the study?

If you choose to take part in this study, there is a risk that:

- **You may lose time at work or home and spend more time in the hospital or doctor's office than usual**
- **You may be asked sensitive or private questions which you normally do not discuss**

The drugs used in this study may affect how different parts of your body work such as your liver, kidneys, heart, and blood. The study doctor will be testing your blood and will let you know if changes occur that may affect your health.

There is also a risk that you could have side effects from the study drug(s)/study approach.

Here are important points about side effects:

- **The study doctors do not know who will or will not have side effects.**
- **Some side effects may go away soon, some may last a long time, or some may never go away.**
- **Some side effects may interfere with your ability to have children.**
- **Some side effects may be serious and may even result in death.**

Here are important points about how you and the study doctor can make side effects less of a problem:

- **Tell the study doctor if you notice or feel anything different so they can see if you are having a side effect.**
- **The study doctor may be able to treat some side effects.**
- **The study doctor may adjust the study drugs to try to reduce side effects.**

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COMMON, SOME MAY BE SERIOUS **In 100 people receiving RVD, more than 20 and up to 100 may have:**
• **High blood pressure which may cause headaches, dizziness** • **Skin changes, rash, acne** • **Swelling of the body, tiredness, bruising** • **Weight gain in belly, face, back and shoulders** • **In children and adolescents: decreased height** • **Pain in belly** • **Infection, especially when white blood cell count is low** • **Damage to the bone which may cause joint pain or loss of motion** • **Bleeding of the eye** • **Glaucoma** • **Difficulty sleeping** • **Mood swings** • **Diabetes** • **Increased appetite and weight gain** • **Loss of bone tissue** • **Anemia which may require blood transfusion** • **Constipation, diarrhea, nausea, vomiting** • **Tiredness, fever** • **Bruising, bleeding** • **Loss of appetite** • **Muscle weakness** • **Numbness, tingling, or pain of the arms and legs** • **Increased sweating**

The tables below show the most common and the most serious side effects that researchers know about. There might be other side effects that researchers do not yet know about. If important new side effects are found, the study doctor will discuss these with you.

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No matter which study Part or Group you are in, you will get treatment with RVD (bortezomib, lenalidomide and dexamethasone), so you may possibly have any of the side effects and risks related to these drugs. Risks and side effects related to these drugs include those which are:

OCCASIONAL, SOME MAY BE SERIOUS **In 100 people receiving RVD, from 4 to 20 may have:**
• **Cloudiness of the eye, visual disturbances**
• **Non-healing wound**
• **Heartburn**
• **Kidney stones**
• **Pain**
• **Bleeding from multiple sites**
• **Internal bleeding which may cause black tarry stool or blood in vomit**
• **Chills**
• **Dehydration**
• **Dizziness, headache**
• **Worry**
• **Cough, shortness of breath, sore throat**
• **Low blood pressure which may cause feeling faint**
• **Weight loss**
• **Muscle spasms**
• **Sores on the skin**
• **Itching**
• **Feeling of "pins and needles" in arms and legs**
• **Blood clot which may cause swelling, pain, shortness of breath**

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RARE, AND SERIOUS In 100 people receiving RVD, 3 or fewer may have:
• **Bleeding from sores in stomach** • **Broken bones** • **A tear or hole in internal organs that may require surgery which may cause difficulty swallowing** • **Brain damage which may cause headache, seizure, blindness (also known as Reversible Posterior Leukoencephalopathy Syndrome)** • **Kidney damage which may require dialysis** • **Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat** • **Cancer of bone marrow caused by chemotherapy** • **Damage to the organs (brain, lungs, blood vessel in lungs) which may cause changes in thinking, shortness of breath** • **Increased tumor size** • **A new cancer resulting from treatment of earlier cancer** • **Severe skin rash with blisters and peeling which can involve mouth and other parts of the body** • **Heart failure which may cause shortness of breath, swelling of ankles, and tiredness** • **Damage to organs in the body when donor cells attack host organs which may cause dry skin, or muscle weakness** • **Stroke which may cause paralysis, weakness** • **Difficulty stimulating enough stem cells in the bloodstream for future transplant** • **Liver damage which may cause yellowing of eyes and skin, swelling** • **Heart attack**

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Venous thrombosis (blood clots) and pulmonary embolism (blood clots in the lungs):
There is a potential risk for patients receiving lenalidomide of venous thrombosis (blood clots) and pulmonary embolism (blood clots in the lungs). The risk of such blood clots is increased when lenalidomide is used with corticosteroids and possibly with interferon, chemotherapy, and erythropoietin compared to using lenalidomide alone. Signs and symptoms of venous thrombosis and pulmonary embolism include the following and require medical evaluation:

- Cough that begins suddenly and/or produces blood
- Sudden onset of shortness of breath at rest or with severe exertion
- Pain in ribs with breathing
- Chest pain (under the breastbone or on one side; especially sharp or stabbing; also may be burning, aching or dull, heavy sensation; may be worsened by breathing deeply, coughing, eating, bending, or stooping)
- Rapid breathing
- Rapid heart rate
- Wheezing
- Clammy skin

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- Increased warmth of one or both legs
- Changes in skin color of one or both legs, redness
- Bluish skin discoloration
- Nasal flaring
- Pelvis pain
- Leg pain or tenderness in one or both legs
- Swelling in the legs
- Lump associated with a vein near the surface of the body, may be painful
- Weak or absent pulse
- Lightheadedness or fainting
- Dizziness
- Sweating
- Anxiety

You can lessen your risk for dangerous blood clots by not smoking, not having very long times of bed rest or being still, and not taking long car or plane rides. Obesity, recent major surgery (especially knee, hip, and stomach operations), childbirth within the last 6 months, the use of medications such as estrogen and hormonal birth control, and injury to an arm or leg also increase your risk for clotting. Also, while it is more common with this drug to have clotting in a vein, clotting in an artery is possible. This could lead to heart attack or stroke.

Please note that the use of lenalidomide in combination with bortezomib may increase the risk of certain nervous system functions. This includes changes in sensation, tingling or numbness, loss of coordination, loss of muscle control, difficulty breathing or swallowing, blurred vision, dizziness, nausea or vomiting, diarrhea, constipation and weight loss.

Sometimes a second primary cancer arises after patients have undergone cancer therapy, including therapy using chemotherapeutic agents used to treat multiple myeloma.

Recently, in clinical trials of patients with newly diagnosed multiple myeloma, a higher number of second cancers has also been reported in patients treated with high doses of chemotherapy (induction therapy) and/or stem cell transplant followed by prolonged (maintenance) lenalidomide therapy compared to those who received induction therapy and/or transplant without maintenance lenalidomide.

We do not know at this time whether prolonged lenalidomide therapy in this clinical setting actually increases the risk of second primary cancers. No increase in second primary cancers has been observed in patients receiving lenalidomide therapy who have relapsed multiple myeloma or other types of cancer.

We will be carefully monitoring these events (second primary cancers) in on-going studies of lenalidomide therapy and will inform you if there are any changes. We want you to be aware of this possibility and to continue to follow standard medical advice for prevention and early detection of other cancers during and after your treatment.

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Because of the reproductive risks of the drugs used on this study, you should not become pregnant or father a child for at least one month after stopping lenalidomide. If you take elotuzumab, you should not become pregnant for at least 2 months after stopping elotuzumab, or father a child for at least 3 months.

Reproductive risks associated with lenalidomide:

Lenalidomide is a similar drug to a drug called thalidomide. Thalidomide is known to cause severe life-threatening birth defects in humans including very short or missing arms/legs, deafness, heart defects, very small or missing eyes, paralysis of the face, kidney or gastrointestinal problems, poor growth and mental retardation. If lenalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby. Females are warned to avoid pregnancy while taking lenalidomide. Because of this risk, all patients taking lenalidomide must read and agree to the list of statements provided by your doctor depending on your sex and ability to become pregnant. If your uterus and/or both ovaries have not been removed, or if you have had at least one menstrual period in the past 24 months and/or your menses stopped due to treatment of your disease, you will be considered a female that is able to become pregnant.

Reproductive risks :

You should not become pregnant or father a baby while in this study. You must use a highly effective birth control method or a combination of 2 additionally effective birth control methods while in this study. Examples of highly effective birth control are a condom or a diaphragm, either with spermicidal jelly; oral, injectable, or implanted birth control; or abstinence. The effect of bortezomib on reproductive capacity and its safety in pregnancy are unknown. If you are a woman capable of becoming pregnant [anyone who has not undergone a hysterectomy (removal of the womb), has not had both ovaries removed or has not been post-menopausal (stopped menstrual periods) for more than 24 months in a row], you must have a negative serum pregnancy test before beginning treatment. In addition, you must not be breastfeeding a baby during this study.

If you think that you have become pregnant or may have fathered a child while taking part in this study you must tell the study doctor immediately. The study doctor will advise you of the possible risks to your unborn baby and discuss options for managing the pregnancy with you. You should also notify the doctor managing your pregnancy that the mother/father received the study drugs bortezomib or lenalidomide.

If you are a female study subject and you become pregnant during your participation in this study, your treatment with study drug will be stopped and you may be withdrawn from some of the study procedures but not from follow-up by your study doctor. The study doctor will ask for your permission to stay in contact with you throughout the length of the pregnancy.

If you are a male study subject and your partner becomes pregnant, the study doctor will ask for your partner's permission to collect information about her pregnancy and the health of the baby.

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Laboratory tests show that bortezomib may damage DNA. Based on this information, it is possible that bortezomib may cause infertility in men and women (not being able to become pregnant or father a child).

Part I and Group 2 of Part II

Patients who are in Part I and Group 2 of Part II will also get treatment with elotuzumab, so you may possibly have additional side effects. Additional risks and side effects related to elotuzumab include those which are:

Likely
- Weight loss
- Cough
- Low white blood cell count

Less Likely:
- Reduced sensitivity to touch
- Night sweats
- Shingles (rash caused by infection)
- Chest pain
- Mood changes
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, difficulty breathing, swelling of the face or throat
- Reaction that can occur during or following the infusion of the drug. The reaction may include fever, chills, rash, high blood pressure and difficulty breathing.

Other unexpected reactions may occur. It is also possible that your immune system could make antibodies against elotuzumab, which would limit how well it works against the myeloma.

For more information about risks and side effects, ask your study doctor.

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Are there benefits to taking part in the study?

Taking part in this study may or may not make your health better. While doctors hope adding elotuzumab will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from this study will help doctors learn more about using elotuzumab as a treatment for cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this study?

Your other choices may include:
- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment
- Getting comfort care, also called palliative care. This type of care helps reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat

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the cancer directly, but instead tries to improve how you feel. Comfort care tries to keep you as active and comfortable as possible.

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- The National Cancer Institute (NCI) and other government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people
- SWOG
- The Cancer Trials Support Unit (CTSU), a research group sponsored by the NCI to provide greater access to clinical trials
- The Alliance for Clinical Trials in Oncology, ECOG-ACRIN Cancer Research Group, and NRG Oncology.
- Bristol-Myers Squibb, the manufacturer of elotuzumab
- Celgene Corporation, the manufacturer of lenalidomide

A description of this clinical trial will be available on http://www.ClinicalTrials.gov. This Web site will not include information that can identify you. At most, the Web site will include a summary of study results. You can search this Web site at any time.

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this study?
You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment.

Bristol-Myer Squibb will supply the elotuzumab at no charge while you take part in this study. Bristol-Myer Squibb does not cover the cost of getting the elotuzumab ready and giving it to you, so you or your insurance company may have to pay for this.

Even though it probably won't happen, it is possible that the manufacturer may not continue to provide the elotuzumab for some reason. If this would occur, other possible options are:

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- You might be able to get the elotuzumab from the manufacturer or your pharmacy but you or your insurance company may have to pay for it.
- If there is no elotuzumab available at all, no one will be able to get more and the study would close.

If a problem with getting elotuzumab occurs, your study doctor will talk to you about these options.

Bortezomib and dexamethasone are commercially available. Beginning at the start of your next Cycle of treatment, Celgene will provide lenalidomide at no cost to you or your insurance company through the Revlimid® REMS™ program.

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at http://m.cancer.gov/topics/clinicaltrials/learningabout/payingfor/how-insurance-companies-decide. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

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Who can answer my questions about the study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number]*.

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).* *[Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

Please note: This section of the informed consent form is about additional research studies that are being done with people who are taking part in the main study. You may take part in these additional studies if you want to. You can still be a part of the main study even if you say 'no' to taking part in any of these additional studies.

You can say "yes" or "no" to each of the following studies. Please mark your choice for each study.

Future Contact

I agree to allow my study doctor, or someone approved by my study doctor, to contact me regarding future research involving my participation in this study.

Yes No

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Consent Form for Use of Specimens for Research

About Using Specimens for Research

You are going to have a blood draw and a bone marrow biopsy to see if you have cancer. Your doctor will remove some body tissue to do some tests. The results of these tests will be given to you by your doctor and will be used to plan your care.

We would like to keep some of the specimens that are left over for future research. If you agree, these specimens will be kept and may be used in research to learn more about cancer and other diseases. Please read the information sheet called "How are Specimens Used for Research" to learn more about specimen research.

The research that may be done with your specimens is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your specimens will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

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Things to Think About

The choice to let us keep the left over specimens for future research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your specimens can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your specimens. Then any specimens that remain will no longer be used for research.

In the future, people who do research may need to know more about your health. While SWOG may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes specimens are used for genetic research (about diseases that are passed on in families). Even if your specimens are used for this kind of research, the results will not be put in your health records.

If your confidential genetic information is discovered, you may suffer from genetic discrimination. Genetic discrimination occurs if people are treated unfairly because of differences in their genes that increase their chances of getting a certain disease. In the past, this could have resulted in the loss of health insurance or employment. Because of this, The Genetic Information Nondiscrimination Act of 2008, also referred to as GINA, was passed by Congress to protect Americans from such discrimination. The new law prevents discrimination from health insurers and employers. This act was signed into federal law on May 21, 2008 and went into effect May 2009. This law does not cover life insurance, disability insurance and long-term care insurance.

While this study has safeguards in place to protect your confidential genetic information and to make it extremely unlikely that your identity would be connected with any special studies that are performed on your tissue, it is possible that this information could be discovered by someone who is unauthorized to have access to it.

Your specimens will be used only for research and will not be sold. The research done with your specimens may help to develop new products in the future.

CLOSED EFFECTIVE 04/15/2018

Benefits

The benefits of research using specimens include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

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Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No." If you have any questions, please talk to your doctor or nurse, or call our research review board at IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. **My specimens may be kept for use in research to learn about, prevent, treat or cure cancer.**

   Yes No

2. **My specimens may be kept for use in research about other health problems (for example: diabetes, Alzheimer's disease, or heart disease).**

   Yes No

3. **Someone may contact me in the future to ask me to allow other uses of my specimens.**

   Yes No

If you decide to withdraw your specimens from a SWOG Specimen Repository in the future, a written withdrawal of consent should be submitted through your study doctor to the SWOG Operations Office. Please designate in the written withdrawal whether you would prefer to have the specimens destroyed or returned to the study doctor.

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Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

1-800-4-CANCER (1-800-422-6237)

You may also visit the NCI Web site at http://cancer.gov/

- For NCI's clinical trials information, go to: http://cancer.gov/clinicaltrials/
- For NCI's general information about cancer, go to http://cancer.gov/cancerinfo/

You will get a copy of this form. If you want more information about this study, ask your study doctor.

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Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered. I agree to take part in this study.

Participant (or legally authorized representative) _____

Date _____

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Specimen Consent Supplemental Sheets

How are Specimens Used for Research?

Where do specimens come from?

A specimen may be from a blood sample or from bone marrow, skin, toenails or other body materials. People who are trained to handle specimens and protect donors' rights make sure that the highest standards of quality control are followed by SWOG. Your doctor does not work for SWOG, but has agreed to help collect specimens from many patients. Many doctors across the country are helping in the same way.

Why do people do research with specimens?

Research with specimens can help to find out more about what causes cancer, how to prevent it, how to treat it, and how to cure it. Research using specimens can also answer other health questions. Some of these include finding the causes of diabetes and heart disease, or finding genetic links to Alzheimer's.

What type of research will be done with my specimen?

Many different kinds of studies use specimens. Some researchers may develop new tests to find diseases. Others may develop new ways to treat or even cure diseases. In the future, some of the research may help to develop new products, such as tests and drugs. Some research looks at diseases that are passed on in families (called genetic research). Research done with your specimen may look for genetic causes and signs of disease.

How do researchers get the specimen?

Researchers from universities, hospitals, and other health organizations conduct research using specimens. They contact SWOG and request samples for their studies. SWOG reviews the way that these studies will be done, and decides if any of the samples can be used. SWOG gets the specimen and information about you from your hospital, and sends the specimen samples and some information about you to the researcher. SWOG will not send your name, address, phone number, social security number or any other identifying information to the researcher.

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Will I find out the results of the research using my specimen?

You will not receive the results of research done with your specimen. This is because research can take a long time and must use specimen samples from many people before results are known. Results from research using your specimen may not be ready for many years and will not affect your care right now, but they may be helpful to people like you in the future.

Why do you need information from my health records?

In order to do research with your specimen, researchers may need to know some things about you. (For example: Are you male or female? What is your race or ethnic group? How old are you? Have you ever smoked?) This helps researchers answer questions about diseases. The information that will be given to

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the researcher may include your age, sex, race, diagnosis, treatments and family history. This information is collected by your hospital from your health record and sent to SWOG. If more information is needed, SWOG will send it to the researcher.

Will my name be attached to the records that are given to the researcher?

No. Your name, address, phone number and anything else that could identify you will be removed before they go to the researcher. The researcher will not know who you are.

How could the records be used in ways that might be harmful to me?

If your confidential genetic information is discovered, you may suffer from genetic discrimination. Genetic discrimination occurs if people are treated unfairly because of differences in their genes that increase their chances of getting a certain disease. In the past, this could have resulted in the loss of health insurance or employment. Because of this, The Genetic Information Nondiscrimination Act of 2008, also referred to as GINA, was passed by Congress to protect Americans from such discrimination. The new law prevents discrimination from health insurers and employers. This act was signed into federal law on May 21, 2008, and went into effect May 2009. This law does not cover life insurance, disability insurance and long-term care insurance.

While this study has safeguards in place to protect your confidential genetic information and to make it extremely unlikely that your identity would be connected with any special studies that are performed on your tissue, it is possible that this information could be discovered by someone who is unauthorized to have access to it.

How am I protected?

SWOG is in charge of making sure that information about you is kept private. SWOG will take careful steps to prevent misuse of records. Your name, address, phone number and any other identifying information will be taken off anything associated with your specimen before it is given to the researcher. This would make it very difficult for any research results to be linked to you or your family. Also, people outside the research process will not have access to results about any one person which will help to protect your privacy.

What if I have more questions?

If you have any questions, please talk to your doctor or nurse, or call our research review board at (Insert IRB's Phone Number).

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