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A PHASE II TRIAL FOR THE TREATMENT OF POEMS SYNDROME WITH DARATUMUMAB

Principal Investigator

Frits van Rhee, MD PhD

Myeloma Center

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PROTOCOL SUMMARY

This trial investigates the use of Daratumumab (DARA), an antibody directed at the human CD38 molecule, for the treatment of patients with POEMS syndrome. This trial will enroll ten subjects, who will complete 12 four-week cycles of DARA, in combination with the immunomodulatory drug (IMiD) lenalidomide. Objectives of this study include improvement in neuropathy and performance status, as well as improvement in laboratory values and survival. Details of the study are outlined herein.

1.0 OBJECTIVES

1.1 Primary Objectives

POEMS syndrome is paraneoplastic to typically a low-grade clonal plasma cell (PC) disorder or isolated plasmacytoma. The preferred therapy of autologous peripheral blood stem cell transplant (PBSCT) poses risks in terms of morbidity and mortality. The study will test the efficacy of DARA and lenalidomide avoiding autologous PBSCT. Patients with POEMS syndrome often have a poor performance status and are significantly debilitated by their progressive polysensorimotor neuropathy. The primary endpoints will address these critical parameters by measuring:

a) Improvement in Overall Neuropathy Limitations Scale (ONLS)

b) Improvement in Eastern Cooperative Oncology Group (ECOG) Performance Status

This study will also evaluate the safety of DARA when used in combination of lenalidomide for subjects with POEMS syndrome.

1.2 Secondary Objectives

Reduction in size of the PC clone often accompanies response. The clonal PC burden will be assessed using the International Myeloma Working Group (IMWG) criteria. Vascular endothelial growth factor (VEGF) is a critical cytokine thought to be crucial to the pathogenesis of POEMS syndrome. VEGF levels will be followed as an additional secondary endpoint. The duration of improvement in ONLS, progression-free survival (PFS) and overall survival (OS) will be further secondary endpoints. In summary secondary endpoints are:

a) PC response using IMWG criteria

b) Reduction in VEGF levels

c) Duration of improvement in ONLS

d) PFS

e) OS

2.0 BACKGROUND AND RATIONALE

2.1 Clinical Description of POEMS Syndrome

POEMS syndrome is a paraneoplastic syndrome secondary to a PC dyscrasia. It is a rare disorder with a reported prevalence of approximately 0.3 per 100,000.[1] The peak incidence of the POEMS syndrome is in the 5th and 6th decades of life, unlike multiple myeloma (MM), which has a peak incidence in the 7th and 8th decades. The acronym POEMS stands for **P**olyneuropathy, **O**rganomegaly, **E**ndocrinopathy, **M**onoclonal Protein, and **S**kin Changes. Other clinical features can be present as well including extravascular volume overload (peripheral edema, pleural effusions, ascites), sclerotic bone lesions, thrombocytosis, Castleman Disease (CD) and elevated levels of vascular endothelial growth factor. The constellation of progressive polysensorimotor neuropathy and any of the following should prompt evaluation for POEMS syndrome: monoclonal protein (especially lambda light chain); thrombocytosis; anasarca; or papilledema. The diagnosis of POEMS syndrome is made based on a composite of clinical and laboratory features (**Appendix I**).[2] The diagnosis of POEMS syndrome is confirmed when both of the mandatory major criteria, one of the three other major criteria, and one of the six minor criteria are present.

POLYNEUROPATHY

The neuropathy is the dominant characteristic of the syndrome. The quality and extent of the neuropathy, which is peripheral, ascending, symmetrical, and affecting both sensation and motor function should be elicited.[3] It starts as a sensory neuropathy and motor symptoms typically dominate over time. Patients are areflexic and typically have a steppage gait and a positive Romberg sign.

Nerve conduction studies in patients with POEMS syndrome show slowing of nerve conduction that is more predominant in the intermediate than distal nerve segments as compared to chronic inflammatory demyelinating polyneuropathy (CIDP), and there is more severe attenuation of compound muscle action potentials in the lower than upper limbs.[1,4-7] In contrast to CIDP, conduction block is rare. The conduction findings could suggest that demyelination is predominant in the nerve trunk rather than the distal nerve terminals and axonal loss is predominant in the lower limb nerves.[1] Axonal loss is greater in POEMS syndrome than it is in CIDP.[7]

MONOCLONAL PC DISORDER AND HEMATOLOGIC FINDINGS

The size of the M-protein on electrophoresis is typically small (median 1.1 g/dL) and is rarely more than 3.0 g/dL. The M-protein is usually IgG or IgA and almost always of the lambda type.[8,9] Laboratory findings are notable for an absence of cytopenias. In fact, nearly half of patients will have thrombocytosis or erythrocytosis.[8] In the series of Li and colleagues, 26% of patients had anemia, which the authors attributed to impaired renal function.[10] Their series was enriched with CD cases (25%), which may have also contributed to this unprecedentedly high rate of anemia. Bone marrow (BM) usually contains < 5% PCs, and again when clonal cells are found they are almost always monoclonal lambda. Little is known about the PCs in POEMS syndrome except that more than 95% of the time they are lambda light chain restricted with restricted immunoglobulin light chain variable gene usage (IGLV1).[11-13] Translocations and deletion of chromosome 13 have been described, but hyperdiploidy is not seen.[14,15] The BM biopsy reveals megakaryocyte hyperplasia and megakaryocyte clustering in 54% and 93% of cases, respectively.[16] One-third of patients do not have clonal PCs on their iliac crest biopsy. These are the patients who present with a solitary or "multiple solitary plasmacytomas." The other two-thirds of patients have clonal PCs in their BM, and 91% of these cases are clonal lambda. Immunohistochemical staining is more sensitive than 6-color flow since the former provides information on BM architecture, which is key in making the diagnosis in nearly half of cases. In a study by Dispenzieri *et al*. of 67 pretreatment BMs biopsies from patients with POEMS syndrome, lymphoid aggregates were found in 49% of cases.[17] Of these, there was PC rimming in all but one, and in 75% and 4% the rimming was clonal lambda and kappa, respectively. This finding was not seen in BMs from normal controls or from patients with monoclonal gammopathy of undetermined significance (MGUS), MM, or amyloidosis. Overall, only 8/67 (12%) of POEMS cases had normal iliac crest BM biopsies, *i.e*. no detectable clonal PCs, no PC rimmed lymphoid aggregates, and no megakaryocyte hyperplasia.

BONE LESIONS

Osteosclerotic lesions occur in approximately 95% of patients and can be confused with benign bone islands, aneurysmal bone cysts, non-ossifying fibromas, and fibrous dysplasia.[9,18-20] Some lesions are densely sclerotic, while others are lytic with a sclerotic rim, while still others have a mixed soap-bubble appearance. Bone windows of CT body images are often very informative, even more so than fluorodeoxyglucose (FDG)-uptake, which can be variable.[21,22] FDG-uptake occurs in those lesions which have a lytic component.[23] The advantage of whole-body CT (computed tomography) – even low dose similar to what is quickly becoming the standard in MM –

or CT- positron emission tomography (PET) is that other features of the disease are also seen: effusions, ascites, adenopathy, and hepatosplenomegaly.

EXTRAVASCULAR VOLUME OVERLOAD

Extravascular fluid overload most commonly manifests as peripheral edema, but pleural effusion, ascites, and pericardial effusions are also common. The composition of the ascites was studied in 42 patients with POEMS syndrome. The ascitic fluid had low serum ascites albumin gradients consistent with an exudative rather than a portal hypertension process in 74% of cases.[24]

VASCULAR ENDOTHELIAL GROWTH FACTOR AND OTHER CYTOKINES

Plasma and serum levels of VEGF are markedly elevated in patients with POEMS and correlate with the activity of the disease.[25-28] The principal isoform of VEGF expressed is VEGF165.[25] VEGF levels are independent of M-protein size, and increased VEGF has been found in ascitic fluid and the cerebrospinal fluid.[25,26,29] IL-1β, TNF-α and IL-6 levels are often also increased. Serum VEGF levels are 10-50 times higher than plasma levels of VEGF.[30] In patients with POEMS, VEGF is found in both PCs and platelets.[31-33] The higher level observed in serum is attributable to the release of VEGF from platelets *in vitro* during serum processing. Because plasma is a product of an anticoagulated sample, there is less platelet activation and therefore less platelet VEGF contributing to the plasma measurement than the serum sample. Tokashiki ***et al.*** suggest that serum VEGF is the better test because it reflects the VEGF contribution from both the serum and platelets.[30] However, the counter-argument is that the amount of VEGF release by platelets may vary due to collection and processing technique, making serum measurements of VEGF less reliable. Investigators from the Mayo Clinic have demonstrated that a plasma VEGF level of 200 pg/mL had a specificity of 95% with a sensitivity of 68% in support of a diagnosis of POEMS syndrome.[17] Other diseases with high VEGF include connective tissue disease, vasculitis, and CD.[27] Others have shown that a serum level of 1,920 pg/mL is diagnostic of POEMS with a specificity of 98% and a sensitivity of 73%.[34]

ORGANOMEGALY

As many as three-quarters of patients will have organomegaly, but other series would suggest that it occurs in only one-quarter of patients. [8-10,18,35,36] Any or all of liver, spleen, and lymph nodes can be enlarged. Between 11-30% of POEMS patients who have a documented clonal PC disorder

also have documented CD or Castleman-like histology.[9,10,18,35,37] In 30 patients with POEMS syndrome, 19 of 32 biopsied lymph nodes showed angiofollicular hyperplasia typical of CD.[18] In another series, 25 of 43 biopsied lymph nodes were diagnostic of CD and 84% of these had hyaline vascular type.[10]

CD (or angiofollicular lymph node hyperplasia) is a rare lymphoproliferative disorder which has many presentations, ranging from an asymptomatic unifocal mass to multifocal masses with a multitude of symptoms. The symptoms can range from simple B-symptoms to various autoimmune phenomenon to a severe inflammatory disorder leading to multi-organ failure and death.[9,18,35,38-59]

ENDOCRINOPATHY

Endocrinopathy is a central but poorly understood feature of POEMS. In one large series, approximately 84% of patients had a recognized endocrinopathy, with hypogonadism as the most common endocrine abnormality, followed by thyroid abnormalities, glucose metabolism abnormalities, and lastly by adrenal insufficiency.[36]

SKIN FINDINGS

A whole skin examination should be performed looking for hyperpigmentation, a recent out-cropping of hemangioma, hypertrichosis, dependent rubor and acrocyanosis, lipodystrophy, white nails, sclerodermoid changes, facial atrophy, flushing or clubbing.[8,10,35,60-64]

The histologic findings of the dermis have been reported to range from non-specific to glomeruloid hemangiomata to vascular abnormalities in apparently normal dermis.[65-67] Biopsies of normal-appearing skin demonstrated an extremely complex subpapillary vascular network with largely dilated and frequently anastomotic vessels.[68] Capillary loops appeared more complex than normal, and most of them were probably clotted.

PAPILLEDEMA

Papilledema is present in at least one-third of patients. Of the 33 patients at the Mayo Clinic referred for a formal ophthalmologic examination during a 10-year period, 67% had ocular signs and symptoms, the most common of which was papilledema in 52% of those examined.[69] The most common ocular symptoms reported were blurred vision in 15, diplopia in 5, and ocular pain in 3. In

another series of 94 patients, papilledema, which was found in approximately 50% of patients, was an adverse prognostic feature for overall survival.[70]

RESPIRATORY FINDINGS

The pulmonary manifestations are protean, including pulmonary hypertension, restrictive lung disease, impaired neuromuscular respiratory function, and impaired diffusion capacity of carbon monoxide, but improve with effective therapy.[71,72] Respiratory complaints are usually limited given patients' neurologic status impairing their ability to induce cardiovascular challenges. In a series of 137 POEMS syndrome patients seen at the Mayo Clinic between 1975 and 2003, at presentation, the frequency with which patients reported dyspnea, chest pain, cough, and orthopnea, were 20%, 10%, 8%, and 7%, respectively.[71] Nearly 25% had significant chest X-ray abnormalities.

Pulmonary hypertension has been reported to occur in approximately 25% of patients with POEMS syndrome.[72,73] It is more likely to occur in patients with extravascular overload. Whether the digital clubbing seen in POEMS is a reflection of underlying pulmonary hypertension and/or parenchymal disease is yet to be determined. Impaired diffusing capacity of the lungs for carbon monoxide (DLCO) has been shown to be an adverse prognostic factor in another series.[70]

RENAL FINDINGS

Serum creatinine levels are normal in most cases. Fewer than 10% of patients have proteinuria exceeding 0.5 g/24 hours, and only 6% have serum creatinine greater than or equal to 1.5 mg/dL. Four percent of patients developed renal failure as preterminal events.[9] In another series from China, 37% of patients had a creatinine clearance (CrCl) of less than 60 ml/min/m2, and 9% had a CrCl of less than 30 ml/min and 15% had microhematuria.[10] The estimate of CrCl less than 60 mL/min/m^2 has recently been revised to 22% of patients by the same group from China.[74] In our experience, renal disease is more likely to occur in patients who have co-existing CD. In POEMS syndrome, the renal histologic findings are diverse with membranoproliferative features and evidence of endothelial injury being most common.[75] On both light and electron microscopy, mesangial expansion, narrowing of capillary lumina, basement membrane thickening, sub-endothelial deposits, widening of the sub-endothelial space, swelling and vacuolization of endothelial cells, and mesangiolysis predominate.[76-82] Standard immunofluorescence is negative, which differentiates it from primary membranoproliferative glomerulitis.[75,77,83] Rarely, infiltration by PCs nests or Castleman-like lymphoma can be seen.[82]

THROMBOSIS

Patients are at increased risk for arterial and/or venous thrombosis during their course, with nearly 20% of patients experiencing one of these complications.[84,85] Lespirit *et al.* observed 4 of 20 patients to have arterial occlusion.[84] In the Mayo series, there were 18 patients suffering serious events such as stroke, myocardial infarction, and Budd-Chiari syndrome.[9] Affected vessels include carotid, iliac, celiac, subclavian, mesenteric, and femoral.[86-89] Ten percent of patients present with a cerebrovascular event, most commonly embolic or vessel dissection and stenosis.[90] The POEMS associated strokes tend to end artery border-zone infarctions.[89] The median time between peripheral neuropathy symptom onset and the cerebrovascular event was 23 months (range 0.5 to 64 months). Risk factors for cerebral events included thrombocytosis and BM plasmacytosis. Aberrations in the coagulation cascade have been implicated in POEMS syndrome.[91]

2.2 Treatment of POEMS Syndrome

The therapy of POEMS syndrome is directed at the clonal PC disorder. Patients with isolated plasmacytomas, without generalized BM involvement, are treated with localized irradiation. Not only does radiation to an isolated (or even two or three isolated) lesion(s) improve the symptoms of POEMS syndrome over the course of 3–36 months, but it can be curative. In a series of 35 patients with POEMS syndrome treated at the Mayo Clinic, radiation was used as primary therapy.[92] This resulted in a 4-year OS of 97% and a 4-year PFS of 52%. More than half the “failures” occurred within 12 months of radiation. An update of this series, which now included 91 patients receiving radiation therapy, the 10-year OS was 70% and the 6-year PFS was 62%.[93,94] In a review of radiation therapy in the management of POEMS syndrome from South Korea, 6 patients had radiotherapy as primary therapy—two of whom had multiple lesions, but were deemed too sick for chemotherapy—and 7 patients received consolidative radiotherapy for persistent M-spike and/or persistent clinical symptoms.[95] The response rates in this series for radiation alone were comparable to that of the Mayo series, but in the Korean series, both OS and PFS were inferior among those patients who received radiation therapy alone largely due to the fact that these patients were sicker at time of treatment.

Patients with a disseminated, clonal PC disorder, typically characterized by BM involvement, are treated with agents used for multiple myeloma. There are no published randomized clinical trials pertaining to POEMS syndrome, treatment recommendations are largely based on case series and anecdotes. Corticosteroids may provide symptomatic improvement, but response duration is limited. The most experience has been with an alkylator-based therapy, either low dose or high

dose with PBSCT. The first prospective clinical trial to treat POEMS syndrome included 31 patients who were treated with 12 cycles of melphalan and dexamethasone.[96] The authors found that 81% of patients had a hematologic response, 100% had VEGF response and 100% with at least some improvement in neurologic status. A limitation of this study is that follow-up was only 21 months, so long-term outcomes are not yet available.

High dose alkylator therapy with melphalan followed by autologous PBSCT is considered by many to be the treatment of choice. It is highly effective, but selection bias may confound reports. Case series suggest 100% of patients achieve significant neurologic improvement.[63,77,97-111] Doses of melphalan ranging from 140 to 200 mg/m^2 have been used, with the lower doses used for sicker patients. Anecdotally, responses are durable, but relapses have been reported.[112,113] Of the 59 patients with POEMS syndrome treated at the Mayo Clinic Rochester, PFS was 98%, 94%, and 75% at 1, 2, and 5 years, respectively.[110] Updated data on a larger dataset of 80 patients revealed a 6-year PFS of 72% and a 10-year OS of 89%.[93] However, there is considerable treatment-related morbidity and mortality associated with PBSCT including engraftment syndrome characterized by fevers, rash, diarrhea, and weight gain, occurring anytime between days 7 and 15 and more severely afflicted patients may be prone to pulmonary complications. Patients with splenomegaly may also have a complicated transplant course with delayed engraftment and more need for red cell and platelet transfusions.

Targeting VEGF with the antibody bevacizumab is attractive, but has been met with mixed results. Five patients who had also received either radiation or alkylator during and/or predating the bevacizumab had benefit, including three who had improvement but was then consolidated with high-dose chemotherapy with autologous PBSCT.[114-116] However, three patients receiving bevacizumab died raising the concern that interruption of ‘dependence’ on VEGF can cause circulatory collapse.[112,117,118] In view of these results most experts avoid the use of bevacizumab in POEMS syndrome.

Thalidomide and bortezomib have also anti-VEGF effects and have been explored in POEMS syndrome. Bortezomib has been used in 25 patients.[119-123] The first report is difficult to interpret since the patient had a number of chemotherapies prior to receiving a bortezomib, doxorubicin, and dexamethasone combination. There was early evidence of improvement even before starting the bortezomib regimen. The other reports as a single agent, with dexamethasone, or with dexamethasone and cyclophosphamide all showed significant improvements in patients without any worsening of the peripheral neuropathy. Finally, the largest series was from Shanghai Changzheng Hospital in which 20 patients with newly diagnosed POEMS syndrome were treated with 3–6 cycles of cyclophosphamide, reduced dose bortezomib, and dexamethasone.[124] The

overall hematologic response rate was 76% with 7 patients achieving complete hematologic response; 88% had VEGF response. Ninety-five percent of patients had a reduction of the ONLS by 1 or more. No neurologic worsening was observed. Thalidomide in combination with dexamethasone has also shown to produce responses in terms of VEGF, peripheral neuropathy, and extravascular volume overload, but hematologic responses have not been reported.[125-128] Enthusiasm for this therapy should be tempered by the risk of peripheral neuropathy induced by this drug. Misawa *et al.* have reported on a 25 patient 24-week randomized double-blind trial of thalidomide plus dexamethasone versus dexamethasone alone for patients ineligible for autologous PBSCT.[129] VEGF levels dropped faster in patients treated with thalidomide, though there were no significant differences in other endpoints between the two groups at 24 weeks. During the 72-week open-label extension study, nerve conduction velocities increased as compared to baseline.

Lenalidomide, which has a low incidence of peripheral neuropathy, is a more attractive alternative to thalidomide. The French have reported in abstract form their results of a Phase 2 study of lenalidomide and dexamethasone for 2 cycles as neoadjuvant therapy preceding radiation or high dose therapy or as primary therapy as 9 cycles followed by 12 cycles of single-agent lenalidomide.[130] They have treated 27 patients: 10 pre-radiation therapy, 8 pre-ASCT, and 9 as primary therapy. Although follow-up is short, the authors report that several patients had a rapid neurological response, no patient had died, and 1 patient had progressed. These results are similar to previous case reports and case series though relapses have been reported.[131-133] In the largest case series of 20 patients, all patients responded, but 4 patients relapsed 3–10 months after the end of treatment.[110] Three of these treatment failures responded to further therapy, including one who responded to reintroduction of the lenalidomide-dexamethasone combination.

The anti-CD38 monoclonal antibody DARA in combination with lenalidomide is an important addition to the anti-MM therapeutic armamentarium. Excellent results have been reported in the treatment of both relapsed and newly diagnosed MM.[134-137] In addition, several reports highlight the efficacy of DARA in AL- amyloidosis, which in analogy to POEMS syndrome, is characterized by the presence of a low-grade PC dyscrasia. Lenalidomide has an immunostimulatory effect, which synergizes with the immunologic effects of DARA. This prompted us to treat a POEMS patient who relapsed after autologous PBSCT with a combination of lenalidomide and DARA, which resulted in normalization of VEGF levels, complete hematologic response and major neurologic improvement. The clinical course of this patient is depicted in **Figure 1.**[138] The combinatorial efficacy of lenalidomide and DARA in PC dyscrasia forms the rational of the present clinical trial exploring these agents in POEMS syndrome as a non-toxic alternative to autologous PBSCT and its

associated risks. Both drugs have an excellent side effect profile and are well-tolerated both alone and in combination.

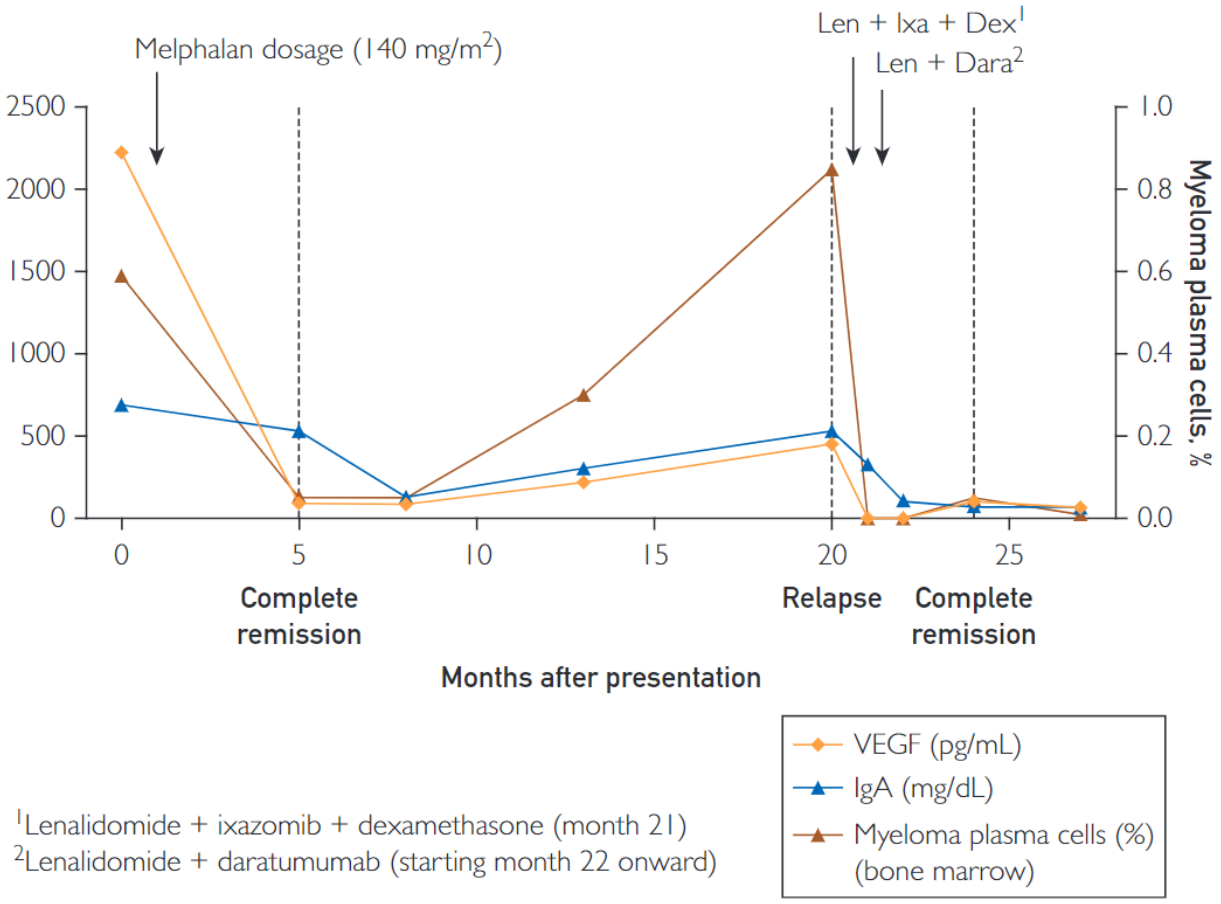


Figure 1. Clinical Course of POEMS Patient Treated with Daratumumab. The percentage of myelomatous PCs by 8-color flow cytometry in the BM (red) and serum levels of VEGF (yellow) and IgA (blue) are depicted. Noted treatments were applied (arrows) and response calls made (dashed lines) at indicated times calculated in months after initial disease presentation (x-axis).

2.3 Monitoring Response of POEMS Syndrome

There is no consensus regarding response to treatment criteria in POEMS syndrome. Evaluating the hematological response can sometimes prove difficult given the small size of the monoclonal peak often associated with a hypergammaglobulinemia and the light chain ratio can be normal. On the other hand, the now routine minimal residual testing does allow for accurate quantification of the number of clonal cells in the BM; hematologic response will, therefore, be a secondary objective and will be assessed by standard criteria from the IMWG. Monitoring the VEGF levels has also been used and will be an additional secondary objective to measure response. Organ toxicity, especially affecting the peripheral nervous system and overall functional status are the most

debilitating features of POEMS syndrome. The performance status is therefore a primary endpoint and will be evaluated by ECOG score. ONLS is a simple tool to evaluate neurologic functioning and will be a further primary endpoint.[139]

2.4 Daratumumab

DARA is a human IgG1$_k$ monoclonal antibody that binds with high affinity to a unique epitope on CD38. It is a targeted immunotherapy that attacks tumor cells that overexpress CD38, a transmembrane glycoprotein, in a variety of hematological malignancies including MM.

DARA induces lysis of CD38-expressing tumor cells, including MM tumor cells that were freshly isolated from patients, by a wide spectrum of mechanisms including complement-dependent cytotoxicity, antibody- dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis through activation of complement proteins, natural killer cells, and macrophages, respectively.[140,141]

DARA is being developed by Janssen Scientific Affairs, LLC and was approved in November 2015 by the United States Food and Drug Administration (FDA) for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an IMiD or who are double refractory to a PI and IMiD. Since then it has received additional approvals to be used in combination with lenalidomide and dexamethasone or bortezomib and dexamethasone for patients that have received at least one prior therapy; in combination with bortezomib, melphalan and prednisone for the treatment of patients with newly diagnosed multiple myeloma who are ineligible for autologous stem cell transplant; and in combination with pomalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least two prior therapies included lenalidomide and a proteasome inhibitor

2.5 Nonclinical Studies with Daratumumab

Safety information on DARA has been derived from human and chimpanzee tissue cross-reactivity studies, a 6-week repeat dose toxicity study in chimpanzees with dose levels of 5 mg/kg and 25mg/kg, and a local tolerance study in rabbits. Additionally, a cynomolgus tissue cross-reactivity study and a 2-dose study in cynomolgus monkeys have been conducted with the surrogate molecule HuMab-CD38. The primary toxicities identified in chimpanzees were infusion-related reactions during the first, but not subsequent, DARA infusions, thrombocytopenia, and neutropenia. The binding affinity of DARA is ≥15-fold higher for chimpanzee platelets than for human platelets, suggesting that thrombocytopenia may be less pronounced in humans. Anemia was observed in cynomolgus monkeys. The cynomolgus anti-CD38 binds strongly to cynomolgus monkey red blood

cells (RBCs), while DARA shows only a low level of binding to human RBCs, suggesting that the anemia may have limited clinical relevance in humans. The effects on platelets and red blood cells were reversible. Depletion of specific lymphocyte phenotypic cell populations, as expected, based on the intended pharmacological effect of DARA, was observed in both chimpanzees and cynomolgus monkeys.

The local tolerability of subcutaneous infusion of DARA in combination with rHuPH20 was evaluated in rabbits. The combination was well tolerated and there were no DARA-related macroscopic or microscopic findings.

2.6 Clinical Studies with Daratumumab

Combination Treatment with Lenalidomide and Dexamethasone

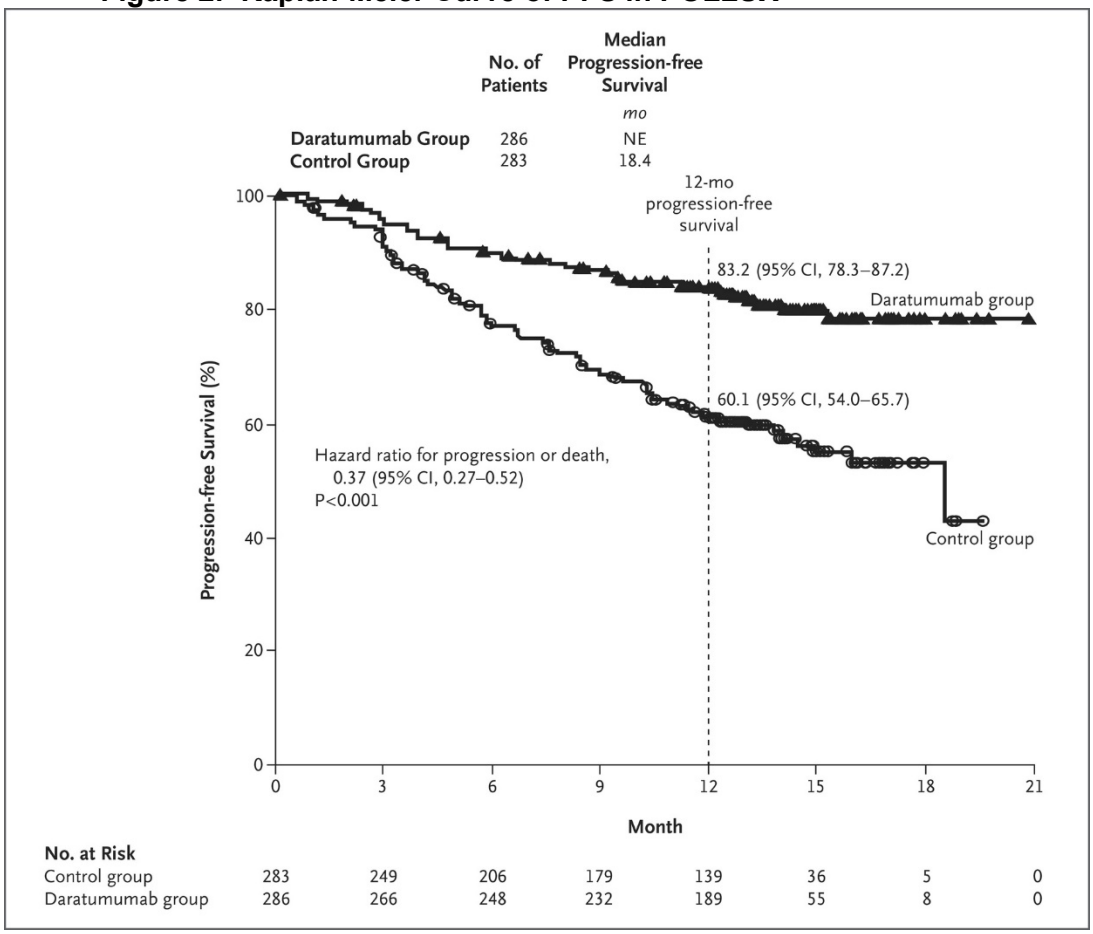
POLLUX (NCT02076009), an open-label, randomized, active-controlled Phase 3 trial, compared treatment with DARZALEX 16 mg/kg in combination with lenalidomide and low-dose dexamethasone (DRd) to treatment with lenalidomide and low-dose dexamethasone (Rd) in patients with multiple myeloma who had received at least one prior therapy. Lenalidomide (25 mg once daily orally on Days 1-21 of repeated 28-day [4-week] cycles) was given with low dose oral or intravenous dexamethasone 40 mg/week (or a reduced dose of 20 mg/week for patients >75 years or body mass index [BMI] <18.5). On DARZALEX infusion days, 20 mg of the dexamethasone dose was given as a pre-infusion medication and the remainder given the day after the infusion. For patients on a reduced dexamethasone dose, the entire 20 mg dose was given as a DARZALEX pre-infusion medication. Dose adjustments for lenalidomide and dexamethasone were applied according to manufacturer's prescribing information. Treatment was continued in both arms until disease progression or unacceptable toxicity.

A total of 569 patients were randomized; 286 to the DRd arm and 283 to the Rd arm. The baseline demographic and disease characteristics were similar between the DARZALEX and the control arm. The median patient age was 65 years (range 34 to 89 years), 11% were ≥75 years, 59% were male; 69% Caucasian, 18% Asian, and 3% African American. Patients had received a median of 1 prior line of therapy. Sixty-three percent (63%) of patients had received prior autologous stem cell transplantation (ASCT). The majority of patients (86%) received a prior PI, 55% of patients had received a prior immunomodulatory agent, including 18% of patients who had received prior lenalidomide; and 44% of patients had received both a prior PI and immunomodulatory agent. At baseline, 27% of patients were refractory to the last line of treatment. Eighteen percent (18%) of patients were refractory to a PI only, and 21% were refractory to bortezomib. Efficacy was

evaluated by progression free survival (PFS) based on International Myeloma Working Group (IMWG) criteria.

POLLUX demonstrated an improvement in PFS in the DRd arm as compared to the Rd arm; the median PFS had not been reached in the DRd arm and was 18.4 months in the Rd arm (hazard ratio [HR]=0.37; 95% CI: 0.27, 0.52; p<0.0001), representing 63% reduction in the risk of disease progression or death in patients treated with DRd.

Figure 2: Kaplan-Meier Curve of PFS in POLLUX



Additional efficacy results from POLLUX are presented in Table 1 below.

Table 1: Additional efficacy results from POLLUX[a]

	DRd (n=286)	**Rd (n=283)**
Overall response (sCR+CR+VGPR+PR)	261 (91.3%)	211 (74.6%)
p value[b]	<0.0001	
Stringent complete response (sCR)	51 (17.8%)	20 (7.1%)
Complete response (CR)	70 (24.5%)	33 (11.7%)
Very good partial response (VGPR)	92 (32.2%)	69 (24.4%)
Partial response (PR)	48 (16.8%)	89 (31.4%)

DRd = daratumumab- lenalidomide-dexamethasone; Rd = lenalidomide-dexamethasone
[a] Based on Intent-to-treat population
[b] p-value from Cochran Mantel-Haenszel Chi-Squared test.

In responders, the median time to response was 1 month (range: 0.9 to 13 months) in the DRd group and 1.1 months (range: 0.9 to 10 months) in the Rd group. The median duration of response had not been reached in the DRd group (range: 1+ to 19.8+ months) and was 17.4 months (range: 1.4 to 18.5+ months) in the Rd group.

With a median follow-up of 13.5 months, 75 deaths were observed; 30 in the DRd group and 45 in the Rd group.

Combination Treatment with Bortezomib and Dexamethasone

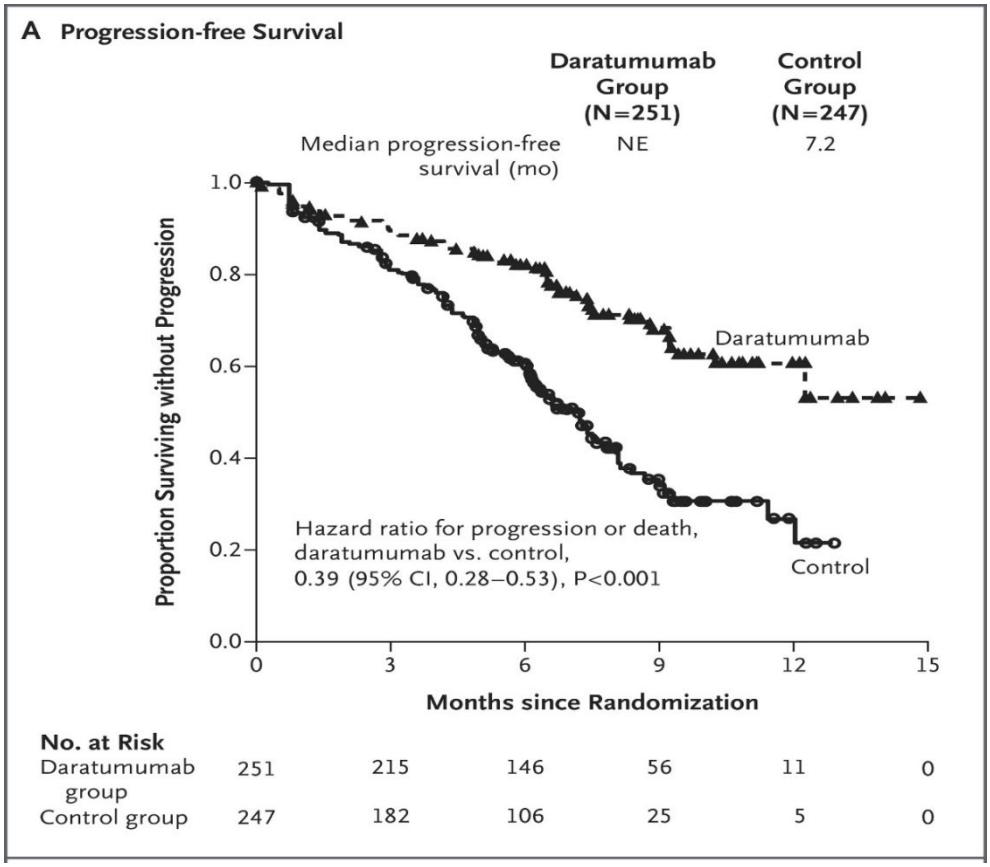
CASTOR (NCT02136134), an open-label, randomized, active-controlled Phase 3 trial, compared treatment with DARZALEX 16 mg/kg in combination with bortezomib and dexamethasone (DVd), to treatment with bortezomib and dexamethasone (Vd) in patients with multiple myeloma who had received at least one prior therapy. Bortezomib was administered by SC injection or IV infusion at a dose of 1.3 mg/m2 body surface area twice weekly for two weeks (Days 1, 4, 8, and 11) of repeated 21 day (3-week) treatment cycles, for a total of 8 cycles. Dexamethasone was administered orally at a dose of 20 mg on Days 1, 2, 4, 5, 8, 9, 11, and 12 of each of the 8 bortezomib cycles (80 mg/week for two out of three weeks of the bortezomib cycle) or a reduced dose of 20 mg/week for patients >75 years, BMI <18.5, poorly controlled diabetes mellitus or prior intolerance to steroid therapy. On the days of DARZALEX infusion, 20 mg of the dexamethasone dose was administered as a pre-infusion medication. For patients on a reduced dexamethasone dose, the entire 20 mg dose was given as a DARZALEX pre-infusion medication. Bortezomib and dexamethasone were given for 8 three-week cycles in both treatment arms; whereas DARZALEX was given until disease progression. However, dexamethasone 20 mg was continued as a DARZALEX pre-infusion medication in the DVd arm.

Dose adjustments for bortezomib and dexamethasone were applied according to manufacturer's prescribing information.

A total of 498 patients were randomized; 251 to the DVd arm and 247 to the Vd arm. The baseline demographic and disease characteristics were similar between the DARZALEX and the control arm. The median patient age was 64 years (range 30 to 88 years); 12% were ≥75 years, 57% were male; 87% Caucasian, 5% Asian and 4% African American. Patients had received a median of 2 prior lines of therapy and 61% of patients had received prior autologous stem cell transplantation (ASCT). Sixty-nine percent (69%) of patients had received a prior PI (66% received bortezomib) and 76% of patients received an immunomodulatory agent (42% received lenalidomide). At baseline, 32% of patients were refractory to the last line of treatment and the proportions of patients refractory to any specific prior therapy were in general well balanced between the treatment groups. Thirty-three percent (33%) of patients were refractory to an immunomodulatory agent only, with 24% patients in the DVd arm and 33% of patients in the Vd arm respectively refractory to lenalidomide. Efficacy was evaluated by progression free survival (PFS) based on International Myeloma Working Group (IMWG) criteria.

CASTOR demonstrated an improvement in PFS in the DVd arm as compared to the Vd arm; the median PFS had not been reached in the DVd arm and was 7.2 months in the Vd arm (HR [95% CI]: 0.39 [0.28, 0.53]; p-value < 0.0001), representing a 61% reduction in the risk of disease progression or death for patients treated with DVd versus Vd.

Figure 3: Kaplan-Meier Curve of PFS in Castor



Additional efficacy results from CASTOR are presented in Table 2 below.

Table 2: Additional efficacy results from CASTOR[a]

	DVd (n=251)	**Vd (n=247)**
Overall response (sCR+CR+VGPR+PR)	199 (79.3%)	148 (59.9%)
P-value[b]	<0.0001	
Stringent complete response (sCR)	11 (4.4%)	5 (2.0%)
Complete response (CR)	35 (13.9%)	16 (6.5%)
Very good partial response (VGPR)	96 (38.2%)	47 (19.0%)
Partial response (PR)	57 (22.7%)	80 (32.4%)

DVd = daratumumab- bortezomib-dexamethasone; Vd = bortezomib-dexamethasone
[a] Based on Intent-to-treat population
[b] p-value from Cochran Mantel-Haenszel Chi-Squared test.

In responders, the median time to response was 0.8 months (range: 0.7 to 4 months) in the DVd group and 1.5 months (range: 0.7 to 5 months) in the Vd group. The median duration of response had not been reached in the DVd group (range: 1.4+ to 14.1+ months) and was 7.9 months (1.4+ to 12+ months) in the Vd group.

With a median follow-up of 7.4 months, 65 deaths were observed; 29 in the DVd group and 36 in the Vd group were observed.

2.7 Safety Profile of Daratumumab

Daratumumab may cause serious reactions, including:

2.7.1 Infusion reactions:

Infusion reactions are common with Daratumumab and can be severe or serious. Infusions temporarily stopped or treatment with Daratumumab completely stopped for the following symptoms:

- shortness of breath or trouble breathing
- dizziness or lightheadedness (hypotension)
- cough
- wheezing
- throat tightness
- runny or stuffy nose
- headache
- itching
- nausea
- vomiting
- chills
- fever
- high blood pressure or low blood pressure
- fluid in the lungs (pulmonary edema)

2.7.2 Changes in blood test:

Daratumumab can affect the results of blood test to match blood type. These changes can occur for up to 6 months after the final dose of Daratumumab. Before

the start of treatment with Daratumumab a blood test to match blood type can be performed.

2.7.3 Decreases in blood cell count:

Daratumumab can decrease white blood counts and platelets.

2.7.4 The most common side effects of Daratumumab include:

- Infusion related reaction (see separate section)
- Infection of the upper respiratory tract such as nose, sinuses throat or upper airway
- Infection of the lower airway (bronchitis)
- Infection of the lung (pneumonia)
- Low platelets; may increase the risk of bruising and bleeding
- Low red blood cells (Anemia) (which can cause fatigue or weakness)
- Low white blood cells (which can make it harder for your body to fight infection)
- Decreased appetite
- Abnormal sensation including numbness/tingling of hands, feet or limbs
- Headache
- Cough
- Shortness of breath, including wheezing
- Constipation
- Diarrhea
- Nausea
- Vomiting
- Rash, a noticeable change in the texture or color of your skin
- Muscle spasms
- Swelling of hands, feet or limbs
- Fatigue, or lack of energy
- Weakness, lack of strength
- Fever
- Back pain
- Sleeplessness (insomnia)
- Joint pain

2.7.5 Other common side effects of Daratumumab include:

- Urinary Tract infection
- Influenza or flu like symptoms
- Sepsis (a life-threatening response to an infection)
- High blood glucose levels (Blood sugar levels)
- Low blood calcium levels
- Dehydration (Loss of body fluids)
- Irregular heartbeat
- Chills
- Fluid in lungs (pulmonary edema)
- Dizziness
- Inflammation of the pancreas(pancreatitis)
- Itchy skin
- Muscular pain in chest
- Fainting
- High blood pressure
- Injection site reaction: local reaction reported as mild pain or a burning sensation at the site of injection in the abdominal wall. Redness and hardening of the skin at the injection site was also observed and usually disappeared within a few hours after the administration

2.8 Daratumumab Pharmacokinetics

Pharmacokinetic (PK) data are available from GEN501, MMY2002, and MMY1002 monotherapy studies. Doses across these studies ranged from 0.005 to 24 mg/kg. The PK profile was consistent with target-mediated disposition with rapid target-related clearance at low doses and slower clearance at higher doses. Preliminary PK data from Study GEN503 show that following both the first dose and multiple repeated doses, the PK profile of DARA in combination with lenalidomide and dexamethasone is similar to what was observed in Study GEN501 following the same dose and schedule. The data suggest that lenalidomide and dexamethasone do not affect the PK profile of DARA.

3.0 STUDY POPULATION

3.1 Number of Subjects

Ten subjects, both males and females, ages 18 years and older, who meet inclusion and exclusion criteria will be eligible for participation in this study. Accrual is expected to take two years to complete.

3.2 Inclusion Criteria

3.2.1 Patients must have POEMS syndrome and meet the diagnostic criteria for POEMS syndrome as described in Appendix I.

3.2.2 Both newly-diagnosed and relapsed POEMS syndrome will be eligible for inclusion.

3.2.3 Patients must have a platelet count of ≥ 50,000/µL.

3.2.4 Patients must be at least 18 years of age.

3.2.5 Participants must have preserved renal function as defined by a serum creatinine level of < 3 mg/dL.

3.2.6 Participants must have an ejection fraction by ECHO or MUGA scan ≥ 40 percent.

3.2.7 Eastern Cooperative Oncology Group ≥ 1,

3.2.8 Overall Neuropathy Limitations Scale (ONLS) ≥ 1.

3.2.9 Patients must have signed an institutional review board (IRB)-approved informed consent indicating their understanding of the proposed treatment and understanding that the protocol has been approved by the IRB.

3.3 Exclusion Criteria

3.3.1 Documented allergy to lenalidomide, DARA, mannitol, other monoclonal antibodies or human proteins and mammalian-derived products.

3.3.2 Prior treatment with DARA or other CD38 monoclonal antibodies

3.3.3 Patients with central nervous system (CNS) MM involvement.

3.3.4 Patients who have received an investigational drug or device within 4 weeks prior to enrollment or received live attenuated vaccine within 4 weeks prior to enrollment.

3.3.5 Poorly controlled hypertension, diabetes mellitus, or other serious medical illness or psychiatric illness that could potentially interfere with the completion of treatment according to this protocol.

3.3.6 Poor performance status will not be an exclusion criterion since POEMS patients can be expected to have significant limitations.

3.3.7 Patients must not have prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, or other cancer for which the patient has not received treatment for one year prior to enrollment. Other cancers will only be accepted if the patient's life expectancy exceeds five years.

3.3.8 Male and Female subjects and their partners of reproductive potential may not participate unless they have agreed to use an effective contraceptive while on study and for 3 months after cessation of DARA.

3.3.9 Males who are unwilling to abstain from sperm donation while on study and for 3 months after cessation of DARA.

3.3.10 Females of childbearing potential must have a negative pregnancy test documented within one week of registration.

3.3.11 Females who are pregnant or nursing women may not participate.

3.3.12 Patients with POEMS syndrome, who do not have disseminated BM involvement and have an isolated plasmacytoma; these patients should be considered for irradiation.

3.3.13 Subjects has had major surgery within 2 weeks prior to enrollment.

3.3.14 Clinically significant cardiac disease, including myocardial infarction within the past 6 months or unstable or uncontrolled conditions (e.g., unstable angina or congestive heart failure) or other cardiac disease which in the opinion of the investigator would constitute a hazard for participating in the study. Some cardiac dysfunction is expected in this population.

3.3.15 Participant has known chronic obstructive pulmonary disease (COPD) (defined as a forced expiratory volume in 1 second [FEV1] <50% of predicted normal, forced vital capacity (FVC), etc.] and diffusion capacity (DLCO) < 40% of predicted.), known moderate or severe persistent asthma within the last 2 years or currently has uncontrolled asthma of any classification (controlled intermittent asthma or controlled mild persistent asthma is allowed). Exception may be granted if the principal investigator documents that the patient is a candidate for therapy since alternative therapies will at least have similar or not more toxicity.

3.3.16 Participant with known or suspected COPD must have an FEV1 test during screening.

3.3.17 Subjects who are seropositive for human immunodeficiency virus (HIV).

3.3.18 Subjects who are seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (i.e., subjects who are HBsAg negative but positive for antibodies to hepatitis B core antigen [anti-HBc] and/or antibodies to hepatitis B surface antigen [anti-HBs]) must be screened using real-time polymerase chain reaction (PCR) measurement of hepatitis B virus (HBV) DNA levels. Those who are

PCR positive will be excluded. EXCEPTION: Subjects with serologic findings suggestive of HBV vaccination (anti-HBs positivity as the only serologic marker) AND a known history of prior HBV vaccination, do not need to be tested for HBV DNA by PCR.

3.3.19 Subjects who are seropositive for hepatitis C except in the setting of a sustained virologic response [SVR], defined as aviremia at least 12 weeks after completion of antiviral therapy).

3.4 Design and Methods

The treatment schema is defined in **Table 3**. Patients will receive DARA in the outpatient setting, with infusions being administered in Infusion 4. Safety and response assessments will occur prior to Cycles 1 through 6, and at the end of DARA treatment. Once DARA is completed, response assessments are completed every 6 months for the first year, then annually until disease progression. Subjects will also be followed for overall survival.

4.0 TREATMENT PLAN

4.1 Treatment Overview

Table 3. Schema

Cycle 1*-2	**Daratumumab**	**16 mg/kg IV Days 1*, 8, 15, 22** *At the discretion of the investigator, the first DARA dose may be split over 2 days, i.e., 8 mg/kg on day 1 and 8 mg/kg on day 2.
	Lenalidomide	**15mg PO Days 1-21 q28**
Cycle 3-6	**Daratumumab**	**16 mg/kg IV Days 1, 15**
	Lenalidomide	**15mg PO Days 1-21 q28**
Cycle 7-12	**Daratumumab**	**16 mg/kg IV Day 1**
	Lenalidomide	**15mg PO Days 1-21 q28**
Cycle 13+ **(At PI Discretion)**	**Lenalidomide**	**15mg PO Days 1-21 q28**

4.2 Investigational Agent

4.2.1. Description

DARA is a human monoclonal antibody that specifically recognizes the CD38 molecule that is expressed at a high level in a variety of hematological malignancies, including myeloma cells. Because MM tumor cells express high numbers of CD38, a treatment regimen targeting CD38 could be beneficial for subjects with MM. Product for the clinical trial will be provided by the manufacturer free of charge and sent to the UAMS Research Pharmacy.

4.2.2 Preparation

Infusion solution will be prepared as a dilution of DARA in sterile, pyrogen-free 0.9% NaCl. Preparation of infusion bags should be done on the day of the planned infusion. DARA must be administered as an IV infusion given through a well-functioning IV catheter by using an infusion pump or syringe pump. The study drug must be filtered by using an inline filter (0.2 µM) during the infusion. Preparation of DARA will be performed according to the package insert.

4.2.3 Guidelines for the Prevention and Management of Infusion Reaction

Pre-Infusion Medication

On DARA infusion days, the subject will initially receive the following medications prior to infusion:

- Acetaminophen 650 mg PO
- An antihistamine (diphenhydramine 25-50 mg, or equivalent)
- Dexamethasone 20 mg IV
- Montelukast 10 mg PO; optional per investigator discretion

Post-Infusion Medication as Prophylaxis

For the prevention of delayed infusion-related reactions, subjects will receive corticosteroid orally (4 mg Dexamethasone) on the two days following DARA infusions (beginning the day after the infusion). For subjects with a higher risk of respiratory complications (e.g., subjects who have an FEV1%PRED<75%), the following post-infusion medication should also be considered:

- Antihistamine (25-50 mg of diphenhydramine or equivalent) on the 2 days following all infusions

(beginning on the day after the infusion)

- Short-acting β2 adrenergic receptor agonist such as salbutamol aerosol
- Control medications for lung disease (e.g., inhaled corticosteroids ± long-acting β2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salbumatol ± inhaled corticosteroids for subjects with chronic obstructive pulmonary disorder)

Investigators may prescribe bronchodilators, antihistamines, and corticosteroids that are deemed necessary to provide adequate supportive care in the event a bronchospasm occurs after subjects are released from the clinic.

Post-infusion medications will be administered after the infusion has completed, per the timing noted above. If, after 3 full doses, an at-risk subject experiences no major infusion-related reactions, then post-infusion medications may be stopped and DARA can be given by rapid infusion over 90 minutes at the investigator's discretion.

4.2.4 Management of Infusion-Related Reactions

Subjects should be carefully observed during DARA infusions. Infusion reactions may occur, and resources necessary for resuscitation (***e.g.***, agents such as epinephrine and aerosolized bronchodilator, medical equipment such as oxygen tanks, tracheostomy equipment, and a defibrillator) must be available.

If an infusion-related reaction develops, then the infusion should be temporarily interrupted or the rate of infusion decreased.

Subjects should be treated with acetaminophen, antihistamine, or corticosteroids as needed. Intravenous saline may be indicated. For bronchospasm, urticarial, or dyspnea, patients may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, patients may require vasopressors.

In the event of a life-threatening infusion-related reaction (which may include pulmonary or cardiac events) or anaphylactic reaction, DARA should be discontinued and no additional DARA should be administered to the subject. Aggressive symptomatic treatment should be applied.

If an infusion is paused or the infusion rate is decreased, then a longer-than-anticipated infusion time may occur. Overnight stays at the hospital because of slow infusion times should not be reported as an SAE. However, if the underlying cause of the delayed infusion time is an AE or SAE, then that should be reported as such.

Infusion-Related Events of Grade 1 or Grade 2

If the investigator assesses an AE to be related to the DARA infusion, then the infusion should be interrupted. When the subject's condition is stable, the infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that used before the interruption. Subsequently, the infusion rate may be increased.

If the subject experiences a Grade 2 or higher event of laryngeal edema or a Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from the onset, then the subject must be withdrawn from DARA treatment.

Infusion-Related Events of Grade 3 or higher

For infusion-related adverse events that are Grade 4, the infusion should be permanently discontinued and treatment with DARA discontinued for that subject.

For infusion-related adverse events that are Grade 3, the DARA infusion must be interrupted, and the subject must be observed until the resolution of the AE or until the intensity of the event decreases to Grade 1, at which point the infusion may be restarted. Upon restart, the infusion rate should be half of that used before the interruption. Subsequently, the infusion rate may be increased.

If the intensity of the adverse event returns to Grade 3 after restart of the infusion, then the procedure described in this section may be repeated. Should the intensity of the adverse event increase to Grade 3 for a third time, then treatment with DARA will be permanently discontinued for that subject.

4.2.5 Dose Modifications

No DARA dose modification (increase or decrease) will be permitted. Subjects who do not tolerate DARA will be removed from the study. Refer to Section 4.2.6.

Revlimid dose reductions are allowed at study entry based on renal function. Refer to Section 5.0 Table 4.

4.2.6 Toxicity Management

Refer to section 4.2.4 for details on management of infusion-related reactions. The DARA dose must be held if any of the following criteria below are met, to allow for recovery from toxicity related to the study treatment. The criteria for a dose delay are:

- Grade 4 hematologic toxicities
- Grade 3 thrombocytopenia with bleeding
- Febrile neutropenia of any grade
- Neutropenia with infection, of any grade
- Grade 3 or higher non-hematologic toxicities with the following exceptions:
    - Grade 3 nausea that responds to antiemetic treatment within 7 days
    - Grade 3 vomiting that responds to antiemetic treatment within 7 days
    - Grade 3 diarrhea that responds to antidiarrheal treatment within 7 days
    - Grade 3 fatigue that was present at baseline or that lasts for <7 days after the last administration of DARA
    - Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of DARA.

DARA treatment should be resumed when the toxicity has resolved to ≤ Grade 2 or baseline, with the exception that Grade 2 laryngeal edema or Grade 2 bronchospasm must be fully recovered. If DARA administration does not commence within the pre-specified window of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned weekly dosing date. If two consecutive doses of DARA are missed due to DARA-related adverse events, DARA should be permanently discontinued. Note that maintenance therapy may continue as described in Section 6.2 even if DARA is permanently discontinued.

A missed dose will not be made up. If a dose is delayed, then the date of all subsequent doses must be adjusted.

Hepatitis B Virus Reactivation Management

Primary antiviral prophylaxis is permitted as per local standard of care. Per protocol, HBV DNA testing by PCR is mandatory for subjects at risk for HBV reactivation see Section 6.1

For subjects who are diagnosed with HBV reactivation while on treatment, study treatment should be interrupted until the infection is adequately controlled. If the benefits outweigh the risks, study treatment may be resumed with concomitant antiviral prophylaxis as per local standard of care. Consult a liver disease specialist as clinically indicated.

4.3 Dosing Schedule

DARA at a dose of 16 mg per kilogram will be intravenously administered weekly (on Days 1, 8, 15, and 22) for 8 weeks during Cycles 1 and 2, every 2 weeks (on Days 1 and 15) for 16 weeks (Cycles 3 through 6), and every 4 weeks thereafter for a total of 6 months (Cycles 7 to 12). DARA treatment will be completed at one year.

Lenalidomide will be given orally in a dose of 15mg Days 1-21 on a 28-day cycle. DARA therapy will cease after 12 cycles, but lenalidomide can be continued beyond one year at the Principal Investigator's discretion. Standard herpes zoster prophylaxis will be given with acyclovir 400mg twice a day or similar drug (*e.g.* valacyclovir). Thrombo-embolic prophylaxis will comprise aspirin 81mg daily unless the patient is already on anticoagulation.

4.4 Drug Accountability

DARA will be supplied for this study from Janssen Scientific Affairs, LLC and will be shipped to the UAMS Research Pharmacy, which will be responsible for drug maintenance and dispensing. Lenalidomide will be supplied via specialty pharmacy per REMS protocol, and is not provided by the study; subjects' insurance will be billed for costs associated with lenalidomide.

DARA (expired or end of study) should be destroyed on site according to the University of Arkansas for Medical Sciences (UAMS) Research Pharmacy's standard operating procedure. Documentation of removal and destruction should be indicated on drug accountability logs.

4.5 Radiation

This study will only enroll patients with disseminate clonal PCs. Patients with isolated plasmacytoma are excluded. However, rare patients with disseminated disease who also have a large plasmacytoma may receive radiation therapy concurrently with DARA and lenalidomide. These are patients in whom the plasmacytoma is unlikely to respond to DARA and lenalidomide if there is compression of a vital structure. Patients who have had plasmacytomas irradiated prior to study entry are eligible to participate.

5.0 DOSAGE MODIFICATIONS

Subjects will be evaluated for adverse events according to the National Cancer Institute (NCI) Common Terminology for Adverse Events, version 5.0 (CTCAE). All subjects who are discontinued due to an adverse event should be followed for as long as necessary to document the resolution or stabilization of the event.

There will be no dose modifications for DARA. However, rules for dose delays and adjustment of infusion times have already been addressed under 4.1. Lenalidomide will most likely to contribute to any cytopenias. Grade 4 hematologic toxicity will have their dose held until toxicity has resolved to Grade 2 or better and then will have their dose reduced one level from the previous dose received. Dose levels of lenalidomide are 15mg, 10mg, and 5mg. The lenalidomide dose will be adjusted based on renal function per **Table 4**.

Table 4. Lenalidomide Dosing by Renal Function

GFR (mL/min)	Dose Delivery
> 60	15 mg Days 1-21 q28
25 - 59	10 mg Days 1-21 q28
< 25	5 mg Days 1-21 q28
< 25 and Dialysis	0

Subjects who are unable to tolerate lenalidomide may be allowed to remain on study, receiving single-agent DARA, at the discretion of the principal investigator. Subjects who do not tolerate DARA will be removed from the study.

6.0 SCHEDULE OF EVALUATIONS

6.1 Laboratory Tests and Evaluations

Table 5. Study Calendar

		Cycle 1				Cycle 2				Cycle 3		Cycle 4		Cycle 5		Cycle 6		Cycles 7-12
Events	**Screen**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**	**Day 15**	**Day 1**
Window	Day -28 to -1	Within 7 days of C1D1				Within 7 days of C2D1				Within 7 days of C3D1		Within 7 days of C4D1		Within 7 days of C5D1		Within 7 days of C6D1		Within 7 days of cycle start
Physical Assessments																		
H&P[1]	X	X				X				X		X		X		X		X
Adverse Events[2]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory																		
CBC with Differential[3]	X	X				X				X		X		X		X		X
Basic Metabolic Panel (BMP)[4]	X	X				X				X		X		X		X		X
Pregnancy Test (WoCBP only)[5/6]	X[5]	X[5]				X[6]				X[6]		X[6]		X[6]		X[6]		X[6]
Serum VEGF levels[7]	X	X				X				X		X		X		X		
Serum Protein Electrophoresis	X	X				X				X		X		X		X		X
Serum Quantitative Immunoglobulins	X	X				X				X		X		X		X		X
24-hour Urine for Total Protein & Electrophoresis[8]	X	X				X				X		X		X		X		X
Serum Free Light Chains	X	X				X				X		X		X		X		X
Serum/Urine IFE[9]	X	X				X				X		X		X		X		X
Hepatitis B Serology[10]	X																	
HBV QPCR[10]	X											X						prior to C7, C10
Blood Type and Indirect Antiglobulin Test	X																	
Research Blood Samples[11]	X									X								
Bone Marrow Aspirate/Biopsy[12]	X									X								

Echo/MUGA	X																	
PFTs	X																	
Treatment																		
Daratumumab[13]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Lenalidomide[14]		Days 1-21 Q28 days				Days 1-21 Q28 days				Days 1-21 Q28 days		Days 1-21 Q28 days		Days 1-21 Q28 days		Days 1-21 Q28 days		Days 1-21 Q28 days

Events	**End of Dara Treatment**[15]	**Cycles 13 and beyond**[16]	**Follow Up for PFS/OS**[17]
Window	Within 8 weeks discontinuation	+/- 4 weeks	+/- 4 weeks
Physical Assessments			
H&P[1]	X	X	X
Adverse Events[2]	X	X	X
Laboratory			
CBC with Differential[3]	X		
Basic Metabolic Panel (BMP)[4]	X		
Pregnancy Test (WoCBP only)[5/6]	X[6]	X[6]	
Serum VEGF levels[7]	X		X
Serum Protein Electrophoresis	X	X	X
Serum Quantitative Immunoglobulins	X	X	X
24-hour Urine for Total Protein & Electrophoresis[8]	X	X	X
Serum Free Light Chains	X	X	X
Serum/Urine IFE[9]	X	X	X
HBV QPCR[10]	X	X	X
Blood Type and Indirect Antiglobulin Test			
Research Blood Samples[11]	X		
Bone Marrow Aspirate/Biopsy[12]	X	X	X
Echo/MUGA			
PFTs			
Treatment			
Daratumumab[13]			
Lenalidomide[14]		Days 1-21 Q28 days	

Patient evaluation for the diagnosis of POEMS syndrome will be outside the realm of this study. Unless otherwise specified, tests completed within 7 days of Cycle 1 day 1 do not have to be repeated.

[1] H&P to include detailed medical and treatment history, weight, height, BSA, and Performance Status by ECOG. ONLS to be recorded.

[2] Subjects will be followed continuously for adverse events (AEs) from the start of treatment through 30 days after the last dose of study treatment. For the remainder of the follow up period, only ongoing AEs and any new AEs possibly related to study treatment or participation will be documented.

[3] CBC with differential.

[4] BMP (Na, K, Cl, CO2, Ca, BUN, Cr, Glucose).

[5] WoCBP must have a documented negative serum or urine pregnancy test (sensitivity of at least 50 mIU/mL) within 2 weeks prior to the start of treatment and then again within 24 hours prior to C1D1.

[6] WoCBP must have a documented negative serum or urine pregnancy test (sensitivity of at least 50 mIU/mL). Pregnancy testing/counseling performed as required through the Revlimid REMS® program.

[7] VEGF levels will be supported by the study.

[8] Per clinical lab SOP, the UPEP is cancelled when the total protein is < 6 mg/dL because the results of the UPEP are not quantifiable at this level. If the UPEP is unable to be performed, the UIFE will be performed to determine the presence or absence of the urine monoclonal protein.

[9] As clinically indicated to assess response (i.e. upon disappearance monoclonal protein on SPEP and UPEP).

[10] Hepatitis B serology: HBsAb, HBcAb, HBsAg. Patients with positive Hepatitis B serology will be excluded, unless HBsAg negative and no clinical evidence of infection, as recommended by the FDA. Eligible patients with positive HBV serology will be monitored for re-activation of HBV every three monthly by QPCR for the duration of DARA therapy and up to 6 months after stopping DARA treatment.

Note all myeloma program patients are screened routinely for HIV, HBV, HCV at their first visit.

[11] Research Peripheral Blood Sample. See Ancillary Studies 10.2.

[12] BM Aspirate & Biopsy are for routine studies (pathology, flow for MRD, cytogenetics, and FISH). Correlative BM scientific studies (Section 10.0) will be obtained at the same time in consenting patients. The screening bone marrow does not have to be repeated if completed per standard of care within the last 42 days.

[13] Daratumumab: Cycle 1-2 weekly on days 1, 8, 15, 22; cycles 3-6 every 2 weeks on days 1, 15; Cycles 7-12 every 4 weeks on day 1 (28 day cycles); discontinued after 12 cycles. At the discretion of the investigator, the first DARA dose may be split over 2 days, i.e., 8 mg/kg on cycle 1 day 1 and 8 mg/kg on cycle 1 day 2.

[14] Lenalidomide can continue beyond 12 cycles per PI discretion

[15] End of Dara Treatment: Visit will occur after the completion of 12 cycles of daratumumab or at the discontinuation of daratumumab if it is discontinued early. Treatment with lenalidomide may continue per PI discretion.

[16] Assessments for cycles 13 and beyond: Completed every 6 months (+/- 4 weeks). BM only as clinically indicated.

[17] Follow up for PFS/OS: PFS testing to be completed to every 6 months (+/- 4 weeks) for the first year then yearly thereafter (+/- 4 weeks) until disease progression. PFS testing will also be completed at disease progression and to confirm response. BM only as clinically indicated. OS will be followed by an annual phone call if the subject is not returning to UAMS for treatment

6.2 Screening Procedures

After written consent has been obtained, subjects will be screened in order to assess eligibility for study participation. All screening laboratory assessments must be performed within 28 days prior to Cycle 1 Day 1. PFTs, Echo/MUGA and Bone Marrow assessments must be performed within 42 days of Cycle 1 Day 1. For WOCPB pregnancy test must be performed within 2 weeks of Cycle 1 Days 1.

Subjects who meet inclusion and exclusion criteria will be eligible to be enrolled in the study.

The results should be available prior to the start of study treatment:

- Confirmation of signed ICF
- H&P (including detailed medical and treatment history, weight, height, BSA, ECOG, and ONLS)
- Adverse Event Assessment
- Laboratory assessments (CBC with differentials, BMP, Pregnancy Test for WOCBP, Serum VEGF levels, SPEP, SIFE, UPEP, UIFE, QIGS, SFLC, hepatitis serology, blood type, indirect antiglobulin test, and research blood samples)
- Bone Marrow Aspirate/Biopsy (pathology, flow for MRD, cytogenetics, and FISH)
- Echo/MUGA
- PFTs

6.3 Treatment Procedures

The following procedures will be completed during the treatment period at the times designated in the Study Calendar (Table 5):

- H&P
- Adverse Event Assessment
- Laboratory assessments (CBC with differentials, BMP, Pregnancy Test for WOCBP, Serum VEGF levels, SPEP, SIFE, UPEP, UIFE, QIGS, SFLC, hepatitis serology, and research blood samples)
- Bone Marrow Aspirate/Biopsy (pathology, flow for MRD, cytogenetics, and FISH)
- Administration of protocol required therapies

6.4 End of Dara Treatment Procedures

The EOT visit will occur after the completion of 12 cycles of daratumumab or within 8 weeks of discontinuation of daratumumab if it is discontinued early. Treatment with lenalidomide may continue per PI discretion.

The following procedures will be completed during the EOT visit:

- H&P (including detailed medical and treatment history, weight, height, BSA, ECOG, and ONLS)
- Adverse Event Assessment
- Laboratory assessments (CBC with differentials, BMP, Pregnancy Test for WOCBP, Serum VEGF levels, SPEP, SIFE, UPEP, UIFE, QIGS, SFLC, hepatitis serology and research blood samples)
- Bone Marrow Aspirate/Biopsy (pathology, flow for MRD, cytogenetics, and FISH)

6.5 Progression Free Survival/Overall Survival Follow Up Procedures

The PFS/OS Follow Up will be completed every 6 months for the first year then yearly thereafter until disease progression occurs. The following procedures may be completed during these time periods:

- H&P (including detailed medical and treatment history, weight, height, BSA, ECOG, and ONLS)
- Adverse Event Assessment
- Laboratory assessments (Serum VEGF levels, SPEP, SIFE, UPEP, UIFE, QIGS, and SFLC,)
- Bone Marrow Aspirate/Biopsy (pathology, flow for MRD, cytogenetics, and FISH)

OS will be followed by an annual phone call if the subject is not returning to UAMS for treatment.

7.0 DEFINITIONS OF SAFETY EVENTS

7.1 Definitions

7.1.1 Adverse Events (AE)

An AE is any untoward medical occurrence in a clinical study subject administered a medicinal (investigational or non-investigational) product. An adverse event does not necessarily have a causal relationship with the treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to that medicinal product. This includes any occurrence that is new in onset or aggravated in severity or frequency from the baseline condition. Abnormal results of diagnostic procedures are considered to be AEs if the abnormality:

- Results in study withdrawal
- Is associated with an SAE

- Is associated with clinical signs or symptoms
- Leads to additional treatment or to further diagnostic tests
- Is considered by the investigator to be of clinical significance

7.1.1.1 Abnormal Laboratory Values Defined as AEs

An abnormal laboratory value is considered to be an AE if the laboratory abnormality is characterized by any of the following:

- Results in discontinuation from the study
- Requires treatment, modification of study drug dose, or any other therapeutic intervention
- Is judged by the Investigator to be of significant clinical impact/importance

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded as an AE. If the laboratory abnormality was not a part of a diagnosis or syndrome, then the abnormality should be recorded as the AE

7.1.1.2 Safety Events of Interest for a Janssen Medicinal Product that Require Expediting Reporting and/or Safety Evaluation including but not limited to:

- Drug exposure during pregnancy (maternal and paternal)
- Overdose of a Janssen medicinal product
- Exposure to a Janssen medicinal product from breastfeeding
- Suspected abuse/misuse of a Janssen medicinal product
- Inadvertent or accidental exposure to a Janssen medicinal product
- Any failure of expected pharmacological action (i.e., lack of effect) of a Janssen medicinal product
- Medication error involving a Janssen medicinal product (with or without patient exposure to the Janssen medicinal product, e.g., name confusion)
- Suspected transmission of any infectious agent via administration of a medicinal product
- Unexpected therapeutic or clinical benefit from use of a Janssen medicinal product

These safety events may not meet the definition of an adverse event; however, from a Janssen Scientific Affairs, LLC perspective, they are treated in the same manner as adverse events. Special situations should be recorded on the Adverse Event page of the CRF

Any special situation that meets the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to Janssen Scientific Affairs, LLC .

7.1.2 Serious Adverse Event (SAE)

An event is “serious” based on ICH and EU Guidelines on Pharmacovigilance for Medicinal Products for Human Use if it involves considerable detriment or harm to one or more persons (who may or may not be participants), or required intervention to prevent one or more persons from experiencing considerable detriment or harm. SAEs include:

- Results in death
- Is life-threatening:(The subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is a suspected transmission of any infectious agent via a medicinal product
- Any other important medical event that, based upon appropriate medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above. Examples include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, the development of drug dependency or drug abuse, suicidal ideation or attempts, or the unintentional revealing of some genetic information to insurers.

NOTE: DEATH FOR ANY REASON SHOULD BE REPORTED AS A SERIOUS ADVERSE EVENT.

7.1.2.1 Hospitalization

For reports of hospitalization, it is the sign, symptom or diagnosis which led to the hospitalization that is the serious event for which details must be provided.

Any event requiring hospitalization or prolongation of hospitalization that occurs during the study must be reported as a serious adverse event, except hospitalizations for the following:

- Hospitalizations not intended to treat an acute illness or adverse event (e.g., social reasons such as pending placement in long-term care facility)
- Surgery or procedure planned before entry into the study. [Note: Hospitalizations that were planned before the start of data collection and where the underlying condition for which the hospitalization was planned has not worsened will not be considered serious

adverse events. Any adverse event that results in a prolongation of the originally planned hospitalization is to be reported as a new serious adverse event.]

7.1.2.2 Life-Threatening Conditions

Disease progression should not be recorded as an adverse event or serious adverse event term; instead, signs and symptoms of clinical sequelae resulting from disease progression/lack of efficacy will be reported if they fulfill the serious adverse event definition.

7.1.2.3 Adverse Events of Special Interest

Adverse events of special interest are events that Janssen Scientific Affairs, LLC is actively monitoring as a result of a previously identified signal (even if non-serious). These adverse events are:

- Infusion reactions: ≥ grade 3
- Infections: ≥ grade 4
- Cytopenias: ≥ grade 4
- Tumor lysis syndrome
- Other malignancies
- Intravascular hemolysis – all grades

  Any Adverse Event of Special Interest that is identified should be recorded on an SAE Report Form and be reported to Janssen within 24 hours of knowledge of the event.

7.1.2.4 Pregnancy

All initial reports of pregnancy must be reported to Janssen Scientific Affairs, LLC using the Serious Adverse Event Form. Abnormal pregnancy outcomes (e.g. spontaneous abortion, fetal death, stillbirth, congenital anomaly, ectopic pregnancy) are considered serious adverse events and must be reported to Janssen within 24 hours of knowledge of the event using the SAE Report Form.

Any subject who becomes pregnant during the study must be promptly withdrawn from the study and discontinue further study treatment.

Because the effect of the Janssen medicinal product on sperm is unknown, pregnancies in partners of male subjects exposed to a Janssen medicinal product will be reported using the Serious Adverse Event Form. Depending on local legislation this may require prior consent of the partner.

Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant will be required.

7.1.3 Individual Case Safety Report (ICSR)

A valid ICSR must contain the four minimum criteria required to meet regulatory reporting requirements.

- an identifiable subject (but not disclosing personal information such as the subject's name, initials or address)
- an identifiable reporter (investigational site)
- a Janssen medicinal product
- an adverse event, outcome, or certain special situations

  The minimum information required is:
- suspected Janssen medicinal product (doses, indication)
- date of therapy (start and end date, if available)
- batch or lot number, if available
- subject details (subject ID and country)
- gender
- age at AE onset
- reporter ID
- adverse event detail (AE verbatim in English), onset date, relatedness, causality, action taken, outcome, (if available)
- Janssen protocol ID

7.1.4 Product Quality Complaint (PQC)

A product quality compliant is defined as any suspicion of a product defect related to a potential quality issue during manufacturing, packaging, release testing, stability monitoring, dose preparation, storage or distribution of the product, or delivery system. Not all PQCs involve a subject. Lot and batch numbers are of high significance and need to be collected whenever available.

Examples of PQC include but not limited to:

- Functional Problem: e.g., altered delivery rate in a controlled release product
- Physical Defect: e.g. abnormal odor, broken or crushed tablets/capsules
- Potential Dosing Device Malfunction: e.g., autoinjector button not working, needle detaching from syringe

- Suspected Contamination
- Suspected Counterfeit

7.1.5 Related

An event is “related” if more likely than not it was caused by the research activity.

7.1.6 Unexpected

An event is “unexpected” when its specificity, nature, severity or incidence is not accurately reflected in the consent form, protocol, or investigator’s brochure previously reviewed and approved by the IRB. Examples include a lower rate of response to treatment or a side effect that is more severe than initially expected. A current list of expected adverse reactions/events can be found at: http://www.darzalex.com/shared/product/darzalex/darzalex-prescribing-information.pdf

7.1.7 Study Period

All AEs will be recorded on the Case Report Forms (CRFs) by the Investigator from the time of the start of study drug until 30 days after the last dose of study treatment. All relevant historical medical conditions that are known/diagnosed prior to the administration of study drug(s) are to be recorded as medical history.

7.2 Monitoring, Recording, and Reporting of Safety Events

7.2.1 Adverse Events (AEs)

All subjects will be monitored for AEs during the study period. Assessments may include monitoring the patient's clinical symptoms; laboratory, pathological, radiological, or surgical findings; physical examination; or other appropriate tests and procedures.

All AEs occurring during the study period must be recorded. The clinical course of each event should be followed until resolution, stabilization, or until it has been determined that the study treatment or participation is not the cause.

AE data collection and reporting are done to ensure the safety of subjects enrolled in the studies and those who will enroll in future protocols. AEs are to be reported in a routine fashion at scheduled times during the trial, such as with the annual reports to the IRB. Certain AEs must be reported in an expedited fashion to allow for more timely monitoring of subject safety and care.

Steps to Determine if the Event Requires Expedited Reporting

1. Identify the type of event using NCI CTCAE version 5.0
2. Grade the event using NCI CTCAE version 5.0
3. Determine whether the adverse event is related to protocol therapy (investigational or commercial). Attribution categories are as follows:

- Related - there is a reasonable possibility that the study drugs and/or procedures caused or contributed to the adverse event
- Not Related - a causal relationship of the adverse event to the study drugs and/or procedures is unlikely

4. Determine expectedness of the event. Expected events are those previously identified resulting from administration of the agent.

An adverse event is considered unexpected when the type or severity of the event is **not** listed in:

- The investigator's brochure or drug package insert (commercial drug)
- Consent form

5. Determine if this event involves a new or increased risk(s) to subjects.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event occurring more than 30 days after the last dose that is possible, probably, or definitely attributable to the agent(s) must be reported according to the instructions above.

7.2.2 Serious Adverse Events (SAEs)

All serious adverse events that have not resolved by the end of the study, or that have not resolved upon discontinuation of the subject's participation in the study, must be followed until any of the following occurs:

- The event resolves
- The event stabilizes
- The event returns to baseline if a baseline value/status is available
- The event can be attributed to agents other than the study drug or to factors unrelated to study conduct

- It becomes unlikely that any additional information can be obtained (subject or health care practitioner refusal to provide additional information, lost to follow-up after demonstration of due diligence with follow-up efforts)

7.2.2.1 Expedited Reporting of SAEs

Any adverse event meeting IRB policy 10.2, Unanticipated Problem Involving Risks to Subjects or Others (UPIRTSO), must be reported to the IRB within 10 days of notification of the event. Per this policy, any problem, event, or new information that meets the following criteria would require expedited reporting as Reportable New Information:

1) unanticipated or unexpected
2) related to the research
3) involves new or increased risk to the subject(s).

All other adverse events not meeting UPIRTSO criteria should be recorded and reported to the UAMS IRB at the continuing review in a summary format. Events which have resulted in death or are life-threatening should be reported immediately to the IRB if these events meet the requirements of IRB policy 10.2. Deaths due to disease progression would be considered anticipated and not related to the research and therefore would not be immediately reported under this policy.

All SAEs, UPIRTSOs and any special situations that meet the criteria of a serious adverse event should be recorded on a Serious Adverse Event Report Form and be reported to Janssen Scientific Affairs, LLC using the MedWatch 3500A form **within 24 hours of becoming aware of the event.** Ensure that the MedWatch 3500A form contains all the ICSR elements in section 7.1.3.

7.2.3 PQC Reporting

A PQC may have an impact on the safety and efficacy of the product. Timely, accurate, and complete reporting and analysis of PQC information from studies are crucial for the protection of patients, investigators, and Janssen Scientific Affairs, LLC, and are mandated by regulatory agencies worldwide. Janssen Scientific Affairs, LLC has established procedures in conformity with regulatory requirements worldwide to ensure appropriate reporting of PQC information. Lot and/or Batch #s shall be collected or any reports failure of expected pharmacological action (i.e., lack of effect). The product should be quarantined immediately and if possible, take a picture.

All initial PQCs involving a Janssen medicinal product under study must be reported to Janssen Scientific Affairs, LLC using the MedWatch 3500A form **within 24 hours after being made aware of the event.** Ensure that the MedWatch 3500A form contains all the PQC elements in section 7.1.4. The Janssen contact will provide additional information/form to be completed.

If the defect for a Janssen medicinal product under study is combined with either a serious adverse event or non-serious adverse event must report the PQC to Janssen Scientific Affairs, LLC according to the serious adverse event reporting timelines. A sample of the suspected product should be maintained for further investigation if requested by Janssen Scientific Affairs, LLC.

7.2.4 Transmission Methods

The following methods are acceptable for transmission of safety information to Janssen Scientific Affairs, LLC:

- Electronically via Janssen SECURE Email service (preferred)
- For business continuity purposes, if SECURE Email is non-functional:
  - Facsimile (fax), receipt of which is evidenced in a successful fax transmission report
- Telephone (if fax is non-functional).

  Please use the contact information and process information provided by Janssen Scientific Affairs, LLC.

7.2.5 Maintenance of Safety Information

All safety data will be maintained in a clinical database in a retrievable format and all adverse events, both serious and non-serious, in report format. However, in certain circumstances more frequent provision of safety data may be necessary, e.g. to fulfill a regulatory request, and as such the data shall be made available within a reasonable timeframe at Janssen Scientific Affairs, LLC request.

7.2.6 Dissemination of Safety Information

IND safety reports for the Study Product will be sent to the IRB in accordance with Federal regulations 21 CFR 312.66.

Janssen Scientific Affairs, LLC agrees to provide to the principal investigator IND safety reports for the Janssen Medicinal Product as they become available until all subjects in the Protocol have completed their last Study visit according to the Protocol (i.e. Last Subject Last Visit has occurred).

7.2.7 Non-Serious AEs

All non-serious adverse events should be reported to Janssen Scientific Affairs, LLC according to the timeframe outlined in the Research Funding Agreement section entitles Reporting of Data.

7.2.8 Final Study Report

The Investigator will prepare a final report including a complete and full summary of all adverse events, special situations, and pregnancy reports according to the timeframe outlined in the Research Funding Agreement.

7.3 Subject Confidentiality

The Myeloma Center affirms the subject's right to protection against invasion of privacy. In compliance with United States Federal regulations, representatives of the FDA, NCI and other regulatory authorities may review medical records and copy relevant research records 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.

7.4 Investigator Responsibilities

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

The Investigator will permit IRB review and regulatory inspection(s) (e.g. FDA, EMEA, TPP), providing direct access to the facilities where the study took place, source documents, and all other study documents.

The Investigator or a designated member of the Investigator's staff must be available at some time during auditing 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. All study documents must be made available to the auditing representative so that the accuracy and completeness of study documents may be confirmed.

7.5 Protocol Amendments

If modification of the protocol is necessary, the modification must be confirmed in writing, and the Investigator will inform the IRB after modifications have been approved by Janssen. Written verification of IRB approval will be obtained before any amendment that affects patient safety or efficacy, is implemented. Amendments that are administrative in nature do not require IRB approval but will be submitted to the IRB for information.

7.6 Suspension of Study

If conditions arise requiring further clarification before the decision to proceed with or terminate the study can be reached, the study will be suspended until the situation has been resolved.

7.7 Protocol Deviations

When an emergency occurs that requires a deviation from the protocol for a study subject, a deviation will be made only for that subject. The Principal Investigator or other physician in attendance in such an emergency will, if circumstances and time permit, contact the IRB immediately by telephone. If time does not allow for this, the Investigator will notify of the IRB of the deviation as soon as possible in writing.

Such contacts will be made as soon as possible to determine whether or not the subject (for whom the deviation from protocol was effected) is to continue in the study. The subjects' medical and/or research record will completely describe the deviation from the protocol and state the reasons for such deviation.

7,8 Early stopping rules

Early stopping rules will be put in place to protect the patients from excess toxicity. The trial will be halted if treatment-related death occurs in two of the first three patients. If ≤ 1 treatment related death occurs in the first 3 patients, then a further 3 patients will be enrolled. The trial will be halted if > 2 treatment-related deaths occur in the first 6 patients. If ≤ 2 treatment-related deaths occur in the first 6 patients, then a further 4 patients will be enrolled completing the enrollment of the 10 patients.

8.0 ETHICAL AND REGULATORY CONSIDERATIONS

8.1 Informed Consent

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

The formal consent of each subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. All subjects for this study will be provided a consent form describing this study and providing sufficient information in language suitable for subjects to make an informed decision about their participation in this study. The person obtaining consent will thoroughly explain each element of the document and outline the risks and benefits, alternative treatments, and requirements of the study. The consent process will take place in a quiet and private room, and subjects may take as much time as needed to make a decision about their participation. Participation privacy will be maintained and questions regarding participation will be answered. No coercion or undue influence will be used in the consent process. This consent form must be signed by the subject or legally acceptable surrogate, and the individual obtaining the consent. A copy of the signed consent will be given to the participant, and the informed consent process will be documented in each subject's research record.

8.2 Institutional Review

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

The Investigator will be responsible for preparing documents for submission to the relevant IRB and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

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

8.3 Case Report Forms

The Principal Investigator and/or his designee(s) will prepare and maintain adequate and accurate case histories with observations and data pertinent to the study. Study-specific CRFs will be used

and should be completed as soon as possible upon completion of a study visit. Information collected on CRFs shall be identical to that appearing in original source documents. In accordance with federal regulations, the Principal Investigator is responsible for the accuracy and authenticity of all clinical and laboratory data entered onto CRFs. The Principal Investigator will review and approve completed CRFs to attest that the information contained is true and accurate.

8.4 Subject Confidentiality

The Myeloma Center affirms the subject's right to protection against invasion of privacy. In compliance with United States Federal regulations, representatives of the FDA, NCI and other regulatory authorities may review medical records and copy relevant research records 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.

8.5 Record Retention

Study documentation includes all CRFs, data correction forms or queries, source documents, Sponsor correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms). All study records will be retained in accordance with applicable institutional policies and regulatory requirements.

9.0 STATISTICAL CONSIDERATIONS

This is a phase II clinical trial with the objective to assess the efficacy and safety of DARA and lenalidomide for POEMS syndrome in a small cohort (n=10) of patients. All subjects meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response. Outcome parameters will be described using simple descriptive statistics.

9.1 Definition of Success

An evaluable patient will be classified as a treatment success of the primary endpoint if:

a) There is a one-point improvement in ECOG performance score; and/or

b) ≥ 50% reduction in ONLS score at Day 360.

Of note, a ≤ 50% reduction in ONLS score will constitute a partial response (PR).

9.2 Accrual and Study Duration

We anticipate an accrual rate of approximately five eligible subjects per year. Thus 10 subjects will be accrued in approximately two years. The primary endpoint will be assessed after all subjects have been accrued and followed for an additional year, approximately three years after the opening of the study.

9.3 Sample Size and Power

The sample size of this rare disorder is too small to allow for formal comparisons. Ten subjects to be enrolled are not through formal sample size/power calculation. Descriptive statistics will be used to measure outcome.

9.4 Toxicity

There is no formal data and safety monitoring committee for Phase II studies. Toxicity and accrual monitoring are done routinely by the principal investigator and the study statistician. In addition, the maximum grade for each type of toxicity regardless of causality will be recorded and reported for each patient and frequency tables will be reviewed to determine toxicity patterns.

9.5 Secondary Endpoints

- Hematologic response will be measured by IMWG response criteria see Appendix III for response criteria definitions.
- Normalization of VEGF levels will be considered a complete response (CR) for the VEGF levels. Rare POEMS patients with normal VEGF levels will not be evaluable for this parameter; such patients will not be replaced.
- Duration of response will be recorded and analyzed using descriptive parameters to characterize the outcome of the cohort.
- OS and PFS will be assessed using Kaplan-Meier Curves see Appendix III for survival outcome definitions.

10.0 ANCILLARY STUDIES

10.1 Participation, Confidentiality, and Future Studies

Participation in laboratory research studies related to this trial is voluntary. The informed consent document shall outline that research is voluntary and allow subjects to opt in or out of these studies.

Subjects who choose to participate shall be notified that their samples, and data attributed to their samples, will be coded; only the principal investigator and his designees shall have access to identifying information or to a key that may be used to decode and link samples to their identities.

Samples will be stored for an indefinite period of time for future research provided the subject consents to such.

In order to initiate any ancillary research utilizing data and specimens from patients who opted in to future research collections for this protocol, authorization from Janssen Scientific Affairs, LLC will be sought.

10.2 Molecular Studies of CD138-purified Plasma Cells and Bone Marrow Biopsies

BM aspirates and biopsies for genetic studies (RNA sequencing), aCGH, and proteomics profiling will be performed. Approximately 10mL of BM aspirate will be collected in an EDTA syringe and sent to the Myeloma Accessioning Lab. Samples will be collected at 3 time points: screening/before the first dose of DARA; prior to Cycle 3 Day 1; and at the end of treatment. All correlative studies will be funded by other mechanisms and not as part of this protocol.

10.3 Mass Cytometry/Proteomics Profiling Studies of Peripheral Blood

PB comprises major components of the immune system, such as T and B cell subsets and NK and dendritic cells, all of which have been shown to be altered/important in MM. We envision that mass cytometry and proteomics profiling of PB, both un-separated and separated into distinct subset components, may provide important information regarding the immunologic profile of POEMS patients.

Approximately 40mL of peripheral blood will be collected at the time points specified in Section 10.2 above.

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12.0 APPENDIX I – DIAGNOSTIC CRITERIA FOR POEMS SYNDROME

Mandatory Major Criteria	1. Polyneuropathy (typically demyelinating) 2. Monoclonal PC proliferative disorder (almost always lambda)
Other Major Criteria (One Required)	3. Castleman Disease 4. Sclerotic bone lesions 5. VEGF elevation
Minor Criteria	6. Organomegaly (splenomegaly, hepatomegaly, or lymphadenopathy) 7. Extravascular volume overload (edema, pleural effusion, or ascites) 8. Endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, pancreatic) 9. Skin changes (hyperpigmentation, hypertrichosis, glomeruloid hemangiomata, plethora, acrocyanosis, flushing, white nails) 10. Papilledema 11. Thrombocytosis / polycythemia
Other Symptoms and Signs	Clubbing, weight loss, hyperhidrosis, pulmonary hypertension/restrictive lung disease, thrombotic diatheses, diarrhea, low vitamin B_{12} values

(Taken from Dispenzieri *Am J Hematol.* 2015;90(10):951-962)

13.0 APPENDIX II – OVERALL NEUROPATHY LIMITATIONS SCALE

Name:
Date:

Overall Neuropathy Limitations Scale (ONLS)

Instructions: The examiner should question **and** observe the patient in order to determine the answers to the following questions. Note should be made of any other disorder other than peripheral neuropathy which limits function at the foot of the page.

ARM SCALE

Does the patient have any symptoms in their hands or arms, eg tingling, numbness or weakness? **Yes** ☐ **No** ☐
(if "no", please go to "legs" section)

Is the patient affected in their ability to:	Not affected	Affected but not prevented	Prevented
Wash and brush their hair	☐	☐	☐
Turn a key in a lock	☐	☐	☐
Use a knife and fork together (or spoon, if knife and fork not used)	☐	☐	☐
Do or undo buttons or zips	☐	☐	☐
Dress the upper part of their body excluding buttons or zips	☐	☐	☐

If all these functions are prevented can the patient make purposeful movements with their bands or arms? Yes ☐ No ☐ Not applicable ☐

Arm Grade
0=Normal
1=Minor symptoms in one or both arms but not affecting any of the functions listed **SCORE=_____**
2=Disability in one or both arms affecting but not preventing any of the functions listed
3=Disability in one or both arms preventing at least one but not all functions listed
4=Disability in both arms preventing all functions listed but purposeful movement still possible
5=Disability in both arms preventing all purposeful movements

LEG SCALE

	Yes	No	Not applicable
Does the patient have difficulty running or climbing stairs?	☐	☐	☐
Does the patient have difficulty with walking?	☐	☐	☐
Does their gait look abnormal?	☐	☐	☐
How do they mobilise for about 10 metres (ie 33 feet)?			
Without aid	☐	☐	☐
With one stick or crutch or holding to someone's arm	☐	☐	☐
With two sticks or crutches or one stick or crutch holding onto someone's arm or frame	☐	☐	☐
With a wheelchair	☐	☐	☐
If they use a wheelchair, can they stand and walk 1 metre with the help of one person?	☐	☐	☐
If they cannot walk as above are they able to make some purposeful movements of their legs, eg reposition legs in bed?	☐	☐	☐
Does the patient use **ankle foot orthoses/braces?** (please circle)	☐	☐ **If yes:** (please circle) **right/left**	

Leg grade
0=Walking/climbing stairs/running not affected
1=Walking/climbing stairs/running is affected, but gait does not look abnormal **SCORE=_____**
2=Walks independently but gait looks abnormal
3=Requires unilateral support to walk 10 metres (stick, single crutch, one arm)
4=Requires bilateral support to walk 10 metres (sticks, crutches, crutch and arm,frame)
5=Requires wheelchair to travel 10 metres but able to stand and walk 1 metre with the help of one person
6=Restricted to wheelchair, unable to stand and walk 1 metre with the help of one person, but able to make some purposeful leg movements
7=Restricted to wheelchair or bed most of the day, unable to make any purposeful movements of the legs

Overall Neuropathy Limitation Scale=arm scale (range 0 to 5)+leg scale (range 0 to 7);
(range: 0 (no disability) to 12 (maximum disability)) **TOTAL SCORE=_____**
Is there any disorder, other than peripheral neuropathy, which affects the above functions **Yes** ☐ **No** ☐
If **yes** please describe:

14.0 APPENDIX III – IMWG RESPONSE CRITERIA AND SURVIVAL OUTCOME DEFINITIONS

Timing of Response Evaluation

Response will be evaluated according to the Schedule of Evaluations listed above (Section 6.0)

Stringent Complete Response (sCR):

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

Complete Response (CR):

- Disappearance of all evidence of serum and urine M proteins on immunofixation electrophoresis studies ***and***
- ≤ 5% plasma cells in BM ***and***
- Disappearance of any soft tissue plasmacytomas

Very Good Partial Response (VGPR):

- Meets all of the criteria for PR ***and***
- Serum and urine M proteins detectable by immunofixation but not on electrophoresis ***or***
- ≥ 90% reduction in serum M protein **and** urine M protein < 100 mg/24 hrs.

Partial Response (PR):

- If the patient had soft tissue plasmacytomas present at baseline and they were assessed at this disease assessment: ≥ 50% reduction in size of soft tissue plasmacytomas (see Appendix; Notes h.) ***and***
- If the patient had ≥ 30% plasma cells in BM at baseline and a BM biopsy was done: ≥ 50% reduction in plasma cells ***and***
- ≥ 50% reduction in serum M protein **and** reduction in urine M protein ≥ 90% or to < 200 mg/24 hours ***or***

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

Stable Disease (STA):

- Patient does not meet criteria for sCR, CR, VGPR, PR, or Progression (PROG).

Progression (PROG): Any one or more of the following:

- Serum M protein increase ≥ 25% from baseline (or an increase of ≥ 1 g/dL if serum M protein was ≥ 5 g/dL at baseline), with an absolute increase of ≥ 0.5 g/dL ***or***
- Urine M protein increase ≥ 25% from baseline, with an absolute increase of ≥ 200 mg/24 hrs ***or***
- If patient had serum M protein < 1 g/dL, urine M protein < 200 mg/24 hrs, and an involved serum free light chain level ≥ 10 mg/dL at baseline: ≥ 25% increase in the difference between involved and uninvolved serum free light chain level, with an absolute increase of ≥ 10 mg/dL ***or***
- BM plasma cell percentage increase ≥ 25% from baseline, with the absolute plasma cell % ≥ 10% ***or***
- New bone lesions or soft tissue plasmacytomas, or definite increase in size of existing bone lesions or soft tissue plasmacytomas (see Appendix III: Note 8.) ***or***
- Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to MM

NOTES:

1. If a disease assessment indicates that a patient is experiencing a sCR, CR, VGPR, PR, or PROG, this should be confirmed by a second disease assessment and this should be done prior to the institution of any new therapy. The second disease assessment may be done at any time.
2. “M protein” may also be known by the following synonyms: M-spike, monoclonal protein, myeloma protein, monoclonal paraprotein, M-component.

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

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

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

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

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

8. Skeletal survey is not required for assessment of response unless clinically indicated, but is recommended once a year in clinical practice. sCR, CR, VGPR, PR, and STA all require no known evidence of progressive or new bone lesions if radiographic studies were performed, but radiographic studies are not required to satisfy these response requirements.

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

Best Response

This is calculated from a sequence of Objective Status evaluations

Stringent Complete Response

An objective status of sCR on at least two sequential disease assessments. Only one BM biopsy, done during one of these two disease assessments, is required to confirm the response.

Complete Response

An objective status of CR on at least two sequential disease assessments. Only one BM biopsy, done during one of these two disease assessments, is required to confirm the response.

Very Good Partial Response

An objective status of VGPR on at least two sequential disease assessments.

Partial Response

An objective status of PR on at least two sequential disease assessments.

Unconfirmed sCR (UsCR)

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

Unconfirmed CR (UCR)

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

Unconfirmed VGPR (UVGPR)

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

Unconfirmed PR (UPR)

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

Stable / No Response

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

Increasing Disease (INC)

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

Inadequate Assessment. Response Unknown (NASS)

Progression greater than eight weeks after registration and either all objective statuses prior to registration are unknown or the only known objective statuses occurred less than three weeks after registration.

Relapse

In patients with a confirmed response as described above, relapse is defined as the first occurrence of any of the following, reconfirmed by repeat analysis of serum and/or 24-hour urine M protein, done more than 2 weeks apart:

- Myeloma protein increase by more than 100% from the lowest level recorded on study, or a rise of 2.0 g/dl (this increase must be to a level > 1.0 g/dL if it is to constitute the sole manifestation of relapse).
- Myeloma protein increase above the response criteria for PR.
- Reappearance of M-protein in blood or urine not related to immune recovery or recent infection.
- Increase in the size and number of lytic bone lesions recognized on radiographs. New skeletal or MRI lesions, preferentially confirmed by fine needle aspirate.
- Myeloma-related cytogenetic abnormalities.
- BM plasmacytosis > 10% or > 5% light chain restricted, non-diploid, plasma cells on clg/DNA.
- Hypercalcemia, not explained by any other cause.

Survival Outcomes

Overall Survival

Measured as the time from initial registration to death from any cause.

Progression-Free Survival

Measured as the time from initial registration to progression/relapse of disease or death from any cause

15.0 APPENDIX IV - PERFORMANCE STATUS SCALE AND ADVERSE EVENT GRADING

ECOG Grading Scale

Participants will be graded according to the current ECOG grading scale:

Grade	Scale
0	Fully active; able to carry on all pre-disease activities without restriction. (Karnofsky 90-100).
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work. (Karnofsky 70-80).
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. (Karnofsky 50-60).
3	Capable of only limited self-care; confined to be or chair more than 50% of waking hours (Karnofsky 30-40).
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair (Karnofsky 10-20).

Adverse Event Criteria

This study will utilize the CTCAE Version 5.0 for toxicity and performance reporting. A copy of the CTCAE version 5.0 can be downloaded from the CTEP home page at http://ctep.info.nih.gov). Additionally, the toxicities are to be reported in the appropriate data collection tools.

16.0 APPENDIX V - CRITERIA FOR REMOVAL FROM TREATMENT AND STUDY

Criteria for Removal from Treatment:

a. Completion of protocol therapy

b. Progressive disease or relapse

c. Delay of > 2 months in the start of subsequent cycles

d. Unacceptable toxicity (i.e., non-reversible Grade 3 or Grade 4 life-threatening toxicity probably or definitely related to protocol therapy)

e. Major deviation in protocol therapy

f. Discontinuation of DARA due to safety or tolerability

g. Development of second neoplasm (SMN)

h. Pregnancy

i. The patient may withdraw from the study at any time for any reason

Notes:

- Subjects may remain on study if lenalidomide intolerance requires discontinuation; the subject may continue on single-agent DARA at the discretion of the principal investigator.
- All reasons for discontinuation of treatment must be clearly documented in source documents and database.

Criteria for Removal from Protocol Follow-Up/Off study Criteria

a. Death

b. Lost to follow-up

c. Withdrawal of consent for any further data collection

17.0 APPENDIX V - INSTITUTIONAL DARATUMUMAB PROTOCOL

17.1 Background

DARA is an IgG1κ human monoclonal antibody directed against CD38. CD38 is a cell surface glycoprotein which is highly expressed on myeloma cells, yet is expressed at low levels on normal lymphoid and myeloid cells. By binding to CD38, DARA inhibits the growth of CD38 expressing tumor cells by inducing apoptosis.

17.2 Usual Dosage

Weeks 1-8: 16 mg/kg once weekly for 8 doses

Weeks 9-24: 16 mg/kg once every 2 weeks for 8 doses

Weeks 25+: 16 mg/kg once every 4 weeks until disease progression

All doses to be based on patient's actual body weight.

17.3 Standard Dilution and Titration Parameters

	Dilution Volume	Initial rate (First Hour)	Rate Increments[+]	Maximum Rate
First infusion*	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Second Infusion	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
Subsequent Infusion	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

*if adverse reaction occurs, use first infusion instructions for all future doses
[+]only increase rate if patient is without adverse reaction

17.4 Rapid Infusion

Rapid infusion parameters may be initiated for the *third dose* of DARA and beyond if the patient has not experienced any prior infusion-related adverse effects.

- Must be denoted on patient's written chemo orders from the physician.
- Intended for outpatient administration only.

- Drug will be diluted in 500 mL of normal saline and infused at 240 mL/hour for first 30 minutes (20% of dose), then 480 mL/hour for remaining 60 minutes (80% of dose). Entire volume of bag should be infused.

17.5 Pre- and Post-Infusion Medications

Indicated to reduce the risk of infusion reactions and delayed infusion reactions, which are frequently respiratory in nature. Administer pre-medications at least 1 hour prior to initiating the infusion. Pre- and post-medications may vary at the discretion of the oncologist.

Standard Pre-and Post-Medications:

- Dexamethasone 20 mg IV prior to infusion
- Tylenol 650 mg PO prior to infusion
- Benadryl 25 mg PO prior to infusion
- Albuterol 90 mcg 2 puffs prior to infusion and PRN
- Singulair 10 mg days 1, 2 and 3
- Allegra 180 mg days 1, 2 and 3
- Dexamethasone 4 mg days 2 and 3

17.6 Recommended Monitoring

- **Standard Infusion:** Patient's vitals (blood pressure, heart rate, respiratory rate, and temperature) should be monitored prior to the start of the infusion, every 30 minutes during the infusion, and repeated at the end of the infusion.
- **Rapid Infusion:** Patient's vitals should be monitored prior to the infusion and every 15 minutes during the first hour, and repeated at the end of the infusion.

17.7 Common Side Effects

Fatigue, nausea, joint pain, back pain, fever, chills, dizziness, cough, shortness of breath, nasal congestion, cold-like symptoms (upper respiratory infection), swollen hands, ankles or feet, thrombocytopenia, anemia.

17.8 Management of Adverse Reactions

- For infusion reactions of any grade/severity, immediately stop infusion, manage symptoms, and notify MD/APRN.
- Grade 1-2 (mild to moderate): Once reaction symptoms resolve, resume the infusion at no more than HALF the rate at which the reaction occurred. If the patient does not experience any further reaction symptoms, infusion rate escalation may resume at increments and intervals as clinically appropriate.
- Grade 3 (severe): Once reaction symptoms resolve, consider restarting the infusion at no more than HALF the rate at which the reaction occurred. If the patient does not experience additional symptoms, resume infusion rate escalation at increments and intervals as appropriate.
- Repeat the procedure above in the event of recurrence of Grade 3 symptoms. Permanently discontinue daratumumab upon the third occurrence of a Grade 3 or greater infusion reaction.

Table 2

Grading of Hypersensitivity Reactions According to the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0[a]

	Grade				
	1	2	3	4	5
Hypersensitivity (allergic reaction)	Transient flushing or rash, drug fever < 38°C (< 100.4°F)	Rash, flushing, urticaria, dyspnea, drug fever ≥ 38°C (≥ 100.4°F)	Symptomatic bronchospasm ± urticaria, parenteral medication(s) indicated, allergy-related edema/ angioedema, hypotension	Anaphylaxis	Death
Acute infusion reaction (cytokine release syndrome)	Mild reaction, infusion interruption not indicated, intervention not indicated	Requires therapy or infusion interruption, but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≥ 24 h	Prolonged (ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion), recurrence of symptoms following initial improvement, hospitalization indicated for other clinical sequelae (eg, renal impairment, pulmonary infiltrates)	Life-threatening, pressor or ventilatory support indicated	Death

NCI = National Cancer Institute; NSAIDs = nonsteroidal anti-inflammatory drugs.

[a]Reprinted, with permission, from NCI (http://ctep.cancer.gov/forms/CTCAEv3.pdf) Cancer Therapy Evaluation Program, NCI Common Terminology Criteria for Adverse Events v3.0. DCTD, NCI, NIH, DHHS. December 12, 2003. NIH Publication #03-5410

- Grade 4 (life threatening): Permanently discontinue daratumumab treatment.
- Notify “DARA INFUSION REACTION” email group, so pharmacist and MD may adjust orders as indicated.

18.0 APPENDIX VI – LIST OF ABBREVIATIONS

aCGH	Microarray-based Comparative Genomic Hybridization
AE	Adverse Event
BM	Bone Marrow
BMP	Basic Metabolic Panel
CBC	Complete Blood Count
CIDP	Chronic Inflammatory Demyelinating Polyneuropathy
CR	Complete Response
CrCl	Creatinine Clearance
CRF	Case Report Form
CT	Computed Tomography
CTCAE	NCI Common Terminology for Adverse Events
DARA	Daratumumab
DLCO	Diffusing Capacity of the Lungs for Carbon Monoxide
ECOG	Eastern Cooperative Oncology Group
FDA	Food and Drug Administration
FDG	Fluorodeoxyglucose
FEV1	Forced Expiration Volume in One Second
FVC	Forced Vital Capacity
GEP	Gene Expression Profiling
H&P	History and Physical
HBV	Hepatitis B Virus
HIPAA	Health Insurance Portability and Accountability Act
ICH	International Conference on Harmonization
IMiD	Immunomodulatory Drug
IMWG	International Myeloma Working Group
INC	Increasing Disease
IRB	Institutional Review Board
MGUS	Monoclonal Gammopathy of Undetermined Significance
MM	Multiple Myeloma
NCI	National Cancer Institute
nCR	Near Complete Response
ONLS	Overall Neuropathy Limitations Scale
OS	Overall Survival
PB	Peripheral Blood

PBSCT	Peripheral Blood Stem Cell Transplant
PC	Plasma Cells
PET-CT	Positron Emission Tomography – Computed Tomography
PFS	Progression Free Survival
PI	Proteasome Inhibitor
PK	Pharmacokinetics
PO	By Mouth
PR	Partial Response
PROG	Disease Progression
RBCs	Red Blood Cells
RNA	Ribonucleic acid
SAE	Serious Adverse Event
sCR	Stringent Complete Response
SoC	Standard of Care
STA	Stable Disease
UAMS	University of Arkansas for Medical Sciences
UCR	Unconfirmed Complete Response
UPR	Unconfirmed Partial Response
UsCR	Unconfirmed Stringent Complete Response
UVGPR	Unconfirmed Very Good Partial Response
VEGF	Vascular Endothelial Growth Factor
VGPR	Very Good Partial Response
WoCBP	Women of Child Bearing Potential