A Randomized Parallel Phase 2 Study of Elotuzumab plus Lenalidomide (Elo/Rev) for the Treatment of Serologic Relapse/Progression while on Lenalidomide Maintenance for Multiple Myeloma

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MCC 19197: A randomized parallel phase 2 study of Elotuzumab plus Lenalidomide (Elo/Rev) for the treatment of serologic relapse/progression while on lenalidomide maintenance for multiple myeloma

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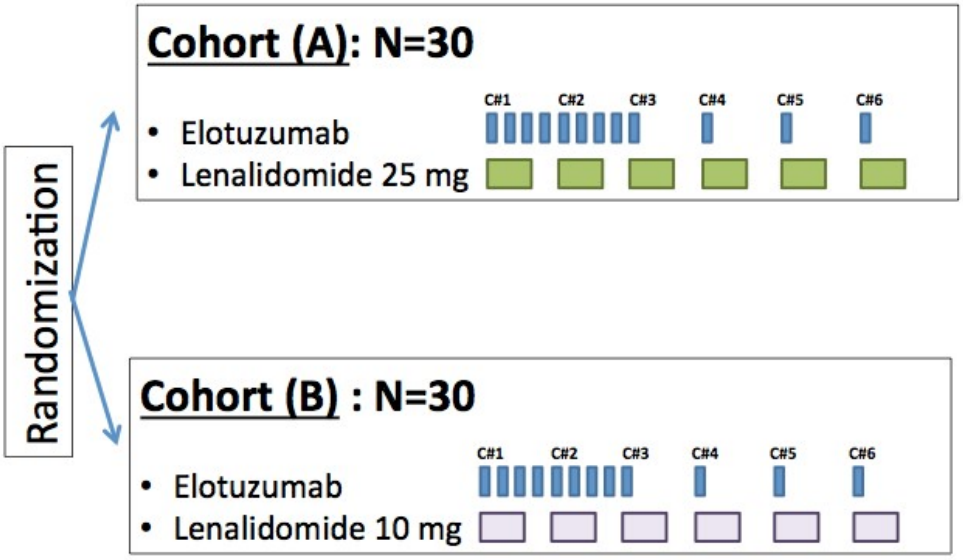
Study Title	A randomized parallel phase 2 study of Elotuzumab plus Lenalidomide (Elo/Rev) for the treatment of serologic relapse/progression while on lenalidomide maintenance for multiple myeloma

Study Rationale	Multiple myeloma constitutes approximately 10% of all hematologic malignancies. High dose chemotherapy followed by autologous HCT remains an integral treatment strategy for multiple myeloma. Lenalidomide is the most commonly prescribed maintenance therapy after autologous HCT, however, disease relapse/progression after autologous HCT remains unavoidable secondary to the existence of minimal residual disease and drug resistance conferred by tumor microenvironment. When patients relapse/progress after autologous HCT, management of disease depends on prior treatment history, organ function and patient tolerability to certain chemotherapeutic agents. There are considerable practice variations in part due to several FDA approved anti-myeloma agents and there is no consensus on how best to treat serologic relapse/progression without symptomatic disease after autologous HCT. With the incorporation of free light chain assay into the standard clinical practice, relapse/progression of myeloma may be captured early and only limited literature is available to characterize the pattern of relapse/progression after autologous HCT. A Spanish group reported 4 distinctive patterns of relapse/progression including (1) extramedullary disease, (2) plasma cell leukemia, (3) clinically symptomatic disease (66%), and (4) insidious increase in serum M-spike (18%).[5] More recently, Zamarin et al. evaluated 273 patients who underwent autologous HCT (79% of them not on maintenance) and showed that 85% of patient had asymptomatic relapse/progression detected by serologic testing whereas only 15% had symptomatic relapse/progression (characterized by anemia, renal failure, hypercalcemia, soft tissue or bone disease) after autologous HCT.[6] The latter study demonstrated increasing frequency of serologic relapse without symptomatic disease after autologous HCT over time. It was also shown that the survival was better with asymptomatic relapse/progression.[6] A Spanish group conducted an observation prospective registry study evaluating the timing and patter of relapsed disease in myeloma patients.[7] The median time from biological/serologic relapse to clinical (symptomatic) relapse was 105 days which is relatively short.[7] Signaling Lymphocyte Activation Molecule family-7 (SLAMF7, also known as CS1 or CD319) is a human membrane glycoprotein and member of the immunoglobulin superfamily.[8,9] SLAMF7 is expressed on myeloma cell surface on both primary human myeloma cells and myeloma cell lines.[9] Soluble SLAMF7 has also been detected in myeloma patients' serum and has been shown to correlate with myeloma disease stage.[8] Additionally, SLAMF7 is expressed in natural killer (NK) cells and T-cell subsets.[10,11] The CS1/SLAMF7 gene is located on the long arm of chromosome 1 (1q23.1-1q24.1), and gains of chromosome 1q are relatively frequent in myeloma.[12] SLAMF7 has been demonstrated to co-localize with CD138 promoting cell-cell adhesion, and plays a role in myeloma cell interactions with bone marrow stromal cells.[8,13] SLAMF7 is a self-ligand for NK cells and promotes activation through selective expression of the adaptor protein, EAT-2.[14-16] Furthermore, SLAMF7 may inhibit T cells that lack EAT-2.[14] Elotuzumab (previously called HuLuc63) is a humanized immunoglobulin G_1 anti-CS1/SLAMF7 monoclonal antibody that has been shown to impair myeloma cell adhesion. *In vitro* studies
	have shown impaired primary myeloma cell survival with or without bone marrow stromal cells.[8] Elotuzumab is thought to exert effects on myeloma cells through antibody-dependent cellular cytotoxicity (ADCC) which is mediated by NK cells through interaction of their Fcγ RIIIa receptor.[8,9,17] Elotuzumab also directly activate NK cells through direct SLAMF7 ligation.[18,19] In a phase 1 dose escalation study of Elotuzumab in 35 advanced myeloma

	patients, there was no maximum tolerated dose (MTD) identified up to 20 mg/kg (given every 14 days for 8 weeks).[20] Nine out of 34 patients (26.5%) had stable disease at day 56, suggesting limited single agent activity. At doses of 10 and 20 mg/kg of Elotuzumab, SLAMF7 receptors on bone marrow-derived myeloma cells were consistently saturated.[20] Mean terminal phase half-life increased with a dose escalation ($T_{1/2}$ □ of 7.8 days with 20 mg/kg) suggesting a saturation of target-mediated elimination.[20] Transient decreases in lymphocyte counts were observed (within hours, in both $CS1^+$ and $CS1^-$ subsets) but returned to baseline levels by day 7.[20] Several phase II and III trials using combination therapy with Elotuzumab have been conducted in myeloma.[21] Most recently, a phase 3 trial comparing Elotuzumab (10 mg/kg days 1, 8, 15, and 22 for first 2 cycles, then on days 1 and 15 with third cycle), lenalidomide and dexamethasone with lenalidomide plus dexamethasone in relapsed/refractory myeloma has been reported.[1] After a median follow-up of 24.5 months, median progression-free survival (PFS) was 19.4 months in Elotuzumab group vs. 14.9 months in control group ($P < 0.001$).[1] This very promising anti-CS1/SLAMF7 monoclonal antibody therapy with Elotuzumab has now been FDA approved and added to the armamentarium of anti-myeloma therapy. Overall, Elotuzumab appears to be well tolerated, with most common adverse events with single agent therapy being infusion-related reactions.[22] In the phase 3 trial, Elotuzumab group had higher grade 3-4 lymphopenia (77% vs. 49%).[1] There was also a suggestion that grade 3 or 4 neutropenia incidence may be lower in Elotuzumab group (34% vs. 44%). Based on the prior clinical studies of Elotuzumab in relapse/refractory myeloma, Elotuzumab was demonstrated to be safe and effective for its treatment at a dose of 10 mg/kg in combination with lenalidomide. As noted previously, it is critical that the Fc portion of Elotuzumab is able to bind to the Fcγ RIIIa receptor expressed on NK cells.[8,9] The Fcγ RIIIa gene has allelic variation that determines the affinity of the Fcγ RIIIa receptor for IgG1 antibodies such as elotuzumab.[9] In a phase 2 study of Elotuzumab plus bortezomib/dexamethasone for relapse/refractory multiple myeloma, Jakubowiak et al. evaluated the associations of Fcγ RIIIa receptor polymorphisms and clinical outcomes.[23] Patients who were homozygous for the high-affinity Fcγ RIIIa V (VV) allele had a longer PFS compared to those with homozygous for the low affinity Fcγ RIIIa F (FF) allele (22.3 months vs. 9.8 months),[23] suggesting the importance of evaluation Fcγ RIIIa polymorphisms to predict better disease control in subsets of myeloma patients. Of note, this advantage in the VV group for Fcγ RIIIa was not seen when Elotuzumab was combined with lenalidomide and dexamethasone in the Eloquent-2[39] Disruption of interactions between myeloma cells and the microenvironment by targeting SLAMF7 using Elotuzumab (anti-CS1/SLAMF7 monoclonal antibody) could potentially abrogate drug-resistance and sensitize cells that are losing response to lenalidomide. Elotuzumab could potentially increase the NK cell activity in the context of lenalidomide therapy. We hypothesize that addition of Elotuzumab to myeloma patients who demonstrate serologic relapse/progression to single agent lenalidomide maintenance may modulate antimyeloma immune response and render those patients into better response and prolong time to progression.
Primary Objectives	Progression free survival with Elotuzumab plus lenalidomide when Elotuzumab is added to multiple myeloma patients with serologic relapse/progression while receiving lenalidomide maintenance for each cohort

Secondary Objectives	• Overall response rate (ORR) with Elotuzumab and lenalidomide for each cohort • Minimum response (MR) or better rate with Elotuzumab and lenalidomide for each cohort • Time to next treatment (TTNT) for each cohort • Comparison of clinical outcomes (cohort A versus B) • Fcγ RIIIa receptor polymorphisms (homozygous for high-affinity V (VV) allele vs. low affinity F (FF) allele) • Effect of Elotuzumab added to lenalidomide on phenotypic characteristics of the immune infiltrate and correlation with therapeutic efficacy
Sample Size	In a randomized phase 2 study of lenalidomide single agent therapy (either 30 mg daily or 15 mg PO twice daily days 1-21 out of 28-day cycle) in relapsed/refractory myeloma where dexamethasone was added after 2 cycles if progressive or stable disease, median PFS was 7.7 months with once-daily lenalidomide (compared to 3.9 months with twice daily lenalidomide).[24] In a phase 3 study, a combination of Elotuzumab/lenalidomide/dexamethasone vs. lenalidomide/dexamethasone in relapsed/refractory myeloma showed PFS of 19.4 months vs. 14.9 months (with 5 months benefit).[1] Based on these results, we assume that in patients receiving single agent lenalidomide maintenance even if the dose of lenalidomide was increased to the maximum dose of 25 mg PO daily, those patients who are experiencing serologic relapse/progression would have at best 7 months of median PFS and a Spanish study indicated approximately 3 months until clinical progression (without any study). We hypothesize that the addition of Elotuzumab to maintenance lenalidomide would improve PFS to 12 months (with addition of 5 months benefit). We anticipate that approximately 3 subjects per month will be accrued over 24 months. The statistical power was computed based on the assumptions; (1) null PFS of 7 months and alternative PFS of 12 months, (2) the projected accrual of 24 months, (3) a follow-up time of 12 months, and (4) an one-sided alpha of 0.05. With these assumptions, **a sample size of 30 patients per cohort** would have 85% power to reject the null hypothesis of 7 months (versus alternative of 12 months, hazard ratio 0.58). As the primary goal of the study is to investigate the clinical benefit of each combination regimen, results of the cohort (A) and cohort (B) will be reported separately and additional comparative analyses will be performed as an exploratory aim. The final analysis for primary endpoint will be conducted if 28 PFS events are observed.

Study Design	Randomized parallel 2-cohort phase 2 study of Elotuzumab given at 10 mg/kg weekly during induction in combination with lenalidomide (either 25 mg or 10 mg) in patients with multiple myeloma who progress or relapse serologically while on single agent lenalidomide maintenance. Patients will be randomized to either (1) cohort A = lenalidomide 25 mg PO daily days 1-21 with Elotuzumab or (2) cohort B = lenalidomide 10 mg PO daily days 1-21 with Elotuzumab. We selected the dose of Elotuzumab at 10 mg/kg weekly dosing followed by monthly infusion of 20 mg/kg based on the safety and tolerability profile in the published phase 3 study and other studies of combination therapy with bortezomib,[1-3] as well as an ongoing study in combination with pomalidomide (NCT02612779). Elotuzumab will be administered intravenously on days 1, 8, 15, and 22 during the first 2 cycles, then on day 1 of each cycle starting third cycle. The combination therapy with Elotuzumab and lenalidomide will be continued until further progression of myeloma (based on response criteria) or intolerability. ***Combination dosing schedule:***

	(1) Cohort A: • Elotuzumab 10 mg/kg IV weekly (days 1, 8, 15 and 22) for 2 cycles, then 20 mg/kg every 4 weeks • Lenalidomide 25 mg PO daily days 1-21 out of a 28-day schedule (2) Cohort B: • Elotuzumab 10 mg/kg IV weekly (days 1, 8, 15 and 22) for 2 cycles, then 20 mg/kg every 4 weeks • Lenalidomide 10 mg PO daily days 1-21 out of a 28-day schedule  ***Response assessment:*** The Consensus on Uniform Reporting of Response will be used to evaluate response.[4] Myeloma patients enrolled in this clinical study will be assessed for disease response after every cycle. Time to disease progression will be defined as the time from the day first Elotuzumab treatment to the time of myeloma progression.
Duration of Treatment	Patients will continue on therapy until clinical relapse as per IMWG criteria; 1.1.1 Clinical relapse 1.1.2 Clinical relapse requires one or more of the following criteria: 1.1.3 Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice;

	1.1.4	Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression);
	1.1.5	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 SPD[§§] of the measurable lesion;
	1.1.6	Hypercalcemia (>11 mg/dL);
	1.1.7	Decrease in hemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions;
	1.1.8	Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma;
	1.1.9	Hyperviscosity related to serum paraprotein
	***Lancet Oncol* 2016; 17: e328–46**	

Inclusion/ Exclusion criteria	**Inclusion criteria** 1. Patients with multiple myeloma who demonstrate evidence of serologic relapse/progression while on lenalidomide maintenance given as part of **first** line therapy (including upfront high-dose chemotherapy followed by autologous hematopoietic cell transplantation (HCT)) without symptomatic relapse/progression. Lenalidomide maintenance is defined as **single agent** lenalidomide therapy of any doses up to 15 mg PO daily for 14-28 days (28-day cycle). Relapse/progression is defined as increase of 25% from lowest confirmed response value in one or more of the following criteria: Serum M –protein(absolute increase must be ≥ 0.5g/dl) Serum M-protein increase >1g/dl, if the lowest M component was >5 g/dl Urine M –protein(absolute increase must be > 200 mg in 24 hours) In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dl) For patients relapsing from complete remission, relapse is defined as: Reappearance of serum or serum M-protein by immunofixation or electrophoresis. 2. 2. Male or female patients aged ≥ 18 years old 3. Ability to provide written informed consent obtained prior to participation in the study and any related procedures being performed 4. Measurable disease with at least 1 of the following assessed within 28 days prior to Cycle 1 Day 1: a. Serum M-protein ≥ 0.5 g/dL, b. Urine M-protein ≥ 200 mg/24 hour, c. In subjects without detectable serum or urine M-protein, serum free light chain (SFLC) > 10 mg/dL (involved light chain) and an abnormal serum kappa lambda ratio 5. Patients must meet the following laboratory criteria within 28 days prior to Cycle 1, day 1:

a) Absolute neutrophil count (ANC) ≥ 1 x 10^9/L

b) Hemoglobin ≥ 10 g/dl

c) Platelet count ≥ 75,000/mm3

d) AST and ALT ≤ 2.5 x ULN

e) Serum bilirubin ≤ 1.5 x ULN

f) Serum Creatinine clearance ≥ 50ml/min

Exclusion criteria

1. Prior Elotuzumab
2. Patients with clinical relapse/progression as per the IMWG uniform criteria defined as one or more of the following criteria:
    a. Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression)

    b. 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 of the measurable lesion
    c. Hypercalcemia (>11 mg/dL);
    d. Decrease in hemoglobin of ≥2 g/dL not related to therapy or other non-myeloma related conditions;
    e. Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma
    f. Hyperviscosity related to serum paraprotein
3. Women who are pregnant or breast feeding or women of childbearing potential (WOCBP) not using an effective method of birth control. WOCBP are defined as sexually mature women who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months). Women of childbearing potential must have a negative serum pregnancy testing within 7 days prior to the administration of drug.
4. Male patients whose sexual partners are WOCBP not using effective birth control
5. Patients with a prior malignancy with in the last 5 years (except for skin basal or squamous cell carcinoma, or *in situ* cancer of the cervix)
6. Patients with known positivity for human immunodeficiency virus (HIV)) or hepatitis C; baseline testing for HIV and hepatitis C is not required
7. Patients with a diagnosis of POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) or plasma cell leukemia (> 2.0 × 109/L circulating plasma cells by standard differential)

Screening Assessments (to be done within 28 days of C1D1)	Signed written informed consent Demographics and medical history (prior therapy) Pregnancy test (if applicable) Physical examination and vital signs (within 28 days of therapy)
	Hematology (CBC) (within 28 days of therapy) Clinical chemistry (within 28 days of therapy) Assessment of disease status (within 28 days of therapy) (SPEP, 24h UPEP, serum free light chain) Bone marrow aspiration and biopsy with cytogenetics, FISH, My PRS (gene expression profile) (within 28 days of therapy) Skeletal survey (within 28 days of therapy) Concomitant medication
Treatment and post treatment assessments	**Day 1 of each cycle** Physical examination and vital signs CBC (also day 8, 15, 22 of cycles 1-2) Complete clinical chemistry (also day 8, 15, 22 of cycles 1-2) Assessment of disease status (SPEP, 24h UPEP, Quantitative Immunoglobulins, serum free light chain) Adverse events and concomitant medication Pregnancy test if applicable
Response	Response will be assessed per the uniform response criteria of the IMWG
Safety variables and analysis	The safety and tolerability of Elotuzumab and lenalidomide given for the treatment of serologic progression after first line therapy to myeloma patients will be evaluated by means of AE reports, physical examinations, and laboratory safety evaluations. Common Terminology Criteria for Adverse Events (CTCAE) V 5.0 will be used for grading of AEs. Investigators will provide their assessment of causality as 1) unrelated, 2) unlikely related, 3) possibly related, or 4) probably or 5) definitely related for all AEs to one both study drugs.

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1.0 Introduction

1.2 Overview and Study Rationale

Multiple myeloma constitutes approximately 10% of all hematologic malignancies. High-dose chemotherapy followed by autologous HCT remains an integral treatment strategy for multiple myeloma. Lenalidomide is the most commonly prescribed maintenance therapy after autologous HCT, however, disease relapse/progression after autologous HCT remains unavoidable secondary to the existence of minimal residual disease and drug resistance conferred by tumor microenvironment. When patients relapse/progress after autologous HCT, management of disease depends on prior treatment history, organ function and patient tolerability to certain chemotherapeutic agents. There are considerable practice variations in part due to several FDA approved antimyeloma agents and there is no consensus on how best to treat serologic relapse/progression without symptomatic disease after autologous HCT.

With the incorporation of free light chain assay into the standard clinical practice, relapse/progression of myeloma may be captured early and only limited literature is available to characterize the pattern of relapse/progression after autologous HCT. A Spanish group reported 4 distinctive patterns of relapse/progression including (1) extramedullary disease, (2) plasma cell leukemia, (3) clinically symptomatic disease (66%), and (4) insidious increase in serum M-spike (18%).[5] More recently, Zamarin et al. evaluated 273 patients who underwent autologous HCT (79% of them not on maintenance) and showed that 85% of patient had asymptomatic relapse/progression detected by serologic testing whereas only 15% had symptomatic relapse/progression (characterized by anemia, renal failure, hypercalcemia, soft tissue or bone disease) after autologous HCT.[6] The latter study demonstrated increasing frequency of serologic relapse without symptomatic disease after autologous HCT over time. It was also shown that the survival was better with asymptomatic relapse/progression.[6] A Spanish group conducted an observation prospective registry study evaluating the timing and patter of relapsed disease in myeloma patients.[7] The median time from biological/serologic relapse to clinical (symptomatic) relapse was 105 days which is relatively short.[7]

Signaling Lymphocyte Activation Molecule family-7 (SLAMF7, also known as CS1 or CD319) is a human membrane glycoprotein and member of the immunoglobulin superfamily.[8,9] SLAMF7 is expressed on myeloma cell surface on both primary human myeloma cells and myeloma cell lines.[9] Soluble SLAMF7 has also been detected in myeloma patients' serum and has been shown to correlate with myeloma disease stage.[8] Additionally, SLAMF7 is expressed in natural killer (NK) cells and T-cell subsets.[10,11] The CS1/SLAMF7 gene is located on the long arm of chromosome 1 (1q23.1-1q24.1), and gains of chromosome 1q are relatively frequent in myeloma.[12] SLAMF7 has been demonstrated to co-localize with CD138 promoting cell-cell adhesion, and plays a role in myeloma cell interactions with bone marrow stromal cells.[8,13] SLAMF7 is a self-ligand for NK cells and promotes activation through selective expression of the adaptor protein, EAT-2.[14-16] Furthermore, SLAMF7 may inhibit T cells that lack EAT-2.[14]

Elotuzumab (previously called HuLuc63) is a humanized immunoglobulin G_1 anti-CS1/SLAMF7 monoclonal antibody that has been shown to impair myeloma cell adhesion. *In vitro* studies have shown impaired primary myeloma cell survival with or without bone marrow stromal cells.[8] Elotuzumab is thought to exert effects on myeloma cells through antibody-dependent cellular cytotoxicity (ADCC) which is mediated by NK cells through interaction of their Fcγ RIIIa receptor.[8,9,17] Elotuzumab also directly activates NK cells through direct SLAMF7 ligation.[18,19] In a phase 1 dose escalation study of Elotuzumab in 35 advanced myeloma patients, there was no maximum tolerated dose (MTD) identified up to 20 mg/kg (given every 14 days for 8 weeks).[20] Nine out of 34 patients (26.5%) had stable disease at day 56, suggesting limited single agent activity. At doses of 10 and 20 mg/kg of Elotuzumab, SLAMF7 receptors on bone marrow-derived myeloma cells were consistently saturated.[20] Mean terminal phase half-life

increased with a dose escalation ($T_{1/2}$ of 7.8 days with 20 mg/kg) suggesting a saturation of target-mediated elimination.[20] Transient decreases in lymphocyte counts were observed (within hours, in both $CS1^+$ and $CS1^-$ subsets) but returned to baseline levels by day 7.[20] Several phase II and III trials using combination therapy with Elotuzumab have been conducted in myeloma.[21] Most recently, a phase 3 trial comparing Elotuzumab (10 mg/kg days 1, 8, 15, and 22 for first 2 cycles, then on days 1 and 15 with third cycle), lenalidomide and dexamethasone with lenalidomide plus dexamethasone in relapsed/refractory myeloma has been reported.[1] After a median follow-up of 24.5 months, median progression-free survival (PFS) was 19.4 months in Elotuzumab group vs. 14.9 months in control group ($P < 0.001$).[1] This very promising anti-CS1/SLAMF7 monoclonal antibody therapy with Elotuzumab has now been FDA approved and added to the armamentarium of anti-myeloma therapy. Overall, Elotuzumab appears to be well tolerated, with most common adverse events with single agent therapy being infusion-related reactions.[22] In the phase 3 trial, Elotuzumab group had higher grade 3-4 lymphopenia (77% vs. 49%).[1] There was also a suggestion that grade 3 or 4 neutropenia incidence may be lower in Elotuzumab group (34% vs. 44%). Based on the prior clinical studies of Elotuzumab in relapse/refractory myeloma, Elotuzumab was demonstrated to be safe and effective for its treatment at a dose of 10 mg/kg in combination with lenalidomide.

As noted previously, it is critical that the Fc portion of Elotuzumab is able to bind to the FcγRIIIa receptor expressed on NK cells.[8,9] The FcγRIIIa gene has allelic variation that determines the affinity of the FcγRIIIa receptor for IgG1 antibodies such as elotuzumab.[9] In a phase 2 study of Elotuzumab plus bortezomib/dexamethasone for relapse/refractory multiple myeloma, Jakubowiak et al. evaluated the associations of FcγRIIIa receptor polymorphisms and clinical outcomes.[23] Patients who were homozygous for the high-affinity FcγRIIIa V (VV) allele had a longer PFS compared to those with homozygous for the low-affinity FcγRIIIa (FF) allele (22.3 months vs. 9.8 months),[23] suggesting the importance of evaluation of FcγRIIIa polymorphisms to predict better disease control in subsets of myeloma patients.

Study Rationale:

Disruption of interactions between myeloma cells and the microenvironment by targeting SLAMF7 using Elotuzumab (anti-CS1/SLAMF7 monoclonal antibody) could potentially abrogate drug-resistance and sensitize cells that are losing response to lenalidomide. Elotuzumab could potentially increase the NK cell activity in the context of lenalidomide therapy. We hypothesize that addition of Elotuzumab to myeloma patients who demonstrate serologic relapse/progression to single agent lenalidomide maintenance may modulate anti-myeloma immune response and render those patients into better response and prolong time to progression.

1.3 Overview of Elotuzumab

Elotuzumab (EMPLICITI™, Bristol-Myers Squibb Company [BMS], New York, NY, USA) is a fully humanized recombinant monoclonal immunoglobulin G1 (IgG1) antibody that binds human SLAMF7 (also CS1, CRACC). The unique epitope of Elotuzumab is located within the membrane proximal C2 domain of SLAMF7. The cell surface glycoprotein SLAMF7 is universally and highly expressed on patient MM cells, irrespective of cytogenetic abnormalities and the degree of disease progression. The exact role of SLAMF7 in myeloma cells is still unknown. Stable knockdown of SLAMF7 in MM cells resulted in decreased cell growth and colony formation in vitro,[25] as well as reduced tumor burden and increased survival of animals in a xenograft mouse model.[26] Homing of myeloma cells to the bone marrow, adhesion, and survival within the bone marrow microenvironment were impacted, indicating an involvement of SLAMF7 in the pathogenesis of MM. Elotuzumab has been evaluated for the treatment of MM in a series of clinical trials. The first-in-human study (Study 1701) assessed safety and tolerability as well as PK of Elotuzumab as a single agent. However, the antitumor effects of Elotuzumab were largely determined in combination with established myeloma therapies. In Study 1701, the safety and tolerability as well

as PK and pharmacodynamics of different doses of Elotuzumab (dose cohorts from 0.5 to 20 mg/kg body weight) were analyzed in 35 patients with RRMM. Saturation of SLAMF7 receptors was observed at Elotuzumab doses of 10–20 mg/kg. Despite plasma cell target saturation, no objective myeloma responses were observed.[20] Based on the European Society of Blood and Marrow Transplantation myeloma response criteria, 25 patients (73.5%) had progressive disease and nine patients (26.5%) were classified as having stable disease, demonstrating minimal single-agent activity of Elotuzumab. These findings substantiate the challenge to effectively activate and direct cells of the immune system to kill myeloma cells in patients with compromised immune function, in particular, with compromised NK cell function. In Study 1701, patients were heavily pretreated and had received a median of 4.5 prior therapies including lenalidomide, thalidomide, and/or bortezomib. To further evaluate the association between NK cell status and the efficacy of Elotuzumab monotherapy, a Phase II biomarker study (Study CA204011) is currently ongoing in patients with high-risk smoldering MM.

1.3.1 Combination studies of Lenalidomide and Elotuzumab

Lenalidomide is an oral IMiD that has been shown to directly kill MM cells, stimulate T cells to produce IL-2, increase NK cell proliferation, and lower the threshold required for NK cell activation.[27,28] Based on data of several Phase III trials, lenalidomide in combination with low-dose dexamethasone (L/d) was approved for treatment of newly diagnosed MM patients ineligible for stem cell transplantation[29] and of patients with relapsed MM who have received at least one prior therapy.[30,31] A meta-analysis of randomized controlled trials confirmed the survival advantage of treatment with L/d compared with other first-line therapies in patients with previously untreated MM.[32]

The triple combination therapy of Elotuzumab, lenalidomide, and dexamethasone (E–L/d) was evaluated in a Phase I/II dose escalation study (Study 1703) and two large Phase III studies (ELOQUENT-1 and -2) in patients with newly diagnosed MM and RRMM, respectively. While ELOQUENT-1 is still ongoing with first results to be expected in 2017, data of ELOQUENT-2 are already available showing substantial evidence of effectiveness for E–L/d in the treatment of patients with RRMM who have received one to three prior therapies.

In this study, a total of 646 patients were enrolled (321 in the E–L/d arm and 325 in the L/d arm). Efficacy results of 635 treated patients showed a significant increase in tumor response of 78.5% versus 65.5% and median progression-free survival (mPFS) of 19.4 versus 14.9 months of E–L/d over L/d, respectively[33]. Based on data of a 3year follow-up analysis, the progression-free survival (PFS) benefit of patients on E–L/d was maintained during this period. Exploratory analysis revealed a median delay of 1 year in the time to next treatment in patients treated with E–L/d compared with L/d-treated patients (33 months on E–L/d vs 21 months on L/d). Preliminary analysis of overall survival (OS) also indicated an advantage for patients treated with E–L/d.[34] Of note, the benefit in PFS and OS of patients on E–L/d was observed for all patient subgroups independent of age, disease stage, response to most recent line of therapy, number and nature of prior therapies, as well as high-risk cytogenetic profile.[33,34]

Based on the Phase III efficacy data and the observed adverse events (AEs) (see “Safety of Elotuzumab treatment”), both the FDA and the EMA approved Elotuzumab in combination with lenalidomide at 25 mg days 121 and dexamethasone for the treatment of patients with RRMM.

Safety and tolerability data showed that minimal incremental toxicity was associated with addition of Elotuzumab to L/d. Significant differences in grade 3/4 AEs were observed for lymphopenia (78% on E–L/d vs 49% on L/d) and neutropenia (35% on E–L/d vs 44% on L/d). The rates for other grade 3/4 AEs including anemia, thrombocytopenia, cardiac or renal disorders were similar between the treatment groups. Infections (any grade) were reported in 83% of patients in the Elotuzumab group versus 75% in the control group. After adjustment for drug exposure, infection rates were equal in the two groups (196 and 193 events per 100 patient-years on E–L/d and L/d, respectively).[35] The incidence of herpes zoster infections was 4.1 versus 2.2 per 100 patient-years, respectively. Despite the finding of increased lymphopenia which may reflect alterations in lymphocyte trafficking, there was no evidence of

increased autoimmunity or other sequelae of immune dysregulation.[33] This confirmed previous results in whole blood samples from healthy individuals tested for the effects of Elotuzumab on the numbers of T, NK, and B cells. Elotuzumab treatment did not result in substantial depletion of major lymphocyte subsets.[36]

Infusion reactions (mostly grade 1/2) occurred in only 11% of patients treated with E–L/d[35] and usually presented as pyrexia, chills, headache, flushing, and/or hypertension. Most infusion reactions were observed during the first dose of Elotuzumab. They were usually mild to moderate and resolved spontaneously within 24 hours or after management as clinically indicated. No patient experienced grade 4–5 reactions, and all but two patients could continue Elotuzumab treatment.[33]

Furthermore, second primary malignancies were observed in 7% of patients on E–L/d compared with 4% on L/d. However, after adjustment for exposure to study therapy, the incidence rates were similar at 3.5 and 2.8 second primary cancers per 100 patient-years, respectively.[33]

In Study CA204-112 (NCT02159365), treatment of Elotuzumab administered over ~1 hour in combination with L/d was evaluated in 70 patients with newly diagnosed or relapsed/refractory MM.[37,38] All patients were required to have a premedication regimen before each dose of Elotuzumab. The infusion rate was accelerated from 0.5 to 5 mL/min at the start of the third dose in treatment cycle 1. At data cutoff, infusion reactions were observed in only two patients. The reactions were of grade 1/2 intensity and both patients continued treatment with Elotuzumab. No grade 3/4 infusion reactions had occurred by the end of treatment cycle 2. The administration of Elotuzumab at a faster rate may provide a safe option to reduce treatment time for patients.

2 Study objectives

2.1 Primary Objective

- Progression free survival with Elotuzumab plus lenalidomide when Elotuzumab is added to multiple myeloma patients with serologic relapse/progression while receiving lenalidomide maintenance for each cohort

2.2 Secondary Objectives

- Overall response rate (ORR) with Elotuzumab and lenalidomide for each cohort
- Minimum response (MR) or better rate with Elotuzumab and lenalidomide for each cohort
- Time to next treatment (TTNT) for each cohort
- Comparison of clinical outcomes (cohort A versus B)
- Fcγ RIIIa receptor polymorphisms (homozygous for high-affinity V (VV) allele vs. low affinity F (FF) allele)
- Effect of Elotuzumab added to lenalidomide on phenotypic characteristics of the immune infiltrate and correlation with therapeutic efficacy

3 Overall study design

Randomized parallel 2-cohort phase 2 study of Elotuzumab given at 10 mg/kg weekly during induction in combination with lenalidomide (either 25 mg or 10 mg) in patients with multiple myeloma who progress or relapse serologically while on single agent lenalidomide maintenance. Patients will be randomized to either (1) cohort A = lenalidomide 25 mg PO daily days 1-21 or (2) cohort B = lenalidomide 10 mg PO daily days 1-21 with Elotuzumab. We selected the dose of Elotuzumab at 10 mg/kg weekly dosing followed by monthly infusion of 20 mg/kg based on the safety and tolerability profile in the published phase 3 study and other studies of combination therapy with

bortezomib,[1-3] as well as an ongoing study in combination with pomalidomide (NCT02612779). Elotuzumab will be administered intravenously on days 1, 8, 15, and 22 during the first 2 cycles, then on day 1 of each cycle staring third cycle. The combination therapy with Elotuzumab and lenalidomide will be continued until further progression of myeloma (based on response criteria) or intolerability.

A total of 60 eligible patients will be randomized into one of two study arms in 1:1 ratio. Stratification factors are risk (standard vs. high) and lenalidomide maintenance post-transplant (yes vs. no). A permuted-block randomization will be applied to ensure a balanced assignment to each treatment arm. Randomization will be accomplished using the Moffitt Cancer Center web-based Subject Registration and Randomization System (SRAR). The SRAR program is accessed using an individual secure identification key that authenticates the user into the Moffitt network.

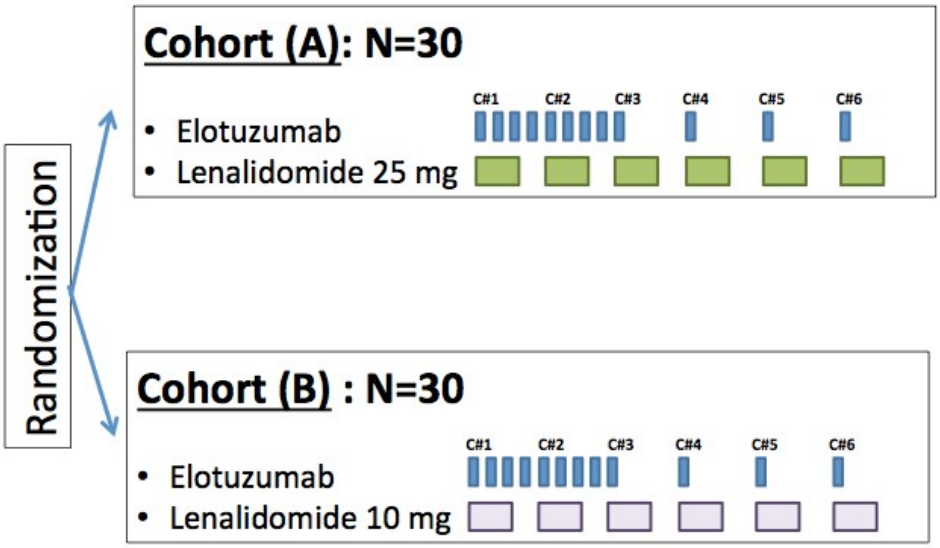
Combination dosing schedule:

(1) Cohort A:

- Elotuzumab 10 mg/kg IV weekly (days 1, 8, 15 and 22) for 2 cycles, then 20 mg/kg every 4 weeks
- Lenalidomide 25 mg PO daily days 1-21 out of a 28-day schedule

(2) Cohort B:

- Elotuzumab 10 mg/kg IV weekly (days 1, 8, 15 and 22) for 2 cycles, then 20 mg/kg every 4 weeks
- Lenalidomide 10 mg PO daily days 1-21 out of a 28-day schedule



Response assessment:

The Consensus on Uniform Reporting of Response will be used to evaluate response.[4] Myeloma patients enrolled in this clinical study will be assessed for disease response after every cycle. Time to disease progression will be defined as the time from the day first Elotuzumab treatment to the time of myeloma progression.

4 Study population

Patients with multiple myeloma who demonstrate evidence of serologic relapse/progression while on lenalidomide maintenance given as part of **first** line therapy (including upfront high-dose chemotherapy followed by autologous hematopoietic cell transplantation (HCT)) without symptomatic relapse/progression. Lenalidomide maintenance is defined as **single agent** lenalidomide therapy of any doses up to 15 mg PO daily for up to 28 days (28-day cycle. Relapse/progression is defined as increase of 25% from the lowest response value (for either serum or urine M-spikes), absolute increase in serum M-spike ≥ 0.5 g/dL, absolute increase in urine M-spike ≥ 200 mg/24hour, or the difference between involved and uninvolved free light chain (FLC) levels of absolute increase with > 10 mg/dl (only for those without measurable serum and urine M-spikes) There will be 30 subjects in each cohort for total accrual of 60 subjects.

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. Results of all baseline evaluations, which assure that all inclusion and exclusion criteria have been satisfied, must be reviewed by the Principal Investigator or Co-investigators prior to enrollment of that patient. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to enrollment. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

4.1 Inclusion criteria

1. Patients with multiple myeloma who demonstrate evidence of serologic relapse/progression while on lenalidomide maintenance given as part of **first** line therapy (including upfront high-dose chemotherapy followed by autologous hematopoietic cell transplantation (HCT)) without symptomatic relapse/progression.

   Lenalidomide maintenance is defined as **single agent** lenalidomide therapy of any doses up to 15 mg PO daily for 14-28 days (28-day cycle). Relapse/progression is defined as increase of 25% from lowest confirmed response value in one or more of the following criteria: Serum M –protein (absolute increase must be > 0.5g/dl)

   Serum M-protein increase >1g/dl, if the lowest M component was >5 g/dl

   Urine M –protein (absolute increase must be > 200 mg in 24 hours)

   In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dl)

   For patients relapsing from complete remission, relapse is defined as:

   Reappearance of serum or serum M-protein by immunofixation or electrophoresis.

2. Male or female patients aged ≥ 18 years old

3. Ability to provide written informed consent obtained prior to participation in the study and any related procedures being performed

4. Measurable disease with at least 1 of the following assessed within 28 days prior to Cycle 1 Day 1:

A. Serum M-protein ≥ 0.5 g/dL,

B. Urine M-protein ≥ 200 mg/24 hour,

C. In subjects without measurable serum or urine M-protein, serum free light chain (SFLC) > 10 mg/dL (involved light chain) and an abnormal serum kappa lambda ratio

5. Patients must meet the following laboratory criteria within 28 days prior to Cycle 1, day 1:

- Absolute neutrophil count (ANC) ≥ 1 x 10^9/L
- Hemoglobin ≥ 10 g/dl
- Platelet count ≥ 75,000/mm3
- AST and ALT ≤ 2.5 x ULN
- Serum bilirubin ≤ 1.5 x ULN
- Serum Creatinine clearance ≥ 50ml/min

4.2 Exclusion criteria

1. Prior Elotuzumab
2. Patients with clinical relapse/progression as per the IMWG uniform criteria defined as one or more of the following criteria:

A. Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression)

B. 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 of the measurable lesion

C. Hypercalcemia (>11 mg/dL);

D. Decrease in hemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions;

E. Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma

F. Hyperviscosity related to serum paraprotein

3. Women who are pregnant or breast feeding or women of childbearing potential (WOCBP) not using an effective method of birth control. WOCBP are defined as sexually mature women who have not undergone a hysterectomy or who have not been naturally postmenopausal for at least 12 consecutive months (i.e., who has had menses any time in the preceding 12 consecutive months). Women of childbearing potential must have a negative serum pregnancy testing within 7 days prior to the administration of drug.

4. Male patients whose sexual partners are WOCBP not using effective birth control

5. Patients with a prior malignancy with in the last 5 years (except for skin basal or squamous cell carcinoma, or *in situ* cancer of the cervix)

6. Patients with known positivity for human immunodeficiency virus (HIV)) or hepatitis C; baseline testing for HIV and hepatitis C is not required

7. Patients with a diagnosis of POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes) or plasma cell leukemia (> 2.0 × 109/L circulating plasma cells by standard differential)

5 Treatments

5.1 Investigational therapy

Elotuzumab will be provided by BMS as investigational product. Elotuzumab (BMS-901608, also known as HuLuc63) is an immune-stimulatory humanized, IgG1 monoclonal antibody (mAb) targeted against signaling lymphocyte activation molecule family 7 (SLAMF7), a glycoprotein expressed on myeloma and natural killer (NK) cells. EMPLICITI™ (Elotuzumab) is commercially available and is indicated in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies. All precautions and restrictions included in the Prescribing Information (e.g., pregnancy testing and contraception) must be observed when dispensing and administering lenalidomide as part of this protocol During the study, Elotuzumab will be administered in combination with lenalidomide at a dose of 10 mg/kg administered intravenously every week for the first two cycles and at a dose of 20 mg/kg monthly thereafter until disease progression or unacceptable toxicity.

Product Description / Class and Dosage Form	Potency	IMP/NonIMP	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Elotuzumab Powder for Solution for Infusion	400 or 300 mg/vial	IMP	Open Label	Vial	*Refer to the label on container*

Lenalidomide is a thalidomide analogue indicated for the treatment of subjects with multiple myeloma, in combination with dexamethasone, in subjects who have received at least 1 prior therapy.

Lenalidomide is a commercially available drug, available for oral administration, depending upon local health authority approvals (Celgene Corporation 2013).

All precautions and restrictions included in the Prescribing Information (e.g., pregnancy testing and contraception) must be observed when dispensing and administering lenalidomide as part of this protocol.

During the study lenalidomide will be administered at 10 or 25 mg PO daily days 1-21 of 28 days cycles until disease progression or discontinuation.

Dexamethasone is a commercially available drug. The description, how supplied, and storage instructions for dexamethasone product are found in the prescribing information.

During the study dexamethasone will be administered as premedication for Elotuzumab as indicated in the package insert.

Treatment assignment

Patients will be randomized to either (1) cohort A = lenalidomide 25 mg PO daily days 1-21 or (2) cohort B = lenalidomide 10 mg PO daily days 1-21 with Elotuzumab.

5.2 Treatment cycle and duration

Treatment cycles will have a duration of 28 days and subjects will receive Elotuzumab on days 1,8,15, and 22 of cycles 1-2 and on day 1 on cycle 3 and beyond, in combination with lenalidomide at either 25 mg (cohort A) or 10 mg (cohort B) on days 1-21. All cycles will start 28 days (± 3) after the start of the prior cycle.

Subjects will continue therapy until one of the following:

1. Disease progression
2. Withdrawal from the study for any reason
3. Death

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5.3 Study Treatment Administration

Cycles 1-2

Elotuzumab/lenalidomide will be given in 28-day cycles:

·Elotuzumab will be administered at a dose of 10 mg/kg weekly IV on Days 1, 8, 15, and 22

·Lenalidomide will be administered at a dose of 25(cohort A) or 10 mg (cohort B) once-daily by mouth on Days 1–21

Day	1	8	15	22	28
Elotuzumab	X	X	X	X	
Lenalidomide					

Cycles 3 and beyond

Elotuzumab/lenalidomide will be given in 28-day cycles:

·Elotuzumab will be administered at a dose of 20 mg/kg monthly IV on Days 1

·Lenalidomide will be administered at a dose of 25(cohort A) or 10 mg (cohort B) once-daily by mouth on Days 1–21

Days	1	8	15	22	28
Elotuzumab	X				
Lenalidomide					

Based on the emerging data on accelerated infusion, the infusion rate of Elotuzumab will be at 0.5 mL/min for the first 30 minutes, 1 mL/min from 30 to 60 minutes, then 2 mL/min from 60 minutes and beyond on cycle 1 day 1. On cycle 1 day 8, infusion rate will be 3 mL/min for the first 30 minutes, then 4 mL/min from 30 minutes and beyond. Infusion rate will be 5 mL/min from cycle 1 day 15 and after. All patients will receive pre-medication with antihistamine (25 – 50 mg of diphenhydramine PO or IV), H2 blocker (such as ranitidine 50 mg IV or 150 mg PO or equivalent) and acetaminophen (650 – 1000 mg) PO for potential infusion reactions. As part of pre-medication, dexamethasone 28 mg PO will be given between 3 and 24 hours before Elotuzumab and 8 mg IV between 45 and 90 minutes before Elotuzumab as prescribed in the package insert.

5.4 Elotuzumab

Elotuzumab will be administered intravenously on days 1, 8, 15, and 22 during the first 2 cycles, then on day 1 of each cycle staring third cycle. Based on the emerging data on accelerated infusion, the infusion rate of Elotuzumab will be at 0.5 mL/min for the first 30 minutes, 1 mL/min from 30 to 60 minutes, then 2 mL/min from 60 minutes and beyond on cycle 1 day 1. On cycle 1 day 8, infusion rate will be 3 mL/min for the first 30 minutes, then 4 mL/min from 30 minutes and beyond. Infusion rate will be 5 mL/min from cycle 1 day 15 and after. All patients will receive pre-medication with antihistamine (25 – 50 mg of diphenhydramine PO or IV), H2 blocker (such as ranitidine 50 mg IV or 150 mg PO or equivalent) and acetaminophen (650 – 1000 mg) PO for potential infusion reactions. As part of pre-medication, dexamethasone 28 mg PO will be given between 3 and 24 hours before Elotuzumab and 8 mg IV between 45 and 90 minutes before Elotuzumab as prescribed in the package insert.

5.5 Lenalidomide

Lenalidomide will be taken once-daily by mouth days 1-21 of each cycle at 25 or 10 mg daily depending on the treatment cohort to whom the subject is randomized to, with or without food. Lenalidomide capsules should be swallowed whole with water. The capsules should not be opened, broken, or chewed. Subjects will be instructed to take the lenalidomide dose at approximately the same time every day. If a planned administration of lenalidomide is missed, it should be taken as soon as possible within the same calendar day with a return to schedule the following day. If a calendar day of dosing is missed, subjects should not make up doses, but should resume the dosing regimen on schedule with the next course. Missed doses must be reported.

For female subjects of childbearing potential, non-pregnant state must be documented prior to the first dose of lenalidomide, and prior to the start of each subsequent cycle.

5.6 Interruption or discontinuation of treatment

For patients who are unable to tolerate the protocol-specified dosing schedule, dose adjustments are permitted in order to keep the patient on study drug. Toxicity will be assessed using the NIH-NCI Common Terminology Criteria for Adverse Events, version 5.0 (CTCAEv5.0), (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev5.pdf)). All interruption or changes to study drug administration must be recorded.

5.7 Dose modifications for Elotuzumab

If a Grade 2 or higher infusion reaction occurs during Elotuzumab administration, interrupt the infusion and institute appropriate medical and supportive measures. Upon resolution to Grade 1 or lower, restart EMPLICITI at 0.5 mL per minute and gradually increase at a rate of 0.5 mL per minute every 30 minutes as tolerated to the rate at which the infusion reaction occurred. Resume the escalation regimen if there is no recurrence of the infusion reaction. In patients who experience an infusion reaction, monitor vital signs every 30 minutes for 2 hours after the end of the Elotuzumab infusion. If the infusion reaction recurs, stop the infusion and do not restart on that day. Severe infusion reactions may require permanent discontinuation of Elotuzumab therapy and emergency treatment.

5.8 Dose modifications for lenalidomide-related toxicity

Dose reduction levels for lenalidomide for toxicity management of individual subjects are provided in Table 6:

Table 6 Dose Decrements for Lenalidomide

Nominal Dose (mg)	**Reduced Lenalidomide Doses (mg)**		
	Dose -1	**Dose -2**	**Dose -3**
25	15	10	5
10	5	Discontinue	—

Treatment guidelines for specific hematologic toxicities and nonhematologic toxicities are outlined below. In addition to dose reductions, administration of lenalidomide may be held temporarily in the event of a treatment related toxicity at the investigator's discretion.

If the lenalidomide dose is reduced during a given cycle, the reduced dose level will be continued for the next cycle. If the reduced dose level is tolerated for a complete cycle, the subject may, at the investigator's discretion, resume the dose level prior to the reduction at the start of the subsequent cycle.

Lenalidomide can be discontinued in the event of a treatment-related toxicity that, in the opinion of the investigator, warrants discontinuation. The subject will be considered still on protocol treatment as long as Elotuzumab is being administered.

5.8.1	**When platelets**	**5.8.2**	**Lenalidomide**
5.8.3	Fall to < 30 × 10^9/L	5.8.4	Hold dose, hold anticoagulation follow CBC weekly, resume at 1 dose decrement after platelets returned to > 30 X10^9/L
5.8.5	**When ANC**		
5.8.6	Falls to < 0.75 × 10^9 /L		Hold dose, administer myeloid growth factor Follow CBC weekly Resume at full dose when ANC ≥ 0.75 × 10^9 /L
5.8.7	For each subsequent drop to < 0.75 × 10^9 /L		Hold dose, administer myeloid growth factor Follow CBC weekly Resume at 1 dose decrement when ANC ≥ 0.75 × 10^9 /L
5.8.8	**Any other drug-related nonhematologic toxicity ≥ Grade 3**	5.8.9	For lenalidomide attribution, hold dose.
		5.8.10	Resume at 1 dose decrement when toxicity has resolved to Grade 2 or less or to baseline grade.

5.9 Study drug discontinuation

It will be documented whether or not each patient completed the clinical study. If for any patient either study treatment or observations were discontinued, the reason will be recorded.

Reasons that a patient may discontinue treatment are considered to constitute one of the following:

1. Subject's condition no longer requires study treatment (e.g. satisfactory therapeutic response)
2. Clinical relapse/progression as per the IMWG uniform criteria defined as one or more of the following criteria:
   a. Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression)
   b. 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 of the measurable lesion
   c. Hypercalcemia (>11 mg/dL);
   d. Decrease in hemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions;
   e. Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma
   f. Hyperviscosity related to serum paraprotein
   g. Adverse event(s)
   h. Abnormal laboratory value(s)

i. Abnormal test procedure result(s)
j. Protocol violation
k. Subject withdrew consent
l. Lost to follow-up
m. Administrative problems
n. New cancer therapy
o. Death

5.9.1.1 Follow-up for toxicities

Patients whose treatment is interrupted or permanently discontinued due to an adverse event or abnormal laboratory value must be followed until resolution or stabilization of the event, whichever comes first.

If a patient requires a dose delay of > 21 days from the intended day of the next scheduled dose, then the patient must be discontinued from the study. If however the patient was clearly benefiting from therapy, the patient may be able to continue treatment with either a 5 mg or 10 mg dose reduction at the Investigator discretion, after resolution of the adverse event. All patients will be followed for adverse events and serious adverse events for at least 4 weeks following the last dose of study treatment.

5.10 Other concomitant medications

Patients must be instructed not to take any additional medications (including over-the-counter products) during the trial without prior consultation with the investigator. All medications taken within 30 days of screening should be recorded. If concomitant therapy must be added or changed, the reason and name of the drug/therapy should be recorded.

In general, the use of any concomitant medication/therapies deemed necessary for the care of the patient are allowed, including drugs given prophylactically (e.g. antiemetics) with the following exceptions:

- No other investigational therapy should be given to patients
- No anticancer agents other than the study medications administered as part of this study protocol should be given to patients. If such agents are required for a patient then the patient must first be withdrawn from the study.
- Leukocyte growth factors (e.g. G-CSF and GM-CSF) are not to be administered systematically but may be prescribed by the investigator for severe neutropenia if this is thought to be appropriate.
- Bisphosphonates are allowed.

5.10.1.1 Required Concomitant medications

Pre-medications on days that Elotuzumab is administered

Dexamethasone- 28 mg PO 3-24 hours prior to Elotuzumab dose

Dexamethasone 8 mg IV 45-90 min prior to Elotuzumab dose

H_1blocker; diphenhydramine (25-50 mg PO/IV) 45-90 min prior to Elotuzumab dose

H_2blocker; Ranitidine or equivalent H2 blocker (50 mg IV or 150 mg PO), 45-90 min prior to Elotuzumab dose

Acetaminophen 650-1000 mg PO 45-90 min prior to Elotuzumab dose

Anticoagulant Prophylaxis

Aspirin (or other anticoagulant or antiplatelet medication such as clopidogrel bisulfate, low-molecular-weight heparin, or warfarin or factor X inhibitors), is a required concomitant medication while taking lenalidomide. In subjects with a prior history of deep vein thrombosis, low-molecular-weight heparin or therapeutic doses of warfarin (for a target international normalized ratio of 2–3) are required. Enteric-coated aspirin once-daily by mouth at the standard prophylactic dose should be administered for the duration of treatment with lenalidomide. Subjects with known high thrombotic risk, e.g., prior deep vein thrombosis, should receive full anticoagulation at the investigator's discretion

Contraception

Females of childbearing potential (FCBP) must:

·Avoid pregnancy for at least 4 weeks before beginning lenalidomide

·Have a negative pregnancy tests within 7 days prior to starting treatment, and each subsequent cycle.

·Pregnancy tests monthly during treatment after the first month or semimonthly for women of childbearing potential with irregular menstruation

·Agree to abstain from heterosexual sexual intercourse or to use 2 methods of effective contraception beginning 4 weeks prior to initiating treatment with lenalidomide, during therapy, during dose interruptions and for 3 months following last dose of drug (more frequent pregnancy tests may be conducted if required per local regulations) An FCBP is defined as a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy, or 2) has not been naturally postmenopausal for at least

24 consecutive months (i.e., no menses at any time in the preceding 24 consecutive months). Amenorrhea following cancer therapy does not rule out childbearing potential.

Male subjects and their partners must use 1 highly effective method of birth control plus 1 additional effective method of birth control (contraception) at the SAME TIME during treatment and for 3 months following the last dose of drug, even if they have undergone a successful vasectomy. Male subjects must not donate sperm while taking lenalidomide and for 28 days after stopping lenalidomide.

Highly effective methods of contraception include:

·Intrauterine device (IUD)

·Hormonal therapy (birth control pills, injections, implants)

·Tubal ligation

·Vasectomy

Additional effective methods include:

·Latex condom

·Diaphragm

·Cervical Cap

5.11 Treatment compliance

Records of study medication used, dosages administered, and intervals between visits will be recorded during the study.

6 Visit schedule and assessments

6.1 Visit schedule

Table 6-1 Evaluation and visit schedule

Assessment	Screening 0-28 days	Day 1 Cycles 1-2	Day 8	Day 15	Day 22	Day 1 Cycle 3 - beyond	End of Study
Assessment	Screening 0-28 days	Day 1 Cycle 1&2 +/-3 days	Day 8	Day 15	Day 22	Day 1 C3-beyond +/- 3 days	End Of Study
Informed Consent	X						
Inclusion/exclusion criteria	X						
Vital signs, Physical examination and ECOG Performance Score[6]	X	X				X	X
Concomitant medications[6]	X	X				X	X
CBC + diff[6]	X	X	X	X	X	X	X
CMP[6] ,Pregnancy Test[6]	X	X	X	X	X	X	X
SPEP/UPEP[8]/immunofixation	X	X				X	X
Serum free light chains	X	X				X	X
Quantitative immunoglobulins	X	X				X	X
Skeletal survey[3]	X					X[3]	X[3]
Bone marrow asp and bx with Cytogenetics, MM Fish Panel Lab correlative studies[1]	X[1]	X[1]					X[1]
MRD Testing	X[2]						
Response Assessment	n/a					X[4]	X
Study Drug Diaries	n/a	X				X[5]	

Adverse Events[7]	n/a	X	X	X		X	X

1. Bone marrow aspirate and biopsy will be done at screening and on cycle 2 day 1, and to confirm CR after 4 cycles, 8 cycles and as indicated and at time of PD for lab correlative studies as outlined in page 26. In parallel a peripheral blood sample will be collected for lab correlative studies at same time points and on day 1 of each cycle. Bone marrow aspirates (30mL volume) for correlative studies will be collected at baseline, Cycle 2 day 1, and thereafter for confirmation of CR, and at time of disease progression to analyze marrow-infiltrating immune populations by MPFC. In parallel, PBMCs, isolated from 20-30mL freshly drawn sample, will be analyzed similarly at 4-week intervals corresponding to Day 1 of each cycle as well as at time of progression.
2. MRD testing will be performed at screening, by flow cytometry and NSG on patients and as indicated on patients in hematologic complete remission. An aliquot of serum will be stored for those patients with IgGk MM who achieved VGPR to evaluate extent of interference by the antibody therapy.
3. Bone survey will be done at screening and once yearly or when clinically indicated. May be substituted by PET scan or MRI as clinically indicated
4. Response assessment will be done every 2 cycles.
5. Study drug diaries will be collected after each cycle
6. Will only capture in CRF if related to adverse event.
7. All females of childbearing potential should complete a serum pregnancy test within 7 days prior to the administration of Elotuzumab and lenalidomide on day 1 of cycle 1. The pregnancy test should be repeated in week 1 of every cycle (except for cycle 1). Postmenopausal women must have been amenorrheic for ≥ 12 months in order to be considered "of non-childbearing potential".
8. Only grade > 2 adverse events possibly related to study drug will be captured in CRF
9. For patients with urine M spike of less than 200 mg/24 hours at screening, 24-hour urine collection with UPEP will be done every other cycle)

6.2 Efficacy assessments

Response will be determined by the investigator based on the disease assessments described above and the IMWG-URC (see definitions in Appendix B). Myeloma response will be assessed at the beginning of each cycle.

The following confirmatory assessments are required for all response categories (stringent complete response [sCR], CR, VGPR, and PR) and progressive disease:

·All laboratory-based progressive disease and all responses require 2 consecutive assessments made at any time before initiation of any new therapy. Confirmatory lab samples should be separated by at least 1 calendar day

·Progressive disease by nonlaboratory-based assessment (i.e.; plasmacytoma or skeletal lesion) does not require confirmatory report

·All response categories also require no evidence of progression including new bone lesions if radiographic studies were performed

·Confirmation of CR or sCR requires bone marrow biopsy or aspirate slides (a confirmatory bone marrow sample is not required)

·Extramedullary plasmacytoma evaluation (if present at baseline)

6.3 Safety assessments

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry, vital signs, ECOG performance status, and the regular physical examinations .

Adverse events will be assessed according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 5.0. This can be accessed on the NIH/NCI website at: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev5.pdf))

6.3.1 Adverse events

Information about all adverse events, whether volunteered by the subject, discovered by investigator questioning, or detected through physical examination, laboratory test or other means, will be collected and recorded and followed as appropriate. Adverse events will be collected from cycle 1, day 1, and while the patients are on study treatment only.

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to study drug. Medical conditions/diseases present before starting study drug are only considered adverse events if they worsen after starting study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments. As far as possible, each adverse event should be evaluated to determine:

1. the severity grade (mild, moderate, severe) or (grade 1-4)
2. its relationship to the study drug(s) (suspected/not suspected)
3. its duration (start and end dates or if continuing at final exam)
4. action taken (no action taken; study drug dosage adjusted/temporarily interrupted; study drug permanently discontinued due to this adverse event; concomitant medication taken; non-drug therapy given; hospitalization/prolonged hospitalization)
5. whether it constitutes a serious adverse event (SAE)

All adverse events should be treated appropriately. Such treatment may include changes in study drug treatment including possible interruption or discontinuation, starting or stopping concomitant treatments, changes in the frequency or nature of assessments, hospitalization, or any other medically required intervention. Once an adverse event is detected, it should be followed until its resolution, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the [Investigators' Brochure] or will be communicated between IB updates in the form of Investigator Notifications. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

Only grade > 2 adverse events possibly related to study drug will be captured in CRF Adverse

events will NOT be collected under following circumstances:

1. Grade 1 unrelated adverse events

2. During screening phase or before cycle 1, day 1 of treatment

6.3.2 Vital signs

Vital sign assessment consists of height (first visit), pulse, blood pressure, respiration rate, temperature and weight.

6.3.3 Physical examination

Physical examination will be performed which must comprise a total body examination.

Significant findings made after the start of study drug which meet the definition of an Adverse Event must be recorded.

6.3.4 Laboratory evaluations

Laboratory evaluation should be done at screening (within 28 days of cycle 1, day 1), and on day 1 of each treatment cycle. Results must be reviewed prior to administering Elotuzumab. More frequent examinations may be performed if medically indicated; results should be recorded.

Hematology

Hematology must include hemoglobin, hematocrit, platelets, total white blood cell count (WBC) and differential.

Blood chemistry

Biochemistry includes the following parameters: BUN, creatinine, sodium, potassium, chloride, CO_2 (HCO_3), glucose, calcium, albumin, total protein, total bilirubin, alkaline phosphatase, AST/SGOT, ALT/SGPT. If total bilirubin is greater than the upper limit of normal, direct and indirect bilirubin should be performed.

Serum pregnancy test

All females of childbearing potential should complete a serum pregnancy test within 7 days prior to the administration of Elotuzumab and lenalidomide on day 1 of cycle 1. The pregnancy test should be repeated in week 1 of every cycle (except for cycle 1). Postmenopausal women must have been amenorrheic for ≥ 12 months in order to be considered “of non-childbearing potential”.

Performance status

Performance status will be assessed by ECOG performance status scale.

6.4 Disease assessments

Disease assessments will be performed at Screening (within 28 days before dosing on Cycle 1 Day 1) and at Day 1 of each treatment cycle.

Disease assessments at Screening (within 28 days before dosing on Cycle 1 Day 1) include the following:

·Serum protein electrophoresis (SPEP), urine protein electrophoresis

(UPEP; 24-hour assessment, no substitute method is acceptable), and immunofixation

·SFLC

·Quantitative immunoglobulins

·Skeletal bone survey

Disease assessments at Day 1 of Cycle 2, and each cycle thereafter, and at the EOT include the following:

·Serum protein electrophoresis (SPEP), urine protein electrophoresis

(UPEP; 24-hour assessment, no substitute method is acceptable. For patients with urine M spike of less than 200 mg/24 hours at screening, 24 hour urine collection with UPEP will be done every other cycle), and immunofixation

·SFLC

·Quantitative immunoglobulins

The following disease assessments will be performed post baseline as noted below:

·Bone marrow sample – On cycle 2 day 1 for lab correlative studies, then only required to confirm a complete response (CR) and at time of clinical relapse

Serum protein electrophoresis, UPEP, SFLC, and quantitative immunoglobulin analyses will be performed at the local laboratory.

6.5 MRD Testing and Lab correlatives (see study calendar)

Analysis of MRD status will be performed on all subjects by 2 methods:

1. Flow cytometry (FC) of cell surface markers and

2. Next Generation Sequencing (NGS) of DNA and/or RNA from the Ig locus.

The MRD analysis by FC will be performed on bone marrow aspirate samples collected at 2 time points: At screening and/or upon achieving a hematologic CR.

3. Identify phenotypic characteristics of the immune infiltrate that predict therapeutic efficacy of Elotuzumab and correlate with survival outcomes in MM care.

Predictive modeling of therapeutic efficacy in an era of immunotherapy must necessarily include parameters derived from immunologic aspects of the tumor microenvironment. The anti-myeloma immune response evolves in conjunction with the progression of disease[25-28] while simple, distinctive patterns identified in the infiltrating immune population can hold prognostic relevance[29,30]. Similarly, characterization of distinct phenotypic changes in peripheral blood lymphocytes (PBL) in high-risk smoldering MM patients exposed a pattern indicative of T cell dysfunction that was reversed with exposure to lenalidomide[28]. In-depth characterization of lymphocytic and myeloid populations infiltrating the marrow of MM patients, monitoring changes in recruitment, phenotype and function of critical effector/regulatory populations, should identify critical queues that will inform clinical decisions to guide optimization of delivery of Elotuzumab in terms of timing and sequencing with ideal therapeutic partners such as IMiDs and checkpoint inhibitors. Furthermore, this signature should be detectable in circulating PBL using enhanced multiparameter flow cytometry (MPFC).

Table 1. MPFC Lymphocyte Analysis Parameters

CD3, CD4, CD8, CD56, Viability			
CD25 (IL-2Rα) CD27 CD45RA CD194 (CCR4) CD195 (CCR5) CD197 (CCR7) CD95 (Fas) CD127 (IL-7Rα) CD94 (NKG2D)	CD25 (IL-2Rα) CD45RA CD194 (CCR4) IFN-γ IL-4 IL-17A FoxP3	CD152 (CTLA-4) CD279 (PD-1) CD223 (Lag-3) CD366 (Tim-3) CD244 (2B4) CD272 (BTLA) CD226 (DNAM-1) TIGIT	Proliferation (CTV) IFN-γ TNF-α Granzyme B
Maturation	Lymphocyte Subset	Exhaustion	Stimulation

We have developed an approach to define these immunologic populations in much greater detail using MPFC. Leukocytes will be isolated from bone marrow aspirates by Ficoll-Hypaque gradient centrifugation after prior extraction of MM cells by CD138 positive magnetic bead selection. In parallel, leukocytes will be isolated in similar fashion from peripheral blood samples from each patient. After adequate viability is determined (>85% viable by trypan blue exclusion), leukocyte cell fractions from each patient sample, will be prepared according to three defined analysis panels (see **Table 1**) to characterize *(a)* maturation state, *(b)* subset composition (e.g. T_H1, T_H2, T_H17, T_{REG}, and $CD8^+$ counterpart populations, as well as NK and NKT cells), and *(c)* exhaustion status. In addition, lymphocyte stimulatory capacity, measured in terms of proliferative capacity and effector cytokine production (i.e. IFN-γ TNF-α and

Granzyme B) will be assessed as a benchmark of immune function. In brief, $CD3^+$ T cells will be isolated from the leukocyte fraction of each sample by magnetic bead selection

(Miltenyi Biotech) to achieve approximately 99% purity. Cells stained with a panel of fluorescently conjugated antibodies for assessment of cell

Table 2. Myeloid Characterization by MPFC.

Myeloid Panel	
CD11b	CD38
CD13	CD71
CD14	CD45
CD15	CD64
CD16	CD80
CD33	CD163
CD34	CD124
CD117	Viability/CD3
HLA-DR	

myeloid compartment will be monitored using a 14-parameter panel designed to detect dendritic cell, myeloid suppressor cell, and macrophage populations, as detailed in Table 2. Immunophenotypic profiles will be discerned from sequential analysis of the individual patient samples at defined intervals Bone marrow aspirates (30mL volume) will be collected at baseline, Cycle 2 day 1, and thereafter for confirmation of CR, and at time of disease progression to analyze marrow-infiltrating immune populations by MPFC. In parallel, PBMCs, isolated from 20-30mL freshly drawn sample, will be analyzed similarly at 4-week intervals corresponding to Day 1 of each cycle as well as at time of progression.

7 **Statistical Methods**

Phase II study

In a randomized phase 2 study of lenalidomide single agent therapy (either 30 mg daily or 15 mg PO daily days 1-21 out of 28-day cycle) in relapsed/refractory myeloma where dexamethasone was added after 2 cycles if progressive or stable disease, median PFS was 7.7 months with once-daily lenalidomide (compared to 3.9 months with twice daily lenalidomide).[24] In a phase 3 study, a combination of Elotuzumab/lenalidomide/dexamethasone vs. lenalidomide/dexamethasone in relapsed/refractory myeloma showed PFS of 19.4 months vs. 14.9 months (with 5 months benefit).[1] Based on these results, we assume that in patients receiving single agent lenalidomide maintenance even if the dose of lenalidomide was increased to the maximum dose of 25 mg PO daily, those patients who are experiencing serologic relapse/progression would have at best 7 months of median PFS and a Spanish study indicated approximately 3 months until clinical progression (without any study). We hypothesize that the addition of Elotuzumab to maintenance lenalidomide would improve PFS to 12 months (with addition of 5 months benefit). We anticipate that approximately 3 subjects per month will be accrued over 24 months. The statistical power was computed based on the assumptions; (1) null PFS of 7 months and alternative PFS of 12 months, (2) the projected accrual of 24 months, (3) a follow-up time of 12 months, and (4) an one-sided alpha of 0.05. With these assumptions, a sample size of 30 patients per cohort would have 85% power to reject the null hypothesis of 7 months (versus alternative of 12 months, hazard ratio 0.58). As the primary goal of the study is to investigate the clinical benefit of each combination regimen, results of the cohort (A) and cohort (B) will be reported separately and additional comparative analyses will be performed as an exploratory aim. The final analysis for primary endpoint will be conducted if 28 PFS events are observed.

7.1 Primary Efficacy Analysis

Progression free survival (PFS) is defined as the time of randomization to date of death from any cause, date of relapse/progression, or the last follow-up date, whichever comes first. The Kaplan-Meier method will be used to estimate PFS for each cohort. The method of Brookmeyer and Crowley will be used to construct 95% confidence interval.

7.2 Secondary Endpoints Analyses

- Overall response rate (ORR) with Elotuzumab and lenalidomide for each cohort
- Minimum response (MR) or better rate with Elotuzumab and lenalidomide for each cohort
- Time to next treatment (TTNT) for each cohort
- Comparison of clinical outcomes (cohort A versus B)
- Fcγ RIIIa receptor polymorphisms (homozygous for high-affinity V (VV) allele vs. low affinity F (FF) allele)
- Effect of Elotuzumab added to lenalidomide on phenotypic characteristics of the immune infiltrate and correlation with therapeutic efficacy

The Kaplan-Meier method or Gray method [40] will be used to estimate the survival rate or incidence rate for the time-to-event endpoints with or without competing risks, respectively. The association of time-to-event endpoints with potential predictors will be explored using Cox proportional regression model or Fine-Gray regression model,[41] as appropriate. The 95% confidence interval for binary endpoint will be computed using the exact binomial distribution (e.g., Clopper-Pearson method) and the association with binary endpoint will be examined by the logistic regression model.

8 REGULATORY CONSIDERATIONS

8.1 Institutional Review Board/Ethics Committee Approval

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB/EC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

The Investigator will be responsible for preparing documents for submission to the relevant IRB/EC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study. The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

Any amendments to the protocol after receipt of IRB/EC approval must be submitted by the Investigator to the IRB/EC for approval. The Investigator is also responsible for notifying the IRB/EC of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

Any advertisements used to recruit subjects for the study must be reviewed and approved by the IRB/EC prior to use.

8.2 Informed Consent

The Investigator must obtain informed consent of a subject or his/her designee prior to any study related procedures as per GCPs as set forth in the CFR and ICH guidelines.

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form signed and dated by the subject and the person obtaining the consent prior to the subject's entry into the study must be maintained in the Investigator's study files.

8.3 Subject Confidentiality

In compliance with United States federal regulations, the Investigator permit its representatives and, when necessary, representatives of the FDA or other regulatory authorities to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

8.4 Study Record Requirements

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; SAE reports, pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medicotechnical departments involved in the clinical study; documents regarding subject treatment and study drug accountability; original signed informed consents, etc.]) be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Investigator agrees to adhere to the document/records retention procedures by signing the protocol.

8.5 Premature Discontinuation of the Study

The responsible local clinical Investigator and the sponsor have the right to discontinue this study at any time for reasonable medical or administrative reasons. Possible reasons for termination of the study could be but are not limited to:

- Unsatisfactory enrollment with respect to quantity or quality.
- Inaccurate or incomplete data collection.
- Falsification of records.
- Failure to adhere to the study protocol.

9 REGULATORY AND REPORTING REQUIREMENTS

9.1 Adverse Events

(All serious adverse events (SAE) must be reported to the Medical Monitor BMS within 24 hours of the investigational staff's knowledge; this includes any event that occurs during the participation of the trial regardless of associated therapy, severity or relationship)

9.2 Serious Adverse Event (SAE) Definition

A serious adverse event is one that at any dose (including overdose):

- Results in death
- Is life-threatening[1]
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity[2]
- Is a congenital anomaly or birth defect
- Is an important medical event[3]
- Suspected positive pregnancy

1 "Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.

2 "Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.

3 Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

9.3 Adverse Drug Reporting

Toxicity will be scored using CTCAE Version 5.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 5.0. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness. Note that only adverse events that are greater than grade 1 will be captured in the case report forms and reported.

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome.

9.4 Investigator Reporting Responsibilities

9.4.1 Reporting to FDA

The conduct of the study will comply with all FDA safety reporting requirements.

IND Annual Reports

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report

Serious adverse events will be forwarded to FDA by the Sponsor-Investigator according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (mild, moderate, severe), relationship to study drug (probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" and as defined above are present.

Adverse drug reactions that are Serious, Unlisted/unexpected, and at least possibly associated to the drug, and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA) in writing by each investigator/physician engaged in clinical research. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

The investigator/physician shall notify the FDA by telephone or by fax of any unexpected fatal or life threatening experience associated with the use of the drug. As soon as possible, but no later than 7 calendar days after the sponsors initial receipt of the information. Each phone call or fax shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND if applicable.

9.4.2 Reporting to Sponsor (NPM)

In addition to reporting to the FDA, Sponsor-Investigator will forward completed SAE and pregnancy forms to representatives of the Sponsor.

- All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 30 days of discontinuation of dosing must be reported to BMS Worldwide Safety. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

- If the BMS safety address is not included in the protocol document (e.g., multicenter studies where events are reported centrally), the procedure for safety reporting must be reviewed/approved by the BMS Protocol Manager. Procedures for such reporting must be reviewed and approved by BMS prior to study activation.

- The BMS SAE form should be used to report SAEs. If the BMS form cannot be used, another acceptable form (i.e., CIOMS or Medwatch) must be reviewed and approved by BMS. The BMS protocol ID number must be included on whatever form is submitted by the Sponsor/Investigator. The CIOMS form is available at: http://www.cioms.ch/index.php/cioms-form-i.

- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.

Worldwide.Safety@bmsaepbusinessprocess@bms.com

- In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of a SUSAR Report.
    - Other important findings which may be reported by BMS as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (e.g., animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.
    - Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.
    - In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).
    - Canada Phase IV AE reporting requirement:
        - The Division 8 of the Food and Drug Regulations in Canada require that any cases of Unusual Failure in Efficacy occurring in Canada be reported to the Canadian Health Authorities in an expedited manner.
        - Canadian sites will record single cases of Unusual Failure in Efficacy as an Adverse Event. This reporting requirement is specific for Canadian sites only.
- This AE is required to be reported to BMS within 24 hours by the
  Investigator/site staff becoming aware of the report
- For transmission purposes, report this AE using the paper SAE form.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on BMS or an approved form; pregnancies must be reported on a Pregnancy Surveillance Form.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

BMS will be provided with a simultaneous copy of all adverse events filed with the FDA.

SAEs should be reported on MedWatch Form 3500A, which can be accessed at: http://www.accessdata.fda.gov/scripts/medwatch/. The website will instruct you where to send the SAE forms.

- An SAE report should be completed for any event where doubt exists regarding its seriousness.
- For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection in the protocol.
- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.
- If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
- If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to BMS using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization. All SAEs should be followed to resolution or stabilization.

9.4.3 Reporting to the IRB

The principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy. The following SAE are reported to the IRB: Unexpected, related events which increase the risk of harm to subjects.

9.5 Adverse Events Updates / IND Safety Reports

BMS shall notify the Investigator via an IND Safety Report of the following information:

- Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected.
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

10 DATA MANAGEMENT

10.1 Data Collection

The Clinical Research Coordinators and Investigators of each site will be responsible for the recording of the site's data into the electronic data capture system, ONCORE.

10.2 Protocol Monitoring Committee

The Protocol monitoring committee (PMC) will be composed of medical and statistical independent reviewers and will meet to review the efficacy and safety data and determine a risk/benefit analysis in this subject population. The purpose of the PMC is to advise on serious safety considerations, lack of efficacy and any other considerations within the charge to the Committee. The PMC may request additional meetings or safety reports as deemed necessary upon discussion with the principal investigator. The PMC may stop the study following review of results from each interim analysis.

10.3 Study Monitoring and Auditing

10.3.1 Investigator responsibilities

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations.

Investigators, or a designated member, must enter study data onto CRFs or other data collection system. The Investigator will permit study-related monitoring visits and audits by BMS or its representatives, IRB/EC review, and regulatory inspection(s) (e.g., FDA, EMEA, TPP), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.

The Investigator, or a designated member of the Investigator's staff, must be available at some time during monitoring visits to review data and resolve any queries and to allow direct access to the subject's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The data collection must be completed prior to each visit and be made available to the BMS representative so that the accuracy and completeness may be checked.

10.3.2 Site responsibilities

A conference call/study meeting will be held weekly for the phase I and monthly for the phase II to review patient enrollment and accrual, safety and toxicity data, and treatment results, as available.

10.3.3 Monitoring

Data will be captured in Oncore, Moffitt's Clinical Trials Database. Regulatory documents and case report forms will be monitored internally according to Moffitt Cancer Center Monitoring Policies. Monitoring will be performed regularly to verify data is accurate, complete, and verifiable from source documents; and the conduct of the trial is in compliance with the currently approved protocol/amendments, Good Clinical Practice (GCP), and applicable regulatory requirements.

11 PROTOCOL AMENDMENTS OR DEVIATIONS

11.1 Protocol Amendments

Any amendment to this protocol must be agreed to by the Principal Investigator and reviewed and approved by BMS. Amendments should only be submitted to IRB/EC after consideration of BMS. review. Written verification of IRB/EC approval will be obtained before any amendment is implemented.

11.2 Protocol Deviations

When an emergency occurs that requires a deviation from the protocol for a patient, a deviation will be made only for that patient. A decision will be made as soon as possible to determine whether or not the patient (for whom the deviation from protocol was effected) is to continue in the study. The patient's medical records will completely describe the deviation from the protocol and state the reasons for such deviation. In addition, the Investigator will notify the IRB/EC in writing of such deviation from protocol. Non-emergency minor deviations from the protocol will be permitted with approval of the Principal Investigator and the local IRB/EC.

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13 Appendices

A. ECOG Performance Status Scale

Grade	Description
0	Normal activity, fully active, able to carry on all predisease performance without restriction.
1	Symptoms, but fully ambulatory, restricted in physically strenuous 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 all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only 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.
5	Dead

B. International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma *Lancet Oncol* 2016; 17: e328–46

	Response criteria*
IMWG MRD criteria (requires a complete response as defined below)	
Sustained MRD-negative	MRD negativity in the marrow (NGF or NGS, or both) and by imaging as defined below, confirmed minimum of 1 year apart. Subsequent evaluations can be used to further specify the duration of negativity (eg, MRD-negative at 5 years)†
Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by NGF‡ on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in multiple myeloma (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
Sequencing MRD-negative	Absence of clonal plasma cells by NGS on bone marrow aspirate in which presence of a clone is defined as less than two identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the LymphoSIGHT platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells§ or higher
Imaging plus MRD-negative	MRD negativity as defined by NGF or NGS plus disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT or decrease to less mediastinal blood pool SUV or decrease to less than that of surrounding normal tissue¶
Standard IMWG response criteria‖	
Stringent complete response	Complete response as defined below plus normal FLC ratio** and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ patients, respectively, after counting ≥100 plasma cells)††
Complete response	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow aspirates
Very good partial response	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
Partial response	≥50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥90% or to <200 mg per 24 h; If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥30%. In addition to these criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required
Minimal response	≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required
Stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease
Progressive disease ¶¶,‖‖	Any one or more of the following criteria:

	Response criteria*
	Increase of 25% from lowest confirmed response value in one or more of the following criteria: Serum M-protein (absolute increase must be ≥0·5 g/dL); Serum M-protein increase ≥1 g/dL, if the lowest M component was ≥5 g/dL; Urine M-protein (absolute increase must be ≥200 mg/24 h); In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL); In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma-cell percentage irrespective of baseline status (absolute increase must be ≥10%); Appearance of a new lesion(s), ≥50% increase from nadir in SPD§§ of >1 lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis; ≥50% increase in circulating plasma cells (minimum of 200 cells per µL) if this is the only measure of disease
Clinical relapse	Clinical relapse requires one or more of the following criteria: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); 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 SPD§§ of the measurable lesion; Hypercalcemia (>11 mg/dL); Decrease in hemoglobin of ≥2 g/dL not related to therapy or other non-myeloma-related conditions; Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; Hyperviscosity related to serum paraprotein
Relapse from complete response (to be used only if the end point is disease-free survival)	Any one or more of the following criteria: Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥5% plasma cells in the bone marrow; Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia see above)
Relapse from MRD negative (to be used only if the end point is disease-free survival)	Any one or more of the following criteria: Loss of MRD negative state (evidence of clonal plasma cells on NGF or NGS, or positive imaging study for recurrence of myeloma); Reappearance of serum or urine M-protein by immunofixation or electrophoresis; Development of ≥5% clonal plasma cells in the bone marrow; Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or

Response criteria*

hypercalcemia)

For MRD assessment, the first bone marrow aspirate should be sent to MRD (not for morphology) and this sample should be taken in one draw with a volume of minimally 2 mL (to obtain sufficient cells), but maximally 4–5 mL to avoid hemodilution. IMWG=International Myeloma Working Group. MRD=minimal residual disease. NGF=next-generation flow. NGS=next-generation sequencing. FLC=free light chain. M-protein=myeloma protein. SPD=sum of the products of the maximal perpendicular diameters of measured lesions. CRAB features=calcium elevation, renal failure, anemia, lytic bone lesions. FCM=flow cytometry. SUV_{max}=maximum standardized uptake value. MFC=multiparameter flow cytometry. ^{18}F-FDG PET=^{18}F-fluorodeoxyglucose PET. ASCT=autologous stem cell transplantation.

*

All response categories require two consecutive assessments made any time before starting any new therapy; for MRD there is no need for two consecutive assessments, but information on MRD after each treatment stage is recommended (e.g., after induction, high-dose therapy/ASCT, consolidation, maintenance). MRD tests should be initiated only at the time of suspected complete response. All categories of response and MRD require no known evidence of progressive or new bone lesions if radiographic studies were performed. However, radiographic studies are not required to satisfy these response requirements except for the requirement of FDG PET if imaging MRD-negative status is reported.

†

Sustained MRD negativity when reported should also annotate the method used (e.g., sustained flow MRD-negative, sustained sequencing MRD-negative).

‡

Bone marrow MFC should follow NGF guidelines.[30] The reference NGF method is an eight-color two-tube approach, which has been extensively validated. The two-tube approach improves reliability, consistency, and sensitivity because of the acquisition of a greater number of cells. The eight-color technology is widely available globally and the NGF method has already been adopted in many flow laboratories worldwide. The complete eight-color method is most efficient using a lyophilized mixture of antibodies which reduces errors, time, and costs. 5 million cells should be assessed. The FCM method employed should have a sensitivity of detection of at least 1 in 10^5 plasma cells.

§

DNA sequencing assay on bone marrow aspirate should use a validated assay such as LymphoSIGHT (Sequenta).

¶

Criteria used by Zamagni and colleagues,[85] and expert panel (IMPetUs; Italian Myeloma criteria for PET Use).[81, 97] Baseline positive lesions were identified by presence of focal areas of increased uptake within bones, with or without

any underlying lesion identified by CT and present on at least two consecutive slices. Alternatively, an SUV_{max}=2·5 within osteolytic CT areas >1 cm in size, or SUV_{max}=1·5 within osteolytic CT areas ≤1 cm in size were considered positive. Imaging should be performed once MRD negativity is determined by MFC or NGS.

‖

Derived from international uniform response criteria for multiple myeloma.[11] Minor response definition and clarifications derived from Rajkumar and colleagues.[14] When the only method to measure disease is by serum FLC levels: complete response can be defined as a normal FLC ratio of 0·26 to 1·65 in addition to the complete response criteria listed previously. Very good partial response in such patients requires a ≥90% decrease in the difference between involved and uninvolved FLC levels. All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments do not need to be confirmed. Each category, except for stable disease, will be considered unconfirmed until the confirmatory test is performed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response.

**

All recommendations regarding clinical uses relating to serum FLC levels or FLC ratio are based on results obtained with the validated Freelite test (Binding Site, Birmingham, UK).

††

Presence/absence of clonal cells on immunohistochemistry is based upon the κ/λ/L ratio. An abnormal κ/λ ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of >4:1 or <1:2.

‡‡

Special attention should be given to the emergence of a different monoclonal protein following treatment, especially in the setting of patients having achieved a conventional complete response, often related to oligoclonal reconstitution of the immune system. These bands typically disappear over time and in some studies have been associated with a better outcome. Also, appearance of monoclonal IgG κ in patients receiving monoclonal antibodies should be differentiated from the therapeutic antibody.

§§

Plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For patients with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by the SPD.

¶¶

Positive immunofixation alone in a patient previously classified as achieving a complete response will not be considered progression. For purposes of calculating time to progression and progression-free survival, patients who have achieved a complete response and are MRD-negative should be evaluated using criteria listed for progressive disease. Criteria for relapse from a complete response or relapse from MRD should be used only when calculating disease-free survival.

‖‖

In the case where a value is felt to be a spurious result per physician discretion (e.g., a possible laboratory error), that value will not be considered when determining the lowest value.