REsponse Adapted Combination Therapy Approaches for High-Risk Multiple Myeloma (REACH)

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Trial Drugs
Commercial Agents: Dexamethasone, Daratumumab, Lenalidomide, Carfilzomib
Drug Company Supplied: None

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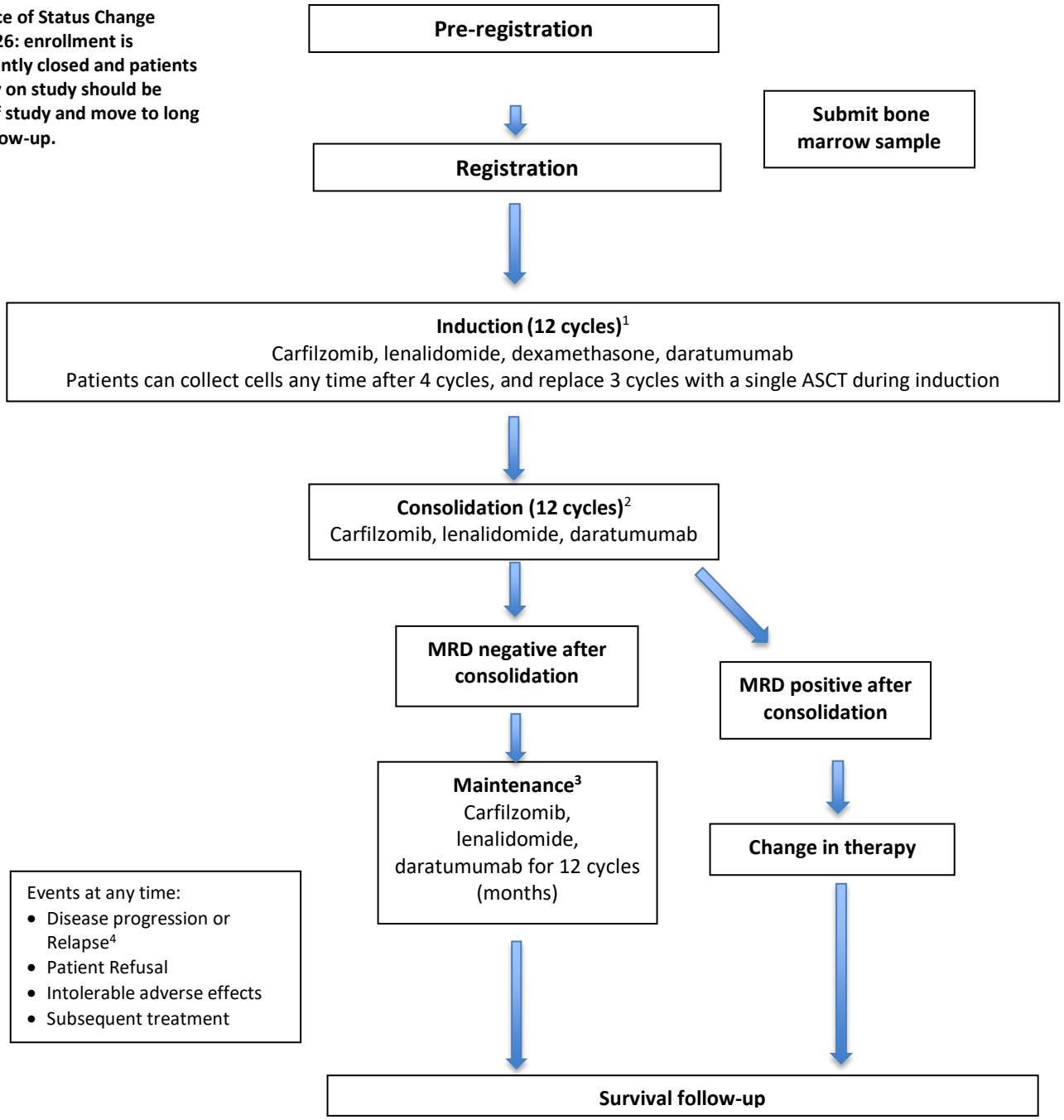
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Per Notice of Status Change 08Jan2026: enrollment is permanently closed and patients currently on study should be taken off study and move to long term follow-up.



Cycle = 28 days (±4 days)

1 Induction cycles 1-12 cycles

2 Consolidation cycles 13-24

3 Maintenance cycles 25-36

4 Confirmation of PD or REL is not required. However, treatment may be discontinued for progressive disease or relapse that is unconfirmed per physician discretion. In this case, an objective status of PD or REL should be entered on the measurement form and progressive disease or relapse should be reported on the patient status form

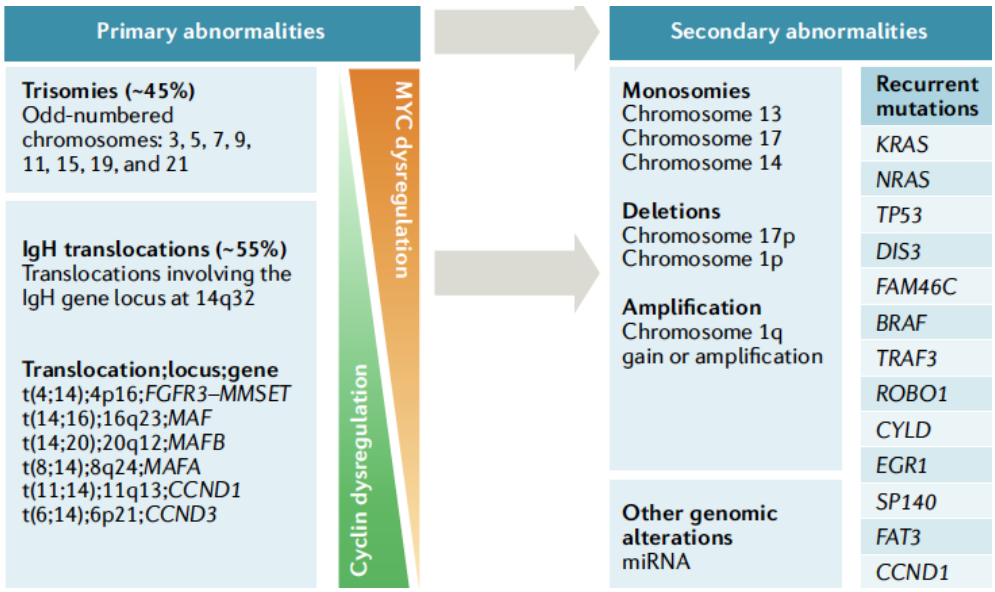
Generic name: carfilzomib Brand name(s): Kyprolis Mayo Abbreviation: Cfz	Generic name: Dexamethasone Brand name(s): Decadron Mayo Abbreviation: DXM	Generic name: Lenalidomide Brand name(s): Revlimid Mayo Abbreviation: REV	Generic name: Daratumumab Brand name(s): Darzalex Mayo Abbreviation: DARA

Availability: Commercial	Availability: Commercial	Availability: Commercial	Availability: Commercial

1.0 Background

1.1 ***Multiple Myeloma:*** Multiple myeloma is a malignancy of the differentiated plasma cells that affect the older patient with a median age at onset of 65-70 years and a slight male predominance. It is characterized by clonal expansion of plasma cells leading to increased production of monoclonal protein in the majority of patients accompanied by end organ damage in the form of lytic bone disease, hypercalcemia, anemia and renal insufficiency.[1] Nearly 24,000 patients with myeloma are diagnosed in the United States each year, and despite considerable improvements in therapy, myeloma remains incurable and uniformly fatal with a median overall survival of around 8 years. Recent improvements in therapies have significantly improved the survival outcomes, but given the inevitable relapses seen in these patients, new approaches to therapy are clearly needed. As the efficacy of therapies have increased and newer classes of drugs have been approved for treatment of myeloma, there is increasing interest on improving the depth of response with the initial therapy of myeloma.

1.2 ***High risk multiple myeloma***: MM remains a very heterogenous disease that appear at least partly driven by presence of a defined set of genomic abnormalities. Chromosomal abnormalities can be identified in nearly all patients with myeloma and can be broadly classified as primary abnormalities that likely originate at the time of the initial clone development, as these are seen at the earliest precursors phase of MGUS, and secondary abnormalities that are often subclonal and increase in frequency as the disease progresses through multiple responses and relapses.[2] The primary abnormalities are of two types, translocations involving immunoglobulin heavy chain region on chromosome 14 and trisomies of various chromosomes, typically odd numbered chromosomes. Secondary abnormalities include monosomies and deletions or amplifications involving different chromosomes (**Figure 1**). In addition, several recurrent gene mutations have been described in myeloma, that again appear to increase in frequency and burden with disease progression.



Risk stratification in myeloma has relied heavily on the FISH testing on plasma cells performed to identify the above describe chromosomal abnormalities. Presence of t(4;14), t(14;16), del17p, *Myc* abnormalities and 1q amplification have been associated with poor outcome. Patients with genetic high-risk MM have median survival of about 3 years, nearly a third of those without the high-risk abnormalities. Testing for genetic mutations, can add to this, but is not commonly used at this time. In particular, mutations involving the TP53 gene in the remaining allele in patients with del17p has been associated with a dismal outcome. In addition, certain laboratory abnormalities such as serum albumin, serum beta2 microglobulin and serum LDH can improve the risk stratification approach as has been described with the use of revised International Staging System. We and others have shown that presence of more than one high risk genetic abnormality can identify a group of patients at the highest risk of poor survival, referred to as 'double hit' MM.[3] Current treatment approaches to the treatment of HR-MM have clearly been inadequate. The only treatment outcome that appears to be associated with a better than anticipated outcomes in HR-MM has been the achievement of minimal residual disease (MRD) negativity. However, it remains to be seen if an MRD directed treatment approach can alter the outcomes of all patients with HR-MM. Recent results from the MASTER trial suggests that early discontinuation based on single MRD negativity is not adequate for long term control of high-risk MM. [4]

1.3 ***Initial therapy of symptomatic multiple myeloma***: The treatment paradigms for multiple myeloma have undergone a significant change in the past decade.[5,6] A decade ago, patients who were considered eligible for transplant underwent the procedure after a brief duration of therapy with a steroid based regimen with or without doxorubicin. Patients ineligible for transplant went on to receive melphalan and prednisone. With these treatment approaches patients had a median survival of 3-4 years, with nearly 10-20% of patients dying in the first year after diagnosis. During the last decade several new drugs were introduced such as thalidomide and its analogue lenalidomide and the proteasome inhibitor bortezomib and these along with continued use of transplant has led to improved survival in myeloma.[7] In fact, in the recent clinical trials 3-year survival has approached 90% and 1-year mortality has dropped to under 2%.[8] This progress has come through a series of investigations examining the efficacy of the new drugs used in various combinations and sequences. Initial trials in the relapsed setting confirmed significant clinical activity for all these new drugs. This was followed by several clinical trials that examined the combination of novel agents with dexamethasone in the setting of newly diagnosed disease. The studies consistently demonstrated superior response rates, deeper responses, and improved progression-free survival for patients undergoing initial therapy with novel agents.[8-11] The trials examined the role of the new drugs in the context of transplant eligible and ineligible patients. This has been followed by three drug regimens that either combined the new drugs together or incorporated an alkylator drug to the novel agent-dexamethasone combination. These have included combinations of bortezomib and dexamethasone with thalidomide (VTD), lenalidomide (VRd) or cyclophosphamide (VCD).[9,10,12,13]

Of particular interest is the VRd regimen, which has shown high efficacy rates and is increasingly used for initial therapy in the community.[9,13] VRd regimen has been associated with high response rates approaching 100% and deep responses with very good partial response rates and complete response rates of over 70 and 40% respectively. It has proven to be a highly effective initial therapy for patients planning stem cell transplantation with no significant effect on the ability to successfully mobilize stem cells.

In the initial phase 1/2 trial of the VRd regimen, 66 patients with newly diagnosed myeloma received 3-week cycles of bortezomib (days 1, 4, 8, 11), lenalidomide (days 1-14), and dexamethasone (days 1, 2, 4, 5, 8, 9, 11, 12). Phase 2 dosing was determined to be bortezomib 1.3 mg/m^2 lenalidomide 25 mg, and dexamethasone 20 mg. Most common toxicities included sensory neuropathy, fatigue, lymphopenia, neutropenia and thrombocytopenia. All patients had a partial response 74% achieving very good partial response or better. In the EVOLUTION trial, patients were randomized to receive bortezomib 1.3 mg/m^2 d 1, 4, 8, 11 and dexamethasone 40 mg d 1, 8, 15, with either cyclophosphamide 500 mg/m^2 d 1, 8 and lenalidomide 15 mg d 1–14 (VDCR), lenalidomide 25 mg d1-14 (VRd), cyclophosphamide 500 mg/m^2 d 1, 8 (VCD) or cyclophosphamide 500 mg/m^2 d 1, 8, 15 (VCD-mod) in a 21 day cycle (maximum 8 cycles).[13,14] This was followed by bortezomib 1.3 mg/m^2 (d 1, 8, 15, 22) for four 42-day maintenance cycles in all arms. VGPR or better was seen in 58, 51, 41 and 53% (CR rate of 25, 24, 22 and 47%) of patients (VDCR, VRd, VCD and VCD-mod arms, respectively); the corresponding progression-free survival (PFS) at 1 year was 86, 83, 93 and 100%, respectively. In a recently presented phase 3 trial, the combination of VRd was associated with increased response rates, deeper responses, increased PFS and improved overall survival compared with lenalidomide and dexamethasone. In the SWOG0777 trial, 525 patients with newly diagnosed myeloma were randomized to lenalidomide with or without bortezomib. Median PFS was 43 months (VRd) versus 31 months (Rd). Median OS was not reached (VRd) versus 63 months (Rd); HR = 0.666; two-sided log-rank p-value = 0.0114.

1.4 ***Carfilzomib:*** More recently, development of a next generation proteasome inhibitor namely carfilzomib (Cfz), has introduced the possibility of enhancing the efficacy of a three drug combination with significantly reduced toxicity. Carfilzomib targets the chymotrypsin-like activity of the 20S proteasome.[15-18] Carfilzomib is a selective inhibitor and binds most specifically to the chymotrypsin-like protease, with less activity against the other subunits. In addition, carfilzomib demonstrates less reactivity against non-proteasomal proteases when compared to bortezomib.

Carfilzomib has been shown to have significant anti-myeloma activity in the setting of relapsed myeloma both in bortezomib naïve as well as bortezomib refractory patients.[19-23] The toxicity pattern suggested that the drug is well tolerated, and in particular seemed to have very low rate of neuropathy. In relapsed or refractory MM patients treated at 20–27 mg/m^2, the most common adverse events (AEs) are anemia, fatigue, nausea, diarrhea, and cyclic thrombocytopenia. Peripheral neuropathy of any grade regardless of relationship to study drug is < 15% despite the majority of patients entering these studies with existing Grade 1 or 2 peripheral neuropathy. The most common Grade 3/4 AEs are anemia (14%), thrombocytopenia (12%), pneumonia (6%), and fatigue (5%). Importantly, Grade 3/4 neutropenia occurs in < 5% and Grade 3/4 peripheral neuropathy in < 3% (includes neuropathy, peripheral neuropathy, and neuropathic pain), despite the fact that nearly all of the patients have these conditions as a result of their prior drug therapies and disease. These results are consistent with the lack of myelosuppressive and neuropathic effects of carfilzomib in preclinical studies.

In the newly diagnosed setting, the combination of carfilzomib with lenalidomide and dexamethasone (KRd) was evaluated in a recent phase 1/2 trial.[24] After 4 cycles of therapy all patients had a response including 59% with VGPR or better and 36% with a nCR or better. After a median of 12 cycles (range, 1-25), 62% (N = 53) achieved at least near-complete response (CR) and 42% stringent CR. Responses were rapid and improved during treatment. In 36 patients

completing 8 or more cycles, 78% reached at least near CR and 61% stringent CR. The toxicities were mostly hematologic and no grade 3 or higher neuropathy was seen. Grade 1 or 2 neuropathy was seen in less than 10% of patients. Stem cell collection was successful in all patients in whom it was attempted. At 6-month median follow up, no disease progression was observed. The overall CR rate with KRd is much higher than those seen with VRd. Higher CR rate have been shown to translate into better overall survival both in the non-transplant and transplant setting.[25-27]This is particularly true when more sensitive tests of minimal residual disease like flow cytometry or PCR have been used to demonstrate a more profound reduction of tumor burden.

Particularly relevant for the current study has been the phase 2 study of KRd in patients with high-risk smoldering myeloma. In a phase 2 study, patients with NDMM or high-risk SMM were treated with eight 28-day cycles of carfilzomib 20/36 mg/m^2 on days 1, 2, 8, 9, 15, and 16; lenalidomide 25 mg on days 1 through 21; and dexamethasone 20/10 mg (cycles 1-4/5-8) on days 1, 2, 8, 9, 15, 16, 22, and 23. Patients who achieved at least stable disease continued on lenalidomide for 24 cycles. Among the 12 patients with high-risk SMM, the most common adverse events were lymphopenia and gastrointestinal disorders. All patients with SMM achieved at least a very good partial response during the study period. Among the 28 patients with NDMM and the 12 with SMM achieving at least a near-complete response, MRD negativity was found in 100%.

KRd in combination with autologous stem cell transplantation has been studied in patients with high risk SMM in the CESAR trial.[19] The HR was defined by the presence of both bone marrow plasma cells (PCs)≥ 10% and serum M-protein ≥3g/dL or if only one criterion was present, patients must have a proportion of aberrant PCs within the total PCs bone marrow compartment by immunophenotyping of 95% plus immunoparesis. Induction therapy consisted of six 4-weeks cycles of KRd followed by ASCT with melphalan conditioning. Three months later, patients received two cycles of KRd consolidation followed by maintenance with lenalidomide. The ORR was 98% for the 43 patients who completed the 6 induction cycles; 46% of ≥CR, MRD by NGF was negative in 38%. Of the 29 patients who received ASCT and were evaluable at 3 months: the ORR was 100% including ≥CR in 69%; MRD was negative in 17 out of these 29 patients (58%). Among the 19 patients who completed the two planned consolidation cycles, 85% had ≥CR, including sCR in 74%, CR in 11% and VGPR in 16%. Toxicity was manageable and ASCT was feasible. After a median f/u of 13 months (1-108), 98% of patients remain free of progression and alive.

1.5 ***Lenalidomide in myeloma:*** Lenalidomide, an immunomodulatory drug, is a thalidomide derivative with a very distinct toxicity profile compared with thalidomide. It has significant activity in the setting of multiple myeloma; both in relapsed and in newly diagnosed disease.

Initial phase I/II study of lenalidomide in relapsed myeloma determined the ideal dose to be 25 mg once daily given for 3 of 4 weeks.[20] The initial trial in the relapsed disease also demonstrated increased activity in combination with pulsed doses of dexamethasone. These findings led to the initial trials of the combination in newly diagnosed disease as well as randomized trials of the combination in relapsed myeloma.[21] In the phase 3 trials of lenalidomide and dexamethasone, the combination was demonstrated to be superior to dexamethasone in terms of response rates and progression free and overall survival.[22] The initial phase 2 study of lenalidomide and dexamethasone in newly diagnosed myeloma, conducted at the Mayo Clinic, also employed the

combination of lenalidomide and pulsed dose dexamethasone (40 mg daily on four days on four days off schedule) for the first four cycles followed by 40 mg weekly for the subsequent cycles. The phase 2 study demonstrated significant response rates and long term follow up demonstrated sustained responses and 1-year survival rates of over 90%. The subsequent phase 3 trial in the ECOG (E4A03) compared the same dosing strategy to one that employed a lower dose of dexamethasone (40 mg weekly) right from the start of therapy.[22] The results of the trial demonstrated a superior overall survival for the lower dose dexamethasone arm.

More recently, lenalidomide has been studied in older patients ineligible for stem cell transplantation, where two different duration of therapy were compared to the combination of melphalan, thalidomide and dexamethasone. In the FIRST trial, 1623 patients were randomized to lenalidomide and dexamethasone in 28-day cycles until disease progression, to the same combination for 72 weeks (18 cycles), or to MPT for 72 weeks. The median progression-free survival was 25.5 months with continuous lenalidomide-dexamethasone, 20.7 months with 18 cycles of lenalidomide-dexamethasone, and 21.2 months with MPT; P<0.001 for both comparisons). Overall survival at 4 years was 59% with continuous lenalidomide-dexamethasone, 56% with 18 cycles of lenalidomide-dexamethasone, and 51% with MPT. Grade 3 or 4 adverse events were less frequent with continuous lenalidomide-dexamethasone compared with MPT (70% vs. 78%). Compared with MPT, continuous lenalidomide-dexamethasone was associated with fewer hematologic and neurologic toxic events, and a moderate increase in infections.

Most relevant to the current study is the randomized phase 3 trial of lenalidomide and dexamethasone in patients with high risk SMM.[23] In a phase 3 trial, 119 patients with high-risk smoldering myeloma were randomly assigned to treatment with lenalidomide and dexamethasone or observation. Patients in the treatment group received an induction regimen (lenalidomide at a dose of 25 mg per day on days 1 to 21, plus dexamethasone at a dose of 20 mg per day on days 1 to 4 and days 12 to 15, at 4-week intervals for nine cycles), followed by a maintenance regimen (lenalidomide at a dose of 10 mg per day on days 1 to 21 of each 28-day cycle for 2 years). After a median follow-up of 40 months, the median time to progression was significantly longer in the treatment group than in the observation group (median not reached vs. 21 months; P<0.001). The 3-year overall survival was also higher in the treatment group (94% vs. 80%; P=0.03). A partial response or better was achieved in 79% of patients in the treatment group after the induction phase and in 90% during the maintenance phase. Toxic effects were mainly grade 2 or lower and managed with dose modifications.

1.6 ***Daratumumab in myeloma***: Daratumumab is a human IgG1κ monoclonal antibody (mAb) that binds with high affinity to a unique epitope on CD38, a transmembrane glycoprotein. It is a targeted immunotherapy directed towards tumor cells that express high levels of CD38, such as plasma cells from patients with multiple myeloma. This target is distinct from those of other approved agents for multiple myeloma therapy.
Nonclinical Studies with daratumumab: Based on preclinical data, daratumumab may utilize multiple effector cell functions, resulting in immune mediated killing of tumor cells. In ex vivo experiments utilizing human bone marrow stromal cells co-cultured with primary multiple myeloma cells, complement-dependent cytotoxicity (CDC) occurs rapidly and demonstrates maximal myeloma cell killing by daratumumab within 1 hour of antibody-mediated activation of the complement proteins. Daratumumab-induced antibody-dependent cell-mediated cytotoxicity (ADCC) is slower in its action, with maximal ADCC by daratumumab observed at 4

hours in vitro. Daratumumab has also been shown to induce antibody-dependent cellular phagocytosis (ADCP) in the presence of macrophages within 4 hours in vitro The precise role of some or all of these effector functions in reducing tumor burden in patients is unknown. In toxicology studies in cynomolgus monkeys and chimpanzees, the major observed toxicities were cytokine release syndrome and thrombocytopenia. A minor decrease in red blood parameters was also observed. Cytokine release was seen only following the first dose and was markedly reduced following implementation of a 10-mg predose of daratumumab. The effect on platelets and red blood cells was reversible.
For the most comprehensive nonclinical and clinical information as well as Reference Safety Information regarding daratumumab, refer to the latest version of the Daratumumab United States Package Insert (USPI).

Clinical studies with daratumumab

Single agent studies: Two large single agent studies have been reported to date; GEN501 and MMY2002.[24-26] In the GEN501 study, daratumumab was administered at doses of 0.005 to 24 mg per kilogram of body weight during the dose escalation phase. No maximum tolerated dose was identified. In the dose-expansion phase, 30 patients received 8 mg per kilogram of daratumumab and 42 received 16 mg per kilogram, administered once weekly (8 doses), twice monthly (8 doses), and monthly for up to 24 months. In the expansion phase, the median time since diagnosis was 5.7 years. Subjects had received a median of four prior treatments; 79% of the subjects had disease that was refractory to the last treatment received (64% had disease refractory to proteasome inhibitors and immunomodulatory drugs and 64% had disease refractory to bortezomib and lenalidomide), and 76% had received autologous stem-cell transplants. Infusion-related reactions were mild (71% of subjects had an event of any grade, and 1% had an event of grade 3), with no dose-dependent adverse events. The most common adverse events of grade 3 or 4 (in ≥5% of subjects) were pneumonia and thrombocytopenia. The overall response rate was 36% in the cohort that received 16 mg per kilogram (15 subjects had a partial response or better, including 2 with a complete response and 2 with a very good partial response) and 10% in the cohort that received 8 mg per kilogram (3 had a partial response). In the cohort that received 16 mg per kilogram, the median progression-free survival was 5.6 months (95% confidence interval [CI], 4.2 to 8.1), and 65% (95% CI, 28 to 86) of the subjects who had a response did not have progression at 12 months.

In the MMY2002 study, subjects with multiple myeloma who were previously treated with at least three lines of therapy (including proteasome inhibitors and immunomodulatory drugs), or were refractory to both proteasome inhibitors and immunomodulatory drugs, were randomized to receive intravenous daratumumab 8 mg/kg or 16 mg/kg in in the initial part of the study. Subjects received 8 mg/kg every 4 weeks, or 16 mg/kg per week for 8 weeks (cycles 1 and 2), then every 2 weeks for 16 weeks (cycles 3–6), and then every 4 weeks thereafter (cycle 7 and higher). In the second part of the study, the dose of 16 mg/kg was taken forward. One-hundred-six subjects with a median of five previous lines of therapy (range 2–14) were treated at the 16 mg/kg dose. 85 (80%) subjects had previously received autologous stem cell transplantation, 101 (95%) were refractory to the most recent proteasome inhibitors and immunomodulatory drugs used, and 103 (97%) were refractory to the last line of therapy. Overall, responses were seen in 31 subjects (29.2%,)—three (2.8%) with a stringent CR, ten (9.4%) with a VGPR, and 18 (17.0%) with a PR. Median duration of response was 7.4 months (95% CI 5.5–not estimable) and progression-free survival was 3.7 months and the 12-month overall survival was 64.8%.

Daratumumab was well tolerated; fatigue (40%) and anemia (33%) were the most common adverse events.

Daratumumab-lenalidomide combinations: Pre-clinically, using bone marrow mononuclear cells from subjects with multiple myeloma, increased killing of tumor cells was demonstrated when daratumumab was combined with lenalidomide as compared with that of either agent alone.

In an open-label phase 1/2 study GEN503 daratumumab administered at 2-16 mg/kg was combined with standard dose of lenalidomide and dexamethasone, leading to a recommended phase 2 dose of dara 16 mg/kg along with lenalidomide 25 mg days 1-21 and dexamethasone 40 mg weekly. DARA 16 mg/kg was administered weekly during the first two 28-day cycles, every other week during Cycles 3 through 6, and monthly in Cycle 7 and beyond until disease progression or unacceptable toxicity. LEN 25 mg was administered orally on Days 1 through 21 of each cycle, and DEX 40 mg was given weekly. Thirty two subjects with median of 2 prior lines of therapy were enrolled. The most common (>25%) TEAEs included neutropenia (81%), muscle spasms (44%), cough (38%), diarrhea (34%), fatigue and hypertension (28% each). Eighteen (56%) subjects had IRRs and these were generally mild to moderate and occurred mostly during the first cycle. IRRs included cough (25%), allergic rhinitis, nausea, and vomiting (9% each), as well as dyspnea, nasal congestion, and hypertension (6% each). The overall response rate was 88%, with 11 (34%) partial responses and 17 (53%) ≥very good partial responses (VGPRs) that included 7 (22%) stringent complete responses, 1 (3%) complete response, and 9 (28%) VGPRs. The median time to first and best response was 1 month and 4.5 months, respectively. Results of this study confirm the efficacy of combining daratumumab with lenalidomide and dexamethasone. A large phase 3 trial of Daratumumab and Rd versus Rd has completed accrual.

Carfilzomib, lenalidomide, dexamethasone and daratumumab (KRd-Dara): This combination has been studied in newly diagnosed myeloma with manageable toxicity and excellent efficacy.[27] In a phase 2 trial, Jakubowiak et al reported on 22 newly diagnosed MM pts receiving daratumumab in combination with KRd. Among the 22 pts enrolled in the study, the median (range) age was 59.5 (34-74) years and 95% of pts had an ECOG score ≤1. After median (range) duration of follow-up of 13.1 (6.6-14.9) months, pts received a median (range) of 12 (1-13) treatment cycles. Treatment discontinuations were due to elective ASCT (n = 6), adverse events (AE; n = 1), and progressive disease (n = 1). The ORR was 100% among the 21 response-evaluable patients including 43% sCR, 14% CR, 33% VGPR, and 10%PR.

1.7 Rationale for the current trial: Myeloma remains incurable with the current approaches. Even though the median overall survival for MM in general has reached 10 years in many recent studies, patients with high-risk MM have survival that has not improved to the same degree. Given that MRD negativity appear to overcome the impact of the poor risk genetic abnormalities, it is reasonable to hypothesize that deep responses using rational combinations of all available drug classes in a response adapted fashion will allow us to improve the outcomes of patients with high-risk MM and may translate into cure or long-term disease quiescence. So we propose to use a 4-drug combination that will utilize the most active agents for initial treatment of HR-MM, and then use a response adapted strategy with a immunotherapeutic approach for those failing to achieve MRD negativity after 24 cycles of one of the most effective combinations.

2.0 Objectives

2.1 Primary Objective

2.11 To estimate the rate of sustained MRD negativity (MRD negative status at any point, with a repeated MRD negative status one year later) in subjects with high-risk multiple myeloma.

2.2 Secondary Objective

2.21. To describe the toxicities associated with this treatment approach in subjects with high-risk MM.

2.22. To estimate the overall response rate, VGPR or better rate and CR rate at the end of induction, end of consolidation, end of maintenance and at two years after the completion of treatment.

2.23. To estimate the progression-free survival and overall survival rate.

2.3 Correlative Research

2.31 To describe the clonal architecture through a combination of genomic, epigenomic, proteomic and metabolomic studies before and after treatment, in subjects with high-risk MM.

2.32 To describe the bone marrow microenvironment through various stages of treatment and the time of MRD negative state and at time of relapse.

3.0 Subject Eligibility

3.1 Pre-registration - Inclusion Criteria

3.11 Age $\geq$18 years and $\leq$80 years

3.12 Patient must have suspected or confirmed newly diagnosed multiple myeloma by International Myeloma Working Group (IMWG) criteria.

3.13 ECOG performance status (PS) 0 or 1 (Appendix VII)

3.14 Provide informed written consent.

3.15 Willing to return to enrolling institution for follow-up during the Active Treatment Phase of the trial.

3.16 Willing to provide blood and bone marrow samples for planned research

3.17 Life expectancy > 6 months

3.18 Able to take aspirin (325 mg) daily as prophylactic anticoagulation. Note: Subjects intolerant to aspirin may use warfarin, novel oral anticoagulants, or low dose molecular weight heparin.

3.19 Patients must have monoclonal protein studies (serum free light chain assay, serum immunofixation or serum MASS-FIX) at time of diagnosis before induction therapy initiated and available for review to be enrolled. Note: Patients are allowed to

participate in this study if urine electrophoresis immunofixation study was not done at time of diagnosis or cannot be obtained

3.2 Pre-registration - Exclusion Criteria

3.21 MGUS, smoldering myeloma, light chain amyloidosis with organ involvement

3.22 Diagnosed or treated for another malignancy ≤ 1 year prior to pre-registration or previously diagnosed with another malignancy and have any evidence of residual disease. NOTE: Subjects with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

3.23 Other co-morbidity which would interfere with subject's ability to participate in trial, e.g. uncontrolled infection, uncompensated heart or lung disease.

3.24 Other concurrent chemotherapy, or any ancillary therapy considered investigational. NOTE: Concurrent chemotherapy is any treatment not related to multiple myeloma.

NOTE: Bisphosphonates are considered to be supportive care rather than therapy, and are thus allowed while on protocol treatment.

3.25 Peripheral neuropathy ≥ Grade 3 on clinical examination or grade 2 with pain ≤30 days prior to registration.

3.26 Major surgery ≤14 days prior to pre-registration.

3.27 Any medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

3.28 Known allergies, hypersensitivity, or intolerance to corticosteroids, monoclonal antibodies or human proteins, or their excipients (refer to respective package inserts or Investigator's Brochure) or known sensitivity to mammalian-derived products. Known allergies, hypersensitivity, or intolerance to trial drugs.

3.29a Inability to comply with protocol/procedures.

3.29b Received prior treatment for multiple myeloma prior to pre-registration. Note: results can still be pending as long as the tests have been performed.

3.3 Registration - Inclusion Criteria

3.31 **High risk myeloma**, which is untreated, defined as any two of:
a) Beta-2 microglobulin >5.5
b) gain or amplification of chr1q
c) del17p or monosomy 17 or TP53 mutation (if known)
d) t(4;14) or t(14;16)
e) ≥5% circulating plasma cells
f) presence of extramedullary disease (does not include bone contiguous disease)

3.32 The following laboratory values obtained ≤14 days prior to registration.
Calculated creatinine clearance (using Cockcroft-Gault equation below)*

- ≥ 30 mL/min
- Absolute neutrophil count (ANC) ≥1000/mm^3 (without the use of growth factors)
- Platelet count ≥75000/mm^3
- Hemoglobin ≥8.0 g/dL
- Total bilirubin ≤ 1.5 x ULN
- ALT and AST ≤ 3 x ULN

*Cockcroft-Gault Equation:
Creatinine clearance for males =
(140 - age)(actual body weight in kg)/ (72)(serum creatinine in mg/dL)
Creatinine clearance for females =
(140- age)(actual body weight in kg)(0.85)/(72)(serum creatinine in mg/dL)

3.33 Registration must be completed ≤30 days after pre-registration.

3.34 Patients must not have received more than one cycle of treatment between pre-registration and registration.

3.35 All 4 drugs in the study regimen approved by insurance.

3.36 LVEF ≥ 40% ≤30 days prior to registration

3.4 Registration - Exclusion Criteria

3.41 If any of the following exist at screening, subject will not be eligible for trial because this trial involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown:

- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception (per protocol)

3.42 Evidence of current uncontrolled cardiovascular conditions, including hypertension, cardiac arrhythmias, congestive heart failure, unstable angina, or myocardial infarction within the past 6 months. Note: Prior to trial entry, any ECG abnormality at screening must be documented by the investigator as not medically relevant.

3.43 NYHA II, III, IV heart failure

3.44 Known human immunodeficiency virus (HIV) positive.

3.45 Seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg]). Subjects with resolved infection (ie., 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.

3.46 Known or suspected active hepatitis C infection.

4.0 Schedule of Events

Tests and procedures	Pre-registration (step 0)[16]	Prior to registration (step 1)	Active monitoring phase					
			Induction C1-12[11]	End of Induction	Consolidation C13-24	End of Consolidation	Maintenance C25-36	End of treatment/ Safety visit[12]
	≤30 days	≤14 days	Every cycle; pre tx	≤7 days prior to C13D1	D1 of each cycle; pre tx	w/in 7 days prior to C25D1	D1 of each cycle; pre tx	
Signed ICF	X							
Complete Med Hx	X							
AE		X	X (weekly for C1,C2)		X		X	X
PE, Wgt, Ht (screen only), Vitals[1]		X	X		X		X	X
ECOG	X		X		X		X	X
CBC w/ diff[2]		X	X (weekly for C1,C2)		X		X	X
Chemistry[2]		X	X (weekly for C1,C2)		X		X	X
Hepatitis B (HBV) Serology[12]		X (≤30 days)						
HBV DNA Testing[13]		X (≤30 days)	X (q 12 wks)		X (q 12 wks)		X (q 12 wks)	X
LDH, B_2 Microglobulin	X					X		X
SPEP/UPEP[3]	X		X		X		X	X
Affected IGs[4]	X		X		X		X	X
Serum & Urine Immunofixation[5]	X		X		X		X	X
Serum FLC[6]	X		X		X		X	X
ECHO or MUGA (to assess LVEF)		X (≤30 days)		X		X		X
ECG		X (≤30 days)		X		X		X
Skeletal Survey (whole body low dose CT, PET/CT, or MRI)[16]		X (≤60 days)	X[15]		X[15]			X

Tests and procedures	Pre-registration (step 0)[16]	Prior to registration (step 1)	Active monitoring phase					
			Induction C1-12[11]	End of Induction	Consolidation C13-24	End of Consolidation	Maintenance C25-36	End of treatment/ Safety visit[12]
	≤30 days	≤14 days	Every cycle; pre tx	≤7 days prior to C13D1	D1 of each cycle; pre tx	w/in 7 days prior to C25D1	D1 of each cycle; pre tx	
Bone marrow aspirate/biopsy w/ FISH (scn only) & flow cytometry[7]	X (≤60 days)			X		X		X
Research bone marrow[7,R] submission per IRB# 521-93 (RST) IRB# 919-04 (ARZ) IRB# 14-009163 (FLA)	X[14]		X[7]	X		X		X
Research blood sample[8,R] per IRB# 521-93(RST) IRB# 919-04 (ARZ) IRB# 14-009163 (FLA)	X		X[8]	X		X		X
Indirect Antiglobulin Test (IAT)[9]		X (≤30 days)						
Chest X-ray		X (≤30 days)						
Serum pregnancy test[10]		X	X		X		X	

Cycle = 28 days (±4 days)

Note: The value closest to the time of starting treatment should be considered as baseline value for response assessment

All scheduled visits will have a window of ± 4 days unless otherwise stated. End of phase visits should be within 7 days of the scheduled start date of the next phase.

1. Vital signs include heart rate and blood pressure (collected via standard of care process).
2. CBC with differential to include Hgb, WBC, and platelets. Chemistry panel to include creatinine, calcium, bilirubin – total and direct, AST, ALT, alkaline phosphatase, albumin and BUN.
3. 24-hour urine for UPEP is required at screening for all patients and then at Day 1 of each cycle only if urine M protein meets the requirement for measurable disease. It is also required for all patients to document VGPR and CR. Once the patient has two negative urine tests to document response, it does not need to be repeated again if patient was not initially being followed by urine tests. See Section 11 for details.
4. Affected Igs refer to the baseline M-protein type, that is, IgG, IgA, or IgD. Not applicable if subject is "non-secretory" or if the subject has no chain, i.e. light chain myeloma.

5. Immunofixation is required at pre-registration and then in the absence of M-spike to document CR or sCR.
6. FLC is required at screening for all subjects. If being followed by FLC, it is required at each cycle as specified. If not being followed by FLC, then only required post screening to confirm a sCR.
7. Bone marrow aspirate and biopsy required at pre-registration, end of cycles 1, 3, 6, 18, and end of induction, end of consolidation, at CR, at progression, and in those shown to be MRD negative, one year after documentation of MRD negativity. MRD assessment will be done using commercial Adaptive clonSEQ test. FISH is required at screening only and should be performed locally. Flow cytometry will be done centrally as part of research assessment. Research aspirate must be collected within 30 days of C1D1, so it is recommended that screening marrow and aspirate are done within this time period to avoid having to repeat the aspirate. If a bone marrow aspirate and biopsy is required for confirmation of CR, and a scheduled marrow is due within 60 days, the testing can be held until the scheduled marrow. If a scheduled bone marrow aspirate and biopsy was done within 60 days of the marrow needed for confirmation of CR and showed < 5% plasma cells, then it does not need to be repeated.
8. Research blood samples are required at pre-registration, end of cycles 1, 3, 6, 18, and end of induction, end of consolidation, at CR, at progression, and in those shown to be MRD negative, one year after documentation of MRD negativity.
9. Daratumumab treatment will affect the indirect antiglobulin test (IAT), so this test should be performed prior to study treatment. Effects can last for 6 months after stopping treatment.
10. For women of childbearing potential only. Must be done with 10-14 days prior to starting treatment and again within 24 hours prior. FCBP with regular or no menstrual cycles must have pregnancy tests weekly for the first 28 days and then every 28 days while on study, at study discontinuation, and 28 days post discontinuation. FCBP with irregular menstrual cycles must have pregnancy tests weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14- and 28-days following discontinuation.
11. SPEP/UPEP, affected immunoglobulins, and serum FLC as well as Physical Exam and ECOG PS do not need to be repeated at C1D1 if done within 14 days of C1D1
12. Tests do not need to be repeated if performed within 14 days. End of treatment HBV DNA testing does not need to be repeated if performed within 12 weeks.
13. Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc) is required for all patients at screening within 90 days of starting study treatment. For subjects with serologic evidence of resolved HBV infection (i.e., positive Anti-HBs or positive Anti-HBc) at screening, HBV DNA testing by PCR must be performed locally at screening, every 12 weeks during treatment, at the end of treatment with daratumumab, and every 12 weeks for up to 6 months after the last dose of daratumumab. Additionally, subjects ongoing in the Treatment Phase who are within 6 months of starting study treatment will be required to have HBV serology. HBV serology is not required at Screening or for subjects ongoing in the Treatment Phase who are within 6 months of starting study treatment if this was performed as part of standard of care within 3 months prior to the first dose. Subjects who are positive for Anti-HBc or Anti-HBs will undergo testing for hepatitis B DNA by PCR. Subjects with serologic finding 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. During and following study treatment, subjects who have history of HBV infection will be closely monitored for clinical and laboratory signs of reactivation of HBV.
14. The research bone marrow can be collected any time before start of treatment. The pre-reg step is to allow for patients to have marrow collected while their risk status was being determined
15. Every 12 cycles. For patients with extramedullary disease only, imaging is required every 3 cycles until complete response and then every 6 months or sooner at the discretion of the treating physician. Results of tests included in pre-registration need to be completed before standard of care therapy, but results may still be pending.
16. Disease measurement parameters are required prior to standard of care therapy. Results of tests included in pre-registration need to be completed before standard of care therapy, but results may still be pending.
R Research funded (see Section 19.0). Will be charged to IRB #521-93/919-04/14-009613 not to patient's account.

4.2 Survival Follow-up

	Survival Follow-up[1] (±30 days)				
	q. 3 months until PD, relapse, or subsequent non protocol therapy (±14 days)	At PD	After PD, relapse, or subsequent non-protocol therapy q. 6 months	Death	New Primary
Survival Follow-up[2]	X	X	X	X	At each occurrence

1. All timelines in this table are approximate and may vary by a month or more
2. If a patient is still alive 3 years after registration, no further follow-up is required.

5.0 Study Cohorts:

5.1 Cohorts: single cohort study

Treatment will include 12 cycles of induction and 12 cycles of consolidation, followed by carfilzomib + lenalidomide + daratumumab maintenance for those who are MRD negative. Those with persistent MRD positivity may proceed to alternate therapy.

6.0 Registration Procedures

6.1 Pre-registration (step 0)

6.11 Registering a patient

To register a patient, access the Mayo Clinic Research Registration Application at [redacted] The Research Registration Application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the website. If unable to access the website, contact the Mayo Clinic Research Site Management Office at [redacted] or [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

Access and training instructions for the registration/randomization application are available on the Mayo Clinical Office of Clinical Trials web page ([redacted]) and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and an MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release

of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact Mayo Clinic Research Site Management at [redacted]. If the patient was fully registered, the Research Site Management staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC Subject ID number (R######) must be assigned. It is the responsibility of the individual submitting the registration for the patient to confirm the process has been successfully completed prior to release of the study agent.

6.12 Verification of information

Prior to accepting the pre-registration, the registration/randomization application will verify the following:

- IRB approval at the registering institution
- Patient pre-registration eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information.

6.13 Pre-registration tests/procedures

Pre-registration tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.2 Registration (step 1):

6.21 Registering a patient

To register a patient, access the Mayo Clinic Research Registration Application at [redacted]. The Research Registration Application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the website. If unable to access the website, contact the Mayo Clinic Research Site Management Office at [redacted] or [redacted] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

The instructions for the registration/randomization application are available on the Mayo Clinical Office of Clinical Trials web page [redacted]) and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and an MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release

of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact Mayo Clinic Research Site Management at [redacted] If the patient was fully registered, the Research Site Management staff can access the information from the centralized database and confirm the registration.
- Refer to "Instructions for Remote Registration" in section "Finding/Displaying Information about A Registered Subject."

Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC Subject ID number (R######) must be assigned. It is the responsibility of the individual submitting the registration for the patient to confirm the process has been successfully completed prior to release of the study agent.

6.2 Correlative Research

A mandatory correlative research component is part of this trial. The subject will be automatically registered onto this component (see Sections 3.1 and 14.0).

6.3 Verification of information

Prior to accepting the registration, registration/randomization application will verify the following:

- IRB approval at the registering institution
- Subject eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information, if applicable.

6.4 Documentation of IRB approval

Documentation of IRB approval must be on file in the Research Site Management Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) with Research Site Management (fax: [redacted] or email [redacted]). If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted, and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Research Site Management Office is no longer necessary.

6.5 Treatment on protocol

Treatment on this protocol must commence at Mayo Clinic under the supervision of a hematologist.

6.6 Treatment start

Treatment cannot begin prior to registration and must begin ≤14 days after registration.

6.7 Pretreatment (Screening)
Pretreatment tests/procedures must be completed within the guidelines specified on the schedule of events (see Section 4.0).

6.8 Baseline symptoms
All required baseline symptoms must be documented and graded.

6.9a Study drug
Study drugs are available

6.9b Study Conduct
The clinical trial will be conducted in compliance with regulations (21 CFR 312, 50, and 56), guidelines for Good Clinical Practice (ICH Guidance E6), and in accordance with general ethical principles outlined in the Declaration of Helsinki; informed consent will be obtained from all participating subjects; the protocol and any amendments will be subject to approval by the designated IRB/IEC prior to implementation, in accordance with 21 CFR 56.103(a); and subject records will be stored in a secure location and subject confidentiality will be maintained. The investigator will be thoroughly familiar with the appropriate use of the trial drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the trial and the integrity of the data collected. Master files should be established at the beginning of the trial, maintained for the duration of the trial and retained according to the appropriate regulations.

7.0 Protocol Treatment

Per Notice of Status Change 08Jan2026: enrollment is permanently closed and patients currently on study should be taken off study and move to long term follow-up.

- This is a phase 2 clinical trial in subjects with high-risk multiple myeloma.
- Dose modifications for toxicity are outlined in Section 8.
- All subjects are planned to receive treatment as outlined in the schema, except for unacceptable toxicity or withdrawal of consent.
- All subjects will take aspirin (325 mg) daily as prophylactic anticoagulation. Subjects intolerant to aspirin may use warfarin, novel oral anticoagulants, or low molecular weight heparin.
- An individual subject will be considered off-treatment following a safety follow-up period after the last cycle of treatment.

7.1 Treatment Schedule

7.11 Induction

Table 7.1 Induction Cycles 1-12

Drug	Route	Dose	Schedule Each cycle is 28 days
Dexamethasone	Oral/IV	40 mg	Days 1, 8, 15 and 22 < 75 years old: 40 mg ≥ 75 years old: 20 mg
Daratumumab**	SQ	1800 mg	Cycles 1 and 2: Days 1, 8, 15, 22 Cycles 3, 4, 5, 6: Days 1, 15 Cycles 7 onwards: Day 1
Carfilzomib*	IV	56 mg/m^2	C1: Days 1,2 (if needed), 8, 15 (C1 Day 1 and Day 2 if needed will be at 20 mg/m^2) C2-12: Days 1, 8, 15
Lenalidomide#	Oral	25 mg	Days 1-21

Cycle = 28 days (± 4 days)

* Maximum dose for carfilzomib is capped at a BSA of 2.2 m^2

In patients with creatinine clearance of 30-59 ml/min, starting dose of lenalidomide should be reduced to 10 mg. If the clearance improves to ≥ 60 ml/min, the dose can be increased to 25 mg (or the next dose level from current dose) provided the patient has not experienced any of the toxicities that would have required a dose reduction for lenalidomide. Starting lenalidomide dosing can be adjusted if patient received lenalidomide in previous cycle of standard of care (SOC) treatment and was found to not tolerate a 25 mg dose.

**Patients who have received up to 4 weekly doses of daratumumab as part of Cycle 1 of a non-protocol regimen prior to the enrollment will receive a modified on-protocol schedule of daratumumab to ensure that they are administered no more than 8 doses in the initial 2 cycles of the antimyeloma regimen (including the non-protocol Cycle 1 of the daratumumab-containing regimen as per the standard loading of daratumumab).

Pre-infusion Medication: On daratumumab injection days, subjects will receive the following medications prior to infusion:

- Acetaminophen (paracetamol) 650-1000 mg orally (PO) approximately 1 hour or less prior to daratumumab injection, or per current institutional standards
- An antihistamine (diphenhydramine 25-50 mg PO, or equivalent) approximately 1 hour prior to injection, or per current institutional standards
- Dexamethasone 40 mg PO (or IV push/injection) approximately 1 hour prior to daratumumab injection during the induction phase. On days when subjects receive this dose of dexamethasone in the clinic, dexamethasone will not be self-administered at home. The dose of dexamethasone premed can be split over two days in case of intolerance.

7.12 Consolidation

Table 7.2 Consolidation Cycles 13-24

Drug	Route	Dose	Schedule Each cycle is 28 days
Daratumumab	SQ	1800 mg	Day 1
Carfilzomib	IV	36 mg/m2	Days 1, 8, 15
Lenalidomide	Oral	15 mg	Days 1-21

Cycle = 28 days (±4 days)

7.13 Maintenance

Table 7.3 Maintenance Cycles 25-36

Drug	Route	Dose	Schedule Each cycle is 28 days
Daratumumab	SQ	1800 mg	Day 1
Carfilzomib	IV	36 mg/m2	Days 1
Lenalidomide	Oral	10 mg	Days 1-21

Cycle = 28 days (±4 days)

7.2 Daratumumab

- Induction: Subjects will receive daratumumab SQ weekly for 8 weeks, then every other week for 16 weeks, then every 4 weeks for 24 weeks Consolidation and Maintenance: subjects will receive daratumumab SQ Day 1 Cycles 13-36.
- Subjects will be observed per Mayo Clinic practice. Reasons for continued observation on daratumumab injections may include but are not limited to the following: subjects with a higher risk of respiratory complications (eg, subjects with mild asthma or subjects with COPD who have an FEV1 < 80% or developed FEV1 < 80% during the study without any medical history), subjects with IRRs with first injection of study drug, or subjects with a decreased condition on day of dosing compared to the prior dosing day.
- Vital signs should be monitored per Mayo Clinic practice.

- Missed doses will not be made up. Procedures for dose reductions and delays are summarized in Section 8.5.
- There are no planned dose reductions.
- Daratumumab is commercially available.

7.3 Carfilzomib

- For cycles 1-24, subjects will receive carfilzomib weekly for 3 weeks (Days 1, 8, 15) with a week off of each 28-day cycle.
- For cycles 25-36, subjects will receive carfilzomib on Day 1 of each 28-day cycle.
- Maximum dose for carfilzomib is capped at a BSA of 2.2 m^2
- Procedures for carfilzomib dose reductions and delays are summarized in Section 8.2, along with the criteria that must be met for retreatment with trial drug. If a dose is missed due to toxicity, the dose will not be made up.
- Carfilzomib is commercially available

7.4 Lenalidomide

- Subjects will receive lenalidomide orally once daily on days 1-21 of the 28 day cycle at about the same time each day (window ±4 days).
- In patients with creatinine clearance of 30-59 ml/min, starting dose of lenalidomide should be reduced to 10 mg. If the clearance improves to ≥ 60 ml/min, the dose can be increased to 25 mg (or the next dose level from current dose) provided the patient has not experienced any of the toxicities that would have required a dose reduction for lenalidomide. Starting lenalidomide dosing can be adjusted if patient received lenalidomide in previous cycle of SOC treatment and was found to not tolerate a 25 mg dose.
- Lenalidomide should be swallowed whole, preferably with water, either with or without food. The capsules should not be opened, broken, or chewed.
- If less than 12 hours has elapsed since missing a dose, the subject can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the subject should not take the dose, but take the next dose at the normal time on the following day. Do not take 2 doses at the same time.
- Procedures for dose reductions and delays are summarized in Section 8.3.
- Lenalidomide is commercially available.

7.5 Dexamethasone (Cycles 1-12 Only)

- Oral dexamethasone may be self-administered by the subject on an outpatient basis.
- Missed doses of dexamethasone will not be made up. Procedures for dose reductions and delays are summarized in Section 8.4.
- Dexamethasone is commercially available.

7.6 Stem cell collection and ASCT during induction

Patients can collect cells any time after 4 cycles. The patient may proceed to a single ASCT during induction and it will replace 3 cycles of induction treatment. Details should be

recorded on the Stem Cell Harvest and Transplant and Engraftment Forms. The subject will have a disease assessment at end of the preceding cycle and at the beginning of the next cycle after ASCT. The ASCT is not considered to be part of protocol treatment.

7.7 Treatment by local medical doctor (LMD)

Treatment by LMD is allowed
Patients will be permitted to receive intravenous carfilzomib and/or subcutaneous daratumumab under the supervision of the local hematologist/oncologists office provided the interval evaluations as required by the protocol can be completed remotely or through the local healthcare facilities. The patient must return to the consenting institution every 28 days.

A written statement outlining drug dosage, method of administration, follow-up tests required, and telephone number to call to discuss any questions with the registering investigator must be sent with the patient to provide necessary information to the LMD. The LMD will be required to supervise the administration of Carfilzomib as stipulated in the protocol and provide written documentation that the drug was administered. The registering investigator is responsible for all treatment decisions and for the collection and submission of the study data in accordance with the approved protocol. Weekly carfilzomib under LMD's supervision can only be administered following weekly phone and laboratory assessments with a Mayo Clinic nurse. If the dose modification or interruption of carfilzomib is required per the local hematologist/oncologist's assessment the Mayo Clinic investigator must be contacted prior to dose adjustments.

If the dose modification or interruption is required per the local hematologist/oncologist's assessment the Mayo Clinic investigator must be contacted prior to dose adjustments. The local hematologist/oncologist may interrupt the dose but must notify the Mayo investigator within 24 hours from the time of dose interruption. Any resumption of the drug(s), with or without dose modifications requires approval of the Mayo investigator. Following external dose adjustments, the patient must be evaluated at Mayo Clinic prior to the beginning of the next cycle.

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in this table for the first **two** cycles, until individual treatment tolerance can be ascertained. Individual drugs can be dose reduced as per the table below depending on the adverse event attribution. Thereafter, these modifications should be regarded as guidelines to limit to mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

NOTE: If carfilzomib, lenalidomide or daratumumab is discontinued, the subject can continue on the other drugs, unless specified otherwise in the dose modification tables. If all three are discontinued, the subject will go to clinical follow-up.

ALERT: ADR reporting may be required for some adverse events (See Section 10)

8.1 Dose Levels for each drug in the combination
(Based on Adverse Events in Sections 8.2-8.5)

NOTE: Toxicities attributable to dexamethasone should lead to dose reduction only for dexamethasone.

Dose reduction steps (each column to be followed independently for each drug)				
Step	***Carfilzomib****	***Lenalidomide***	***Daratumumab***	***Dexamethasone***
0	56 mg/m^2	25 mg	NA	40 mg
-1	45 mg/m^2	25 mg	NA	40 mg
-2	27 mg/m^2	15 mg		24 mg
-3	27 mg/m^2 days 1, 15	10 mg		12 mg
-4	10 mg/m^2 days 1, 15	5 mg		4 mg
-5	Discontinue	Discontinue		Discontinue

*Maximum dose for carfilzomib is capped at a BSA of 2.2 m^2

8.11 Instruction for initiation of a new cycle of treatment or restarting treatment after interruption during a cycle for toxicities.

A new cycle of treatment may begin on the scheduled Day 1 of a new cycle if:

- The ANC is ≥1000/µL
- The platelet count is ≥75,000/µL
- Any other non-hematologic treatment -related adverse event that may have occurred has resolved to ≤Grade 1 or baseline severity.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of treatment will be held until the toxicity has resolved as described above.

If any drug dosing was halted during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on Day 1 of the new cycle.

If any drug dosing was omitted for the remainder of the previous cycle or if the new cycle is held due to known hematologic toxicity newly encountered on the scheduled Day 1, then the new cycle will be started with a one-level dose reduction. If a new cycle of treatment cannot be restarted within 4 weeks of the scheduled Day 1 due to non-resolution of drug related toxicities, the subject will be removed from protocol treatment and will go to survival follow-up.

Since lenalidomide is primarily excreted unchanged by the kidney, starting dose adjustment is recommended in subjects with renal impairment to maintain an effective and safe exposure to lenalidomide. Based on a PK study in subjects with renal impairment due to nonmalignant conditions, lenalidomide starting dose adjustments are recommended for subjects with ClCr < 60 mL/min. Please refer to the US Package Insert for standard dose reductions.

For overlapping toxicities, selective discontinuation or reduction of one agent will be at the discretion of the treating physician. It is acceptable for one agent to be held during a cycle while the others are continued.

8.2 Dose modifications for carfilzomib based on adverse events during a cycle

Hematologic Toxicity	**Recommended Action**
ANC less than 0.5×10^9/L	• Withhold dose ○ If recovered to greater than or equal to 0.5×10^9/L, continue at the same dose level • For subsequent drops to less than 0.5×10^9/L, follow the same recommendations as above and consider 1 dose level reduction when restarting carfilzomib
Febrile neutropenia ANC less than 0.5×10^9/L and an oral temperature more than 38.5 ^{0}C or two consecutive readings of more than 38.0 ^{0}C for 2 hours	• Withhold dose ○ If ANC returns to baseline grade and fever resolves, resume at the same dose level
Platelet count <50,000-25,000/mm^3 or <50-25 X10^9/L)	• Withold carfilzomib and check platelet count weekly until resolution to grade ≤2, then resume at the same dose. • If toxicity lasts more than 3 weeks, reduce dose
Grade 4 Platelet count <25,000/mm^3 or <25 X10^9/L (grade 4)	• First or second occurrences: Withhold carfilzomib and check platelet count weekly until resolution to grade ≤2 and no bleeding. Resume therapy at one level dose reduction. • Third occurrence- Discontinue drug
Renal Toxicity	**Recommended Action**

Serum creatinine greater than or equal to 2 × baseline
 	
Creatinine clearance less than 15 mL/min, or creatinine clearance decreases to less than or equal to 50% of baseline, or need for dialysis
	• Withhold dose and continue monitoring renal function (serum creatinine or creatinine clearance)
	  ○ If attributable to carfilzomib, resume when renal function has recovered to within 25% of baseline; start at 1 dose level reduction
	  ○ If not attributable to carfilzomib, dosing may be resumed at the discretion of the physician
	• For subjects on dialysis receiving carfilzomib, the dose is to be administered after the dialysis procedure

Other Non-hematologic Toxicity	Recommended Action
Hepatic Impairment	• Reduce the dose of carfilzomib by 25% in patients with mild or moderate hepatic impairment. Dosing recommendation cannot be made for patients with severe hepatic function [The pharmacokinetics and safety of carfilzomib were evaluated in patients with advanced malignancies who had either normal hepatic function, or mild (bilirubin > 1 to 1.5×ULN or AST > ULN), moderate (bilirubin > 1.5 to 3×ULN), or severe (bilirubin > 3×ULN) hepatic impairment. The AUC of carfilzomib increased by approximately 50% in patients with mild and moderate hepatic impairment compared to patients with normal hepatic function. PK data were not collected in patients with severe hepatic impairment. The incidence of serious adverse events was higher in patients with mild, moderate, and severe hepatic impairment combined (22/35 or 63%) than in patients with normal hepatic function (3/11 or 27%) • Monitor liver enzymes regularly, regardless of baseline values, and modify dose based on toxicity.
TMA	• If the diagnosis is suspected, hold carfilzomib and manage per standard of care including plasma exchange as clinically appropriate. • If TMA is confirmed, permanently discontinue carfilzomib. • If the diagnosis is excluded, carfilzomib can be restarted.
PRES	• If PRES is suspected, hold carfilzomib. Consider evaluation with neuroradiological imaging, specifically MRI, for onset of visual or neurological symptoms suggestive of PRES. • If PRES is confirmed, permanently discontinue carfilzomib. • If PRES is excluded, carfilzomib administration may resume at the same dose, if clinically appropriate. If condition recurs, permanently discontinue carfilzomib.
CHF greater than or equal to grade 2 10% or more reduction in LVEF	• Discontinue carfilzomib with no rechallenge.
All other severe or life-threatening non-hematological toxicities	• Withhold until resolved or returned to baseline • Consider restarting the next scheduled treatment at 1 dose level reduction

8.3 Dose modifications for lenalidomide based on adverse events during a cycle

CTCAE System/ Organ/ Class (SOC)	ADVERSE EVENT	ACTION
Blood and lymphatic system disorders	Neutropenia associated with fever (ANC less than 1 × 109/L and temperature ≥ 38.5º C)	• Omit lenalidomide dose. • Follow CBC weekly. • If neutropenia has resolved to ≤ grade 2 prior to Day 21 and fever has resolved, restart lenalidomide at next lower dose level and continue the cycle through Day 21. If febrile neutropenia is the only toxicity for which a dose reduction is required. G-CSF may be used and the lenalidomide dose maintained.
Investigations	Grade 3 neutrophil decreased and sustained for 7 days or Grade 4 neutropenia Platelet count decreased ≥ Grade 3 (platelet count < 50,000/mm³)	• Omit lenalidomide dose. • Follow CBC weekly. • Hold anticoagulation until platelets > 50,000 • If platelet count resolves to ≤ grade 2 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle through Day 21. • If neutropenia has resolved to ≤ grade 2 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle through Day 21. If neutropenia is the only toxicity for which a dose reduction is required. G-CSF may be used and the lenalidomide dose maintained.
Skin and subcutaneous tissue disorders	Rash maculo papular Grade 2 or 3	• Omit lenalidomide dose. Follow weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle through Day 21.
	Any rash Grade 4	• Discontinue lenalidomide. Remove subject from all trial treatment. • Go to survival follow-up.
Nervous system disorders	Peripheral sensory Neuropathy Grade 3	• Omit lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle through Day 21.
	Grade 4	• Discontinue lenalidomide. Remove subject from all trial treatment. • Go to survival follow-up.

CTCAE System/ Organ/ Class (SOC)	ADVERSE EVENT	ACTION
Immune system disorders	Allergic reaction Grade 2-3	• Omit dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 15 restart at next lower dose level and continue the cycle until Day 21.
	Grade 4	• Discontinue lenalidomide. Remove subject from all trial treatment. • Go to survival follow-up.
Vascular disorders	Thromboembolic event ≥ Grade 3	• Omit dose and start anticoagulation; restart at investigator's discretion (maintain dose level).
	Hyperthyroidism or Hypothyroidism ≥ grade 2	• Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. • See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level.
Other non-hematologic adverse event	Other non-hematologic toxicity ≥ Grade 3	• Omit lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 2 prior to Day 21, restart lenalidomide at next lower dose level and continue the cycle through Day 21.

8.4 Dose modifications for dexamethasone (Dex) based on adverse events during a cycle

CTCAE System/Organ/ Class (SOC)*	**ADVERSE EVENT**	**ACTION****
Gastrointestinal disorders	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2 (Symptomatic; altered GI function; medical intervention indicated; limiting instrumental ADL)	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.
	Dyspepsia, gastric or duodenal ulcer, gastritis ≥Grade 3 (Severely altered GI function; TPN indicated; elective operative or endoscopic intervention indicated; limiting self-care ADL; disabling)	Omit dexamethasone until symptoms adequately controlled. Restart one dose level below along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Gastrointestinal disorders	Pancreatitis ≥Grade 3 (Severe pain; vomiting; medical intervention indicated (e.g., analgesia, nutritional support))	Discontinue dexamethasone and do not resume.
General disorders and administration site conditions	Edema ≥Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and decrease dexamethasone dose by 1 dose level. If edema persists despite above measures, decrease dose another dose level. Discontinue dexamethasone and do not resume if symptoms persist despite second reduction.
Psychiatric disorders	Confusion or Mood alteration ≥Grade 2 (Severe disorientation; limiting self-care ADL)	Omit dexamethasone until symptoms resolve Restart with one dose level reduction. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Musculoskeletal and connective tissue disorders	Muscle weakness ≥ Grade 2 Weakness limiting self-care ADL; disabling	Decrease dexamethasone dose by one dose level; if weakness persists despite above measures decrease dose by one additional dose level. Discontinue dexamethasone and do not resume if symptoms continue to persist.
Metabolism and nutrition disorders	Hyperglycemia Grade 3 or higher (>250 - 500 mg/dL; >13.9 - 27.8 mmol/L); hospitalization indicated	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by one dose level at a time until levels are satisfactory.

* Located at [redacted]

** Use the following to describe actions in the Action column:

- Omit = The current dose(s) for the specified drug(s) during a cycle is skipped. The subject does not make up the omitted dose(s) at a later time
- Hold/Delay = The current dose(s) of all drugs during a cycle is delayed. The subject does make up the delayed dose(s) when the subject meets the protocol criteria to restart drugs.
- Discontinue = The specified drug(s) are totally stopped.

8.5 Dose modifications for daratumumab based on adverse events during a cycle

Dose modification of daratumumab is not permitted, but dose delay is the primary method for managing daratumumab-related toxicities.

8.51 Daratumumab-Related Toxicity Management

Refer to Section 9.7 for details on management of infusion-related reactions. ONLY if any of the following criteria are met and the event cannot be ascribed to the other drugs, the daratumumab infusion must be held to allow for recovery from toxicity. The criteria for a dose delay are:

- Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding
- Grade 4 neutropenia, if this is the second occurrence despite growth factor support
- Febrile neutropenia of any grade
- Neutropenia with infection, of any grade
- Grade 3 or higher nonhematologic 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 daratumumab
  - Grade 3 asthenia that was present at baseline or that lasts for <7 days after the last administration of daratumumab

If a daratumumab 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 dosing date.

Table 8.5: Daratumumab-Related Toxicity Management

Cycles	**Frequency**	**Dose Held**	**Dosing Re-start**
1 and 2	Weekly (q1wk)	>3 days	next planned weekly dosing date
3 to 6	Biweekly (q2wks)`	>1 week	next planned biweekly dosing date
7+	Every 4 weeks (Q4W)	>2 weeks	next planned every 4 weeks dosing date

A missed dose will not be made up. Doses of daratumumab may be delayed up to 4 weeks. If a dose is delayed, then the dates of the subsequent doses must be adjusted. Any adverse event deemed to be related to daratumumab and unrelated to lenalidomide that requires a dose hold of more than 4 weeks will result in permanent discontinuation of daratumumab.

9.0 Ancillary Treatment/Supportive Care

9.1 Oral hydration

Subjects are encouraged to drink at least 6 to 8 cups of liquid per day.

9.2 Disallowed concomitant treatment

The following treatments are not permitted during the trial:

- Any other investigational treatment
- Any other systemic anti-neoplastic therapy including, but not limited to, immunotherapy, hormonal therapy or monoclonal antibody therapy.
- Any external beam radiotherapy

9.3 Nausea and/or vomiting

Standard anti-emetics including 5-hydroxytryptamine 3 serotonin receptor antagonists are recommended for emesis if it occurs once treatment is initiated; prophylactic anti-emetics may also be considered at the physician's discretion. Dexamethasone should not be administered as an anti-emetic. Fluid deficit should be corrected before initiation of trial drug and during treatment.

9.4 Blood products and growth factors

Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the Journal of Clinical Oncology, Vol 24, No 18 (June 20), 2006: pp. 2932-2947.

9.5 Diarrhea

Prophylactic antidiarrheals can be used in this protocol. Diarrhea should be managed according to clinical practice, including the administration of antidiarrheals such as loperamide once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Fluid deficit should be corrected before initiation of treatment and during treatment. Additional doses of loperamide at 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day). Alternative anti-diarrheals can be used at the discretion of the treating physician. In the event of Grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.

If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Subjects with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

Please monitor subjects carefully for development of ileus.

9.6 Herpes Zoster prophylaxis

Subjects may be at an increased risk of infection including reactivation of herpes zoster and herpes simplex viruses. Prophylaxis with acyclovir 400 mg PO BID is recommended while on trial treatment and for 1 month beyond the end of treatment.

9.7 Management of Hepatitis B Virus Reactivation

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 Schedule of Events).

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. Consultation with a liver disease specialist is recommended as clinically indicated.

9.8 Guidelines for Prevention of Infusion Reactions

Pre-infusion Medication: During Cycle 1 for daratumumab infusion, subjects will receive the following medications prior to infusion:

- Acetaminophen (paracetamol) 650-1000 mg IV or orally (PO) approximately 1 hour or less prior to daratumumab infusion
- An antihistamine (diphenhydramine 25-50 mg IV or PO, or equivalent) approximately 1 hour prior to infusion
- Acetaminophen and antihistamine may be discontinued after cycle 1 per provider preference
- Dexamethasone 40 mg PO (or IV) approximately 1 hour prior to daratumumab infusion during the induction phase. Dexamethasone 20 mg PO (or IV), approximately 1 hour prior to daratumumab infusion during the consolidation and maintenance phases. On days when subjects receive this dose of dexamethasone in the clinic, dexamethasone will not be self-administered at home. The dose of dexamethasone premed can be split over two days in case of intolerance.

Post-infusion Medication: For subjects with higher risk of respiratory complications (i.e., subjects who have a FEV1 <80%), the following post infusion medications should be considered:

- Antihistamine (diphenhydramine or equivalent)
- 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 COPD)

In addition, these at-risk subjects may be hospitalized for monitoring for up to 2 nights after an infusion. If subjects are hospitalized, then their FEV1 should be measured before discharge. If these subjects are not hospitalized, then a follow up telephone call should be made to monitor their condition within 48 hours after all infusions. If the subject has not experienced a significant medical event but is hospitalized overnight

only for observation, then the hospitalization should not be reported as a serious adverse event. 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 hospital/clinic.

9.8 Management of Infusion-related Reactions

Subjects should be carefully observed during daratumumab infusions. Trained trial staff at the clinic should be prepared to intervene in case of any infusion reactions occurring, and resources necessary for resuscitation must be available at the bedside.

If an infusion-related reaction develops, then the infusion should be temporarily interrupted or slowed down. Subjects who experience adverse events during the infusion must be treated according to the investigator's judgment and best clinical practice. The following guidelines may apply:

- Subjects should be treated with acetaminophen, antihistamine, or corticosteroids. Intravenous saline may be indicated. For bronchospasm, urticaria, or dyspnea, subjects may require antihistamines, oxygen, corticosteroids, or bronchodilators. For hypotension, subjects may require vasopressors.
- In the event of a life-threatening infusion-related reaction (which may include pulmonary or cardiac events), or anaphylactic reaction, daratumumab should be discontinued and no additional daratumumab 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 a serious adverse event. However, if the underlying cause of the delayed infusion time is an adverse event or serious adverse event, then that should be reported as such.

Infusion-Related Events of Grade 1 or Grade 2: If the investigator assesses an adverse event to be related to the daratumumab infusion, then the infusion should be paused. 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 at the investigator's discretion.

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 treatment and does not resolve within 6 hours from the onset, then the subject must be withdrawn from treatment.

Infusion-Related Reactions of Grade 3 or Higher: For infusion-related adverse events that are Grade 4, the infusion should be stopped and treatment with daratumumab will be discontinued for that subject.
For infusion-related adverse events that are Grade 3, the daratumumab infusion must be stopped, and the subject must be observed carefully until the resolution of the adverse event or until the intensity of the event decreases to Grade 1, at which

point 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 at the investigator's discretion.

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 at the investigator's discretion. Should the intensity of the adverse event increase to Grade 3 for a third time, then treatment with daratumumab will be discontinued for that subject.

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Definitions

10.11 Investigator

An investigator includes the Site Principal Investigator (PI) or a designated Sub-Investigator.
Sub-Investigator:
A Sub-Investigator is a medically qualified delegate who has been identified and confirmed by the Site PI. Medically qualified designations may include, but are not limited to:

- Medical Doctorate (M.D.), or equivalent medical school graduate degree
- Physician Assistant (P.A.)
- Certified Nurse Practitioner (C.N.P.)
- Registered Nurse (R.N.)

10.12 Adverse Event (AE)

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. (FDA, 21 CFR 312.32; ICH E2A and ICH E6)
The definition of AEs includes:

- Worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition or underlying disease (e.g., diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration more than would be expected and/or has an association with a significantly worse outcome than expected.
  NOTE: A pre-existing condition that has not worsened more than anticipated (i.e., more than usual fluctuation of disease) during the study, or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an AE.
- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject

In general, abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.

Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

The investigator is responsible for ensuring that any AEs observed by the investigator or reported by the subject are recorded in the subject's medical record.

10.13 Serious Adverse Event (SAE)

A serious adverse event is defined as an adverse event that meets ***at least one*** of the following serious criteria (FDA, 21 CFR 312.32; ICH E2A and ICH E6):

- Fatal
- Life threatening (places the subject at immediate risk of death)
- Requires inpatient hospitalization for >= 24 hours or prolongation of existing hospitalization.
  NOTE: Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered SAEs.
- Results in persistent or significant disability/incapacity. Congenital anomaly/birth defect.
- Is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed in the definition above).
  NOTE: Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions not resulting in hospitalization; or the development of drug dependency or drug abuse. **(See Table 10.1)**
  If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a SAE under the criterion of "other medically important serious event."
  NOTE: Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug induced liver injury (DILI), or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

10.14 Suspected Adverse Reaction

Any AE for which there is a reasonable possibility that the drug caused the AE.

10.15 Adverse Events of Special Interest (AESI)

Events that would not typically be considered to meet the criteria for expedited reporting, but that for a specific protocol are being reported via expedited means in order to facilitate the review of safety data (may be requested by the FDA or the sponsor).

10.16 Protocol Violation/Deviation

Any change, divergence or departure from the study design or research procedures that has not been approved by the IRB.
Major Protocol Violation/Deviation: Any change that affects the rights and welfare of subjects and others, increases risks to subjects and others, decreases

potential benefits, compromises the integrity or validity of the research, or represents willful or knowing misconduct.
Minor Protocol Violation/Deviation: Any change that did not increase the risk or decrease the benefit or significantly affect the subject's rights, safety or welfare and/or the integrity of research data (e.g., a routine lab missed at a visit and re-drawn, shortening the duration between a planned study visit, using an outdated HIPAA form or consent form when there are no differences between the two forms other than the approval date).

10.17 Medication error
A **medication error** is defined as any accidental incorrect administration or dosing of a medicinal product.

10.18 Expedited Reporting
Events immediately reported to sponsor using the appropriate iMedidata Rave SAE eCRF(s) once study team has become aware of the event.

10.19a Routine Reporting
Events reported to sponsor via the appropriate iMedidata Rave AE eCRF(s).

10.19b Expected versus Unexpected Events
Expected events are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure (IB), (if an investigator brochure is not required, otherwise described in the general investigational plan).
Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.
Unexpected also refers to AEs or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.
An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.
NOTE: Refer to protocol or IB for reporting needs.

10.19c Relatedness
A problem or event is "related" if it is possibly related and/or attributed to the research procedures including (but not limited to) investigational product(s), assay process and/or study procedures or activity.

Specifically, they will be categorized using the following terms:

Unrelated	AE is ***not*** *related to study agent(s) or research procedure(s)*
Unlikely	AE is ***doubtfully*** *related to study agent(s) or research procedure(s)*
Possible	AE ***may be*** *related to study agent(s) or research procedure(s)*
Probable	AE is ***likely*** *related to study agent(s) or research procedure(s)*
Definite	AE is ***clearly*** *related to study agent(s) or research procedure(s)*

10.19d Severity Criteria

An assessment of the Adverse Events severity grade will be made by the investigator according to the NCI CTCAE Version 5.0.

A copy of this CTCAE version can be downloaded from the CTEP web site: [redacted].

10.2 Site Reporting

Subject data accrued on this study will be reported in accordance with 21CFR 312.32.

All AEs and SAEs will be reported using iMedidata Rave electronic data capture system. Please refer to the "Mayo Clinic Cancer Center Electronic Case Report Form (eCRF) Completion Guidelines" for additional instructions.

All AEs and SAEs must be evaluated, diagnosed, and assessed for safety reporting by an ***investigator***.

The AE grading scale for this study will be Common Terminology Criteria for AEs (CTCAE) version 5.0. All appropriate treatment areas must have access to this CTCAE version.

10.21 Adverse Events

10.211 Site Requirements for Reporting AEs

From the time of registration until ≤ 30 days after the administration of the last dose of study drug/agent or therapy, or until a new anti-cancer treatment starts, whichever occurs first, the Site Principal Investigator (PI) is responsible for ensuring that all AEs (observed by study team, provided by external sources, etc.) are reported to the sponsor.

After 30 days from last dose of administration of the last dose of study drug/agent or therapy, only adverse events that are attributed to the study drug (possible, probable, or definite) are required to be recorded on the adverse event forms. Also refer to Section 10.231 for the reporting of any possible SAEs as applicable.

The investigator(s) is responsible for:

- AE diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- Severity,
- Assessment of the relationship to study treatment(s),

- As applicable, identify and clarify if an adjustment in treatment dose occurred due to an AE
- Determine the relationship of the AE with any study mandated activity (e.g., administration of investigational product, protocol-required therapies, and/or procedure (including any screening procedure(s)).
- Reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject's baseline values.
    - In general, abnormal laboratory findings without clinical significance (based on the Investigator's judgment) are not to be recorded as AEs. Exceptions may include but are not limited to:
        - Baseline and Adverse Events Evaluations (Section 10.213)
    - However, laboratory value changes that require treatment or adjustment in current therapy are considered AEs.
    - Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the AE.
    - Asymptomatic laboratory abnormalities that do not require treatment will not be collected as AEs.
- Following reported AEs until resolution.

The delegated study team member(s) must document and report AEs as follows:

- All AEs must be documented in the subject's medical record and recorded on the appropriate study specific iMedidata Rave "Adverse Events" eCRF. Information documented on the iMedidata Rave "Adverse Events" eCRF must be consistent with that recorded on the source document.
    - AEs will be recorded regardless of whether or not they are considered related to the study drug(s). AEs considered related to study drug(s) will be followed until resolution to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first. Exceptions may include non-clinically significant labs if they meet non-critical reporting criteria.
- If a subject is permanently withdrawn from protocol-required therapies because of an AE, the subject status must be submitted, via the appropriate iMedidata Rave eCRF.
- If an AE results in adjustment in treatment dose (i.e., dose delay, dose reduction, etc.):
    - the individual AE needs to be documented on iMedidata Rave "Adverse Events" eCRF and,
    - the details of the dose adjustment due to the individual AE need to be documented on the iMedidata Rave "Treatment" (Intervention) eCRF.

10.213 Baseline and Adverse Events Evaluations

Pretreatment symptoms/conditions to be graded at baseline and adverse events to be graded at each evaluation. Grading is per CTCAE v5.0 unless alternate grading is indicated in the table below:

CTCAE System/Organ/Class	Adverse event/Symptoms	Baseline	Each evaluation
Injury, poisoning and procedural complication	Infusion related reaction		X
Investigations	White blood cell decreased	X	X
	Platelet count decreased	X	X
	Neutrophil count decreased	X	X
	Lymphocyte count decreased	X	X
Blood and lymphatic system disorders	Anemia	X	X
Metabolism and nutrition disorders	Tumor lysis syndrome		X

10.22 Serious Adverse Events

10.221 Site Requirements for Reporting SAEs

From the time of registration until ≤ 30 days after the administration of the last dose of study drug/agent or therapy, or until a new anti-cancer treatment starts, whichever occurs first, the Site Principal Investigator (PI) is responsible for ensuring that all SAEs (observed by study team, provided by external sources, etc.) are reported immediately to the sponsor.

In addition to reporting to Mayo Clinic, the investigator is responsible for reporting to their appropriate IRB/IEC in accordance with local regulatory requirements and procedures.

Initial reporting:

The investigator/study team must report SAEs as follows:

- All SAEs must be immediately submitted to Mayo Clinic following the study team's knowledge of the event via the iMedidata Rave "Adverse Events" eCRF .
  NOTES: This eCRF will generate the "SAE: Event Information" eCRF when the event is indicated as "serious." Information documented on the iMedidata Rave "SAE: Event Information" eCRF must be consistent with that recorded on the source document.
  Once the SAE information has been captured and submitted in iMedidata Rave, a report can be generated. A copy of this completed report must be kept within the study file at the study site.
- The investigator must assess whether the SAE is possibly related to the investigational product.
- The investigator is expected to follow reported SAEs until stabilization, resolution or patient death. (See section below on

Follow-Up Reporting.)

Follow-Up Reporting:

New information relating to a previously reported SAE needs to be submitted to Mayo Clinic:

- Immediately upon site becoming aware of updated information
- Sites may be required to:
  - Provide additional information including but not limited to discharge summaries, medical records, etc.
  - Query external locations for additional information if events occurred outside the participating site (i.e., Hospitalization records)
  - Respond to Sponsor query(ies) if additional information is needed
- All SAEs regardless of relation to study drug will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant, until a new anti-cancer treatment starts, or death whichever occurs first.
- Revise the previously documented SAE on the appropriate iMedidata Rave eCRF.

NOTE: Information documented on the iMedidata Rave eCRF must be consistent with that recorded on the source document.

Once the updated SAE information has been captured and submitted in iMedidata Rave, a report can be generated. A copy of this updated report must be kept within the study file at the study site.

NOTE: Refer to Section 10.23 for additional reporting requirements.

Table 10.1 Expedited Reporting Requirements for Adverse Events/Serious Adverse Events

EXPEDITED REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS
(21 CFR Part 312)

Investigators MUST immediately report to Mayo Clinic **ANY** Serious Adverse Events (SAE), whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).
Mayo Clinic will report to FDA, per regulations [21 CFR 312.32(c)(d)].
The definition of a SAE can be found in **Section 10.13**.
Detailed site requirements for reporting SAEs can be found in **Section 10.221**.

Initial Reporting		**Follow-Up Reporting**	
Hospitalization >= 24 hours (any grade and/or attribution)	**IMMEDIATELY,** upon study team's awareness of event. (Not to exceed 24 hours.)	**Hospitalization >= 24 hours** (any grade and/or attribution)	**IMMEDIATELY,** upon receiving any updated information regarding initial event. (Not to exceed 24 hours.)
GRADE 3 Attribution of Possible, Probable, or Definite		**GRADE 3** Attribution of Possible, Probable, or Definite	
GRADES 4 and 5 Regardless of Attribution		**GRADES 4 and 5** Regardless of Attribution	

Refer to Section 10.23 for detailed reporting requirements related to Important Medical Events (IME), Adverse Events of Special Interest (AESI), > 30 days post treatment, Dosing errors, Pregnancy, Fetal Death, Neonatal Death, Lactation.

Offline reporting when iMedidata Rave is unavailable:
If the iMedidata Rave system is unavailable to the site staff to report the SAE, the information is to be reported to Mayo Clinic by completing, scanning, and submitting a hard copy of the "Adverse Events" CRF and related "SAE: Event Information" CRFs within 24 hours of the investigator's knowledge of the event. See the study forms packet for printable copy of these forms. Completed forms are to be submitted to [redacted]
For studies where the first notification of a SAE is reported to Mayo Clinic using the Offline reporting instructions, the data must be entered into iMedidata Rave when the system is again available. The originally submitted forms and the email correspondence must be kept within the study file at the study site.

10.222 Exceptions for Site(s) Regarding Expedited Reporting Timelines for SAEs

For this protocol only, the following AEs/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via iMedidata Rave (see **Section 10.22**):

- Specific protocol exceptions to expedited reporting should be reported immediately by investigators **ONLY** if they exceed the expected grade of the event.

CTCAE System Organ Class (SOC)	Adverse event/ Symptoms	CTCAE Grade at which the event will not be reported via expedited mechanisms[1]
Blood and lymphatic system disorders	Anemia	≤Grade 4
Investigations	Lymphocyte count decreased	≤Grade 4
	Neutrophil count decreased	≤Grade 4
	Platelet count decreased	≤Grade 4
	White blood cell decreased	≤Grade 4

[1] These exceptions only apply if the AE does not result in hospitalization. If the AE results in hospitalization, then the standard expedited AEs reporting requirements must be followed.

The following hospitalizations are not considered to be SAEs because there is no "AE" (i.e., there is no untoward medical occurrence) associated with the hospitalization:

- Hospitalizations for respite care.
- Planned hospitalizations required by the protocol.
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration).
- Hospitalization for elective procedures unrelated to the current disease and/or treatment on this trial.
- Hospitalization for administration of study drug or insertion of access for administration of study drug.
- Hospitalization for routine maintenance of a device (e.g., battery replacement) that was in place before study entry.
- Hospitalization or other serious outcomes for signs and symptoms of progression of the cancer.

10.23 Other Reporting

10.231 >30 days post treatment

Immediately, upon study team's awareness of event, submit initial and follow-up (as applicable) reporting as follows:

- SAEs that occur > 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite should be reported to Mayo Clinic (refer to **Section 10.22**).
- For AEs occurring > 30 days after the last administration of investigational agent/intervention, refer to **Section 10.211** for reporting requirements.

10.232 Medication Errors

Medication Error: An error made in prescribing, dispensing, administration, and/or use of the study drug.

The following errors (including but not limited to) are to be reported as a deviation (refer to **Section 10.237**):

- The dispensing, administration and/or use of the unassigned study drug.
- The administration and/or use of an expired study drug.
- Persistent or sporadic, intentional excessive use of medicinal products, which is accompanied by harmful physical or psychological effects.
- Intentional and inappropriate use of a medicinal product not in accordance with the prescribed or authorized dose, route of administration, and/or the indication(s) or not within the legal status of its supply.
- Administration of a quantity of study drug given per administration or per day, which is above the assigned dose.

For Medication Errors that result in an AE or SAE, the event must be reported via the appropriate iMedidata Rave eCRF (refer to Sections 10.21 and 10.22).

10.233 Pregnancy, Pregnant Partner, Fetal Death, Neonatal Death and Lactation

If a female subject becomes pregnant, or a male subject fathers a child, while the subject is on protocol report the pregnancy to Mayo Clinic as specified below.

NOTES:

Pregnancies and/or lactations that occur after registration but before treatment allocation/randomization must be reported by the investigator if they cause the subject to be ineligible from continued participation on the trial.

Pregnancies and lactations that occur from the time of treatment allocation/randomization through 90 days following cessation of study drug/agent, or 30 days following cessation of treatment if the subject initiates new anticancer therapy, whichever is earlier, must be reported by the investigator.

10.2331 Pregnancy

Immediately, upon the Investigator becoming aware of a pregnancy, the site must contact [redacted] for reporting instructions. Mayo Clinic Cancer Center FDA Coordination Team will follow-up with the investigator regarding additional information that may be required.

If a female subject becomes pregnant during the study, the investigator should attempt

to obtain information regarding the birth outcome and health of the infant. If the outcome of the pregnancy meets a criterion for immediate classification as a Serious Adverse

Event (i.e., female subject experiences a spontaneous abortion, stillbirth, or neonatal death or there is a fetal or neonatal congenital anomaly) the investigator will report the event as a Serious Adverse Event.
Pregnancy must be reported in an expedited manner as **Grade 3 "Pregnancy, puerperium and perinatal conditions - Other (pregnancy)"** under the Pregnancy, puerperium and perinatal conditions System Organ Class (SOC). Pregnancy should be followed until the outcome is known.

10.2332 Pregnant Partner

If a male subject's female partner becomes pregnant, the investigator should discuss
obtaining information regarding the birth outcome and health of the infant from the pregnant partner. **Prior to obtaining private information about a pregnant woman and her infant, the Investigator must obtain consent from the pregnant woman and the newborn infant's parent or legal guardian before any data collection can occur. A consent form will need to be submitted to the IRB for these subjects if a pregnancy occurs**.
NOTE: If informed consent is not obtained, no information may be collected.
The site must contact [redacted] for reporting instructions. Mayo Clinic Cancer Center FDA Coordination Team will follow-up with the investigator regarding additional information that may be required.

10.2333 Lactation

If a female breastfeeds while taking protocol-required therapies, report the lactation case
to Mayo Clinic as specified below.
Immediately upon the Investigator's knowledge of any lactation case, the site must contact [redacted] for reporting instructions. Mayo Clinic Cancer Center FDA Coordination Team will follow-up with the investigator regarding additional information that may be required.
Investigators should report lactation cases that occur through 3 months after the last dose of protocol-required therapies.

10.2334 Pregnancy Loss/Fetal Death and Neo-Natal Death

In cases of fetal death, miscarriage or abortion, the mother is the patient. In cases where the child/fetus experiences a SAE other than fetal death, the child/fetus is the patient.
Pregnancy outcomes of spontaneous abortion, missed abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage and stillbirth must be

reported as serious events (Important Medical Events). If the pregnancy continues to term, the outcome (health of infant) must also be reported.
Pregnancy loss is defined in CTCAE as "A disorder characterized by death in utero."
Fetal loss at any gestational age must be reported expeditiously, as **Grade 4 "Pregnancy loss" under the SOC of "Pregnancy, puerperium and perinatal conditions."**
Neonatal death, defined in CTCAE as "Newborn death occurring during the first 28 days after birth" must be reported expeditiously as **Grade 4 "Death neonatal" under the SOC of "General disorders and administration site conditions**."
NOTE: When submitting Mayo Expedited Adverse Event Report reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) must be documented in the "Description of Event" section. Include any available medical documentation.
In addition to reporting to Mayo Clinic, sites are responsible to report any of the above instances to their IRB per Institutional guidelines.

10.234 Death

A death occurring between the time of registration and **≤** 30 days after last dose of study treatment requires iMedidata Rave reporting regardless of causality. Attribution to treatment or other cause must be provided.

Reportable categories of Death

- Death Not Otherwise Specified (NOS): A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
- Death due to progressive disease that cannot be attributed to a CTCAE term associated with Grade 5 should be reported as **Grade 5 "Disease progression"** under the SOC of General disorders and administration site conditions. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.
- All other causes of "Death" must be attributable to a Grade 5 CTCAE term.
- Neonatal and Fetal Death: Refer to **Section 10.2334**.

10.235 Second*ary* Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.
- All secondary malignancies that occur following treatment with an agent under an IND will be reported. Three options are available to describe the event:
  - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])
  - Myelodysplastic syndrome (MDS)
  - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via iMedidata Rave.

10.236 Second Malignancy

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

10.237 Protocol Violation/Deviation Reporting

The Mayo Clinic [redacted] inbox must be notified immediately, of any Major Deviation (defined in Section 10.16).
Mayo Clinic Sites: All Major and Minor deviations must be entered in PTrax immediately upon the study team becoming aware of the violation/deviation. Mayo Clinic staff are responsible for reporting to the Mayo Clinic IRB per IRB policy.

Sponsor-Investigator Reporting

Per FDA, 21 CFR 312.32, Mayo Clinic will report SAEs and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IRBs/IECs in compliance with all reporting requirements according to local regulations and Good Clinical Practice.

Mayo Clinic Cancer Center (MCCC) FDA Coordination Team will assist the sponsor-investigator in the processing of expedited reports (i.e., IND Safety reports, deviations, dosing errors, pregnancy, etc.), as appropriate.

11.0 Treatment Evaluation

The International Myeloma Working Group (IMWG) uniform response criteria (Kumar et al, 2016) will be used to assess response to therapy.

11.1 Terms and definitions

Serum or urine M spike of any level is not a requirement for entry into the trial. If present, and meets criteria for measurable disease, this will be followed for M protein response using IMWG uniform response criteria as described below.

M-protein: synonyms include M-spike, monoclonal protein and myeloma protein, paraprotein, M-component.

Serum M-protein level is quantitated using densitometry on SPEP except in cases where the SPEP is felt to be unreliable.

- M-proteins migrating in the β-region (usually IgA M-proteins)
- Cases in which the M-spike is so large and narrow on agarose (some specimens >4 g/dL) that they underestimate the actual immunoglobulin level (by greater than 1500 mg/dL) due to technical staining properties of the agarose gel
- Cases in which there are multiple peaks of same monoclonal protein (aggregates or dimers)

If SPEP is not available or felt to be unreliable (above examples) for routine M-protein quantitation, then quantitative immunoglobulin levels derived from nephelometry or turbidometry can be accepted. However, this must be explicitly reported at baseline, and only nephelometry can be used for that subject to assess response. SPEP derived M-spike values and quantitative nephelometric immunoglobulin values cannot be used interchangeably.

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

- **FLC estimation** is currently carried out using the serum FLC assay (Freelite, The Binding Site Limited, UK). Subjects with kappa/lambda FLC ratio <0.26 are defined as having monoclonal lambda FLC and those with ratios >1.65 as having a monoclonal kappa FLC. The monoclonal light chain isotype is considered the involved FLC isotype, and the opposite light chain type as the uninvolved FLC type.
- **Response terms:** The following response terms will be used to define M protein response: stringent Complete Response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), Minimal Response (MR), stable disease (SD), and progressive disease (PD).

In addition, for each response category, there will be an "unconfirmed" response category, which will be for internal use, for the purpose of guiding decision making and test ordering. These designations will be applied at the time of the first measurement at which the quantitative aspect of the response category has been satisfied without the confirmation step having been satisfied. The designation "u" will precede the standard abbreviations, and will include usCR, uCR, uVGPR, uPR, uMR, uPD.

- **Measurable disease:** Subjects who have a measurable serum or urine M-protein.
  - Serum M-protein ≥1 g/dl
    NOTE: Quantitative IgG may not be used for defining measurable disease

Patients with IgA myeloma in whom serum protein electrophoresis is deemed unreliable, due to co-migration of normal serum proteins with the para protein in the beta region, may be considered eligible as long as total serum IgA level is elevated above normal range.

- Urine M-protein ≥200 mg/24 h
- Serum FLC assay: Involved FLC level ≥10 mg/dl provided serum FLC ratio is abnormal

For studies that include patients with non-secretory or oligosecretory myeloma:

- Bone marrow plasma cells ≥ 30%
- Measurable extramedullary/soft tissue plasmacytoma (at least one lesion that has a single diameter of ≥2 cm) .

The serum free light chain (FLC) assay is of particular use in monitoring response to treatment in subjects who have oligo-secretory or non-secretory disease and **should be used in assessing response only if the baseline serum and/or urine M proteins are not "measurable" as above, and the baseline level of the involved FLC is "measurable."** When using this assay, it is important to note that the FLC levels vary considerably with changes in renal function and in subjects with renal insufficiency, the levels of both the kappa and lambda may remain elevated, but the ratio normalizes with achievement of CR. Thus, both the level of the involved and the uninvolved FLC isotype (i.e., the involved/uninvolved ratio or involved-uninvolved difference) should be considered in assessing response. **Subjects included on the trial on the basis of FLC alone (i.e., no measurable serum/urine m-spike) should be the only ones who are evaluated using FLC response criteria. The others should follow usual criteria and ignore FLC results** with the exception of defining stringent complete response.

- **Evaluable disease**: Subjects who do not have a "measurable" serum M-spike, serum free light chain, or urine M-spike.
- **Oligosecretory myeloma:** Subject with multiple myeloma who has NEVER had "measurable" serum M-spike or urine M-spike, but has had a detectable monoclonal protein in his/her serum and/or urine and/or measurable serum free light chain.
- **Non-secretory myeloma:** Subject with multiple myeloma who has NEVER had a detectable monoclonal protein in his/her serum and/or urine.

11.2 Clarification of test indications

Listed below are the minimal required tests required to assess response based on the characteristics of their disease at on trial.

Table 11.2					
Tests Required To Assess Response (Must Be Done At Each Disease Measurement Visit except as indicated[1,2])					
On Study Baseline Value	**SPEP[4]**	**24 hr UPEP[2]**	**Ig FLC**	**BM Bx**	**Imaging**
Serum M-protein ≥1 g/dl, and urine M-protein≥ 200 mg/24 hrs	X	X			
Serum M-protein ≥ 1 g/dl, but urine M-protein < 200 mg/24 hrs	X				
Serum M-protein <1 g/dl, and urine M-protein≥ 200 mg/24 hrs		X			
Serum M-protein < 1 g/dl, urine M-protein < 200 mg/24 hrs, but involved Ig FLC is ≥10 mg/dL			X		
Serum M-protein < 1 g/dl, urine M-protein< 200 mg/24 hrs, involved Ig FLC is <10 mg/dL, bone marrow ≥30% plasma cells				X[3]	
Measurable extramedullary/soft tissue plasmacytoma (at least one lesion that has a single diameter of ≥2 cm) at baseline)					X[5]

[1] **Immunofixation studies of both serum and urine** are required to document CR regardless of registration values, and in addition **FLC** measurement and **bone marrow immunophenotyping** is required to document sCR. SPEP and UPEP are required to document VGPR regardless of registration values.

[2] For serum measurable subjects, if there is an improvement in response (for example, VGPR to CR) 24 hour urine should be repeated as needed to meet the specified criteria for the improved response category.

[3] Bone marrow biopsy results do not need to be confirmed (i.e. repeated after documented response).

[4] If serum M-protein is being followed by quantitative immunoglobulin levels (in patients with IgA, IgD myeloma) follow up quantitative immunoglobulins are required. Immunofixation is required to document CR and must be confirmed per Section 11.3.

[5] If a measurable extramedullary/soft tissue plasmacytoma is present at baseline, imaging should be repeated every 3-4 cycles.

11.3 Confirmation of response

In order to be classified as an M protein response, confirmation of each component of the standard IMWG response category per Table 11.5 must be made by verification on two consecutive determinations, except bone marrow and extramedullary/soft tissue plasmacytomas, as detailed below.

- **For VGPR:**
  - If a patient has a UPEP with M protein <100 mg/24 hours at baseline, only one additional UPEP with M protein <100 mg/24 hours is needed to confirm for VGPR (assuming a sample ≥100 mg/24 hours was not seen in between). If UPEP at baseline had ≥100 mg /24h hrs UPEP <100 mg/24 hours is required on two consecutive assessments for VGPR.
  - If a patient has non-quantifiable SPEP at baseline, only one additional SPEP

is needed to confirm for VGPR (assuming a positive was not seen in between). If SPEP is quantifiable at baseline or at any time during treatment, SPEP meeting VGPR criteria is required on two consecutive assessments for VGPR.

- **For CR or sCR:**
  - If a patient has a negative urine immunofixation at baseline, only one additional negative urine immunofixation is needed to confirm for CR/sCR (assuming a positive was not seen in between). If urine immunofixation is positive at baseline or at any time during treatment, negative urine immunofixation is required on two consecutive assessments for CR/sCR.
  - If a patient has a negative serum immunofixation at baseline, only one additional negative serum immunofixation is needed to confirm for CR/sCR (assuming a positive was not seen in between). If serum immunofixation is positive at baseline or at any time during treatment, negative serum immunofixation is required on two consecutive assessments for CR/sCR.
- **NOTE:** Two consecutive assessments refers to the initial test that showed the specified component of the standard IMWG response category was met and then the next occurrence of that test, regardless of the window in between. The confirmation could be as soon as the same day or it could occur multiple cycles later.
- Bone marrow aspirate and biopsy are **only** required to document CR or sCR, except for subjects with marrow evaluable disease **only**, where a bone marrow is required to document all response categories including progression. However, a second confirmatory bone marrow is **not** required to confirm response in any case. Bone marrow biopsy for documentation of CR/sCR may be done +/- 2 cycles from the serologic/urine testing as long as the intervening measures did not show an increase.
- A second confirmatory assessment of extramedullary/soft tissue plasmacytomas is not required to confirm response in any case.
- Radiographic studies are not required to satisfy these response requirements; however, if radiographic studies were performed, there should be no evidence of progressive or new bone lesions.

Appropriate tests required to document and confirm response are listed in Table 11.2

Each category, except for stable disease, will have a working subcategory of "unconfirmed" [prefix 'u"] to designate first time point at which response category MAY have been achieved if confirmed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response.

Unconfirmed response: An unconfirmed response must meet all components of the standard IMWG response category per Table 11.5, except bone marrow may be pending. This includes the first occurrence of the urine criteria being met, as applicable, which may have occurred at baseline as detailed above.

Confirmed response: For confirmation of response, bone marrow and extramedullary/soft tissue plasmacytoma criteria must be met as applicable for the standard IMWG response category. Confirmation of all other components of the

standard IMWG response category is required on a second consecutive assessment. If any component other than bone marrow and extramedullary/soft tissue plasmacytomas has not been confirmed on a second assessment, the response will remain designated as unconfirmed. In this case, the objective status for both cycles should be downgraded to the highest level of confirmed response that the patient has achieved.

NOTE: All measurable components reported at baseline need to be reassessed for response determination. If the measured values are not showing progression but not all components are reassessed, the objective status should be entered as Stable disease until all measurable components are reevaluated and all specified criteria are met for response. Once the patient has achieved a response, the objective status will be entered as a continued response (at the same level of response) if the measured values are not showing progression until all measurable components are reevaluated and all specified criteria for an improved response category are met. For example, if the patient is measurable by serum and has a measurable extramedullary/soft tissue plasmacytoma at baseline, the objective status will be entered as Stable disease if serum was reevaluated with no progression until the extramedullary/soft tissue plasmacytoma is remeasured and all specified criteria are met for response. If the patient achieved a PR, the objective status will continue to be entered as PR if serum was reevaluated with no progression until the extramedullary/soft tissue plasmacytoma is remeasured and all specified criteria are met for the improved response category

11.4 Bone progression:

Caution must be exercised to avoid rating progression or relapse on the basis of variation of radiologic technique alone. Compression fracture does not exclude continued response and may not indicate progression. When progression is based on skeletal disease alone, it should be discussed with the Medical Monitor before removing the subject from the trial.

11.5 Response and Progression:

Criteria for response and progression are listed in Table 11.5. Progressive disease for all subjects as defined in Table 11.5. Although the definition for “relapse from CR (or sCR) is listed, this will be documented as a response category in ONLY those protocols evaluating disease free survival.

Table 11.5: IMWG Criteria for response assessment including criteria for MRD in **Treatment Evaluation**		
Response subcategory		**Response criteria [1]**
IMWG MRD negativity criteria (Requires CR as defined below)	***Sustained MRD negative***	MRD negative in the marrow (Next-generation flow and/or Next-generation sequencing) and by imaging as defined below, confirmed one year apart. [2] Subsequent evaluations can be used to further specify the duration of negativity (e.g., MRD negative @ 5 years etc)
	Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by next-generation flow cytometry[4] on bone marrow aspirates using the EuroFlow standard operation procedure for MRD detection in MM (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells or higher
	Sequencing MRD negative	Absence of clonal plasma cells by next generation sequencing on bone marrow aspirates in which presence of a clone is defined as less than 2 identical sequencing reads obtained after DNA sequencing of bone marrow aspirates using the Lymphosight® platform (or validated equivalent method) with a minimum sensitivity of 1 in 10^5 nucleated cells[5] or higher
	Imaging+ MRD-negative	MRD negative as defined by Next-generation flow or Next-generation sequencing **PLUS** Disappearance of every area of increased tracer uptake found at baseline or a preceding PET/CT[3]
Standard IMWG Response criteria[6]	***sCR (stringent complete response)***	CR as defined below PLUS Normal FLC ratio[10] AND Absence of clonal cells in bone marrow biopsies by immunohistochemistry (κ/λ ratio ≤4:1 or ≥1:2 for κ and λ subjects, respectively, after counting ≥100 PCs)[7] Note: When the FLC ratio is abnormal due to the FLC ratio being inverted, this will also be considered acceptable for sCR.
	CR (complete response)	All of the following are required to be met: • Negative immunofixation on the serum AND urine[12] • <5% plasma cells in bone marrow aspirates (If cellular MRD is to be performed, the first BM aspirate should be sent to MRD and morphological evaluation is not mandatory) In addition, the following must be met as applicable: • If the only measurable disease is FLC, a normal FLC ratio[6] • If the only measurable disease is IgA, less than ULN and negative immunofixation of serum and urine[12] • If extramedullary/ (soft tissue) plasmacytoma is present at baseline: a) FDG-avid or PET positive prior to therapy: Mass of any size permitted if PET negative and b) Variably FDG-avid or PET negative: Regression to normal size on CT. For patients with only skin involvement, these same criteria apply to skin lesions measured with a ruler[11]

	VGPR (very good partial response)	All of the following are required to be met: • Serum and urine M-protein detectable by immunofixation but not on electrophoresis OR • ≥90% reduction in serum M-protein PLUS • urine M-protein level <100mg per 24 hours In addition, the following must be met as applicable: • If the only measurable disease is FLC, a >90% reduction in the difference between involved and uninvolved FLC levels • If the only measurable disease is IgA, a ≥90% decrease in IgA level and serum and urine M-protein by (detectable) immunofixation but not on electrophoresis or IgA below the ULN and positive immunofixation of serum and urine[12] • If extramedullary/soft tissue plasmacytoma is present at baseline: ≥90% decrease in SPD of up to 6 largest dominant masses and a) FDG-avid or PET positive prior to therapy: one or more PET positive at previously involved sites OR b) Variably FDG-avid or PET negative: regression on CT or by measurements with a ruler in patients with only skin involvement[11] NOTE: A response status of VGPR is Not applicable for those patients who do not have a "measurable" serum M-spike, serum free light chain, or urine M-spike at baseline.
	PR (partial response)	All of the following are required to be met, as applicable: • If present at baseline, ≥50% reduction of serum M-protein • if present at baseline reduction in 24-h urinary M-protein by ≥90% or to <200mg per 24 hours • If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If the only measurable disease is IgA, 50-89% decrease in IgA level • If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30% • If extramedullary/soft tissue plasmacytoma is present at baseline: ≥50% decrease in SPD of up to 6 largest dominant masses and a) FDG-avid or PET positive prior to therapy: one or more PET positive at previously involved sites OR b) Variably FDG-avid or PET negative: regression on CT or by measurements with a ruler in patients with only skin involvement [11]
	MR (minimal response)	All of the following are required to be met, as applicable: • If present at baseline, ≥25% but ≤49% reduction of serum M protein • If present at baseline, reduction in 24-hour urine M-protein by 50%-89% which still exceeds 200mg/24 hours[3] • If the only measurable disease is IgA, 25-49% decrease in IgA • If extramedullary/ (soft tissue) plasmacytoma is present at baseline: ≥25% decrease in SPD of up to 6 largest dominant masses and a) FDG-avid or PET positive prior to therapy: one or more PET positive at previously involved sites OR b) Variably FDG-avid or PET negative: regression on CT or by measurements with a ruler in patients with

		only skin involvement[11] NOTE: A response status of MR is Not applicable for those patients who are measurable by bone marrow only.
	SD (stable disease)	(Not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates) Not meeting criteria for CR, VGPR, PR, MR, or progressive disease (PD)
	PD (progressive disease) [8,9]	Any one or more of the following: • Increase of 25% from lowest confirmed response value in one or more of below: ▪ Serum M-protein (absolute increase must be ≥0.5 g/dl) ▪ Serum M-protein increase ≥1 g/dl, if the lowest M component was ≥5 g/dl ▪ Urine M-protein (absolute increase must be ≥200 mg/24 h) ▪ If the only measurable disease is IgA, IgA value (absolute increase must be ≥ 500 mg/dL0.5) ▪ In subjects without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dl) ▪ In subjects without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma cell percentage irrespective of baseline status (absolute % increase must be ≥10%) • Appearance of a new lesion(s), ≥50% increase from nadir in SPD[12] of more than one lesion, or ≥50% increase in the longest diameter of a previous lesion >1 cm in short axis. Lesions PET positive if PET positive prior to therapy[11] • ≥50% increase in circulating plasma cells (minimum of 200/mcl) if this is the only measure of disease
	Clinical Relapse	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) felt related to the underlying clonal plasma cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice • Development of new soft tissue/extramedullary plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression) • Definite increase in the size of existing soft tissue/extramedullary plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the SPD[12] of the measurable lesion • Hypercalcemia (>11 mg/dl) • Decrease in hemoglobin of ≥2 g/dl not related to treatment or other non-myeloma related conditions • Rise in serum creatinine by 2 mg/dl or more from the start of the treatment and attributable to myeloma • Hyperviscosity related to serum paraprotein

Abbreviations: MRD, minimal residual disease; CR, complete response; FLC, free light chain; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response.

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

[2] Sustained MRD negative when reported should also annotate the method used, eg., Sustained Flow MRD negative, Sustained sequencing MRD negative, etc.

[3] Criteria used by Zamagni et al, which, so far, was the only one showing the prognostic value of PET/CT in the MRD setting.[28] Imaging should be performed once MRD negativity is determined by MFC or NGS.

[4] Bone marrow flow cytometry should follow Next Generation Flow (NGF) guidelines.[29] The reference NGF method is an 8 color 2 tube approach which has been extensively validated. The 2 tube approach improves reliability, consistency and sensitivity because of the acquisition of a greater number of cells. The 8 color technology is widely available globally and the NGF method has already been adopted in most many flow laboratories across the world. The complete 8 color method is most efficient using the lyophilized mixture of antibodies which reduces errors, time and costs. It is recommended that 5 million cells be assessed. Flow cytometry method employed should have a sensitivity of detection of plasma cells of at least 1 in 10^5.

[5.] DNA sequencing assay on marrow aspirate should use an assay such as Lymphosight® (Sequenta) since this is the only one validated so far

[6] Derived from International uniform response criteria for multiple myeloma. Durie BG, et al. Leukemia. 2006 Sep;20(9):1467-73. Minor response definition and clarifications derived from Rajkumar SV et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011 May 5;117(18):4691-5. For coding CR and VGPR in subjects in whom the only measurable disease is by serum FLC levels: CR in such subjects indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above. VGPR in such subjects requires a ≥90% decrease in the difference between involved and uninvolved FLC levels. All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. Each category, except for stable disease, will be considered unconfirmed until the confirmatory test is performed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response. When the ratio is abnormal due to the FLC ratio being inverted, this will also be considered acceptable for CR.

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

[8] Positive immunofixation alone in a subject previously classified as CR will not be considered progression. For purposes of calculating time to progression and progression-free survival, CR subjects and MRD negative subjects should be evaluated using criteria listed above for progressive disease (PD). Criteria for relapse from CR or relapse from MRD be used only when calculating DFS. When the FLC ratio is abnormal due to the FLC ratio being inverted, this will also be considered acceptable for sCR.

[9] In the case where a value is felt to be a spurious result per physician discretion (for example, a possible lab error), that value will not be considered when determining the lowest value.

[10] All recommendations regarding clinical utilities relating to serum free light chain levels or FLC ratio is based on results obtained with the Freelite® test. Whether this test can be substituted by other tests, which have made available by other manufacturers in several countries have not been validated up to now.

[11] Extramedullary/soft issue plasmacytoma measurements should be taken from the CT portion of the PET/CT, or MRI scans, or dedicated CT scans where applicable. For subjects with only skin involvement, skin lesions should be measured with a ruler. Measurement of tumor size will be determined by adding the sum of the products of the maximal perpendicular diameters of measured lesions (SPD).

[12] If more than one M protein spike meets the criteria for measurable disease at baseline (for example, both serum and urine are measurable), then both need to be followed for response. Otherwise, only follow the measurable M protein spike for response. SPEP, UPEP, Immunofixation studies of both serum and urine, and Bone marrow biopsy are required to document CR regardless of registration values, and in addition FLC measurement and bone marrow immunophenotyping are required to document sCR. SPEP and UPEP are required to document VGPR regardless of registration values.

12.0 Descriptive Factors

12.1 Parameters followed for hematologic response (pick one): serum M-spike ≥1 g/dL and urine M-spike ≥200 mg/24 hours vs. serum M-spike ≥1g/dL only vs. urine M-spike ≥200 mg/24 hours only vs. serum immunoglobulin free light chain ≥10 mg/dL. Distinguish between SPEP measurements versus quantitative IgA measurement for serum M-spike.

13.0 Treatment/Follow–up Decision at Evaluation of Subject

Per Notice of Status Change 08Jan2026: enrollment is permanently closed and patients currently on study should be taken off study and move to long term follow-up.

13.1 Progressive Disease and Lack of response
Subjects who develop progressive disease will go off treatment and into survival follow-up.

13.2 Subsequent Treatment
Subjects who receive subsequent non-protocol therapy will go to the survival follow-up. Patients who fail to achieve a PR after 4 cycles of consolidation therapy are recommended to go to alternate subsequent treatment, at which time they will go to survival follow-up. Similarly, patients who are still MRD positive at the end of consolidation therapy are also recommended to go on to subsequent therapy, at which time they will go to survival follow-up.

13.3 Discontinuation of treatment for reasons other than subsequent treatment or PD
Subjects who go off protocol treatment for reasons other than subsequent treatment or PD (e.g. off for adverse reactions) will go to survival follow-up.

13.4 After completion of clinical follow-up per the test schedule, patients will enter survival follow-up. During this phase, subjects will be followed for survival status and subsequent (new) non-protocol therapy. These visits may be via phone or mail.

13.5 Criteria for Discontinuation of Treatment
Subjects may discontinue treatment for the following reasons:

- Progressive multiple myeloma
- Subject refuses further treatment on the trial
- Subject develops an intercurrent illness that precludes further participation, or requires a prohibited concomitant treatment
- The Investigator withdraws the subject in the subject's best interest
- Subject is lost to follow-up (defined as the inability to contact the subject on 3 separate occasions over 2 years)
- Administrative reasons (e.g., the subject is transferred to hospice care)
- An adverse event, which in the opinion of the Investigator, precludes further trial participation

13.6 Subject Discontinuation and Trial Discontinuation
The trial may be temporarily or permanently discontinued at any site and at any time. Reasons for trial discontinuation may include, but are not limited to, the following:

- Safety concerns
- Poor enrollment
- Non-compliance with the protocol, Good Clinical Practice guidance or other regulatory requirements by the Investigator(s)
- Request to discontinue the trial by a regulatory or health authority or an IRB/IEC
- Manufacturing difficulties/concerns

All Investigators and the requisite regulatory authorities will be notified if the trial is suspended or terminated for safety reasons. In the case of such termination, the Investigator will notify the IRB/IEC.

13.7 Ineligible Subject

A patient is deemed ineligible if after registration, it is determined that at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry.

- If the patient received treatment, the patient may continue treatment at the discretion of the physician as long as there are not safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, as per section 4.0 of the protocol.
- If the patient never received treatment, on-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

13.8 Major violation

A patient is deemed a major violation, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. If the patient received treatment, the patient may continue treatment at the discretion of the physician as long as there are not safety concerns. The patient will continue in the Active Monitoring/Treatment phase of the study, as per section 4.0 of the protocol.

13.9 Cancel

A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. Baseline material and the End of Protocol Treatment/Intervention Form must be submitted. No further data submission is necessary.

14.0 Biospecimens

14.1 Summary Table of Research Blood and Body Fluid Specimens to be collected for this Protocol

Note: Rochester Research blood and bone marrow collection per protocol IRB 521-93 will be done after consenting for 521-93 and according to that protocol. All processing will be done on Stabile 6.

Arizona Research blood and bone marrow collection per protocol IRB 919-04 will be done after consenting for 919-04 and according to that protocol.

Florida Research blood and bone marrow collection per protocol IRB 14-009163 will be done after consenting for 14-009163 and according to that protocol.

Table 14.1 Summary Table of Research Blood and Body Fluid Specimens to be collected for this Protocol

Correlative Trial (Section for more information)	Mandatory or Optional	Blood or Body Fluid being Collected	Type of Collection Tube (color of tube top)	Volume to collect per tube (# of tubes to be collected)	Pre-Registration	End of cycles 1, 3, 6, 12 (end of induction), 18, 24 (end of consolidation)	At suspected CR and at progression	Process at site? (Yes or No)	Temperature Conditions for Storage /Shipping
Flow cytometry for circulating plasma cells	Mandatory	Peripheral blood	No anticoagulant (red) ACD (yellow)	10 mL (1) 6 mL (3)	X	X	X	No	Cool Pak
Immune profiling									
Flow cytometry for MRD	Mandatory	Bone marrow aspirate	EDTA (lavender) ACD (yellow)	5 ml (1) 6 ml (6)	X	X	X	No	Cool Pak
Genomic studies									
Bone marrow microenvironment assessment									

14.3 Shipping and Handling of Laboratory Specimens

14.31 Kits

14.311 Sites will use their supply of tubes to create kits. if sites are unable to create their own kits, kits may be requested by emailing [redacted] at [redacted]

14.312 The kit contains supplies and instructions for collecting, processing, and shipping specimens.

14.133 Kits will be sent via Fed Ex® Ground at no additional cost to the participating institutions. Allow at least two weeks to receive the kits.

14.134 Kits will not be sent via rush delivery service unless the participating institution provides their own Fed Ex® account number or alternate billing number for express mail. Cost for rush delivery of kits will not be covered by the study.

14.316 **All specimens must be collected and shipped Monday-Thursday ONLY.**

14.32 Shipping (if applicable)

Bone marrow and blood samples can be shipped with Cool Pak the same day they are collected (Monday-Thursday). They should be shipped priority overnight taking care to avoid Friday collection and shipping. If unavoidable, Friday shipping with Saturday delivery can be arranged contacting the laboratory **in advance**.

Please notify Mayo Clinic by email [redacted] or phone [redacted] to notify laboratory when specimens are being shipped.

Predolin Foundation Biobank
Attn: [redacted]
Hematology Research, Stabile 613
Mayo Clinic
[redacted]

14.33 Sample storage and access

Residual samples will be stored at the Mayo Clinic Predolin Foundation Biobank, with access to use of sample limited to the study staff.

15.0 Drug Information

15.1 Carfilzomib (PR-171, Kyprolis™)

Please consult the most current package insert for complete drug information.

15.11 Background: Carfilzomib is an analog of epoxomicin and eponemycin; a tetrapeptide epoxyketone-based irreversible inhibitor of the chymotrypsin-like activity of the 20S proteasome. Proteasome inhibition leads to the accumulation of polyubiquitinated protein substrates within cells and to the selective induction of apoptosis in malignant cells while sparing non-malignant cells.

15.12 Formulation: Carfilzomib for Injection is supplied as an individually cartoned single-use vial containing a dose of 60 mg, 30 mg or 10 mg of carfilzomib as a white to off-white lyophilized cake or powder. Carfilzomib vials contain no antimicrobial preservatives and are intended only for single use.

15.13 Preparation and storage: Unopened vials of carfilzomib are stable until the date indicated on the package when stored in the original package at 2°C to 8°C (36°F to 46°F). Retain carfilzomib in the original package to protect from light. The reconstituted solution contains carfilzomib at a concentration of 2 mg/mL. Read the complete preparation instructions prior to reconstitution.

Reconstitution/Preparation Steps:
1. Remove vial from refrigerator just prior to use.
2. Aseptically reconstitute each vial by slowly injecting Sterile Water for Injection, USP, directing the solution onto the INSIDE WALL OF THE VIAL to minimize foaming to a reconstituted concentration of 2mg/mL (29 mL SWFI in 60 mg vials, 15mL SWFI in 30 mg vials, and 5mL SWFI in 10 mg vials)
3. Gently swirl and/or invert the vial slowly for about 1 minute, or until complete dissolution of any cake or powder occurs. DO NOT SHAKE to avoid foam generation. If foaming occurs, allow solution to rest in vial for about 2 to 5 minutes, until foaming subsides.
4. After reconstitution, carfilzomib is ready for intravenous administration. The reconstituted product should be a clear, colorless solution. If any discoloration or particulate matter is observed, do not use the reconstituted product.
5. When administering in an intravenous bag, withdraw the calculated dose from the vial and dilute into 50 mL 5% Dextrose Injection, USP intravenous bag.
6. Immediately discard the vial containing the unused portion.

Please note: The use of closed system drug transfer devices, where multiple stopper punctures in close proximity to one another can occur, is not recommended as it could result in coring.

Prepared IV bags are stable in the refrigerator for 24 hours, or at room temperature for 4 hours. Total time from reconstitution to administration should not exceed 24 hours.

15.14 Administration:

Current clinical experience indicates that carfilzomib should be administered as a 30-minute infusion.

The IV administration line should be flushed with 5% dextrose in water or normal saline, immediately before and after carfilzomib administration. Carfilzomib should not be administered as a bolus.

15.15 Pharmacokinetic information:

a) Absorption – The C_{max} and AUC following a single IV dose of 27 mg/m^2 was 4232 ng/mL and 379 ng•hr/mL, respectively. Following repeated doses of carfilzomib at 15 and 20 mg/m^2, systemic exposure (AUC) and half-life were similar on Days 1 and 15 or 16 of Cycle 1, suggesting there was no systemic carfilzomib accumulation. At doses between 20 and 36 mg/m^2, there was a dose-dependent increase in exposure.

b) Distribution – The mean V_{ss} of a 20 mg/m^2 dose of carfilzomib was 28 L. When tested in vitro, the binding of carfilzomib to human plasma proteins averaged 97% over the concentration range of 0.4 to 4 micromolar.

c) Metabolism – Carfilzomib was rapidly and extensively metabolized. The predominant metabolites measured in human plasma and urine, and generated in vitro by human hepatocytes, were peptide fragments and the diol of carfilzomib, suggesting that peptidase cleavage and epoxide hydrolysis were the principal pathways of metabolism. Cytochrome P450-mediated mechanisms played a minor role in overall carfilzomib metabolism. The metabolites have no known biologic activity.

d) Excretion – Following intravenous administration of doses ≥ 15 mg/m^2, carfilzomib was rapidly cleared from the systemic circulation with a half-life of ≤ 1 hour on Day 1 of Cycle 1. The systemic clearance ranged from 151 to 263 L/hour, and exceeded hepatic blood flow, suggesting that carfilzomib was largely cleared extrahepatically. The pathways of carfilzomib elimination have not been characterized in humans. Carfilzomib is eliminated primarily in the form of inactive peptide fragments with less than 1% excreted as parent drug.

15.16 Potential Drug Interactions: Carfilzomib is primarily metabolized via peptidase and epoxide hydrolase activities, and as a result, the pharmacokinetic profile of carfilzomib is unlikely to be affected by concomitant administration of cytochrome P450 inhibitors and inducers. Carfilzomib is not expected to influence exposure of other drugs.

15.17 Known potential toxicities:

Please refer to the current package insert for a complete list of toxicities.

15.18 Drug procurement:

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.19 Nursing Guidelines:

15.191 Fatigue is the most commonly reported side effect. Instruct subject in energy conserving lifestyle and monitor for effectiveness.

15.192 Anemia and thrombocytopenia are also commonly seen. Monitor CBC closely and instruct subject to report any unusual bruising or bleeding to the health care team.

15.193 GI side effects are commonly seen, but are usually mild in nature (nausea, diarrhea). Treat symptomatically and monitor for effectiveness.

15.194 Pneumonia and pulmonary hypertension have been seen. Instruct subject to report any shortness of breath, cough and/or chest pain to the trial team.

15.195 Elevated creatinine and isolated cases of renal failure (some associated with tumor lysis syndrome) have been seen. Make sure subject is well hydrated prior to administration and monitor creatinine levels closely. Urinary tract infections can also be seen, instruct subject to report signs and symptoms to trial team.

15.196 Take a detailed history of subject's concomitant medications including OTC and herbal preparations. Instruct subjects not to start any new medications without checking with the trial first.

15.197 Cardiac side effects, including peripheral edema, hypertension, hypotension can be seen. Instruct subject to report any signs or symptoms to health care team.

15.198 Monitor LFT's and instruct subject to report any hepatic symptoms (abdominal pain, jaundice) to trial team immediately.

15.2 **Lenalidomide (Revlimid®, CC-5013, CDC-501)**

Please consult the most current package insert for complete drug information.

15.21 **Background**: Lenalidomide has a wide range of effects, including the inhibition of hematopoietic tumor cell proliferation, the enhancement of T cells and natural killer (NK) cell activity, the modulation of stem cell differentiation, the inhibition of angiogenesis, and the inhibition of inflammation.

15.22 **Formulation**: For clinical trial, lenalidomide is provided as 1.25-, 2.5-, 5-, 10-, 15-, 20-, and 25-mg capsules for oral administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

The lenalidomide capsules are supplied in push-through blister foil or tamper-evident, child-resistant, opaque, high-density polyethylene (HDPE) containers with HDPE caps.

15.23 **Preparation and storage**: Lenalidomide should be stored at room temperature, between 59 and 86ºF (15-30ºC). Store drug away from direct sunlight.

15.24 **Administration:** Capsules are administered by mouth daily with water. Subjects should not break, chew or open the capsules.

15.25 **Pharmacokinetic information**:

a) Absorption – Lenalidomide is rapidly absorbed following oral administration to healthy subjects, with maximum plasma concentrations occurring between 0.5 and 1.5 hours post-dose. Co-administration with a high-fat and high-calorie meal in healthy subjects reduced the extent of absorption, resulting in an approximately 20% decrease in AUC and 50% decrease in C_{max} in plasma.

In the pivotal MM and MDS registration trials where the efficacy and safety were established for lenalidomide, the drug was administered without regard to food intake. Thus, lenalidomide can be administered with or without food.

Multiple dosing (up to 100 mg BID) did not cause marked drug accumulation. In plasma, the relative exposures of the S- and R-enantiomers of lenalidomide are approximately 55% and 45% respectively.

b) Distribution – In vitro (^{14}C)-lenalidomide binding to plasma proteins was low, with mean plasma protein binding at 22.7% and 29.2% in multiple myeloma subjects and healthy volunteers, respectively. In a multiple dose trial in healthy subjects administered 25 mg/day for 4 days, a small amount of lenalidomide (<0.01% of the dose) was detected in semen. Three days after stopping the drug, the amount of drug in semen was undetectable.

c) Metabolism – Results from in vitro metabolism studies showed that lenalidomide was neither metabolized by nor inhibited or induced the CYP pathway. In healthy subjects, lenalidomide undergoes limited metabolism and the parent compound is the predominant circulating component.

d) Excretion – Approximately 65% to 85% of lenalidomide is eliminated unchanged through urinary excretion in subjects with normal renal function. The half-life of elimination is approximately 3 to 4 hours at the clinically relevant doses (5 to 50 mg/day). Steady-state levels are achieved within 4 days.

Analyses in subjects with impaired renal function indicate that as renal function decreases, the total drug clearance decreases proportionally resulting in an increase in AUC. The $t_{½}$ of lenalidomide of lenalidomide was longer by approximately 6 to 12 hours in subjects with moderate or worse RI.

15.26 **Potential Drug Interactions**: Results from human in vitro metabolism studies indicated that lenalidomide is not metabolized by CYP enzymes, suggesting that administration of lenalidomide with drugs that inhibit CYP enzymes is not likely to result in metabolic drug interactions. Lenalidomide did not inhibit or induce marker enzyme activities for human CYP1A2, 2C9, 2C19, 2D6, 2E1, or 3A4 in vitro. In cultured human hepatocytes, lenalidomide did not induce the catalytic activities of CYP1A2, 2B6, 2C9, 2C19, or 3A4/5. Results from in vitro studies showed that lenalidomide is not a substrate of human MRP1, MRP2, or MRP3 efflux transporters. Results from in vitro studies also

demonstrated that lenalidomide is not a substrate of human OAT1, OAT3, OATP1B1 (OATP2), nor OCT1. Lenalidomide is a weak substrate of P-glycoprotein, but does not inhibit P-glycoprotein. Therefore, clinically relevant drug-drug interactions are unlikely between lenalidomide and P-glycoprotein substrates or inhibitors.

Co-administration of multiple doses of 10 mg of lenalidomide had no effect on the single dose pharmacokinetics of R- and S-warfarin. Co-administration of single 25-mg dose warfarin had no effect on the pharmacokinetics of lenalidomide. However, it is not known whether there is an interaction during clinical use.

Concomitant administration with lenalidomide 10 mg/day increased the plasma exposure of digoxin (0.5 mg, single dose) by 14%. It is not known whether the effect will be different in the therapeutic situation (higher lenalidomide doses and concomitant treatment with dexamethasone).

15.27 **Known potential toxicities**:

Please refer to the current package insert for a complete list of toxicities.

15.28 **Drug procurement:**

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Lenalidomide will be used in accordance with Celgene Corporation's Revlimid REMS® program. Per standard Revlimid REMS® program requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in, and must comply with, all requirements of the Revlimid REMS® program.

Further information about the Revlimid REMS® program is available at [redacted]

15.29 **Nursing Guidelines:**

- The most common side effects are neutropenia and thrombocytopenia.
- Due to the highly teratogenic potential of the closely related thalidomide, it is highly recommended that all women of childbearing age group and all men use effective contraception during therapy. All staff who are pregnant or who can become pregnant should not handle this drug outside of its original packaging.
- Instruct subject to report any rash immediately to the trial team.
- Lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened.
- If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.

- Subjects who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact trial staff immediately.

15.3 Dexamethasone for Oral Administration

15.31 **Background**: Dexamethasone is an adrenal corticosteroid compound. Dexamethasone decreases inflammation by suppression of neutrophil migration, decreased production of inflammatory mediators, and reversal of increased capillary permeability; suppresses normal immune response. Dexamethasone's mechanism of antiemetic activity is unknown.

15.32 **Formulation**: Commercially available for oral administration as:
Tablets [scored]: 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, and 6 mg
Solution, oral: 0.5 mg/mL (500 mL)
Solution, oral concentrate: Dexamethasone Intensol: 1 mg/mL (30 mL)

15.33 **Preparation, storage, and stability**: Refer to package insert for complete preparation and dispensing instructions. Store oral tablets at room temperature between 20ºC to 25ºC (60ºF to 77ºF). Protect from moisture. Dispense in a well-closed, light-resistant container as defined in the USP/NF. Store oral liquid at room temperature, do not freeze. Do not use if solution contains a precipitate. Refer to commercial package for drug expiration date.

15.34 **Administration:** Refer to the treatment section for specific administration instructions. May be taken with meals to decrease GI upset.

15.35 **Pharmacokinetic information**:
Onset of action: Prompt
Duration of metabolic effect: 72 hours
Metabolism: Hepatic
Half-life elimination: Normal renal function: 1.8-3.5 hours; **Biological half-life:** 36-54 hours
Time to peak, serum: Oral: 1-2 hours
Excretion: Urine and feces

15.36 **Potential Drug Interactions**:
Cytochrome P450 Effect: Substrate of CYP3A4 (major); **Induces** CYP2A6 (weak), 2B6 (weak), 2C8 (weak), 2C9 (weak), 3A4 (strong)
Increased Effect/Toxicity: Aprepitant, azole antifungals, calcium channel blockers, cyclosporine, estrogens, and macrolides may increase the serum levels of corticosteroids. Corticosteroids may increase the hypokalemic effects of amphotericin B or potassium-wasting diuretics (loop or thiazide); monitor. Refer to the package insert for a listing of other drugs.
Decreased Effect: Antacids and bile acid sequestrants may reduce the absorption of corticosteroids; may reduce the absorption of corticosteroids; separate administration by 2 hours. Aminoglutethimide, barbiturates, and CYP3A4 inducers may reduce the

serum levels/effects of dexamethasone and dexamethasone may decrease the levels/effects of other CYP3A4 substrates. Serum concentrations of isoniazid may be decreased by corticosteroids. Corticosteroids may lead to a reduction in warfarin effect. Corticosteroids may suppress the response to vaccinations.
Ethanol/Nutrition/Herb Interactions:
Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).
Food: Dexamethasone interferes with calcium absorption. Limit caffeine.
Herb/Nutraceutical: Avoid cat's claw (*Uncaria tomentosa)*, echinacea (have immunostimulant properties)

15.37 **Known potential adverse events:** Consult the package insert for the most current and complete information.
Common known potential toxicities, frequency not defined:
Fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, exacerbation of infection, exacerbation or symptoms of diabetes, psychosis, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, esophagitis, peptic ulcer, dermatologic disturbances, convulsions, vertigo and headache, endocrine abnormalities, ophthalmic changes, and metabolic changes. Some subjects have experienced itching and other allergic, anaphylactic or hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia and arthralgia.

15.38 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.4 Daratumumab and hyaluronidase-fihj (Darzalex Faspro®)

15.41 **Background**: Daratumumab is an immunoglobulin G1 kappa (IgG1κ) human monoclonal antibody against CD38 antigen, produced in a mammalian cell line (Chinese Hamster Ovary [CHO]) using recombinant DNA technology. The molecular weight of daratumumab is approximately 148 kDa.

CD38 is a transmembrane glycoprotein (48 kDa) expressed on the surface of hematopoietic cells, including multiple myeloma and other cell types and tissues and has multiple functions, such as receptor mediated adhesion, signaling, and modulation of cyclase and hydrolase activity. Daratumumab is an IgG1κ human monoclonal antibody (mAb) that binds to CD38 and inhibits the growth of CD38 expressing tumor cells by inducing apoptosis directly through Fc mediated cross linking as well as by immune-mediated tumor cell lysis through complement dependent cytotoxicity (CDC), antibody dependent cell mediated cytotoxicity (ADCC) and antibody dependent cellular phagocytosis (ADCP). Myeloid derived suppressor cells (MDSCs) and a subset of regulatory T cells (CD38+Tregs) expresses CD38 and is susceptible to daratumumab mediated cell lysis.

15.42 **Formulation**: Daratumumab and hyaluronidase-fihj injection is a sterile, preservative-free, colorless to yellow, and clear to opalescent solution supplied in a single-dose vial for subcutaneous administration. Each 15 mL single-dose vial contains 1800 mg

daratumumab and 30,000 units hyaluronidase, L-histidine, L-histidine hydrochloride monohydrate, L-methionine, polysorbate 20, sorbitol, and Water for Injection, USP.

15.43 **Preparation and storage**:

Daratumumab SQ study drug vials must be stored in the original carton in a refrigerator ranging from 2°C to 8°C and must not be utilized after the expiry date printed on the label. The product must be protected from light and must not be frozen. Daratumumab SC does not contain preservatives; therefore, any unused portion remaining in the vial must be discarded.

For SQ daratumumab, remove daratumumab vial from refrigerated storage and equilibrate to ambient (15 to 30 ℃) temperature. Store the unpunctured vial at ambient temperature and light for a maximum of 24 hours.
Withdraw 15 mL into a syringe.

Daratumumab and hyaluronidase-fihj SQ injection is directly drawn from the vial into a syringe and is compatible with polypropylene or polyethylene syringe material; polypropylene, polyethylene, or polyvinyl chloride (PVC) subcutaneous infusion sets; and stainless-steel transfer and injection needles. To avoid needle clogging, attach the hypodermic injection needle or subcutaneous infusion set to the syringe immediately prior to injection. Once withdrawn from the vial, the solution may be stored at ambient temperature for up to 4 hours

15.44 **Administration:** Administer pre-injection and post-injection medications. Refer to section 7 of the protocol.

Utilizing a hypodermic injection needle or subcutaneous infusion set, inject 15 mL of the daratumumab and hyaluronidase-fihj solution into the subcutaneous tissue of the abdomen approximately 3 inches to the right or left of the navel over approximately 3-5 minutes. No data are available on performing the injection at other sites of the body.

15.45 **Pharmacokinetic information**:
Following the administration of the recommended dose of 1,800 mg daratumumab and 30,000 units hyaluronidase subcutaneously once weekly for 8 weeks, the mean ± standard deviation (SD) maximum trough concentrations (Ctrough following the 8th dose) were 593±306 µg/mL compared to 522±226 µg/mL for daratumumab 16 mg/kg administered intravenously, with a geometric mean ratio of 108% (90% CI: 96, 122). The estimated median daratumumab area under the concentration-time curves (AUC0-7 days) and daratumumab peak concentration (Cmax) following the 8th dose were comparable between subcutaneous and intravenous daratumumab (4017 µg/mL•day vs. 4,019 µg/mL•day for AUC0-7 days and 592 µg/mL vs. 688 µg/mL for Cmax).
The absolute bioavailability of daratumumab-hyaluronidase is 69%, with peak concentrations occurring around 3 days (Tmax). The estimated mean (coefficient of variation, CV) volume of distribution for the central compartment is 5.2 L (37%) and peripheral compartment was 3.8 L with the daratumumab-hyaluronidase formulation. Daratumumab is cleared by parallel linear and nonlinear saturable

target mediated clearances. The estimated mean (CV%) linear clearance of daratumumab is 119 mL/day. The estimated mean (CV%) elimination half-life associated with linear clearance is 20 days (22%).

15.46 **Potential Drug Interactions**: No drug interaction studies have been performed.

15.47 **Known potential toxicities**:

Please refer to the current package insert for a complete list of toxicities.

15.48 **Drug procurement:**

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.49 **Nursing Guidelines:**

- All subjects should have blood pressure monitored before and after all infusions. For the first infusion, blood pressure should also be recorded more frequently.

- All subjects should have ancillary treatment as specified in section 9.

16.0 Statistical Considerations and Methodology

16.1 Overview

This trial is designed to estimate the rate of sustained MRD negativity (MRD negative status at any point, with a repeated MRD negative status one year later) of adapted treatment in subjects with high-risk MM. The one-stage binomial phase 2 trial design will be used to evaluate the sustained MRD negativity rate.

16.11 Primary Endpoint

The primary endpoint of this trial is the rate of sustained MRD negativity (MRD negative status at any point, with a repeated MRD negative status one year later). All subjects meeting the eligibility criteria, who have signed a consent form and have begun treatment, will be evaluable, with the exception of subjects determined to be a major violation.

16.12 Sample Size

The one-stage binomial trial design to be used is fully described below. A maximum of 67 evaluable subjects will be accrued into this phase 2 trial unless undue toxicity is encountered. We anticipate accruing an additional 8 subjects to account for ineligibility, cancellation, major treatment violation, or other reasons for a maximum of 75 subjects overall.

16.13 Accrual Rate and Trial Duration

The anticipated accrual rate is 3-4 subjects per month, translating to duration of approximately two years for accrual.

16.2 Statistical Design:

16.21 Decision Rule: The largest sustained MRD negativity proportion where the proposed treatment regimen would be considered ineffective in this population is 40%, and the smallest sustained MRD negativity proportion that would warrant subsequent studies with the proposed regimen in this subject population is 60%. The following one-stage binomial design requires 67 evaluable subjects to test the null hypothesis that the true sustained MRD negativity proportion in this subject population is at most 40%.

In the presentation of the FORTE Trial by Francesca Gay at ASCO 2019, the pre-maintenance MRD negativity rate was 49% in 94 patients with R-ISS II/III risk disease on the carfilzomib, lenalidomide, and dexamethasone arm without transplantation (KRd12). Within 33 of those patients with MRD testing available 1 year later, 72% has sustained MRD negativity, translating to a sustained MRD negativity rate overall of approximately 35% (49%x72%). Thus, a sustained MRD negativity rate of 40% or less (null hypothesis) would be considered uninteresting.

16.211 Final Decision Rule: If 33 or fewer subjects with sustained MRD negativity are observed in the first 67 evaluable subjects, we will consider this regimen ineffective in this subject population. Otherwise, if the number of subjects with sustained MRD negativity is at least 34, this will be considered evidence of promising activity and the treatment regimen may be recommended for further testing in subsequent studies.

16.212 Over Accrual: If more than the target number of subjects are accrued, the additional subjects will not be used to evaluate the final decision rule or used in any decision-making process. Analyses involving over accrued subjects are discussed in Section 16.313.

16.22 Power and Significance Level: Assuming that the number of subjects with sustained MRD negativity is binomially distributed, the significance level is 0.05, i.e., there is a 5% chance of finding the regimen to be effective when it truly is not. The probability of declaring that this regimen warrants further trial (i.e., statistical power) under various sustained MRD negativity proportions can be tabulated as a function of the true sustained MRD negativity proportion as shown in the following table.

If the true sustained MRD negativity proportion is...	0.40	0.45	0.50	0.55	0.60
Then the probability of declaring that the regimen warrants further trial is…	0.05	0.21	0.50	0.79	0.95

16.23 Other considerations: Adverse events, quality/duration of response, and patterns of treatment failure observed in this trial, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the trial.

16.3 Analysis Plan

The analysis for this trial will commence at planned time points (see Section 16.2) and at the time the subjects have become evaluable for the primary endpoint. The Statistician and Trial Chair will make the decision, in accord with Standard Operating Procedures, availability of data for secondary endpoints (e.g., laboratory correlates), and the level of data maturity. It is anticipated that the earliest date in which the results will be made available via manuscript, abstract, or presentation format is when last subject has been followed for at least 3 years (5 years after study activation).

16.31 Primary Outcome Analyses:

16.311 Definition: The primary endpoint of this trial is the rate of sustained MRD negativity (MRD negative status at any point, with a repeated MRD negative status one year later). All subjects meeting the eligibility criteria, who have signed a consent form and have begun treatment, will be evaluable for response, with the exception of subjects determined to be a major violation. For the purpose of the repeated MRD measurement one year later, a window of +/-1 month will be employed to allow inclusion of as many test results as possible. Sensitivity analysis will include only repeated MRD measurements within a window of +/-2 weeks.

16.312 Estimation: The proportion of subjects with sustained MRD negativity will be estimated by the number of subjects with sustained MRD negativity divided by the total number of evaluable subjects. Exact binomial 95% confidence intervals for the true sustained MRD negativity proportion will be calculated. In supplemental analysis, the likelihood of MRD negativity over time (i.e., at each time point) will be estimated based on a generalized linear mixed model with logit link function and time as a categorical variable representing planned cycle/time point of assessment

16.313 Over Accrual: If more than the target number of subjects are accrued, the additional subjects will not be used to evaluate the stopping rule or used in any decisionmaking processes; however, they will be included in final point estimates and confidence intervals.

16.32 Secondary Outcome Analyses

16.321 Overall response rate (≥ confirmed VGPR) will be evaluated at the end of induction, end of consolidation, and every 3 cycles of maintenance. Exact binomial 95% confidence intervals for the true response proportion at each time point will be calculated.

16.322 Overall survival is defined as the time from registration to death due to any cause. The distribution of overall survival will be estimated using the method of Kaplan-Meier (Kaplan and Meier, 1958).

16.323 Progression-free survival is defined as the time from registration to the earliest date of documentation of disease progression or death due to any cause. The distribution of progression-free survival will be estimated using the method of Kaplan-Meier.

16.324 Adverse Events: All eligible subjects that have initiated treatment will be considered evaluable for assessing adverse event rate(s). The maximum grade for each type of adverse event will be recorded for each subject, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse event(s) to the trial treatment will be taken into consideration. AEs will be summarized overall, as well as by treatment phase (induction, consolidation, maintenance with carfilzomib+lenalidomide+daratumumab).

16.33 Correlative Analyses: Due to the small overall sample size, the results of these analyses will be considered exploratory and hypothesis generating in nature.

16.331 Extensive omics based analyses are planned as part of this clinical trial. A translational statistical analysis plan (SAP) will be developed as a separate document to allow for integration of the most advanced analytic techniques available at time of analysis. The SAP will be finalized prior to initiation of any statistical analysis. Analyses will be a joint effort of statistics and bioinformatics groups at Mayo Clinic directed by the Investigative Team (PI and Co-investigators). Final data will include multi-omics assessment from up to 75 MM patients each studied at 6 pre-defined intervals (450 time points with up to 9 different assays creating 4,050 datasets). We will employ standard statistical methods (e.g., univariate comparisons between groups and within groups over time and multivariate techniques) as well as innovative methods using machine-learning, network analysis and high-performance computing to address the challenges of integrating multi-omics data in a time series experiment, in order to dissect mechanisms influencing MM pathogenesis and progression. Appropriate transformation of data (e.g., log transformation), checking of assumptions, and multiplicity adjustment will be employed through all analyses, where applicable. Two key aims of investigation will include:

16.3311 To determine the clonal architecture before treatment, after treatment in subjects with residual disease and in subjects who have disease progression after attaining MRD negativity.

16.3312 To evaluate the bone marrow microenvironment before and after treatment and the time of MRD negative state.

16.4 Data & Safety Monitoring:

16.41 The principal investigator(s) and the trial statistician will review the trial every 6 months or more frequently as required to identify accrual, adverse event, and any endpoint problems that might be developing. Teleconferences will be scheduled with the study PI and all investigators at least quarterly to review progress of the study and discuss concerns. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing safety data for this trial per the study specific Clinical Monitoring Plan (CMP).

16.42 Adverse Event Stopping Rules: The stopping rules specified below are based on the knowledge available at trial development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the trial re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The trial team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

16.422 Accrual will be temporarily suspended if at any time we observe events with an attribution of possibly, probably, or definitely related to trial treatment that satisfy one of the following:

- if 3 or more subjects in the first 12 treated subjects during each of the 3 phases of treatment (induction, consolidation and maintenance) experience a grade 4 or higher non-hematologic adverse event

- if after the first 12 subjects have been treated, 20% of all subjects treated during each of the 3 phases of treatment (induction, consolidation and maintenance) experience a grade 4 or higher non-hematologic adverse event

- In addition, if there are 3 or more grade 5 events with an attribution of possibly, probably, or definitely related to trial treatment during the first 25 patients or more than 10% at any time during the trial, the study will be stopped for further assessment and redesign as appropriate.

We note that we will review grade 4 and 5 adverse events deemed “unrelated” or “unlikely to be related”, to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

16.5 Results Reporting on [redacted]:

At trial activation, this trial will have been registered within the "[redacted]" website. The Primary and Secondary Endpoints along with other required information for this trial will be reported on [redacted]. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this trial is 5 years after the trial opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this trial is at the time the last subject registered has been followed for at least 3 years.

16.6 Inclusion of Women and Minorities

16.61 This trial will be available to all eligible subjects, regardless of race, gender, or ethnic origin.

16.62 There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.

16.63 The geographical region served by accruing centers has a population which includes approximately 3-15% minorities. Based on prior studies involving similar disease sites, we expect about 3-5% of subjects will be classified as minorities by race and about 33% of subjects will be women. Expected sizes of racial by gender subsets are shown in the following table:

Table 16.63 Accrual Estimates by Gender/Ethnicity/Race

Ethnic Category	**Sex/Gender**			
	Females	**Males**	**Unknown**	**Total**
Hispanic or Latino	1	2	0	3
Not Hispanic or Latino	22	50	0	72
Ethnic Category: Total of all subjects*	23	52	0	**75**
Racial Category				
American Indian or Alaskan Native	0	1	0	1
Asian	0	1	0	1
Black or African American	5	7	0	12
Native Hawaiian or other Pacific Islander	0	1	0	1
White	17	43	0	60
Racial Category: Total of all subjects*	23	52	0	**75**

Ethnic Categories: **Hispanic or Latino –** a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term "Spanish origin" can also be used in addition to "Hispanic or Latino."

Not Hispanic or Latino

Racial Categories:

American Indian or Alaskan Native – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa.

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations/Tissue Biospecimens

See section 14.0

18.0 Records and Data Collection Procedures

18.1 Submission Timetable

Data submission instructions for this study can be found in the Data Submission Schedule.

18.2 Survival Follow-up

See Section 4.

18.3 CRF completion

This study will use Medidata Rave® for remote data capture (rdc) of all study data. Data collection for this study will be done exclusively through the Medidata Rave® clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active account and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on the organization roster at the enrolling site.

Note: The value closest to the time of starting treatment should be considered as baseline value for response assessment

18.4 Site responsibilities

Each site will be responsible for ensuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.5 Supporting documentation (update required documentation based on protocol requirements)

This study requires supporting documentation for diagnosis prior to study entry as well as for evidence of response to study therapy and progression after study therapy. Supporting documentation for diagnosis will include either a pathology report or a laboratory report demonstrating multiple myeloma (including SPEP, UPEP, FLC, Serum and Urine Immunofixation, Bone Marrow Biopsy and Aspirate, skeletal bone survey, PET scan, Plasma Cell Proliferation and Assessment and FISH). These reports should be uploaded into the Supporting Documentation: Baseline form within 14 days of registration.

For response to treatment, supporting documentation may include SPEP, UPEP, FLC, Serum and Urine Immunofixation, Bone Marrow Biopsy and aspirate, skeletal bone survey, and PET scan. These documents should be uploaded into the Supporting Documentation form.

For patients who progress after study therapy supporting documentation may include any of the following: SPEP, UPEP, FLC, serum and urine immunofixation, bone marrow

biopsy and aspirate, skeletal bone survey, and PET scan. These documents should be uploaded into the Supporting Documentation form.

18.6 Labeling of materials

Each site will be responsible for ensuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.7 Overdue lists

A list of overdue forms and outstanding queries will be available in Rave through the Rave Task Summary. In addition to this, the Overdue Materials report will be distributed monthly by the data manager.

19.0 Budget

19.1 Costs charged to patient: routine clinical care

19.2 Tests to be research funded:
Research testing and analysis on blood and BM specimens

19.3 Other budget concerns:
The Multiple Myeloma SPORE grant will provide Mayo Clinic with funding to support the costs of running this study.

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Multiple Myeloma Diagnostic Criteria

Clonal BMPC ≥10% or biopsy-proven plasmacytoma PLUS

-***Either a myeloma defining event*:**

C: Hypercalcemia: serum calcium >1 mg/dL higher than the upper limit of normal or >11 mg/dL

R: Renal insufficiency: creatinine clearance <40 mL per min or serum creatinine >2 mg/dL

A: Anemia: hemoglobin >20 g/L below the lower limit of normal, or a hemoglobin <100 g/L

B: Bone lesions: osteolytic lesions on x-ray, CT, or PET-CT

-OR *a biomarker of early progression*

- Clonal bone marrow plasma cell percentagen≥60%
- Involved: uninvolved serum free light chain ratio ≥100
- >1 focal lesion on MRI studies

NYHA Classification

Class I: NO Symptoms with ordinary activity

Class II: Symptoms with ordinary activity

Class III: Symptoms with minimal activity

Class IV: Symptoms at rest

ECOG Performance Status Scale

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