

Academic and Community Cancer Research United (ACCRU)

Open Label, Phase 2, Single-Arm Study of Selinexor, Daratumumab, Carfilzomib and Dexamethasone for High-Risk, Relapsed and Relapsed/Refractory Multiple Myeloma Patients Who Have Received 1 – 3 Prior Lines of Therapy

For any communications regarding this protocol, please contact the person indicated on the Protocol Resource page. This is a stand-alone document found on the ACCRU web site [REDACTED]

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Drug Availability

Commercial Agents: Carfilzomib, Daratumumab, Dexamethasone

Drug Company Supplied: Selinexor -IND: 153581

√ Study contributor(s) not responsible for patient care.

Research Coordinating Center

[REDACTED]

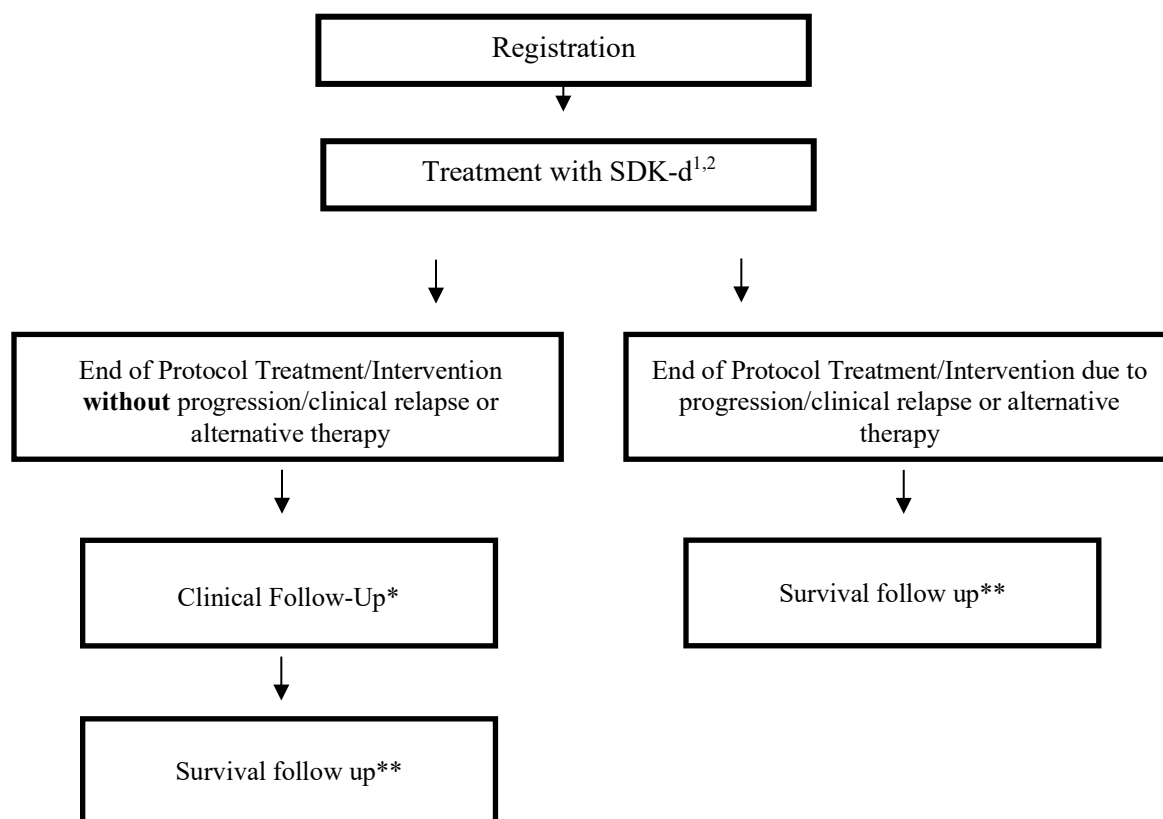
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Schema

Safety Run-in patients only: Prior to discussing protocol entry with the patient, call the ACCRU Registration Office (507-284-2753) for dose level and to ensure that a place on the protocol is open to the patient.



¹Cycle length = 28 days; refer to Section 7.0 for dosing information

²Treatment until progression or alternative therapy

*Clinical Follow- up, every 3 months until 5 years after registration, unless progression/clinical relapse or alternative therapy

**Survival Follow-up, every 6 months until 5 years after registration.

Generic name: Selinexor Brand name(s): Xpovio™, KPT-330 Availability: Karyopharm Therapeutics Inc.	Generic name: Daratumumab Brand name(s): Darzalex® Availability: Commercial
Generic name: Carfilzomib Brand name(s): Kyprolis™, PR-171 Availability: Commercial	Generic name: Dexamethasone Brand name(s): Decadron Availability: Commercial

1.0 Background

Multiple myeloma (MM) is a plasma cell disorder that makes up to ~13% of hematological malignancies. (*National Cancer Institute Surveillance, Epidemiology and End Results Program (SEER)*, n.d.). New treatment options for MM, include new proteasome inhibitors (i.e., carfilzomib, ixazomib), immunomodulators (lenalidomide, pomalidomide), monoclonal antibodies (i.e., daratumumab, elotuzumab), and recently selinexor. Despite the new advances in therapeutic options, MM remains incurable. Survival rates vary between two years for high-risk disease up to ten years in standard-risk disease. (Kazmi et al., 2015) Hence, high-risk MM remains a medical challenge; new advances changed the face of standard-risk disease while high-risk MM is in a stay-behind situation.

High-risk MM (HRMM) makes about 15-20% of a newly diagnosed disease. Overall survival (OS) for HRMM is poor (H. Avet-Loiseau, 2010). HRMM can be identified either by clinical behavior or by cytogenetics. The revised international myeloma group staging system (RISS) is the most commonly used. RISS divides patients into three groups. (Palumbo et al., 2015) Patients presenting with R-ISS stage III have a 5-years progression-free survival (PFS) of 24%. The RISS takes into account the presence of high LDH, del(17p), t(4;14), or t(14;16) and disease burden as per ISS.

In addition to those cytogenetics abnormalities identified by RISS, HRMM can be identified by using the gene expression profile (GEP) of purged plasma cells from bone marrow biopsies. The GEP data from the University of Arkansas indicated that patients with high GEP-70 scores correspond to poor prognosis with a hazard ratio (HR) of 4.75; $P < .001$. (Shaughnessy et al., 2007) Also, the same group showed that the deregulated expression of genes, in the GEP-70 model, are mostly mapped on chromosome 1. Most upregulated genes mapped to chromosome 1q, and most down-regulated genes mapped on chromosome 1p. Therefore, the abnormalities of both short and long arms of chromosome 1 were associated with shorter survival (Shaughnessy et al., 2007). Specifically, highly expressed PSMD4 correlates to 4 copies of 1q21 (CKS1B) and leads to a bortezomib refractory disease in Total Therapy 3 protocols. High PSMD4 gene expression is associated with 68% overall survival in 2-years. (Shaughnessy et al., 2011).

Amplification of CKS1B is frequently associated with the deletion of the CDKN2C gene at the chromosome 1p32.3 locus. Deletion of CDKN2C, a tumor suppressor gene, leads to the deregulation of the G1/S transition, resulting in an increased proliferative rate of plasma cells in patients with MM. Either hemizygous or homozygous deletion of CDKN2C had a worse OS compared with cases with intact CDKN2C (22 months versus 38 months; $P = 0.003$). (Leone et al., 2008)

Clinically, median PFS to front-line of therapy ranges between 36 months without ASCT to 50 months post-ASCT. In a retrospective analysis, patients with early relapse (< 12 months post ASCT) have a 1-year post-relapse OS of 65% vs. 80% in standard-risk group. (S. K. Kumar et al., 2018) In a similar fashion, 2-year post-relapse OS was 50% for early post-ASCT relapse vs. 66% for last post- ASCT relapse. (S. K. Kumar et al., 2018) Hence, early relapse is considered a feature of HRMM. Therefore, early relapse, defined as progression of MM within 12 months of first-line therapy, is an indicator of an ultra-risk feature regardless of the initial depth of response. The median PFS to second-line therapy for those patients is five months vs. 19 months for those with a late relapse ($P < .001$). This short PFS translates into a median OS of 18 months. (Kastritis E. et al., 2017). Similar results were reported by another retrospective study, regardless of ASCT, the median OS for early relapse is significantly low (around 21.0 months). Survival outcomes

remained poor even among patients undergoing early ASCT with a median OS from ASCT of 23 months vs. 122 months for late relapse post-ASCT ($P < 0.001$). (Majithia et al., 2016) Modest improvement in PFS in HRMM was achieved by implementing high dose chemotherapy in the setting of double transplant (Cavo M. et al., 2017) or combinations of multi-chemotherapy regimens. (Lakshman A. et al., 2017) Results from clinical trials were humbled by an OS around 17 months, even less in primary refractory disease. Hence, high-risk MM is associated with dismal survival; therefore, more clinical trials are needed to improve outcomes for this group of patients.

Factors identifying high-risk multiple myeloma.			
Risk Factor	PFS	OS	Ref.
ISS-III	-	29 months	(Greipp et al., 2005)
R-ISS-III	29 months	43 months	(Palumbo et al., 2015)
Plasma cell leukemia	-	6-15 months	(Granell et al., 2017)
Circulating plasma cells	17 months	15 months	(An et al., 2015; Ravi et al., 2018)
Early relapse post ASCT (within 12 months)	-	23.1 months	(Majithia et al., 2016)
Early relapse (within 12 months) post- non-ASCT regimen	-	21 months	(Majithia et al., 2016)
High risk GEP	-	19 months	(Shaji K. Kumar et al., 2011)
Elevated LDH	-	21 months	(Dimopoulos et al., 1991; Terpos et al., 2010)
IMiD-14 gene: High	At 3 years: 52%	At 3 years: (49-70)%	(Bhutani et al., 2017)

1.1 Clinical Activity

1.11 Rationale, for using carfilzomib, daratumumab, and dexamethasone combinations:

Carfilzomib is a keto-epoxide tetrapeptide proteasome inhibitor with proven efficacy in relapsed refractory MM. The ENDEAVOR trial compared

dexamethasone with carfilzomib, at a dose of 56 mg/m², to dexamethasone and bortezomib. The trial showed that carfilzomib was associated with a doubling of the PFS, up to 18 months. The overall response rate was superior with the use of carfilzomib plus dexamethasone compared to bortezomib plus dexamethasone (77% vs. 63%), respectively. During their interim analysis, in January of 2017, carfilzomib improved overall survival by seven months. (Chng et al., 2017; Goldschmidt et al., 2018)

Daratumumab (DARA) is a new monoclonal antibody against CD38, which showed promising results in the setting of relapsed/ refractory disease. Benefits from daratumumab are durable across all responders even those with a minimal response or stable disease. DARA induced at least a PR in 20% of patients with high-risk cytogenetics. Furthermore, in the CASTRO trial, the combination of DARA with a proteasome inhibitor resulted in high response rates with acceptable safety profiles.(Palumbo et al., 2016) The addition of DARA to the standard of care regimens for RRMM has increased complete response (CR) and minimal residual disease (MRD)-negative rates. In the CASTOR trial, adding DARA to bortezomib and dexamethasone increased MRD (10⁻⁵) from 1.7% to 7.2%. MRD negativity (to the level 10⁻⁵) was 5% for all patients and 2% for lenalidomide refractory patients. (Hervé Avet-Loiseau et al., 2016) In the POLLUX trial, adding DARA to lenalidomide and dexamethasone increased MRD (10⁻⁵) from 4.6% to 22.4%. The combination was safely administered to patients without a significant change in the toxicity profile.

High-dose carfilzomib, target up to 70 mg/m², was added to daratumumab and dexamethasone (DKd) in a phase 1b study (MMY1001). (Chari et al., 2018) The combination was associated with overall response rates of 84%. At data cut-off, the median duration of treatment was four cycles. Due to a short median follow up, the median PFS was not reached; 12-month PFS rates were 74% for all-treated patients and 65% for lenalidomide-refractory patients. MRD data was available on 11 patients who achieved ≥CR. Out of 11 patients, only four patients achieved MRD negativity 10⁻⁵ by clonoSEQ®.

Building on MMY1001, the phase 3 CANDOR trial reported results from combining DKd vs. Kd. (Usmani et al., 2019) Patients received 1-3 prior lines of therapy, and 33% of patients were lenalidomide-refractory. After a median follow-up around 16.5 months, the median PFS was not reached for the DKd arm vs. 15.8 months for the Kd arm. The incidence of grade ≥3 AEs was 82.1% and 73.9% in the DKd and Kd arms, respectively. Serious AEs occurred in 56.2% DKd and 45.8% Kd.

Table (1): Clinical trials using Dara/Selinexor/CFZ/dexamethasone Combination for relapsed/refractory MM

Combination for relapsed/refractory MM			ORR	CR	MRD (10-5)	Ref
Daratumumab	Dexamethasone	Selinexor	74%	-	-	(Gasparetto, Lentzsch, et al., 2020)
Daratumumab	Dexamethasone	Carfilzomib	85%	13%	36%	MMY1001

Daratumumab	Dexamethasone	Carfilzomib	84.3%	28.5%	12.5% at 12	CANDOR
Selinexor	Dexamethasone	Carfilzomib	75%	0%	-	(Gasparetto, Lipe, et al., 2020)
Daratumumab	Dexamethasone	Lenalidomide	84%	54%	22.4%	POLLUX
Daratumumab	Dexamethasone	Bortezomib	80%	21%	7.2%	CASTOR

1.12 The rationale for adding selinexor:

Selinexor is a nuclear export protein inhibitor, exportin1 (XPO1), inhibitor. Exportin1 controls nuclear cytoplasm transportation, by which tumor suppressor proteins are exported out of the plasma cell nucleus, hence inhibiting exportin -1 allows tumor suppressor protein to remain functional inside the nucleolus. Selinexor at doses up to 80 mg twice weekly, with dexamethasone is active against MM even in the setting of disease refractory to lenalidomide, pomalidomide, bortezomib, carfilzomib, and daratumumab. An impressive overall response rate of about 20% was reported in such highly resistant MM. (Chari et al., 2019) Side effect profile was acceptable. Nausea and asymptomatic hyponatremia are the most common non-hematological grade 3 adverse events. Also, combining selinexor with bortezomib proved to be safe, with doses up to 100mg weekly, in the setting of the STOMP trial. (Bahlis et al., 2018) Overall response rates in RRMM were around 77%.

Preclinical data showed promising results from the synergistic effects of combining selinexor with carfilzomib. (Rosebeck et al., 2014; Sullivan et al., 2015; Turner et al., 2016) A phase I trial tested the safety of combining Selinexor with carfilzomib and enrolled a total of 18 patients. The recommended phase 2 dosing (RP2D) was established as carfilzomib (27 mg/m² twice a week), selinexor (60 mg biweekly), and dexamethasone (20 mg weekly) combination. (Jakubowiak et al., 2019) The median PFS was 3.7 months, and overall survival was 22.4 months in the overall population. During ASCO-2000 meeting results of another phase I trial with this combination were reported (Gasparetto, Lipe, et al., 2020). Twenty- four patients were enrolled. The majority of patients were lenalidomide exposed (n=23), and a previous autologous transplant was done on about 79% of patients. The overall response rate was around 70%. Deep responses ($\geq$ VGPR) were reported on 50% of the patients. The most notable non-hematological toxicity was nausea, with incidents around 66%. All grades of hyponatremia were reported in 3 patients, only one patient had grade 3 hyponatremia.

Also, selinexor was combined with daratumumab in a phase I trial. The phase 2 recommended dose of selinexor was 100 mg QW. The trial enrolled a total of 34 patients. Thirty-one patients received the recommend phase 2 dose. Overall response rates were 74% in daratumumab naïve patients. Median PFS was 12.5 months. The most common non-hematological adverse event was nausea in about 60% of patients; however, grade-3 nausea was reported in about 9% of the total population. (Gasparetto, Lentzsch, et al., 2020) STOMP trial (NCT02343042).

Minimal residual disease (MRD) as an endpoint:

MRD testing was used as a secondary endpoint for most of those trials. To help define the correlation between MRD negativity and clinical outcomes, Landgren et al. published a meta-analysis of four studies with available MRD data. MRD negativity favored longer PFS compared to those who did not have MRD negativity among patients who achieve CR or sCR with a hazard ratio of 0.35; 95% CI, 0.27- 0.46; $p < 0.001$. (Landgren et al., 2016).

The federal drug administration (FDA) published non-binding guidance for MRD negativity testing for MM patients. MRD testing is recommended in patients with clinical CR per IMWG criteria. Therefore, MRD negativity is considered an acceptable endpoint. (Anderson et al., 2017)

Daratumumab is an IgG-kappa monoclonal antibody. Hence, treatment with daratumumab results in a positive immunofixation and SPEP even in patients with CR “daratumumab interference.” (Tang et al., 2018) Therefore, MRD testing will be allowed for patients with VGPR if the investigator estimates that VGPR is a result of daratumumab interference.

Selinexor (S) has demonstrated clinical efficacy in high-risk MM in combination with dexamethasone (d) and daratumumab (D). Also, the safety profile of carfilzomib (K) combined with either S or D is acceptable. Based on its safety profile and efficacy, it is feasible to propose a phase II study combining SKD-d in RRMM.

1.13 Clinical Safety

Multiple clinical trials reported an acceptable safety profile for different triplet-based combinations of selinexor, daratumumab, and carfilzomib with dexamethasone. Below is a summary of the most common non-hematologic adverse events $\geq$ grade 3. The overall safety profile is acceptable.

Combination for relapsed/refractory MM			Most common non- Hem-toxicity $\geq$ grade 3	Ref
Daratumumab	Dexamethasone	Selinexor	Nausea (3%), vomiting (1%), diarrhea (1%), fatigue (6%), hyponatremia (4%).	(Gasparetto, Lentzsch, et al., 2020)
Daratumumab	Dexamethasone	Carfilzomib	hypertension (18%), and asthenia (12%). Grade 3/4 infections (19%). cardiac failure was 3.9%	MMY1001 (Chari et al., 2018); CANDOR (Usmani et al., 2019)

Selinexor	Dexamethasone	Carfilzomib	Fatigue (17%), and infections (11%). The most common all grade AEs: GI (78%), fatigue (72%), dyspnea (33%), and elevated liver and pancreatic enzymes (28%). 2 serious AEs, 1 URI & 1 lower GI bleeding.	BJH, 2019(Jakubowiak et al., 2019)
Daratumumab	Dexamethasone	Lenalidomide	PNA (12%), diarrhea (5.3%), fatigue (6.4%), dyspnea (3.2%), URI and constipation (1.1%).	POLLUX (Dimopoulos M.A. et al., 2017)
Daratumumab	Dexamethasone	Bortezomib	Neuropathy (4.5%), Diarrhea (3.7%), Fatigue (4.5%), dyspnea (3.7%), PNA (8.2%), Hypertension (6.6%)	CASTOR(Palumbo et al., 2016)

URI: upper respiratory tract infection, PNA: pneumonia.

2.0 Goals

2.1 Primary Objective:

To evaluate the MRD negativity rate, at 10^{-5} level of sensitivity by flow cytometry in bone marrow, with the addition of selinexor to daratumumab, carfilzomib and dexamethasone (SDKd) in patients with high-risk, relapsed or relapsed/refractory Multiple Myeloma.

2.2 Secondary Objective:

- 2.21 To evaluate the overall response rate (PR or better) of patients receiving SDKd combination for high risk, relapsed or relapsed/refractory MM and assess depth of response (VGPR, CR, sCR).
- 2.22 To evaluate the time to response in patients receiving SDKd combination for MM.
- 2.23 To evaluate the duration of response in patients receiving SDKd combination for MM.
- 2.24 To evaluate the progression free survival in patient receiving SDKd.
- 2.25 To evaluate the overall survival in patient receiving SDKd.
- 2.26 To evaluate the MRD negativity rates to the level of sensitivity 10^{-6} by flow cytometry in bone marrow.
- 2.27 To evaluate the safety profile of the SDKd combination.

2.3 Correlative Research

- 2.31 Quality of life assessment utilizing QLQ-C30 and QLQ-MY20 (Cocks et al., 2007; Wisloff et al., 1996)

3.0 Patient Eligibility

3.1 Registration – Inclusion Criteria

- 3.11 Age $\geq$ 18 years.
- 3.12 Patients must have a documented history of relapsed or relapsed / refractory MM as defined by IMWG criteria. (Rajkumar et al., 2014)
- Patients must be selinexor and carfilzomib sensitive (i.e. non-refractory)
 - Prior daratumumab exposure is allowed, provided that it has been $\geq$ 6 months (24 weeks) from the time of registration
- 3.13 High risk disease defined as 1 or more of the following:
- High risk cytogenetics (any of the following):
 - i. t(4;14), t(14;16), t(14;20)
 - ii. del(17p)
 - iii. del(1p)
 - iv. Gain 1q ($\geq$ 3 copies)
 - LDH $>$ upper limit of normal at relapse
 - ISS stage 3 disease at relapse
 - Extramedullary disease at diagnosis or relapse
 - $\geq$ 5% circulating plasma cells at diagnosis or relapse
 - High risk by gene expression profiling, if known, at diagnosis or relapse
 - Early relapse with first-line therapy
 - i. $\leq$ 18 months from registration for patients not undergoing ASCT
 - ii. $\leq$ 36 months from registration for patients undergoing ASCT and post-ASCT maintenance
- 3.14 Measurable disease as defined in Section 11.0.
- 3.15 1 – 3 prior lines of therapy. See Exclusion criteria 3.21 for daratumumab wash-out period.
- 3.16 ECOG Performance Status (PS) 0, 1, or 2 (Form is available on the ACCRU website)
- 3.17 Patients must have evidence of adequate bone marrow reserves, obtained $\leq$ 28 days prior to registration, as defined by the following:
- Absolute neutrophil count (ANC) $\geq$ 1,000 cells/mm³ without filgrastim or its equivalent (lab draw must be $\geq$ 7 days from completion of growth factor therapy) or peg- filgrastim or its equivalent (lab draw must be $\geq$ 14 days from completion of growth factor therapy).

- Platelet count of $\geq 100,000$ cells/mm³ for patients who have bone marrow plasmacytosis of $< 50\%$, or $\geq 50,000$ cells/mm³ for patients who have bone marrow plasmacytosis of $> 50\%$, both without platelet transfusion support (lab draw must be ≥ 7 days from completion of platelet transfusion) or the use of TPO mimetics.

NOTE: If your site laboratory reports use different units of measurements than what is required by the protocol eligibility requirements, please use the “Lab Test Unit Conversion Worksheet” available on the ACCRU website under “General Forms”.

- 3.18 Patients must have evidence of adequate hepatic function, obtained ≤ 28 days prior to registration, as defined by the following:
- Total bilirubin ≤ 2.0 times the upper limit of the institutional normal values except in subjects with congenital bilirubinemia, such as Gilbert syndrome (in which case a direct bilirubin $\leq 1.5 \times \text{ULN}$ is required)
 - Total AST and ALT ≤ 2.5 times the upper limit of the institutional normal values
- 3.19a Patients must have adequate cardiac function defined as LVEF $\geq 45\%$ by echocardiogram, MRI or MUGA scan.
- 3.19b For those with symptomatic pulmonary disease (e.g. COPD, asthma) or other signs / symptoms of pulmonary disease, adequate pulmonary function as defined by a FEV1 $\geq 50\%$ of predicted and DLCO/VA $\geq 50\%$ of predicted ≤ 28 days prior to registration.
- Note: Baseline pulmonary function tests are only required on an as needed basis.
- 3.19c Patients must have evidence of adequate renal function, obtained ≤ 28 days prior to registration, as defined by the following: Creatinine clearance (CrCl) ≥ 30 mL/min., as measured by a 24-hour urine collection, **or** estimated by the Cockcroft and Gault formula.
- Calculated creatinine clearance must be ≥ 30 ml/min using the Cockcroft-Gault formula below:

Cockcroft-Gault Equation:

$$\text{Creatinine clearance for males} = \frac{(140 - \text{age})(\text{weight in kg})}{(72)(\text{serum creatinine in mg/dL})}$$

$$\text{Creatinine clearance for females} = \frac{(140 - \text{age})(\text{weight in kg})(0.85)}{(72)(\text{serum creatinine in mg/dL})}$$

- 3.19d Negative pregnancy test done ≤ 7 days prior to registration, for women of childbearing potential only.

- 3.19e Female patients of childbearing potential must have a negative serum pregnancy test at screening and agree to use highly effective (dual methods of) contraception throughout the study and for 6 months following the last dose of study drug; and male patients must use an effective barrier method of contraception throughout the study and for 3 months following the last dose of study drug if sexually active.
- 3.19f Ability to complete questionnaire(s) by themselves or with assistance.
- 3.19g Provide informed written consent ≤ 28 days prior to registration.
- 3.19h Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study).
- 3.19i Willing to provide mandatory bone marrow aspirate biopsies for research purposes (see Sections 6.0 and 14.0).

3.2 Registration – Exclusion Criteria

- 3.21 Prior treatment with daratumumab ≤ 24 weeks prior to registration.
- 3.22 Patient with carfilzomib-refractory disease defined as disease progression ≤ 60 days of last carfilzomib dose.

Exception: If carfilzomib was dosed at or below 36 mg/m² weekly, or if carfilzomib was dosed at or below 45 mg/m² every other week maintenance dosing.
- 3.23 Any of the following because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects:
 - Pregnant women
 - Nursing women
 - Men or women of childbearing potential who are unwilling to employ adequate contraception
- 3.24 Co-morbid systemic illnesses or other severe concurrent disease which, in the judgment of the investigator, would make the patient inappropriate for entry into this study or interfere significantly with the proper assessment of safety and toxicity of the prescribed regimens.
- 3.25 Uncontrolled hypertension, defined as a systolic blood pressure of ≥ 160 mmHg or a diastolic blood pressure of ≥ 90 mmHg.
- 3.26 Significant cardiac disease, including any of the following:
 - $\geq$ Class 3 New York Heart Association (NYHA) congestive heart failure (Resource located on the ACCRU Website)
 - EKG evidence of acute ischemia
 - Unstable angina
 - Myocardial infarction ≤ 6 months prior to registration

- Clinically significant arrhythmias or conduction block (PACs, PVCs, rate controlled atrial fibrillation, sinus arrhythmia, asymptomatic sinus bradycardia or sinus tachycardia and 1st degree heart block are not considered clinically significant)
- $\geq$ Grade 2 QTcF prolongation (i.e. > 480 ms)

Note: Prior to registration, any EKG abnormality at screening not felt to put the patient at risk must be documented by the investigator as not medically significant.

3.27 A diagnosis of HIV does not exclude the patient from participation. However, the viral load must be < 50 copies/mm³ and CD4 count ≥ 200 on anti-HIV therapy ≤ 28 days prior to registration.

3.28 Positive hepatitis C antibody test result or positive hepatitis C RNA test result ≤ 28 days prior to registration.

NOTE: Patients with positive Hepatitis C antibody due to prior eradicated disease can be enrolled if a confirmatory negative Hepatitis C RNA test is obtained.

3.29a Is seropositive for hepatitis B (defined by a positive test for hepatitis B surface antigen [HBsAg] ≤ 28 days prior to registration). Patients with resolved infection (i.e. patients 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. Patients who are PCR positive will be excluded.

Exception: Patients with serologic findings suggestive of HBV vaccination.

3.29b Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, or psychiatric illness/social situations that would limit compliance with study requirements.

3.29c Discontinuation of prior carfilzomib or daratumumab due to treatment toxicity.

3.29d Radiation ≤ 14 days prior to registration.

Note: Palliative XRT to $< 5\%$ of the total marrow volume as assessed by the treating investigator is allowed ≤ 14 days of registration.

3.29e Major surgery ≤ 4 weeks (28 days) prior to registration.

3.29f Any multiple myeloma therapy ≤ 14 days prior to registration.

3.29g Receiving any other investigational agent which would be considered a treatment for the primary neoplasm.

3.29h Active central nervous system (CNS) involvement.

- 3.29i Concomitant AL amyloidosis or POEMS syndrome.
- 3.29j Patients cannot have other prior or concomitant malignancies except for:
- Non-melanoma skin cancer
 - In situ malignancy
 - Low-risk prostate cancer after curative therapy
 - Prostate cancer Gleason grade 6 AND with stable Prostate Specific Antigen (PSA) levels off treatment
 - Other cancer for which the patient has been treated with curative intent or disease free for ≥ 3 years

4.0 Test Schedule

Tests and procedures			Active Monitoring Phase						
	Prior to Registration		Prior to treatment on Day 1 of each cycle (± 2 days)	Days 8 and 15 of each cycle	Every 3 cycles (± 2 days)	At suspected CR or better response (± 14 days)	End of Protocol Treatment (± 14 days)	30-Day Follow-up after last dose (± 7 days)	Clinical Follow-up ¹⁴
	≤ 28 days	≤ 7 days							
Informed Consent	X								
History and exam, ECOG PS	X		X				X		
Vital Signs (BP, heart rate, SaO ₂ , temp)	X		X	X			X		
Height and weight ¹	X		X				X		
Adverse event assessment ¹³	X		X				X	X	X
Hematology: CBC/differential	X		X	X			X		X
Comprehensive chemistries ²	X		X				X		
Limited chemistry panel ²				X					X
Myeloma markers: Serum immunofixation and protein electrophoresis (SPEP) ⁴ , IgG, IgA, IgD ³ , IgE ³ , urine immunofixation and protein electrophoresis (UPEP) ⁴ , serum free light chains ⁴ .	X		X			X	X		X
B2M, LDH, Uric acid	X								
Assessment of extramedullary disease: CT, MRI or PET-CT scan. ⁵	X				X				
Forced expiratory volume test ⁶	X								

Tests and procedures	Active Monitoring Phase								
	Prior to Registration		Prior to treatment on Day 1 of each cycle (± 2 days)	Days 8 and 15 of each cycle	Every 3 cycles (± 2 days)	At suspected CR or better response (± 14 days)	End of Protocol Treatment (± 14 days)	30-Day Follow-up after last dose (± 7 days)	Clinical Follow-up ¹⁴
	≤ 28 days	≤ 7 days							
Hepatitis B (HBV) virus serology and HBV DNA testing ⁷	X		X						
Hepatitis C Testing	X								
HIV Testing	X								
ECG	X								
Echo, Cardiac MRI, or MUGA	X								
BNP or NT-proBNP ¹⁵	X			X ¹⁵					
Mandatory Bone Marrow Biopsy (See Section 14.0) ^{8,R}						X			
Myeloma panel: fluorescence in situ hybridization (FISH) ¹⁶	X								
Conventional cytogenetics ¹⁶	X								
MRD assessment by flowcytometry ¹²						X			
Pregnancy blood ⁹		X							
Patient Medication Diary (Appendix II) ¹⁰			X						
Patient Questionnaire quality of life assessment (Appendix III, Appendix IV) ¹¹			X		X		X		

1 If a subject's weight changes by more than 10% from induction C1D1, the dose of carfilzomib and daratumumab should be re-calculated. Height only needs to be checked once ≤ 28 days prior to registration.

2 Comprehensive serum chemistries including: sodium, potassium, chloride, CO₂, BUN, creatinine, glucose, calcium, phosphorus, magnesium, albumin, total protein, total bilirubin, alkaline phosphatase, AST and ALT. Limited serum chemistries include sodium, potassium, chloride, CO₂, BUN, creatinine and glucose.

- 3 Testing for IgD and IgE will only be performed for subjects with IgD and IgE-type myeloma.
- 4 Refer to Section 11 for details on testing schedule. At suspected CR, all restaging tests will be repeated including: SPEP, UPEP, serum immunofixation, urine immunofixation, and FLC.
- 5 Assess extramedullary plasmacytomas disease for subjects with suspected or prior known extramedullary involvement. Subsequent every 3- cycle monitoring of extramedullary disease applies only to those patients with extramedullary disease at baseline.
- 6 Only for subjects with symptomatic COPD, asthma, or other pulmonary disease.
- 7 Serology include hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (Anti-HBs), and hepatitis B core antibody (Anti-HBc). For subjects with serologic evidence of resolved HBV infection (i.e. positive anti-HBs or positive anti-HBc) ≤ 28 days prior to registration, HBV DNA testing by PCR must be performed locally with each cycle. 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. During and following study treatment, subjects who have a history of HBV infection will be closely monitored for clinical and laboratory signs of reactivation of HBV with monthly DNA by PCR.
- 8 Mandatory bone marrow aspirate collected for MRD analyses. See Section 14.0.
- 9 For women of childbearing potential only. Must be completed ≤ 7 days prior to registration.
- 10 The diary must begin the day the patient starts taking the medication and must be completed per protocol and returned to the treating institution OR compliance must be documented in the medical record by any member of the care team.
- 11 Baseline questionnaire to be completed after registration and prior to treatment on C1D1. After Baseline, this questionnaire will be completed every 3 cycles and at the end of protocol treatment. These are available as standalone documents located on the ACCRU website.
- 12 Minimal residual disease (MRD) test will be completed on the mandatory bone marrow aspirate collected at suspected CR. See Section 14.0.
- 13 To be performed every cycle, at the end of protocol treatment, and until 30 days after the last dose of protocol treatment. If the patient begins a new antineoplastic therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started.
- 14 Clinical Follow-Up every 3 months (± 14 days) until progression/clinical relapse or alternative therapy, or a maximum of 5 years from registration, whichever occurs first.
- 15 The same test should be performed ≤ 28 days prior to registration and C1D15 prior to treatment (either cardiac BNP or NT-proBNP)
- 16 If the non-decalcified diagnostic tissue used for FISH and conventional cytogenetics was collected ≥ 6 months prior to registration, a fresh biopsy must be collected and FISH/conventional cytogenetics analysis must be completed ≤ 28 days prior to registration.
- R Research funded

- 4.1 Survival Follow-up: Patients who have documented disease progression and/or have initiated alternative therapy will move to Survival Follow-up. This will occur every 6 months (± 30 days) until death, withdrawal of consent, or until 5 years after registration. If the patient is alive 5 years after registration, no further follow-up is required.

5.0 Grouping Factor:

Cohort: Safety Run-In vs Phase II

6.0 Registration Procedures

6.1 Site Procedures

- 6.11 Study staff will need to complete the required training prior to gaining access to the registration application. This is located on the ACCRU webpage at [REDACTED] Refer to Study Resources → Applications. Near the bottom of the page there will be a link to the “Research Registration Application Training.” After training is complete, study staff must complete the “Attestation of Training” and send to the ACCRU Registration Office at [REDACTED]

- 6.12 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients. Approvals should be uploaded using the online ACCRU Regulatory Management System (ARMS).

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) with ACCRU. Approvals should be uploaded using the online ACCRU Regulatory Management System (ARMS). 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.

Submission of annual IRB approval is required until the study has been closed through your IRB.

6.2 Safety Run-In:

Prior to discussing protocol entry with the patient, call the ACCRU Registration Office (507-284-4130) to ensure that a place on the protocol is open to the patient.

- 6.21 To register a patient, fax [REDACTED] or email [REDACTED] a completed eligibility checklist to the Academic and Community Cancer Research United (ACCRU) Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.

6.3 For all Phase II patients

- 6.31 To register a patient, access the ACCRU web page at [REDACTED] go to the Study Resources → Application section and click on “Registration” and enter the registration application. The registration application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the Academic and Community Cancer Research United (ACCRU) Registration Office at [REDACTED] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

Instructions for the registration application are available on the above web page

under the Study Resources → Application section. Please refer to the “Research Registration Application Training” or Quick Reference Guide for instructions.

Prior to initiation of protocol study intervention, this process must be completed in its entirety and a ACCRU subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration application can be confirmed in any of the following ways:

- Contact the ACCRU Registration Office [REDACTED] If the patient was fully registered, the Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to the Research Registration Application training on the ACCRU website under Study Resources → Applications.

6.4 For all patients

6.41 Prior to accepting the registration, the registration application will verify the following:

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

6.5 Treatment cannot begin prior to registration and must begin ≤ 28 days after registration.

6.6 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.7 All required baseline symptoms (see Section 10.52) must be documented and graded.

6.8 Treatment on this protocol must commence at an ACCRU institution under the supervision of a hematologist/oncologist.

6.9a Study drug is available on site.

6.9b Patient questionnaire booklet is available on site.

7.0 Protocol Treatment

7.1 Overall Treatment and Safety Plan

Although selinexor has been safely combined with daratumumab-dexamethasone and carfilzomib- dexamethasone in patients with RRMM, there are no data on the safety of selinexor in a 4-drug combination. Therefore, we will first pursue a safety run-in phase to identify the RP2D of selinexor when incorporated into the daratumumab, carfilzomib and

dexamethasone backbone.

The safety run-in will be followed by a single arm, phase II study. Patients treated at the RP2D in the safety run-in will be included in the phase II analysis.

7.2 Treatment Schedule

7.21 Pretreatment medication

Agent	Dose	Route	Day
Acetaminophen	650-1000 mg	oral	30-60 minutes prior to daratumumab
Diphenhydramine (or equivalent)	25-50 mg	IV or oral	30-60 minutes prior to daratumumab
Montelukast*	10 mg	oral	The night prior to and 30 – 60 minutes prior to the first two doses of daratumumab
Normal Saline	250 or 500 ml	IV	Prior to carfilzomib during Cycle 1; as needed thereafter
Ondansetron*	8 mg	Oral	Every 8 hours the day prior to, the day of, and for 2 days after selinexor.
Olanzapine*	5 mg	Oral	Once a day at night

*Highly recommended pre-treatment medication. See Section 9.4 for additional dosing recommendations for olanzapine.

NOTE: For recommended concomitant medications see Section 9.3. For post infusion medications and high-risk patients see section 9.7.

7.22 Chemotherapy schedule:

Chemotherapy schedule			
Drug	Route	Dose	Schedule Each cycle is 28 days ⁵
Carfilzomib ¹	IV over 30 minutes	20mg/m ² 56 mg/m ²	Day 1 Days 8 and 15
Daratumumab	IV or SQ per prescribing information ²	16 mg/kg (IV) OR 1800 mg (SQ)	Cycles 1 and 2: Days 1, 8, 15, 22 Cycles 3 - 6: Days 1, 15 Cycles 7+: Day 1
Dexamethasone ³	Oral	40 mg	Days 1, 8, 15 and 22
Selinexor ⁴	Oral	60 mg	Days 1, 8, 15

Cycle = 28 days

¹ Maximum dose for carfilzomib is capped at a BSA of 2.2 m². Carfilzomib will be dosed at 20 mg/m² on C1D1, and 56 mg/m² thereafter.

² Rapid daratumumab administration over 90 minutes may be used with dose 3 and beyond if no IRR was encountered with dose 2. Subcutaneous (SQ) administration is permitted (See Section 15.4 for additional SQ administration

guidance).

³Dexamethasone dose is reduced to 20 mg for patients with diabetes or ≥ 75 years.

⁴Dosing dependent on dose level assignment in the safety run-in and the RP2D identified in the safety run-in

⁵ ± 2 days for scheduled visits.

7.23 Selinexor

7.231 Oral Selinexor may be self-administered by the patient on an outpatient basis. Missed doses and delayed procedures are summarized in Section 8.

7.232 Accurate records will be kept in the source documents of all drug administration (including dispensing and dosing).

7.233 See Section 15 for details on Selinexor description, formulation, storage, and accountability.

7.24 Carfilzomib

7.241 Subjects will receive carfilzomib once weekly for 3 weeks (Days 1, 8, and 15) during each 28-day cycle.

7.242 Maximum dose for carfilzomib is capped at a BSA of 2.2 m². If a subject's weight changes by more than 10% from baseline, the dose of carfilzomib will be re-calculated.

7.243 Procedures for carfilzomib dose reductions and delays are summarized in Section 8, 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.

7.25 Daratumumab

7.251 Subjects will receive daratumumab intravenously or subcutaneously weekly for the first 2 cycles, then every other week for Cycles 3 – 6, then every 4 weeks from Cycle 7 and beyond.

7.252 For IV administration: Each patient's dose will be calculated based on the subject's weight rounded to the nearest kilogram. There is no cap on the absolute dose allowed, as long as the dose does not exceed 16 mg/kg. If a subject's weight changes by more than 10% from baseline, the dose of daratumumab will be re-calculated.

For SQ administration: Each patient's dose will be a fixed dose of daratumumab 1800 mg/30,000 units hyaluronidase.

7.253 Vital signs should be monitored extensively on Cycle 1 Day 1 before, during (per local practice), and after the first infusion of daratumumab. For all other infusions, vital signs should be measured immediately before the start of infusion and as needed thereafter.

7.254 Missed doses and delayed procedures are summarized in Section 8.

7.255 There are no planned dose reductions.

7.26 Dexamethasone

7.261 Oral dexamethasone may be self-administered by the subject on an outpatient basis.

7.262 Missed doses and delayed procedures are summarized in Section 8.

7.263 Dexamethasone is commercially available. Accurate records will be kept in the source documents of all drug administration (including dispensing and dosing).

7.264 See Section 15.3 for details on dexamethasone description, formulation, storage, and accountability.

7.3 Safety Run-In

Table 7.3 Dose Levels of Selinexor, Daratumumab, Carfilzomib and Dexamethasone for the Safety Run-In

Cohorts	Selinexor	Daratumumab	Carfilzomib	Dexamethasone+
Dose Level 0*	60 mg	16 mg/kg	56 mg/m ²	40 mg
Dose Level -1	40 mg	16 mg/kg	56 mg/m ²	40 mg

*Starting Dose Level

+ Patients ≥ 75 years old will received dexamethasone dose of 20 mg.

7.31 Rules for Dose De-escalation in Safety Run-In

Dose de-escalation will be considered if Dose Level 0 per table 7.3 proves excessively toxic, with 2 or more subjects having significant toxicities as defined in section 7.32. If this is the case, an additional 6 patients will be enrolled at Dose Level -1 with dose de-escalation.

Dose de-escalation will proceed per the table below:

Dose Level 0

If there are	Then
0 -1/6 subjects with significant toxicity per section 7.32	Proceed to Phase II
$\geq 2/6$ subjects with significant toxicity per section 7.32	Enroll 6 subjects at dose level -1

Dose Level -1

If there are	Then
0 -1/6 subjects with significant toxicity per section 7.32	Proceed to Phase II
$\geq 2/6$ subjects with significant toxicity per section 7.32	STOP. Will need to reconsider dosing scheme

7.32 Definition of Significant Toxicity

Toxicity that meets the criteria as defined below will be considered a significant toxicity if it occurs in the first cycle of treatment and is possibly, probably, or definitely related to study treatment:

- Grade 4 neutrophil count decreased lasting > 7 days.
- Grade 4 platelet count decreased lasting > 7 days.
- Grade 3 or higher non-hematologic toxicity except: grade 3 nausea, vomiting or diarrhea that can be controlled within 48 hours with appropriate supportive care, grade 3 hyperglycemia that can be controlled within 48 hours with appropriate supportive care, asymptomatic grade 3 or higher electrolyte disturbances that can be controlled with repletion within 24 hours, and grade 3 fatigue that in part is related to the underlying myeloma.
- Any Grade 4 infusion related reaction (IRR)
- Treatment-related death.

Patients will be considered evaluable for significant toxicity if they have:

- a) Completed 1 cycle of therapy and received adequate dosing (all 3 doses of selinexor and carfilzomib, ≥ 3 out of 4 doses of daratumumab and ≥ 3 out of 4 doses of dexamethasone)

OR

- b) Received less than adequate dosing due to significant toxicity. If a patient fails to receive adequate dosing in the first cycle for reasons other than significant toxicity, an additional patient will be enrolled to replace this patient. Patients who discontinue treatment due to a daratumumab infusion reaction may be replaced.

Patients participating in the safety run-in who are receiving Erythropoiesis-Stimulating Agents (ESAs) or require red blood cell transfusion during Cycle 1 of therapy will be evaluable for significant toxicity. However, platelet transfusions, thrombopoietin (TPO) mimetics and neutrophil growth factors may not be used during Cycle 1 for the sole purpose of significant toxicity avoidance. If a safety run-in patient requires platelet transfusions or neutrophil or platelet growth factors during Cycle 1 as standard of care and does not incur a significant toxicity, the ACCRU Study Team will meet to determine if that patient is evaluable for significant toxicity or needs to be replaced.

8.0 Dosage Modification Based on Treatment-Related Adverse Events

Strictly follow the modifications in this table for the first **two** cycles, until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines to produce 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 or increases apply to treatment given in the preceding cycle and are based on treatment-related adverse events observed since the prior dose.

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

NOTE: If the patient experiences a significant treatment-related adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered for that entire subsequent cycle. If that cycle is completed with no further treatment-related adverse events > Grade 2, then the dose may be increased, at the investigator's discretion, one level at a time, in the following cycles. If a drug was discontinued due to toxicity, protocol therapy may continue with the other drugs.

Dose Levels (Based on treatment-related Adverse Events in the following sections)

Dose reduction steps (each column to be followed independently for each drug)

Dose Level	Carfilzomib**	Daratumumab	Selinexor	Dexamethasone
0*	56 mg/m ²	16 mg/kg (IV) OR 1800 mg (SQ)	60 mg	40 mg
-1	45 mg/m ²	N/A	40 mg	20 mg
-2	36 mg/m ²			12 mg
-3	27 mg/m ²			

* Dose level 0 refers to the starting dose.

** Maximum dose for carfilzomib is capped at a BSA of 2.2 m²

Dose Modification Guidelines for Treatment-Related Hematologic Toxicity

	1 st Occurrence	2 nd Occurrence	3 rd Occurrence	4 th Occurrence
Grade 4 Neutrophil count decreased or Febrile Neutropenia	Hold SKD-d until ANC recovers to $\geq 1 \times 10^9 / \text{L.}$	Hold SKD-d until ANC recovers to $\geq 1.0 \times 10^9 / \text{L.}$ Resume selinexor at 1 level dose reduction	Hold SKD-d until ANC recovers to $\geq 1.0 \times 10^9 / \text{L.}$ Resume carfilzomib at 1 level dose reduction	Hold SKD-d until ANC recovers to $\geq 1.0 \times 10^9 / \text{L.}$ discontinue selinexor
Grade 4 Platelet count decreased	Hold SKD-d until platelets recovers to $\geq 25 \times 10^9 / \text{L.}$ Resume Selinexor at 1 level dose reduction	Hold SKD-d until ANC recovers to $\geq 25 \times 10^9 / \text{L.}$ Resume carfilzomib at 1 level dose reduction	Hold SKD-d until ANC recovers to $\geq 25 \times 10^9 / \text{L.}$ discontinue selinexor	Hold SKD-d until ANC recovers to $\geq 25 \times 10^9 / \text{L.}$ discontinue selinexor

8.1 Dose Modifications for carfilzomib based on carfilzomib related adverse events during a

cycle

Dose Modifications for carfilzomib based on adverse events	
Adverse Event	Action
Renal Toxicity	Recommended Action
Serum creatinine greater than or equal to $2 \times$ baseline, or 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 1 level 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 $1.5 \times$ ULN or AST $>$ ULN), moderate (bilirubin > 1.5 to $3 \times$ ULN), or severe (bilirubin $> 3 \times$ 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.

Dose Modifications for carfilzomib based on adverse events	
Adverse Event	Recommended Action

Thrombotic microangiopathy (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.
Posterior reversible encephalopathy syndrome (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

Carfilzomib doses that are delayed or missed can be made up within 48 hours. If a carfilzomib dose was delayed by more than 48 hours, it will be missed and will not be replaced. Any adverse event deemed to be related to carfilzomib that requires a dose hold of > 4 weeks will result in permanent discontinuation of carfilzomib.

8.2 Dose modifications for dexamethasone (Dex) based on dexamethasone-related adverse events during a cycle

Dose modifications for dexamethasone (Dex) based on adverse events		
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 $\geq$ 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.
	Pancreatitis $\geq$ 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 $\geq$ 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 $\geq$ 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 $\geq$ 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
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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

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.

8.3 Dose modifications for daratumumab based on daratumumab-related adverse events during a cycle

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

8.31 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/injection must be held to allow for recovery from toxicity.

The criteria for a dose delay are:

- Grade 4 platelet count decreased or Grade 3 platelet count decreased with bleeding
- Grade 4 neutrophil count decreased, if this is the second occurrence despite growth factorsupport
- Febrile neutropenia of any grade

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.

Daratumumab-Related Toxicity Management; delayed/ missed doses 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

If the dose is held longer than indicated in the above table, the dose of daratumumab should be omitted. Daratumumab can resume at the next schedule dose if appropriate.

8.4 Dose modifications for selinexor based on selinexor-based adverse events during a cycle

Non-hematological toxicity	
Toxicity	Action

Hyponatremia	Sodium level 130 mmol/L or less: • Interrupt selinexor and provide appropriate supportive care. Monitor until sodium levels return to 130 mmol/L or higher. • Restart selinexor at 1 dose level lower
Fatigue	Grade 2 lasting > 7 days OR Grade 3: • Interrupt selinexor. • Monitor until fatigue resolves to Grade 1 or baseline. • Restart selinexor at 1 dose level lower
Nausea and Vomiting	Grade 3 nausea (inadequate oral caloric or fluid intake) OR Grade 3 or higher vomiting (6 or more episodes per day): • Interrupt selinexor. • Monitor until nausea or vomiting has resolved to Grade 2 or lower or baseline. • Initiate additional anti-nausea medications. • Restart selinexor at 1 dose level lower
Diarrhea	Grade 2 (increase of 4 to 6 stools per day over baseline): • Institute supportive care. If not better in two weeks then reduce selinexor by 1 dose level Grade 3 or higher (increase of 7 stools or more per day over baseline; hospitalization indicated): • Interrupt selinexor and institute supportive care. • Monitor until diarrhea resolves to Grade 2 or lower. • Restart selinexor at 1 dose level lower
Weight Loss and Anorexia	Weight loss of 10% to less than 20% OR anorexia associated with significant weight loss or malnutrition: • Interrupt selinexor and institute supportive care. • Monitor until weight returns to more than 90% of baseline weight. • Restart selinexor at 1 dose level lower
Any other non-hematological Grade 4 (life Any threatening) toxicity	• Interrupt selinexor. • Monitor until resolved to Grade 2 or lower, restart selinexor at 1 dose level lower

Selinexor doses that are delayed or missed can be made up within 48 hours. If a selinexor dose was delayed by more than 48 hours, it will be omitted and will not be replaced. Any adverse event deemed to be related to selinexor that requires a dose hold of > 4 weeks will result in permanent discontinuation of selinexor.

9.0 Ancillary Treatment/Supportive Care

Patients should receive appropriate supportive care measures as deemed necessary by the treating investigator.

9.1 Radiation Therapy

Patients may receive palliative radiation during protocol therapy (e.g. for palliation of myeloma-related bone pain) provided: 1) the need for radiation is not an indicator of disease progression; and 2) the size of the radiation field will not impact assessment of disease response. Any decision to pursue palliative radiation must be made in consultation with the study principal investigator.

9.2 Cardiac Monitoring

Patients with an elevated cardiac BNP $\leq$ 28 days prior to registration or C1D15 or who have > 1 underlying cardiovascular risk factor should be monitored closely for signs / symptoms of cardiopulmonary toxicity. Recommend repeat assessment of cardiac function and PFTs as symptoms dictate.

9.3 Concomitant Medication Recommended Medications

9.31 Antiresorptive Therapy

Antiresorptive therapy with zoledronic acid or denosumab is recommended for all subjects.

9.32 Antimicrobial Prophylaxis

Acyclovir or an equivalent antiviral must be given to all patients to decrease the risk of herpes zoster reactivation, per institutional prophylaxis guidelines, unless contraindicated.

Primary antiviral prophylaxis is permitted for prevention of hepatitis B virus reactivation as per local standard of care. Serial HBV DNA testing by PCR is mandatory for patients at risk for HBV reactivation. For patients 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 prophylaxis as per local standard of care. Consult a Hepatologist as clinically indicated.

Levofloxacin prophylaxis is recommended for the first 3 cycles of therapy unless contraindicated (e.g. prior allergic or significant reaction to a quinolone-based antibiotic) (Drayson et al., 2019).

It is recommended that patients with significant hypogammaglobulinemia (non-clonal IgG level of approximately < 400 mg/dL) receive prophylactic IVIG therapy once every 4 weeks.

PJP prophylaxis is recommended for patients with a CD4 count < 200 .

9.33 Prohibited Medications

Concomitant administration of investigational agents, other than those mandated by the protocol, is prohibited. No investigational or commercial agents or therapies other than those described may be administered with the intent to treat the patient's myeloma.

- 9.34 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.

9.35 Permitted Medications

Patients may receive antiemetics and antidiarrheal agents as necessary. Growth factors to support neutrophils (i.e. filgrastim or pegfilgrastim or their equivalents), red blood cells (i.e. erythropoietin-stimulating agents [ESAs]) and platelets (TPO mimetics such as romiplostim or eltrombopag) may be used per institutional guidelines. Patients may receive platelet and red blood cell transfusions if clinically indicated in accordance with institutional guidelines.

9.4 Highly recommended Antiemetics:

- Ondansetron 8 mg po on the day prior to, the day of, and for 2 days after selinexor
- Olanzapine 5 mg po at night. Olanzapine to be tapered after 2 cycles or modified based on tolerability to NK1 receptor antagonist.

- 9.5 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

- 9.6 Diarrhea: This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).

In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and other 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. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.

9.7 Guidelines for Prevention of daratumumab Infusion Reactions:

- Pretreatment Medication: per table 7.21

- 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 β 2 adrenergic receptor agonist such as salbutamol aerosol
 - Control medications for lung disease (e.g., inhaled corticosteroids $\pm$ long-acting β 2 adrenergic receptor agonists for subjects with asthma; long-acting bronchodilators such as tiotropium or salbutamol $\pm$ inhaled corticosteroids for subjects with COPD)

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. 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 hospitalization if hypotension did not improve with IV normal saline.
- 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.

For 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.

9.9 Oral hydration; subjects are encouraged to drink at least 6 to 8 cups of liquid per day.

10.0 Adverse Event (AE) Reporting and Monitoring

The site principal investigator is responsible for reporting any/all adverse events to the sponsor as described within the protocol. Refer to the adverse event and serious adverse event sections of the protocol for detailed information.

The sponsor/sponsor-investigator is responsible for notifying FDA and all participating investigators in a written safety report of any of the following:

- Any suspected adverse reaction that is both serious and unexpected.
- Any findings from laboratory animal or *in vitro* testing that suggest a significant risk for human subjects, including reports of mutagenicity, teratogenicity, or carcinogenicity.
- Any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND and whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug.
- Any clinically important increase in the rate of a serious suspected adverse reaction over the rate stated in the protocol or Investigator's Brochure (IB).

Definitions

Adverse event (AE):

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related.

Suspected adverse reaction:

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

Expedited Reporting

Events reported to sponsor within 24 hours, 5 days or 10 days of study team becoming aware of the event.

Routine Reporting

Events reported to sponsor via case report forms

Events of Interest

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).

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site:

- a. Adverse event monitoring and reporting is a routine part of every clinical trial.
- b. Identify the grade and severity of the event using the CTCAE version 5.0.
- c. Determine whether the event is expected or unexpected (see Section 10.2).
- d. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).
- e. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4)
- f. Determine if other reporting is required (see Section 10.5).
- g. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.5 and 18.0).

Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).

NOTE: A severe AE, as defined by the above grading scale, is NOT the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. 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, (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 adverse events 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.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

- Definite - The adverse event *is clearly related* to the agent(s).
- Probable - The adverse event *is likely related* to the agent(s).
- Possible - The adverse event *may be related* to the agent(s).
- Unlikely - The adverse event *is doubtfully related* to the agent(s).
- Unrelated - The adverse event *is clearly NOT related* to the agent(s).

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug/device and the adverse event.

10.31 AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME (Combination)Arm

When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the **entire combination (arm) is then considered an investigational intervention for reporting**. These AEs should be assessed as specified in the appropriate IND/IDE reporting guidelines in Section 10.4

10.32 **EXPECTED Serious Adverse Events: Protocol Specific Exceptions to Expedited Reporting.**

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.5). *

System Organ Class (SOC)	Adverse event/ Symptoms*	CTCAE Grade at which the event will not be expeditedly reported ¹
Blood and lymphatic system disorders	Anemia	≤ Grade 4
General disorders and administrations site conditions	Fatigue	≤ Grade 3
Gastrointestinal	Vomiting	≤ Grade 3
	Nausea	≤ Grade 3
	Diarrhea	≤ Grade 3
Investigations	Neutrophil count decreased	≤ Grade 4
	Platelet count decreased	≤ Grade 4

	Lymphocyte count decreased	≤ Grade 4
	White blood cell decreased	≤ Grade 4
Metabolism and Nutrition Disorders	Hyperglycemia	≤ Grade 3

¹These exceptions only apply if the adverse event does not result in hospitalization. If the adverse event results in hospitalization, then the standard expedited adverse events reporting requirements must be followed.

*Report any clinically important increase in the **rate** of a serious suspected adverse reaction (at your study) site over that which is listed in the protocol or investigator brochure as an expedited event.

*Report an expected event that is greater in severity or specificity than expected as an expedited event

*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.

A list of known/expected AEs is reported in the investigator brochure, package insert or the literature, including AEs resulting from a drug overdose.

10.321 Death

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent requires expedited reporting within 24-hours.
- Any death occurring greater than 30 days of last dose with an attribution of possible, probable, or definite requires expedited reporting within 24-hours.
- Reportable categories of Death
 - Death attributable to a CTCAE term.
 - Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
 - Death 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 system organ class (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.

10.322 Secondary 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/IDE to be reported. Three options are available to describe the event:
 - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloid Leukemia (AML))
 - Myelodysplastic syndrome (MDS)
 - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.323 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.

10.324 Pregnancy

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. If informed consent is not obtained, no information may be collected.

In cases of fetal death, miscarriage or abortion the mother is the patient. In cases where the child/fetus experiences a serious adverse event other than fetal death, the child/fetus is the patient.

NOTE: When submitting [REDACTED] the potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section. Include any available medical documentation.

10.4 Expedited Adverse Event Reporting Requirements for IND/IDE Agents

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention¹

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

NOTE: Investigators MUST immediately report to the sponsor ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

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

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

(FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 timeframes
Resulting in hospitalization ≥ 24 hrs	7 Calendar Days			24-Hour/ 3 Calendar Days
Not resulting in hospitalization ≥ 24 hrs	Not required		7 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in section 10.32 of the protocol.

Expedited AE reporting timelines are defined as:

- “24-Hour; 3 Calendar Days” - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- “7 Calendar Days” - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

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

Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 4, and Grade 5

AEs Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

Special Instructions:

- Follow site-specific reporting guidelines.
- Submit the ACCRU Adverse Event Expedited Report Form to the ACCRU SAE Coordinator via email [REDACTED]. The ACCRU SAE Coordinator will forward to Karyopharm Pharmacovigilance Department via email: [REDACTED]

- and the Associate Director [REDACTED] via email: [REDACTED] These reports must be forwarded to Karyopharm within 24 hours of learning of the occurrence.
- The ACCRU SAE Coordinator will forward to ACCRU IND Coordinator [REDACTED] as appropriate. The ACCRU IND Coordinator will assist the sponsor-investigator in notifying the FDA if required.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

If the event meets the criteria for an UPIRTSO, submit to your IRB as required by your institutional policies.

10.52 Baseline and Adverse Events Evaluations

The following pre-treatment symptoms/conditions are to be graded at baseline and adverse events are to be graded at each evaluation using CTCAE v5.0 grading. If CTCAE v5.0 grading is not used, note the grading scale used in the table below

CTCAE SYSTEM/ORGAN/CLASS	Adverse event/Symptoms	Baseline	Each evaluation
Blood and lymphatic system	Febrile neutropenia	X	X

disorders			
Cardiac disorders	Heart failure	X	X
	Ventricular arrhythmia	X	Per symptoms
General disorders and administration site conditions	Fatigue	X	X
Gastrointestinal Disorders	Nausea	X	X
	Vomiting	X	X
	# of Stools	X	
	Diarrhea		X
Infections and infestations	Sepsis	X	X
Injury, poisoning and procedural complications	Infusion related reaction		X
Investigations	Creatinine increased	X	X
	Neutrophil count decreased	X	X
	Platelet count decreased	X	X
Nervous system disorders	Peripheral sensory neuropathy	X	X
	Peripheral motor neuropathy	X	X
Respiratory, thoracic and mediastinal disorders	Pulmonary hypertension	X	Per symptoms
Vascular disorders	Hypertension	X	X

10.53 Submit via appropriate ACCRU Electronic Case Report Forms the following AEs experienced by a patient and not specified in Section 10.52:

10.531 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.

10.532 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.

10.523 Grade 5 AEs (Deaths)

10.5231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.

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

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 b-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 monoclonal protein level ≥ 0.5 g/dL and urine monoclonal protein ≥ 200 mg/24 hours
 - Serum Monoclonal protein ≥ 0.5 g/dL only

- Urine Monoclonal protein $\geq 200\text{mg}/24$ hours only
- Serum immunoglobulin FLC assay: Involved FLC level $\geq 10\text{mg}/\text{dl}$ provided serum FLC ratio is abnormal

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.

Tests Required To Assess M protein Response (Must Be Done At Each Disease Measurement Visit except as indicated ^{1,2})				
On Trial Baseline Value	SPEP	24 h UPEP	FLC	Bone marrow biopsy ³
Serum M-spike ≥ 0.5 g/dl, and urine M-spike ≥ 200 mg/24 hrs	X	X		
Serum M-spike ≥ 0.5 g/dl, but urine M-spike < 200 mg/24 hrs	X			
Serum M-spike < 0.5 g/dl, and urine M-spike ≥ 200 mg/24 hrs		X		
Serum M-spike < 0.5 g/dl, urine M-spike < 200 mg/24 hrs, but involved Ig FLC is ≥ 10 mg/dL			X	
At suspected CR	X	X	X	X

¹Immunofixation 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.

²For serum measurable subjects, 24 hour urine does not need to be confirmed (i.e. repeated after

documented response) for any response category

³Bone marrow biopsy results do not need to be confirmed (i.e. repeated after documented response). However, bone marrow biopsy results are needed at suspected CR to measure minimal residual disease status.

11.2 Confirmed response

In order to be classified as an M protein response, confirmation of serum monoclonal protein, serum immunoglobulin free light chain (when primary determinant of response) and urine monoclonal protein (when primary determinant of response) results must be made by verification on two consecutive determinations.

- Bone marrow aspirate and biopsy are **only** required to document CR or sCR, except for subjects with 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.
- 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. For patients with minimal residual disease (MRD)-test negativity and a positive baseline PET, repeat PET scan is required to confirm MRD negative status by IMWG criteria in table 11.5.
- Appropriate tests required to document and confirm response are listed in Table 11.5

11.3 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 treating and study principal investigators before removing the subject from the trial.

11.4 Response and Clinical Relapse/Progression:

Criteria for response and clinical relapse/ progression are listed in Table 11.5. Clinical relapse and 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:

Table 11.5: IMWG Criteria for response assessment including criteria for MRD in Multiple Myeloma		
Response subcategory		Response criteria (S. Kumar et al., 2016; Rajkumar et al., 2011)
IMWG MRD negativ	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 2 negative @ 5 years etc)

Standard IMWG Response criteria ⁶	Flow MRD-negative	Absence of phenotypically aberrant clonal plasma cells by next-generation flow cytometry ² 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 ³ 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
	sCR (stringent complete response)	CR as defined below PLUS Normal FLC ratio ⁷ AND Absence of clonal cells in bone marrow biopsies by immunohistochemistry (κ/λ ratio $\leq 4:1$ or $\geq 1:2$ for κ and λ subjects, respectively, after counting ≥ 100 PCs) ⁸
	CR (complete response)	Negative immunofixation on the serum AND urine AND ⁹ Disappearance of any soft tissue plasmacytomas AND < 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 patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above.
	VGPR (very good partial response)	Serum and urine M-protein detectable by immunofixation but not on electrophoresis OR $\geq 90\%$ reduction in serum M-protein PLUS urine M-protein level <100mg per 24 hours. In patients in whom the only measurable disease is by serum FLC levels: VGPR in such patients requires a > 90% decrease in the difference between involved and uninvolved FLC levels.
	PR (partial response)	$\geq 50\%$ reduction of serum M-protein PLUS reduction in 24-h urinary M-protein by $\geq 90\%$ or to < 200mg per 24 hours. If the serum and urine M-protein are unmeasurable, a $\geq 50\%$ decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, $\geq 50\%$ reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was $\geq 30\%$. In addition to the above listed criteria, if present at baseline, a $\geq 50\%$ reduction in the size (SPD) ¹² of soft tissue plasmacytomas is also required
	MR (minimal response)	$\geq 25\%$ but $\leq 49\%$ reduction of serum M protein AND reduction in 24-hour urine M-protein by 50%-89% In addition to the above listed criteria, if present at baseline, a $\geq 50\%$ reduction in the size (SPD) ¹⁰ of soft tissue plasmacytomas is also required
	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) ¹¹	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) ○ 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 $\geq 10\%$) • Appearance of a new lesion(s), $\geq 50\%$ increase from nadir in SPD¹² of more than one lesion, or $\geq 50\%$ increase in the longest diameter of a previous lesion > 1 cm in short axis. $\geq 50\%$ 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 plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression) • Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the SPD¹² 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 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. Bone marrow flow cytometry should follow Next Generation Flow (NGF) guidelines. 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 .
4. DNA sequencing assay on marrow aspirate should use an assay such as Lymphosight® (Sequentia) since this is the only one validated so far.
5. Imaging is strongly recommended once MRD negativity is determined by MFC or NGS. (Moreau et al., 2019; Zamagni et al., 2015)
6. Derived from International uniform response criteria for multiple myeloma. (Durie et al., 2006) Minor response definition and clarifications derived from the Consensus recommendations for the uniform reporting of clinical trials (Rajkumar et al., 2011). 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 $\geq 90\%$ 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.
7. 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 been made available by other manufacturers in several countries have not been validated up to now.
8. 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. 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.
9. Special attention should be given to the emergence of a different monoclonal protein following treatment, especially in the setting of subjects having achieved a conventional complete response, often related to oligoclonal reconstitution of the immune system. These bands typically disappear over time and in some studies have been associated with a better outcome. Also, appearance of monoclonal IgG kappa in subjects receiving monoclonal antibodies should be differentiated from the therapeutic antibody.
10. 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).

11. 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. 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.

12.0 Descriptive Factors

- 12.1 Parameters followed for hematologic response: serum monoclonal protein level ≥ 0.5 g/dL and urine monoclonal protein ≥ 200 mg/24 hours vs. serum monoclonal protein ≥ 0.5 g/dL only vs. urine monoclonal protein ≥ 200 mg/24 hours only vs. serum immunoglobulin free light chain ≥ 10 mg/dL

If parameter followed is serum monoclonal protein, then distinguish between: SPEP measurements vs. quantitative IgA measurement vs. quantitative IgD measurement

- 12.2 Prior lines of therapy – 1 vs 2 vs 3
- 12.3 Lenalidomide refractory disease – yes vs no
- 12.4 Bortezomib refractory disease – yes vs no
- 12.5 Disease that is refractory Lenalidomide and bortezomib doublet- yes vs no
- 12.6 Daratumumab prior exposure – yes vs no
- 12.7 Pomalidomide refractoriness – yes vs no

13.0 Treatment/Follow-up decision at Evaluation of patient

- 13.1 Patients who are sCR, CR, VGPR, PR, MR, or SD (or usCR, uCR, uVGPR, uPR) will continue treatment per protocol until a maximum of 5 years from registration.
- 13.2 Patients who develop PD while receiving therapy or discontinue protocol therapy for alternative therapy will go to Survival Follow-Up per Section 4.1.
- 13.3 Patients who go off protocol treatment for reasons other than PD or alternative therapy will go to Clinical Follow-up per Section 4.0.
- 13.4 Criteria for Discontinuation of Treatment

Patients may discontinue treatment for the following reasons:

- Relapse or progressive multiple myeloma
- Patient refuses further treatment on the trial
- Patient develops an intercurrent illness that precludes further participation, or requires a prohibited concomitant treatment

- The treating investigator withdraws the patient in the patient's best interests
- Administrative reasons (e.g., the patient is transferred to hospice care)
- The drug manufacturer can no longer provide the study agent (if applicable)
- An adverse event, which in the opinion of the treating investigator, precludes further trial participation

All attempts should be made to complete the End of Study procedures when the patient discontinues treatment. Patients should go to Survival Follow-Up per Section 4.1, unless the patient refuses further study participation or is lost to follow-up.

- 13.5 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. The patient may continue treatment off-protocol at the discretion of the treating physician as long as there are no safety concerns, and the patient was properly registered. The patient will go directly to the Survival Follow-up phase of the study (or off study, if applicable).
- If the patient received treatment, all data up until the point of confirmation of ineligibility must be submitted. Survival Follow-up per Section 4.1 of the protocol.
 - If the patient never received treatment, On-study material and the Off Treatment Form must be submitted. No further data submission is necessary.
- 13.6 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. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the Survival Follow-up phase of the study. The patient may continue treatment off-protocol at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. Survival Follow-up will be required per Section 4.1 of the protocol.
- 13.7 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the Off Treatment Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

14.1 Bone Marrow specimens

Research	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)	At suspected CR or better response	Process at site? (Yes or no)	Temperature Conditions for Storage/Shipping ¹
NGF-MRD Testing	Mandatory	Bone Marrow Aspirate	K-2 EDTA (purple top)	3 ml x 2 tubes	X	No	Room temperature/ Ambient

1. Specimen must be shipped on the same day of collection, so specimens must be procured Monday-Thursday and shipped via overnight courier.

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

14.3 Standard Collection Instructions for Fresh Bone Marrow Specimens

14.31 Use 2 purple top K2-EDTA tubes to collect bone marrow aspirate.

14.32 Pre-label EDTA tubes as indicated below.

All bone marrow specimens must be labeled with protocol number, ACCRU patient ID number, Sample type (BM), and time and date bone marrow aspirate is drawn.

14.33 Instructions for Labels

14.331 Large Labels (download large label template):

- Use Avery 5160 labels*
- Use for all specimens submitted
- Type or write information
- Place on outside bag or container, depending on specimen type

14.332 Small Labels (download small label template):

- Use Avery 5160 labels*
- Use for all specimens submitted
- Type or write information on right side of line
- Cut the label on the line
- Place only the right side of the label on each specimen

*If Avery 5160 labels are not available, the label may be printed on regular paper and taped to the specimen container.

14.34 Collection and Processing

14.341 Use aseptic techniques to collect 3 mL of the first pull (or technical first pull after needle repositioning) of bone marrow aspirate into an EDTA tube; rotate bevel 45° to aspirate and add an additional 3 mL into a second EDTA tube (6 mL aspirate total).

14.342 Immediately after the bone marrow is collected, thoroughly mix the bone marrow with the anticoagulant by gently inverting the EDTA tube multiple times.

14.343 If the amount of bone marrow specified by the protocol cannot be obtained on any individual patient, send the actual specimen obtained. Note on the specimen shipping form if required amount was not obtained.

14.344 Store bone marrow at room temperature until ready to ship. Storage time longer than 24 hours should be noted on the specimen shipping form.

14.35 Standard Shipping Instructions for Fresh Bone Marrow Specimens

14.351 Bone marrow aspirate must be shipped the same day of collection, Monday-Thursday via overnight courier to arrive at the Hematology Research Biobank at Mayo Clinic Rochester the following day (Tuesday-Friday), preferably using Federal Express Priority Overnight service. Use of other courier services may delay package receipt.

14.352 Avoid collecting specimens the day before a federal holiday.

14.353 Bone marrow specimens should be transported at room temperature and avoid as much as possible wide variations in temperature (preferably about 20-25 degrees Celsius range with an average of 23° C or about 73.4 ° F).

14.354 Ship specimens according to IATA shipping regulations.

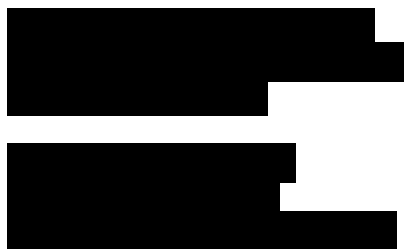
14.3541 Shipping guidelines for ambient specimens:

- The specimen must be wrapped in absorbable material.
- Place the specimen in an AIRTIGHT container (must have a primary and secondary container, ex a Saf-T-Pak).
- Place packaged specimen in an appropriate shipping container (ex. FedEx box or clinical pack).
- Mark the outside shipping container with an "Exempt Human Specimen" label.

14.355 Specimen Submission

Sites to complete the Biospecimen Requisition Form found on the ACCRU website under 'Manuals & Forms'.

Ship to:



14.4 Blood product samples will be collected for the following research

14.41 Minimal residual disease assessment by next generation flow cytometry (NGF-MRD): upon achieving CR or better, patient's MRD status will be assessed via NGF-MRD (Flores-Montero et al., 2017). Briefly, 10 markers will be tested (CD138, CD38, CD45, CD19 CD56, CD27, CD117, CD81, κ / λ light chains) to identify plasma cells, differentiate normal from MM-PC and determine PC clonality. Actual MRD data will be collected from the central testing laboratory,

including percent of cells detected and total cells collected. Unless the sample is limiting, 1×10^7 events will be collected for a standard multiple myeloma MRD sensitivities of 0.001% (10^{-5} sensitivity).

15.0 Drug Information

15.1 Carfilzomib (Kyprolis™)

- 15.11 **Background:** Carfilzomib inhibits proteasomes, which are responsible for intracellular protein homeostasis. Specifically, it is a potent, selective, and irreversible inhibitor of chymotrypsin-like activity of the 20S proteasome, leading to cell cycle arrest and apoptosis.
- 15.12 **Formulation:** Commercially available as single-dose vial containing 10 mg, 30 mg or 60 mg. Carfilzomib is white to off-white lyophilized cake or powder.
- 15.13 **Preparation, storage, and storage:** Unopened vials should be stored refrigerated 2°C to 8°C (36°F to 46°F). Retain in original package to protect from light. Carfilzomib vials contain no antimicrobial preservatives.

Remove vial from refrigerator just prior to use. Aseptically reconstitute each carfilzomib vial only with Sterile Water for Injection, USP.

Strength	Amount of Sterile Water for Injection, USP required for reconstitution
10 mg vial	5 mL
30 mg vial	15 mL
60 mg vial	29 mL

Use a 21-gauge or larger needle (0.8 mm or smaller external diameter needle) to reconstitute each vial by slowly injecting Sterile Water for Injection, USP through the stopper and directing the Sterile Water for Injection, USP onto the inside wall of the vial to minimize foaming. There is no data to support the use of closed system transfer devices with carfilzomib. Gently swirl and/or invert the vial slowly for about 1 minute, or until complete dissolution. Do not shake. Visually inspect for particulate matter and discoloration prior to administration (should be a clear, colorless solution). Carfilzomib can be administered in a 50 mL to 100 mL bag containing 5% Dextrose Injection, USP.

Discard any unused portion of the vial. Do not administer more than one dose from a vial.

Storage conditions of reconstituted carfilzomib	Stability per Container		
	Vial	Syringe	Intravenous D5W bag

Refrigerated 2°C to 8°C (36°F to 46°F)	24 hours	24 hours	24 hours
Room temperature 15°C to 30°C (59°F to 86°F)	4 hours	4 hours	4 hours

15.14 Administration:

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

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

In Cycle 1, carfilzomib is administered at a dose of 20 mg/m². If tolerated in Cycle 1, the dose should be escalated to 56 mg/m² beginning in Cycle 2 and continued at 56 mg/m² in subsequent cycles. Treatment may be continued until disease progression or until unacceptable toxicity occurs.

The dose is calculated using the patient's actual body surface area (BSA) at baseline. Patients with a BSA greater than 2.2 m² should receive a dose based upon a BSA of 2.2 m².

15.15 Pharmacokinetic information:

Distribution: V_{dss}: 28 L (based on 20 mg/m² dose); penetrates all tissues extensively except the brain.

Protein binding, plasma: 97% to human plasma proteins

Metabolism: Rapid and extensive; peptidase cleavage and epoxide hydrolysis; minimal metabolism through cytochrome P450 mediated mechanisms

Half-life elimination: Doses ≥ 15 mg/m²: ≤ 1 hour on Day 1 of Cycle 1

Excretion: Urine (~25% as metabolites; < 1% as parent drug); feces (<1% as parent drug)

15.16 Potential Drug Interactions:

Substrate of P-glycoprotein/ABCB1

Increased Effect/Toxicity: Carfilzomib may increase the levels/effects of: lozapine, contraceptives (estrogens); contraceptives (progestins); deferiprone

The levels/effects of carfilzomib may be increased by pipyrone, lumacaftor, P-glycoprotein/ABCB1 inhibitors; ranolazine

Decreased Effect: Carfilzomib may decrease the levels/effects of BCG

The levels/effects of carfilzomib may be decreased by lumacaftor; P-glycoprotein/ABCB1 inducers.

- 15.17 **Known potential adverse events:** Consult the package insert for the most current and complete information including U.S. Boxed Warnings pertaining to severe diarrhea and severe myelosuppression.

Common known potential toxicities, > 10%:

Blood and lymphatic system disorders: anemia, thrombocytopenia, neutropenia, lymphocytopenia, leukopenia

Cardiac disorders: Chest pain

Gastrointestinal disorders: vomiting, constipation, abdominal pain, nausea, diarrhea

General disorders and administration site conditions: fatigue, fever, peripheral edema, asthenia, chills, hypoesthesia

Infections and Infestations: upper respiratory infection, lung infection (pneumonia)

Investigations: creatinine increased

Metabolism and nutrition disorders: anorexia, hypokalemia, hyperglycemia

Musculoskeletal and connective tissue disorders: back pain, muscle cramps

Nervous system disorders: headache, dizziness, peripheral neuropathy

Psychiatric disorders: insomnia

Respiratory, thoracic, and mediastinal disorders: dyspnea, cough

Vascular disorders: hypertension

Less common known potential toxicities, 1% - 10%:

Blood and lymphatic system disorders: febrile neutropenia

Cardiac disorders: cardiac failure, tachycardia, palpitations, atrial fibrillation, myocardial infarction

Eye/Ear disorders: blurred vision, cataracts, tinnitus

Gastrointestinal disorders: dyspepsia, toothache, gastrointestinal hemorrhage

General disorders and administration site conditions: malaise, flu like symptoms

Infections and Infestations: nasopharyngitis, urinary tract infections, sepsis, bronchitis, influenza, viral infection, rhinitis, gastroenteritis, lung infection

Injury, poisoning, and procedural complications: infusion related reaction,

Investigations: ALT increased, AST increased, increased gamma glutamyltransferase, blood uric acid increased, creatinine renal clearance decreased, C-reactive protein increased, ejection fraction decreased, blood bilirubin increased

Metabolism and nutritional disorders: hypocalcemia, hyperkalemia, hypercalcemia, hypophosphatemia, hyponatremia, hypomagnesemia, hyperuricemia, dehydration, hypoalbuminemia

Musculoskeletal and connective tissue disorders: myalgia, musculoskeletal pain, musculoskeletal chest pain, muscular weakness, bone pain

Nervous system disorders: paresthesia, peripheral sensory neuropathy

Psychiatric disorders: anxiety

Renal and urinary disorders: acute kidney injury, renal failure, renal impairment

Respiratory, thoracic, and mediastinal disorders: epistaxis, pulmonary edema, oropharyngeal pain, dysphonia, wheezing, pulmonary hypertension, pulmonary embolism

Skin and subcutaneous tissue disorders: rash, pruritus, erythema, hyperhidrosis

Vascular disorders: hypotension, DVT, flushing

Rare known potential toxicities, < 1% (Limited to important or life-threatening):

Blood and lymphatic system disorders: hemolytic uremic syndrome, thrombotic microangiopathy, thrombotic thrombocytopenic purpura

Cardiac disorders: cardiac arrest, myocardial ischemia, pericardial effusion, pericarditis, myocardial infarction, cardiomyopathy

Gastrointestinal disorders: gastrointestinal perforation

General disorders and administration site conditions: multi-organ dysfunction syndrome

Hepatobiliary disorders: hepatic failure, cholestasis

Immune system disorders: drug hypersensitivity

Infections and infestations: Clostridium difficile colitis, cytomegalovirus disease

Metabolism and nutrition disorders: tumor lysis syndrome

Nervous system disorders: cerebrovascular accident, intracranial hemorrhage, reversible posterior leukoencephalopathy syndrome, peripheral motor neuropathy

Respiratory, thoracic, and mediastinal disorders: pneumonitis, acute respiratory distress syndrome, acute respiratory failure, interstitial lung disease, pulmonary hemorrhage

Vascular disorders: hypertensive crisis/emergency, hemorrhage

Potential risks (unknown if there is a causal association between the event and carfilzomib):

Herpes zoster infections (The risk of herpes zoster infections can be minimized with antiviral prophylaxis).

Detailed safety information for carfilzomib, including contraindications, warnings, and precautions, adverse reactions, and overdose can be found in the current prescribing information. Carfilzomib should be administered under the supervision of a physician experienced in the use of anti-neoplastic therapy.

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

15.19 Nursing Guidelines

15.19a Fatigue is the most commonly reported side effect. Instruct patient in energy conserving lifestyle and monitor for effectiveness.

15.19b Anemia and thrombocytopenia are also commonly seen. Monitor CBC closely and instruct patient to report any unusual bruising or bleeding to the health care team.

15.19c GI side effects are commonly seen, but are usually mild in nature (nausea, diarrhea). Treat symptomatically and monitor for effectiveness.

15.19d Pneumonia and pulmonary hypertension have been seen. Instruct patient to report any shortness of breath, cough and/or chest pain to the study team.

- 15.19e Elevated creatinine and isolated cases of renal failure (some associated with tumor lysis syndrome) have been seen. Make sure patient is well hydrated prior to administration and monitor creatinine levels closely. Urinary tract infections can also be seen, instruct patient to report signs and symptoms to study team.
- 15.19f Take a detailed history of patient's concomitant medications including OTC and herbal preparations. Instruct patients not to start any new medications without checking with the study first.
- 15.19g Cardiac side effects, including peripheral edema, hypertension, DVT and PE can be seen. Instruct patient to report any signs or symptoms to health care team.
- 15.19h Monitor LFT's and instruct patient to report any hepatic symptoms (abdominal pain, jaundice) to study team immediately.
- 15.19i The IV line should be flushed with D5W or NS immediately before and after carfilzomib administration. Do not administer as a bolus.
- 15.19j Dosing is calculated using patient's actual body surface area (BSA). Patients with a BSA greater than 2.2 m² should receive dose based upon a BSA of 2.2 m².
- 15.19k Monitor electrolytes. Administer replacement doses as ordered and follow labs for effectiveness.
- 15.19l Patient may experience peripheral neuropathy. Assess with each infusion and report any changes to treating provider.

15.2 **Daratumumab (Darzalex®, Darzalex Faspro™, JNJ-54767414):**

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

- 15.21 **Background:** Daratumumab is an immunoglobulin G1 kappa (IgG1κ) human monoclonal antibody directed 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.

Hyaluronidase, a naturally occurring enzyme, increases permeability of the subcutaneous tissue by depolymerizing hyaluronan. In the doses administered, hyaluronidase acts locally. The effects of hyaluronidase are reversible, and permeability of the subcutaneous tissue is restored within 24 to 48 hours.

15.22 Formulation:

- IV Formulation: Daratumumab IV drug solution is a colorless to yellow liquid and sterile concentrate of 20 mg/mL in a vial with a nominal fill of 5 mL or 20 mL. It will be manufactured and provided under the responsibility of Janssen Biotech. Refer to the Product Insert for a list of excipients
- SQ 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. .

15.23 Preparation and storage: IV Formulation : Store daratumumab vials under refrigeration at 2°C to 8°C (36°F- 46°F). Protect daratumumab from light by storing in the original package until time of use. Do not freeze or shake.

Daratumumab vials are single use only. Preparation of the infusion as follows:

- Calculate the dose (mg), total volume (mL) of daratumumab required and the number of daratumumab vials needed based on patient actual body weight.
- Remove a volume of 0.9% Sodium Chloride Injection, USP from the infusion bag/container that is equal to the required volume of daratumumab.
- Withdraw the necessary amount of daratumumab solution and dilute to the appropriate volume by adding to the infusion bag/container containing 0.9% Sodium Chloride USP as specified in the table in 15.24. Infusion bags/containers must be made of either polyvinylchloride (PVC), polypropylene (PP), polyethylene (PE) or polyolefin blend. Dilute under appropriate aseptic conditions. Discard any unused portion left in the vial.
- Gently invert the bag/container to mix the solution. Do not shake.
- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The diluted solution may develop very small, translucent to white proteinaceous particles, as daratumumab is a protein. Do not use if visible opaque particles, discoloration or foreign particles are observed.
- Administer the diluted solution immediately at room temperature 15-25°C (59-77°F) and in room light. Diluted solution may be kept at room temperature for a maximum of 15 hours (including infusion time).
- If not used immediately, the diluted solution can be stored prior to administration for up to 24 hours at refrigerated conditions 2-8°C

(36-46°F) and protected from light. Do not freeze.

SQ Formulation: Store vials in the original carton in a refrigerator ranging from 2°C to 8°C (36°F – 46°F). The product must be protected from light and must not be frozen or shaken.

Preparation as follows: 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. Vials should be removed from the refrigerator and allowed to equilibrate to ambient temperature (15°C to 30°C). Store the unpunctured vial at ambient temperature for a maximum of 24 hours. Withdraw 15 mL from the vial into a syringe. After the solution is withdrawn into the syringe, replace the transfer needle with a syringe cap. To avoid needle clogging, attach the hypodermic injection needle or subcutaneous infusion set to the syringe immediately prior to injection. If not used immediately, store the withdrawn solution for up to 4 hours at ambient temperature and light.

- 15.24 **Administration:** Administer pre-treatment and post-treatment medications per Section 7.21 and 9.7 of the protocol.

IV Administration: Administer daratumumab infusions intravenously using an infusion set fitted with a flow regulator and with an in-line, sterile, non-pyrogenic, low protein-binding polyethersulfone (PES) filter (pore size 0.22 or 0.2 micrometer) at the infusion rate described below. Polyurethane (PU), polybutadiene (PBD), PVC, PP or PE administration sets must be used. Consider incremental escalation of the infusion rate only in the absence of infusion reactions. Do not infuse daratumumab concurrently in the same line with other medications.

	Dilution volume	Initial rate	Rate increment	Maximum rate
First infusion	1000 mL	50 mL/hour (first hour)	50 mL/hour every hour	200 mL/hour
Second infusion	500 mL	50 mL/hour (first hour)	50 mL/hour every hour	200 mL/hour
Subsequent infusions: either Standard infusion or Rapid infusion at the discretion of the treating investigator				
Standard infusion rate (only if patient tolerates rate ≥ 100 mL/hr)	500 mL	100 mL/ hour for 60 minutes	50 mL/hour every hour	200 mL/hour
Rapid infusion protocol (only if patient	500 mL	400 mL/ hour for 30 minutes	No titration; 150 mL/hour for 60 minutes	600 mL/hour

tolerates rate ≥ 100 ml/hr)				
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SQ Administration: 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. Never inject daratumumab into areas where the skin is red, bruised, tender, hard or areas where there are scars.

15.25 **Pharmacokinetic information:**

IV Administration: The pharmacokinetics (PK) of daratumumab following intravenous administration were evaluated in patients with relapsed and refractory multiple myeloma at dose levels from 0.1 mg/kg to 24 mg/kg, and included the recommended 16 mg/kg dose and regimen. Over the dose range from 1 to 24 mg/kg, increases in area under the concentration-time curve (AUC) were more than dose-proportional.

The mean (SD) predose (trough) serum concentration at the end of weekly dosing was 573 (332) µg/mL.

At the recommended dose of 16 mg/kg, the mean ± SD central volume of distribution was 4.7 ± 1.3 L when daratumumab was administered as monotherapy and 4.4 ± 1.5 L when daratumumab was administered as combination therapy.

Daratumumab showed target-mediated disposition with rapid clearance (CL) at low doses and slower CL at higher doses and with multiple doses. Following the first administration at the recommended dose of 16 mg/kg, non-compartment model derived CL was 0.42 ± 0.42 mL/hr/kg and the half-life ($t_{1/2}$) was 9.0 ± 4.3 days. The model-derived half-life associated with linear elimination was approximately 18 ± 9 days. Apparent steady state seems to be reached approximately 5 months into the every 4 week dosing period of the 16 mg/kg with a schedule of weekly for 8 weeks, every 2 weeks for 16 weeks, and then every 4 weeks thereafter.

SQ Administration: 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 (C_{trough} 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 (C_{max}) 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 C_{max}). The absolute bioavailability of daratumumab-hyaluronidase is 69%, with peak concentrations occurring around 3 days (T_{max}). 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%).

Special Populations

Geriatric use: Based on population PK analyses in patients receiving monotherapy or combination therapies, age (range: 31-93 years) had no clinically important effect on the PK or effectiveness of daratumumab. The most common serious adverse events that occurred more frequently in elderly (≥ 65 years of age) were pneumonia and sepsis.

Renal Impairment: The population PK analysis included 592 patients receiving IV daratumumab 16 mg/kg with normal renal function (creatinine clearance [CrCL] ≥ 90 mL/min), 757 patients with mild renal impairment (CrCL < 90 and ≥ 60 mL/min), 604 patients with moderate renal impairment (CrCL < 60 and ≥ 30 mL/min), and 34 patients with severe renal impairment or end stage renal disease (CrCL < 30 mL/min). No formal studies of daratumumab SC formulation in patients with renal impairment have been conducted. No clinically important differences in exposure to daratumumab were observed between patients with renal impairment and those with normal renal function in both daratumumab IV and SC.

Hepatic Impairment: The population PK analysis included 1,742 patients with normal hepatic function (TB and AST $\leq$ ULN), 224 with mild hepatic impairment (TB $1.0\times$ to $1.5\times$ ULN or AST $>$ ULN) patients, and 10 patients with moderate (TB > 1.5 to $3\times$ ULN; n=9) or severe hepatic impairment (TB $> 3\times$ ULN; n=1). No clinical differences in the exposure to daratumumab were observed between patients with hepatic impairment and those with normal hepatic function. The effect of moderate (TB $> 1.5\times$ to $3\times$ ULN and any AST) or severe (TB $> 3\times$ ULN and any AST) hepatic impairment on daratumumab IV or SC pharmacokinetics is unknown. Population PK analysis demonstrated no clinically important differences in the exposure to daratumumab were observed between patients with normal hepatic function and mild hepatic impairment in studies of both daratumumab IV and SC. There were few patients with moderate-severe hepatic impairment to make meaningful conclusions for these populations.

15.26 Potential Drug Interactions:

Clinical PK assessments with daratumumab IV and SQ formulations and lenalidomide, bortezomib, thalidomide, pomalidomide, melphalan, prednisone, cyclophosphamide, dexamethasone, and carfilzomib indicated no clinically relevant drug-drug interactions.

Effects on laboratory tests:

Interference with Indirect Antiglobulin tests: Daratumumab binds to CD38 and RBCs and interferes with compatibility testing, including antibody screening and cross matching and may persist for up to 6 months after the last daratumumab administration. Daratumumab interference mitigation methods include treating reagent RBCs with dithiothreitol (DTT) to disrupt daratumumab binding or

genotyping. Since the Kell blood group system is also sensitive to DTT treatment, K-negative units should be supplied after ruling out or identifying alloantibodies using DTT-treated RBCs. If an emergency transfusion is required, non-cross matched ABO/RhD compatible RBCs can be given per local blood bank practices.

Interference with Serum Protein Electrophoresis and Immunofixation Tests: Daratumumab may be detected on serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for monitoring disease monoclonal immunoglobulins (M protein). This can lead to false positive SPE and IFE assay results for patients with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In patients with persistent very good partial response, where daratumumab interference is suspected, consider using an FDA approved daratumumab-specific IFE assay to distinguish daratumumab from any remaining endogenous M protein in the patient's serum, to facilitate determination of a complete response.

- 15.27 **Known potential toxicities:** Consult the package inset for the most current and complete information.

Warnings and Precautions:

Daratumumab can cause severe and/or serious infusion reactions including anaphylactic reactions. To reduce the risk of acute and delayed infusion reactions, administer with recommended pre-/post supportive care.

Daratumumab binds with CD38 on red blood cells and results in a positive Indirect Antiglobulin Test (indirect Coombs test). Daratumumab-mediated positive indirect antiglobulin test may persist for up to 6 months after the last daratumumab infusion. Type and screen patients prior to starting daratumumab.

Very common known potential toxicities (> 10%):

Blood and lymphatic system disorders: Anemia

Gastrointestinal disorders: Nausea, diarrhea, constipation, vomiting

General disorders and administration site conditions: Fatigue, fever, chills, peripheral edema, asthenia, non-cardiac chest pain, pain

Infections and infestations: Upper respiratory infection, lung infection (pneumonia), bronchitis, nasopharyngitis

Injury, poisoning and procedural complications: Infusion related reaction

Investigations: White blood cell decreased (lymphocytopenia), neutrophil count decreased (neutropenia), platelet count decreased (thrombocytopenia)

Metabolism and nutrition disorders: Anorexia (decreased appetite), hypokalemia, hyperglycemia

Musculoskeletal and connective tissue disorders: Back pain, arthralgia, limb pain, musculoskeletal chest pain, muscle spasms, bone pain

Nervous system disorders: Dizziness, headache, tremor

Psychiatric disorders: Insomnia, anxiety

Respiratory, thoracic and mediastinal disorders: Cough, nasal congestion, dyspnea

Vascular disorders: Hypertension

Common known potential toxicities (1%-10%):**Blood and lymphatic system disorders:** Febrile neutropenia**Cardiac disorders:** Atrial fibrillation**General disorders and administration site conditions:** Injection site reaction**Infections and infestations:** Influenza, sepsis, sinusitis, rhinitis, laryngitis, tonsillitis, shingles**Respiratory, thoracic, and mediastinal disorders:** Pulmonary edema, hypoxia, laryngeal edema, pneumonitis, bronchospasm**Uncommon and rare known potential toxicities, < 1%:** Anaphylaxis, positive indirect Coombs test

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

15.29 Nursing Guidelines

15.29a Daratumumab can cause severe infusion reactions, usually during the first infusion. Patients who have experience a reaction may experience further reactions with subsequent infusions. Most reactions occur during or within 4 hours of infusion, however, reactions may occur up to 48 hours after an infusion. Warn patient of this possibility. Monitor patient throughout infusion for bronchospasm, hypoxia, SOB, and hypertension. Patients may also experience symptoms of anaphylaxis. Administer emergency medication as ordered.

15.29b Patients may experience infections, including URI and pneumonia. Patients who have an ongoing infection should not receive agent.

15.29b Patients may experience gastrointestinal side effects including diarrhea and nausea. Treat symptomatically and monitor for effectiveness.

15.29d Warn patients about the possibility of peripheral neuropathy, dizziness, and insomnia.

15.29e Fatigue is common. Instruct patient in energy conserving lifestyle.

15.29f Rarely patients may experience cardiac issues including, atrial-fibrillation, peripheral edema, and hypertension. Instruct patient to report any chest pain, heart palpitations, and swelling to the study team.

15.29g Monitor CBC w/diff as cytopenias (thrombocytopenia, neutropenia, anemia, and lymphopenia) have been seen. Instruct patient to report any unusual, bruising, bleeding and/or infections/fever to the study team.

15.3 **Dexamethasone for Oral Administration (DXM)**

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/5 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 20°C to 25°C (60°F to 77°F). 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: 4 ± 0.9 hours;
Biological half-life: 36-54 hours
Time to peak, serum: Oral: 1-2 hours
Excretion: Urine (~10%)
- 15.36 **Potential Drug Interactions:**
Cytochrome P450 Effect: Substrate of CYP3A4 (major), P-glycoprotein/ABCB1; **Induces** CYP2A6 (weak/moderate), 2C9 (weak/moderate), 3A4 (weak), UGT1A1
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, separate administration by 2 hours. Aminoglutethimide, barbiturates, and CYP3A4 inducers may reduce the serum levels/effects of dexamethasone. 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, 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 patients 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.

15.39 Nursing Guidelines:

15.39a Monitor regularly for hypertension, CHF and other evidence of fluid retention.

15.39b Advise patient of possible mood or behavioral changes, i.e., depression, euphoria, insomnia, even psychosis. Instruct patient to report any suspected changes to healthcare team.

15.39c Assess for symptoms of gastric ulcer, heartburn, or gastritis. Suggest antacids. Instruct patient to report symptoms to healthcare team if unable to control.

15.39d Evaluate signs of infection, particularly local candidal infections and treat appropriately.

15.39e Monitor blood glucose frequently.

15.39f Instruct patient to report frequent, unrelenting headaches or visual changes to healthcare team.

15.39g Advise patient that easy bruising is a side effect.

15.4 Selinexor (Xpovio™, KPT-330):

IND: 153581

Investigator brochures: Investigator brochure for selinexor is available on the ACCRU web site under study ACCRU-MY-1901.

15.41 **Background:** Selinexor is a small molecule, oral, first-in-class, potent selective inhibitor of nuclear export (SINE) compound. It inhibits the NF-κB and JAK/STAT pathways and shows single-agent anticancer activity in Kirsten ras oncogene homolog (KRAS) mutant cells. Selinexor is FDA approved in combination with dexamethasone for the treatment of adult patients with relapsed

or refractory multiple myeloma who have received at least 4 prior therapies and whose disease is refractory to at least 2 proteasome inhibitors, at least 2 immunomodulatory agents, and an anti-CD38 monoclonal antibody. Additionally, the combination of selinexor, bortezomib, and dexamethasone has been approved in MM patients who have received at least one prior line of therapy and as monotherapy in patients with diffuse large B-cell lymphoma status post 2 lines of systemic therapy.

- 15.42 **Formulation:** Selinexor is supplied as 20-mg, 40-mg, 50-mg, and 60-mg tablets for oral administration for all studies. Selinexor tablets are blue, round, bi-convex, film-coated tablets. The 20-mg tablets have “K20” debossed on one side and nothing on the other side, while the 40-mg tablets are debossed with “X40” on both sides. Similarly, the 50-mg tablets have “X50” and the 60-mg tablets read “X60” on both sides. The inactive ingredients are colloidal silicon dioxide, croscarmellose sodium, magnesium stearate, microcrystalline cellulose, Opadry 200 clear, Opadry II blue, povidone K30, and sodium lauryl sulfate.
- 15.43 **Preparation and storage:** Selinexor tablets should be stored at room temperature (at or below 30 °C [86 °F]).
- 15.44 **Administration:** Administer at approximately the same time of day with or without food. Swallow whole with water; do not break, chew, crush, or divide tablets. If a dose of selinexor is missed or delayed, patients should take their next dose at the next regularly scheduled time. If a patient vomits a dose of selinexor, the patient should not repeat the dose and the patient should take the next dose on the next regularly scheduled day.

Selinexor may be associated with nausea and vomiting; antiemetics are recommended prior to and during treatment to prevent nausea and vomiting. Maintain adequate hydration and caloric intake throughout treatment; consider IV hydration in patients at risk of dehydration.

- 15.45 **Pharmacokinetic information:**
Absorption: The absorption is moderately rapid with a median time to the maximum concentration (t_{max}) of 2 to 4 hours. Selinexor exhibits dose-proportional exposure with moderate-to-high inter-patient variability across a wide dose range of doses in patients with advanced hematologic malignancies or solid tumors.
Distribution: $V_d = 133$ L in patients with cancer. Protein binding = 95%
Metabolism: Hepatic via CYP3A4, multiple UDP-glucuronosyltransferases, and glutathione S-transferases
Half-life elimination: 6 to 8 hours
Excretion: Clearance = 18.6 L/hour in patients with cancer
- 15.46 **Potential Drug Interactions:**
The potential for drug interaction due to inhibition of major human cytochrome (CYPs) (CYP1A2, 2B6, 2C8, 2C9, 2C19, 2D6 and 3A4/5) is low. No demonstrable CYP induction by selinexor was observed in vitro. Selinexor did not inhibit solute carrier transporters except for marginal inhibition of OATP1B1 and 1B3. Based on in vitro results and expected exposure at therapeutic doses, selinexor twice-weekly is not expected to alter the exposures of other drugs.

Although CYP3A4 strong inhibitor was identified to be a significant covariate in the population PK model, the concomitant medication effect was very small and not likely to be clinically relevant.

High doses of acetaminophen can deplete CSH levels and potentially interact with selinexor. Doses up to 1 g daily were shown to have little impact on selinexor metabolism, however larger doses have not been studied.

15.47 Known potential toxicities:

Very Common (>10%): Fatigue, asthenia, thrombocytopenia, nausea, anemia, anorexia, weight loss, diarrhea, vomiting, hyponatremia, neutropenia, leukopenia, constipation, dizziness, dysgeusia, blurred vision, edema, hypotension, dehydration, hypocalcemia, hypophosphatemia, hyperglycemia, hypokalemia, hyperkalemia, increased alanine aminotransferase, increased bilirubin, increased aspartate aminotransferase, infection, insomnia, mental status changes, asthenia, musculoskeletal pain, increased serum creatinine, cough, dyspnea, epistaxis, pneumonia, upper respiratory tract infection, increase in the creatinine phosphokinase (CPK) level, fever

Less Common (1% to 10%): Cardiac failure, syncope, abdominal pain, urinary tract infection, febrile neutropenia, hemorrhage, herpes virus infection, sepsis, falling, headache, peripheral sensory neuropathy, cataract

15.48 Drug procurement: Selinexor is provided free of charge to study participants by Karyopharm Therapeutics.

The initial drug supply order for each site will be placed by Karyopharm Therapeutics. Sites must complete the 'FORM FRM-IST-0008' (located on the ACCRU website under 'Manuals & Forms') and provide to Karyopharm Therapeutics per the instructions on the form. Site pharmacy contact(s) and delivery address for the study drug to Karyopharm Therapeutics via email: [REDACTED] and include 'IST-322/ACCRU' in the subject header. Pharmacists will receive a notification from the DRIVE portal when they are registered and will then need to log in to set up the portal for their site.

After the initial drug shipment, all subsequent orders will be the sites responsibility, through the [REDACTED] Training slides are located on the ACCRU website under 'Manuals & Forms' and include instructions on how to set up and maintain the DRIVE portal accounts. Slide 4 of these training slides describes the specific pharmacy contact information to send to Karyopharm as mentioned above. For troubleshooting the DRIVE portal, contact Karyopharm via email: [REDACTED]

Please allow up to 7 – 10 business days for drug shipment.

15.49 Nursing Guidelines:

15.49a Selinexor should be swallowed whole, and not crushed, chewed or broken. Patients who miss a dose should take their next dose at the next regularly scheduled time. If patient vomits a dose, do not repeat the dose.

- 15.49b Patients may experience nausea/vomiting. It is recommended that patients potentially pre-medicate with antiemetics before their dosing.
- 15.49c Fatigue is very common. Instruct patients in energy conserving lifestyle and to alternate rest with activity.
- 15.49d Patients may experience weight loss.
- 15.49e Electrolyte abnormalities are common. Monitor electrolytes and contact oncology provider if lab abnormalities are noted. Treat as indicated.
- 15.49f Additional GI side effects include diarrhea, constipation, decreased appetite and taste changes. Treat symptomatically and monitor for effectiveness.
- 15.49g Cytopenias are common, with relatively high rates of $\geq$ grade 3. Monitor CBC w/differential closely and instruct patients to report any unusual bruising/bleeding and/or signs/symptoms of infection to the study team immediately.
- 15.49h Respiratory symptoms can be seen with agent including but not limited to: dyspnea, URI, cough, and pneumonia.
- 15.49i Rarely cardiac arrhythmias can occur. Instruct patients to report any chest pain, palpitations, etc to the study team immediately.

16.0 Statistical Considerations and Methodology

16.1 Overview:

This is a single arm Phase II study of a combination of selinexor added to carfilzomib, daratumumab, and dexamethasone in patients with high risk, relapsed or refractory multiple myeloma. This study is designed to assess the rate of minimum residual disease (MRD) negativity at 10^{-5} level of sensitivity using Simon's two stage phase II design with an interim analysis. An early safety analysis will be conducted before continuing accrual in this phase II study.

- 16.11 Primary Endpoint: The primary endpoint of this trial is the rate of MRD negative status. MRD negative status at 10^{-5} level of sensitivity will be considered synonymous with "success", unless specified otherwise. All patients meeting the eligibility criteria, who have signed a consent form and have begun treatment, will be evaluable for response, unless they are determined to be a major violation.

16.2 Statistical Design

- 16.21 Decision Rule: The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 10%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 25%. The following two-stage design with an interim analysis is based on a Simon optimum design and requires 42 evaluable patients to test the null hypothesis that the true success proportion in

this patient population is at most 10%.

16.211 Interim Analysis: Enter 14 evaluable patients into the study. If 1 or fewer successes are observed in the first 14 evaluable patients, we will consider this regimen ineffective in this patient population and terminate the study. Otherwise, if the number of successes is at least 2, we will continue accrual.

16.212 Final Decision Rule: Enter an additional 28 evaluable patients into the study. If 6 or fewer successes are observed in the first 42 evaluable patients, we will consider this regimen ineffective in this patient population. Otherwise, if the number of success is at least 7, this will be considered evidence of promising activity and the treatment may be recommended for further testing in subsequent studies in this population.

16.213 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision- making process. Analysis involving over accrued patients is discussed in section 16.313.

16.214 NOTE: We will not suspend accrual at the interim analysis to allow the first 14 patients to become evaluable, unless undue toxicity is observed. Given the limited overall sample size and the inclusion of an AE stopping rule, we feel it is ethical to not halt accrual for the interim analysis. However, if accrual is extremely rapid, we may temporarily suspend accrual in order to obtain safety data on these patients before re-opening accrual to further patients.

16.215 Dose de-escalation in safety analysis: A safety analysis will be performed in the first 6 evaluable patients per Section 16.4. In the case of unacceptable toxicity as described in section 7.31, the dose will be de-escalated (as per Table 7.3). If this occurs, the first 6 patients will be evaluated separately and will not be included in any decision-making criteria.

16.22 Sample Size: The Simon's two stage design with an interim analysis to be utilized is fully described above. A minimum of 14 and a maximum of 42 evaluable patients will be accrued onto this phase II study unless undue toxicity is encountered. Patients treated at the final dose level in the early safety analysis will be included in phase II primary endpoint analysis. If dose de-escalation is required during the safety analysis, an additional 6 evaluable patients will be accrued per section 16.4. We anticipate accruing an additional 4 (10%) patients to account for ineligibility, cancellation, major treatment violation, or other reasons for a maximum possible sample size of 52 patients.

16.23 Accrual Rate and Study Duration: The anticipated accrual rate is 4-5 evaluable patients per month. At this rate, it will likely take about 12 months to enroll the patients. The maximum total study duration is expected to be approximately 6 years, or until the last patient accrued has been observed for at least 5 years. The earliest date anticipated for presentation of results is at approximately 2 years for the primary endpoint, or when the last patient accrued has been observed for at

least 12 months.

- 16.24 Power and Significance Level: Assuming that the number of successes is binomially distributed, the significance level is .10, i.e., there is a 10% chance of finding the treatment regimen to be effective when it truly is not. The probability of declaring that this regimen warrants further study (i.e., statistical power) and the probability of stopping at the interim analysis under various success proportions can be tabulated as a function of the true success proportion as shown in the following table.

If the true success proportion is...	0.10	0.15	0.20	0.25
Then the probability of declaring that the regimen warrants further studies is...	0.09	0.37	0.67	0.85
And the probability of stopping at the interim analysis is...	0.58	0.35	0.19	0.10

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

16.3 Analysis Plan

The analysis for this trial will commence at planned time points (see 16.2) and at the time the patients have become evaluable for the primary endpoint. The Statistician and Study Chair will make the decision, in accord with CCS 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 patient has been followed for at least 12 months.

16.31 Primary Outcome Analysis

- 16.311 Definition: The primary endpoint of this trial is the MRD negative rate. A success is defined as MRD negative status at 10^{-5} level of sensitivity measured by flow cytometry which is assessed when patient achieve an objective status of CR or better using IMWG response criteria. The CR status does not have to be confirmed for performing MRD testing. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response, unless they are determined to be a major violation. Only patients treated at the final safety run-in dose level will be included when evaluating the decision rules in Sections 16.211 and 16.212.

- 16.312 Estimation: The proportion of success will be estimated by the number of success divided by the total number of evaluable patients. Confidence intervals for the true success proportion will be calculated according to the approach of Duffy and Santner (Duffy & Santner, 1987).

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

16.32 Secondary Outcome Analysis

- 16.321 The overall response rate (ORR) with combination of selinexor to carfilzomib, daratumumab, and dexamethasone will be estimated by the total number of patients who achieve a confirmed response at any time divided by the total number of evaluable patients. A confirmed response is defined as a PR, VGPR, CR or sCR noted as the objective status on two consecutive evaluations at least two weeks apart. Exact binomial 95% confidence intervals for the true overall response rate will be calculated. The depth of response (PR vs. VGPR vs. CR vs. sCR) will also be summarized.
- 16.323 The Time to Response is defined in patients who achieve a confirmed response as the time from registration to the earliest date of documentation of response (objective status of VGPR, PR, CR, sCR) using IMWG criteria. Time to response will be summarized descriptively (median, range).
- 16.324 Duration of Response is defined in patients who achieve a confirmed response as the time from first documentation of objective status (VGPR, PR, CR, sCR) to the earliest date of progression or death, censoring patients who are alive and progression free at the time of the last disease assessment. The distribution of duration of response will be estimated using the method of Kaplan-Meier. (Kaplan & Meier, 1958).
- 16.325 Progression free survival (PFS) is defined as the time from registration to the earliest date of documentation of disease progression or death due to any cause. Patients who receive subsequent treatment for myeloma before disease progression will be censored on the date of their last disease assessment prior to initiation of the subsequent treatment. The distribution of PFS will be estimated using method of Kaplan-Meier.
- 16.326 Overall survival (OS) is defined as the time from registration to death due to any cause. The distribution of OS will be estimated using method of Kaplan-Meier.
- 16.327 MRD negativity rate at 10^{-6} level of sensitivity by flow cytometry in the bone marrow will be estimated as the number of patients who have achieved MRD negative result at 10^{-6} level of sensitivity at any time divided by the total number of evaluable patients. Exact 95% binomial confidence intervals for the true rate of MRD negative response will also be calculated.
- 16.328 Adverse Events (AE): All eligible patients that have initiated treatment will be considered evaluable for assessing AE rate(s). The maximum

grade for each type of AE from each patient will be used for analysis, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the AE(s) to the study treatment will be taken into consideration.

16.33 Correlative Outcome Analysis

- 16.331 Quality of life will be assessed at baseline, every 3 cycles, and at progression, withdrawal or end of treatment as indicated in section 4.0. QOL will be measured using the EORTC QLQ-C30 and QLQ-MY20 (Cocks et al., 2007; Wisløff et al., 1996), a 30-item patient-reported questionnaire about patient ability to function, symptoms related to the cancer and its treatment, overall health and quality of life, and perceived financial impact of the cancer and its treatment. Changes in raw score from baseline to each timepoint will be assessed, in each of the physical and mental health domains. The Wilcoxon signed-rank test will be utilized to assess changes in raw scores. Mean change, along with standard deviation will be reported.

16.4 Early Safety Analysis

An early safety analysis will be performed after the first 6 evaluable patients have been accrued to the study and observed for one cycle. Accrual will be temporarily halted while these patients are evaluated. If 2 or more of the first 6 patients experience a significant toxicity as described in section 7.32, then the dose of Selinexor may be de-escalated (as per Table 7.3). In this case, another safety analysis will be conducted on the next set of first 6 evaluable patients treated at the reduced dose level (40 mg).

Safety will be assessed through summaries of adverse events and changes from baseline laboratory results. All adverse events occurring on or after first study treatment will be summarized by NCI CTCAE v5.0 grade. Deaths reported during the treatment period and during post-treatment follow-up will be listed and summarized.

16.5 Data & Safety Monitoring

- 16.51 The principal investigator(s) and the study statistician will review the study at least twice a year to identify accrual, AE, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.
- 16.52 Adverse Event Stopping Rules (to be evaluated in all patients treated at the dose determined in the safety run-in): The stopping rules specified below are based on the knowledge available at study development. We note that the AE Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the AE profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected AE profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe

events considered at least possibly related to study treatment (i.e., an AE with attribute specified as “possible,” “probable,” or “definite”) that satisfy one of the following:

- If 4 or more patients in the first 14 treated patients experience a grade 4 or higher non-hematologic AE at least possibly related to treatment.
- If after the first 14 patients have been treated, 30% of all patients experience a grade 4 or higher non-hematologic AE at least possibly related to treatment. We note that we will review grade 4 and 5 AEs deemed “unrelated” or “unlikely to be related”, to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related AE.

Note: If safety analysis fails in first 6 patients, those patients will not be used to evaluate the stopping rule.

16.6 Results Reporting on ClinicalTrials.gov

At study activation, this study will have been registered within the “ClinicalTrials.gov” website. The Primary and Secondary Endpoints along with other required information for this study will be reported on [REDACTED]. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 2.5 years after the study opens to accrual. The definition of “Primary Endpoint Completion Date” (PECD) for this study is at the time all patients registered have achieved MRD negativity status at 10^{-5} level of sensitivity by flow cytometry or have discontinued treatment before achieving MRD negativity.

16.7 Subset Analysis for Minorities

- 16.71 Study availability: This study will be available to all eligible patients, regardless of gender, race or ethnic origin.
- 16.72 Statistical analysis by subset: 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.
- 16.73 Regional population: The geographical region served by MCCC has a population which includes approximately 5% minorities. Based on prior MCCC studies involving similar disease sites, we expect about 5-7% of patients will be classified as minorities by race and about 25% of patients will be women.

Accrual Estimates by Gender/Ethnicity/Race

Ethnic Category	Sex/Gender			
	Females	Males	Unknown	Total
Hispanic or Latino	0	2	0	2

Not Hispanic or Latino	20	30	0	50
Ethnic Category: Total of all Patients *	20	32	0	52
Racial Category				
American Indian or Alaskan Native	0	0	0	0
Asian	0	0	0	0
Black or African American	1	1	0	2
Native Hawaiian or other Pacific Islander	0	0	0	0
White	20	30	0	50
Racial Category: Total of all Patients*	21	31	0	52

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, 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. Terms such as “Haitian” or “Negro” can be used in addition to “Black or African American.”

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:

None

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 (DSS) located on the ACCRU website.

18.2 Survival Follow-up

See [Section 4.1](#).

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.

18.4 Site responsibilities

Each site will be responsible for ensuring that all materials contain the patient's initials, ACCRU registration number, and ACCRU protocol number. All PHI must be redacted from any documentation.

18.5 Supporting documentation

Upload a copy of documentation of response or progression in RAVE on the Supporting Documentation Form.

Baseline: The following documents are required for diagnosis and eligibility verification: (Imaging report, Pathology report, Operative report, Lab report, Clinic note, etc.). These documents should be submitted within 14 days of registration.

Treatment: The following documents as applicable: Imaging report, Lab report, Clinic note

At patient progression or restaging for evidence of response: (Imaging report, Pathology report, Operative report, Lab report, Clinic note, etc.)

18.6 Labeling of materials

Each site will be responsible for ensuring that all materials contain the patient's initials, ACCRU registration number, and ACCRU 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 is available on the ACCRU website. Only site staff rostered with the Rave CRA role will have access to these reports.

All data must be entered by Remote Data Entry (RDE) and completed by qualified and authorized personnel. Access the RAVE RDE system through the iMedidata portal at [REDACTED] All data on the CRF must reflect the corresponding source document. Please refer to the ACCRU website for instructions [REDACTED]

19.0 Budget

- 19.1 Each site should review the test schedule (Section 4.0), taking into account local and regional coverage policies, to determine which items are standard of care and which are research at their site. Refer to the payment synopsis for funding provided per accrual for covering study costs, as well as any additional invoiceables that may be allowed.

20.0 References:

- An, G., Qin, X., Acharya, C., Xu, Y., Deng, S., Shi, L., Zang, M., Sui, W., Yi, S., Li, Z., Hao, M., Feng, X., Jin, F., Zou, D., Qi, J., Zhao, Y., Tai, Y.-T., Wang, J., & Qiu, L. (2015). Multiple myeloma patients with low proportion of circulating plasma cells had similar survival with primary plasma cell leukemia patients. *Annals of Hematology*, 94(2), 257–264. <https://doi.org/10.1007/s00277-014-2211-0>
- Anderson, K. C., Auclair, D., Kelloff, G. J., Sigman, C. C., Avet-Loiseau, H., Farrell, A. T., Gormley, N. J., Kumar, S. K., Landgren, O., Munshi, N. C., Cavo, M., Davies, F. E., Di Bacco, A., Dickey, J. S., Gutman, S. I., Higley, H. R., Hussein, M. A., Jessup, J. M., Kirsch, I. R., ... Zamagni, E. (2017). The Role of Minimal Residual Disease Testing in Myeloma Treatment Selection and Drug Development: Current Value and Future Applications. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*, 23(15), 3980–3993. <https://doi.org/10.1158/1078-0432.CCR-16-2895>
- Avet-Loiseau, H. (2010). Ultra High-Risk Myeloma. *Hematology*, 2010(1), 489–493. <https://doi.org/10.1182/asheducation-2010.1.489>
- Avet-Loiseau, Hervé, Casneuf, T., Chiu, C., Laubach, J. P., Lee, J.-J., Moreau, P., Plesner, T., Nahi, H., Khokhar, N. Z., Qi, M., Schecter, J., Carlton, V., Qin, X., Liu, K., Wu, K., Zhuang, S. H., Ahmadi, T., Sasser, A. K., & San-Miguel, J. (2016). Evaluation of

- Minimal Residual Disease (MRD) in Relapsed/Refractory Multiple Myeloma (RRMM) Patients Treated with Daratumumab in Combination with Lenalidomide Plus Dexamethasone or Bortezomib Plus Dexamethasone. *Blood*, 128(22), 246–246.
- Bahlis, N. J., Sutherland, H., White, D., Sebag, M., Lentzsch, S., Kotb, R., Venner, C. P., Gasparetto, C., Del Col, A., Neri, P., Reece, D., Kauffman, M., Shacham, S., Unger, T. J., Jeha, J., Saint-Martin, J.-R., Shah, J., & Chen, C. (2018). Selinexor plus low-dose bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma. *Blood*, 132(24), 2546–2554. <https://doi.org/10.1182/blood-2018-06-858852>
- Bhutani, M., Zhang, Q., Friend, R., Voorhees, P. M., Druhan, L. J., Barlogie, B., Sonneveld, P., Morgan, G. J., Symanowski, J. T., Avalos, B. R., Copelan, E. A., & Usmani, S. Z. (2017). Investigation of a gene signature to predict response to immunomodulatory derivatives for patients with multiple myeloma: An exploratory, retrospective study using microarray datasets from prospective clinical trials. *The Lancet. Haematology*, 4(9), e443–e451. [https://doi.org/10.1016/S2352-3026\(17\)30143-6](https://doi.org/10.1016/S2352-3026(17)30143-6)
- Cavo M., Gay F.M., Patriarca F., Zamagni E., Montefusco V., Galli M., Dozza L., Bringhen S., Grasso M., Testoni N., Ballanti S., Tacchetti P., Semenzato G., Liberati A.M., Benevolo G., Spriano M., Di Bartolomeo P., Di Toritto T.C., Palmas A.D., ... Sonneveld P. (2017). Double autologous stem cell transplantation significantly prolongs progression-free survival and overall survival in comparison with single autotransplantation in newly diagnosed multiple myeloma: An analysis of Phase 3 EMN02/HO95 Study. *Blood*, 130((Cavo M.; Dozza L.; Testoni N.; Tacchetti P.) Seragnoli Institute of Hematology, Bologna University, School of Medicine, Bologna, Italy). Embase. <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L620311207>
- Chari, A., Martinez-Lopez, J., Mateos, M.-V., Blade, J., Lonial, S., Benboubker, L., Rocafiguera, A. O., Arnulf, B., San-Miguel, J., Pineiro, L., Jakubowiak, A. J., De Boer, C., Wang, J., Schecter, J. M., & Moreau, P. (2018). Daratumumab (DARA) in combination with carfilzomib and dexamethasone (D-Kd) in lenalidomide (Len)- refractory patients (Pts) with relapsed multiple myeloma (MM): Subgroup analysis of MMY1001. *Journal of Clinical Oncology*, 36(15_suppl), 8002–8002. https://doi.org/10.1200/JCO.2018.36.15_suppl.8002
- Chari, A., Vogl, D. T., Gavriatopoulou, M., Nooka, A. K., Yee, A. J., Huff, C. A., Moreau, P., Dingli, D., Cole, C., Lonial, S., Dimopoulos, M., Stewart, A. K., Richter, J., Vij, R., Tuchman, S., Raab, M. S., Weisel, K. C., Delforge, M., Cornell, R. F., ... Jagannath, S. (2019). Oral Selinexor-Dexamethasone for Triple-Class Refractory Multiple Myeloma. *The New England Journal of Medicine*, 381(8), 727–738. <https://doi.org/10.1056/NEJMoa1903455>
- Chng, W.-J., Goldschmidt, H., Dimopoulos, M. A., Moreau, P., Joshua, D., Palumbo, A., Facon, T., Ludwig, H., Pour, L., Niesvizky, R., Oriol, A., Rosiñol, L., Suvarov, A., Gaidano, G., Pika, T., Weisel, K., Goranova-Marinova, V., Gillenwater, H. H., Mohamed, N., ... Hájek, R. (2017). Carfilzomib-dexamethasone vs bortezomib-dexamethasone in relapsed or refractory multiple myeloma by cytogenetic risk in the phase 3 study ENDEAVOR. *Leukemia*, 31(6), 1368–1374. <https://doi.org/10.1038/leu.2016.390>
- Cocks, K., Cohen, D., Wisløff, F., Sezer, O., Lee, S., Hippe, E., Gimsing, P., Turesson, I., Hájek, R., Smith, A., Graham, L., Phillips, A., Stead, M., Velikova, G., Brown, J., & EORTC Quality of Life Group. (2007). An international field study of the reliability and validity of a disease-specific questionnaire module (the QLQ- MY20) in assessing the quality of life of patients with multiple myeloma. *European Journal of Cancer (Oxford, England: 1990)*, 43(11), 1670–1678. <https://doi.org/10.1016/j.ejca.2007.04.022>
- Dimopoulos, M. A., Barlogie, B., Smith, T. L., & Alexanian, R. (1991). High serum lactate dehydrogenase level as a marker for drug resistance and short survival in multiple

- myeloma. *Annals of Internal Medicine*, 115(12), 931–935. <https://doi.org/10.7326/0003-4819-115-12-931>
- Dimopoulos M.A., White D.J., Benboubker L., Cook G., Leiba M., Morton J., Ho P.J., Kim K., Takezako N., Trivedi S., Casneuf T., Wu K., Schecter J., Chiu C., & Moreau P. (2017). Daratumumab, lenalidomide, and dexamethasone (DRD) versus lenalidomide and dexamethasone (RD) in relapsed or refractory multiple myeloma (RRMM): Updated efficacy and safety analysis of pollux. *Blood*, 130((Dimopoulos M.A.) National and Kapodistrian University of Athens, Athens, Greece). Embase.
- Duffy, D. E., & Santner, T. J. (1987). Confidence Intervals for a Binomial Parameter Based on Multistage Tests. *Biometrics*, 43(1), 81. <https://doi.org/10.2307/2531951>
- Durie, B. G. M., Harousseau, J.-L., Miguel, J. S., Bladé, J., Barlogie, B., Anderson, K., Gertz, M., Dimopoulos, M., Westin, J., Sonneveld, P., Ludwig, H., Gahrton, G., Beksac, M., Crowley, J., Belch, A., Boccadaro, M., Cavo, M., Turesson, I., Joshua, D., ... International Myeloma Working Group. (2006). International uniform response criteria for multiple myeloma. *Leukemia*, 20(9), 1467–1473. <https://doi.org/10.1038/sj.leu.2404284>
- Flores-Montero, J., Sanoja-Flores, L., Paiva, B., Puig, N., García-Sánchez, O., Böttcher, S., van der Velden, V. H. J., Pérez-Morán, J.-J., Vidriales, M.-B., García-Sanz, R., Jimenez, C., González, M., Martínez-López, J., Corral- Mateos, A., Grigore, G.-E., Fluxá, R., Pontes, R., Caetano, J., Sedek, L., ... Orfao, A. (2017). Next Generation Flow for highly sensitive and standardized detection of minimal residual disease in multiple myeloma. *Leukemia*, 31(10), 2094–2103. <https://doi.org/10.1038/leu.2017.29>
- Gasparetto, C., Lentzsch, S., Schiller, G. J., Callander, N. S., Tuchman, S., Bahlis, N. J., White, D., Chen, C., Baljevic, M., Sutherland, H. J., Kotb, R., Sebag, M., LeBlanc, R., Venner, C. P., Bensinger, W., Rossi, A. C., Sheehan, H., Arazy, M., Kai, K., & Lipe, B. (2020). Selinexor, daratumumab, and dexamethasone in patients with relapsed/refractory multiple myeloma (MM). *Journal of Clinical Oncology*, 38(15_suppl), 8510–8510. https://doi.org/10.1200/JCO.2020.38.15_suppl.8510
- Gasparetto, C., Lipe, B., Tuchman, S., Callander, N. S., Lentzsch, S., Baljevic, M., Rossi, A. C., Bahlis, N. J., White, D., Chen, C., Sutherland, H. J., Kotb, R., LeBlanc, R., Sebag, M., Venner, C. P., Bensinger, W., Sheehan, H., Ju, Y., Kai, K., & Schiller, G. J. (2020). Once weekly selinexor, carfilzomib, and dexamethasone (SKd) in patients with relapsed/refractory multiple myeloma (MM). *Journal of Clinical Oncology*, 38(15_suppl), 8530–8530. https://doi.org/10.1200/JCO.2020.38.15_suppl.8530
- Goldschmidt, H., Moreau, P., Ludwig, H., Niesvizky, R., Chng, W.-J., Joshua, D., Weisel, K., Spencer, A., Orlowski, R. Z., Feng, S., Iskander, K. S., & Dimopoulos, M. A. (2018). Carfilzomib-dexamethasone versus subcutaneous or intravenous bortezomib in relapsed or refractory multiple myeloma: Secondary analysis of the phase 3 ENDEAVOR study. *Leukemia & Lymphoma*, 59(6), 1364–1374. <https://doi.org/10.1080/10428194.2017.1376743>
- Granell, M., Calvo, X., Garcia-Guiñón, A., Escoda, L., Abella, E., Martínez, C. M., Teixidó, M., Gimenez, M. T., Senín, A., Sanz, P., Campoy, D., Vicent, A., Arenillas, L., Rosiñol, L., Sierra, J., Bladé, J., de Larrea, C. F., & GEMMAC (Grup per l'estudi del mieloma i l'amiloïdosi de Catalunya). (2017). Prognostic impact of circulating plasma cells in patients with multiple myeloma: Implications for plasma cell leukemia definition. *Haematologica*, 102(6), 1099–1104. <https://doi.org/10.3324/haematol.2016.158303>
- Greipp, P. R., San Miguel, J., Durie, B. G. M., Crowley, J. J., Barlogie, B., Bladé, J., Boccadoro, M., Child, J. A., Avet-Loiseau, H., Harousseau, J.-L., Kyle, R. A., Lahuerta, J. J., Ludwig, H., Morgan, G., Powles, R., Shimizu, K., Shustik, C., Sonneveld, P., Tosi, P., ... Westin, J. (2005). International staging system for multiple myeloma. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, 23(15), 3412–

3420. <https://doi.org/10.1200/JCO.2005.04.242>
- Jakubowiak, A. J., Jasieles, J. K., Rosenbaum, C. A., Cole, C. E., Chari, A., Mikhael, J., Nam, J., McIver, A., Severson, E., Stephens, L. A., Tinari, K., Rosebeck, S., Zimmerman, T. M., Hycner, T., Turowski, A., Karrison, T., & Zonder, J. A. (2019). Phase 1 study of selinexor plus carfilzomib and dexamethasone for the treatment of relapsed/refractory multiple myeloma. *British Journal of Haematology*. <https://doi.org/10.1111/bjh.15969>
- Kaplan, E. L., & Meier, P. (1958). Nonparametric estimation from incomplete observations. *Journal of the American Statistical Association*, 53(282), 457–481.
- Kastritis E., Roussou M., Eleutherakis-Papaiakovou E., Gavriatopoulou M., Migkou M., Gika D., Fotiou D., Kanellias N., Ziogas D.C., Ntanas-Stathopoulos I., Mparmparousi D., Gatou A., Katopi D., Manios E., Lontos M., Giannouli S., Tsigotis P., Terpos E., & Dimopoulos M.A. (2017). Early relapse post autologous transplantation is associated with very poor survival and identifies an ultra high risk group of myeloma patients. *Blood*, 130((Kastritis E.; Roussou M.; Eleutherakis-Papaiakovou E.; Gavriatopoulou M.; Migkou M.; Gika D.; Fotiou D.; Kanellias N.; Ziogas D.C.; Ntanas-Stathopoulos I.; Manios E.; Lontos M.; Terpos E.; Dimopoulos M.A.) Department of Clinical Therapeutics, National and Kapodistrian University of Athens, School of Medicine, Athens, Greece). Embase. <http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L620335627>
- Kazmi, S. M., Nusrat, M., Gunaydin, H., Cornelison, A. M., Shah, N., Kebriaei, P., Nieto, Y., Parmar, S., Popat, U. R., Oran, B., Shah, J. J., Orlowski, R. Z., Champlin, R. E., Qazilbash, M. H., & Bashir, Q. (2015). Outcomes Among High-Risk and Standard-Risk Multiple Myeloma Patients Treated With High-Dose Chemotherapy and Autologous Hematopoietic Stem-Cell Transplantation. *Clinical Lymphoma, Myeloma & Leukemia*, 15(11), 687–693. <https://doi.org/10.1016/j.clml.2015.07.641>
- Kumar, S. K., Dispenzieri, A., Fraser, R., Mingwei, F., Akpek, G., Cornell, R., Kharfan-Dabaja, M., Freytes, C., Hashmi, S., Hildebrandt, G., Holmberg, L., Kyle, R., Lazarus, H., Lee, C., Mikhael, J., Nishihori, T., Tay, J., Usmani, S., Vesole, D., ... D'Souza, A. (2018). Early relapse after autologous hematopoietic cell transplantation remains a poor prognostic factor in multiple myeloma but outcomes have improved over time. *Leukemia*, 32(4), 986–995. <https://doi.org/10.1038/leu.2017.331>
- Kumar, S., Paiva, B., Anderson, K. C., Durie, B., Landgren, O., Moreau, P., Munshi, N., Lonial, S., Bladé, J., Mateos, M.-V., Dimopoulos, M., Kastritis, E., Boccadoro, M., Orlowski, R., Goldschmidt, H., Spencer, A., Hou, J., Chng, W. J., Usmani, S. Z., ... Avet-Loiseau, H. (2016). International Myeloma Working Group consensus criteria for response and minimal residual disease assessment in multiple myeloma. *The Lancet. Oncology*, 17(8), e328–e346. [https://doi.org/10.1016/S1470-2045\(16\)30206-6](https://doi.org/10.1016/S1470-2045(16)30206-6)
- Kumar, Shaji K., Uno, H., Jacobus, S. J., Van Wier, S. A., Ahmann, G. J., Henderson, K. J., Callander, N. S., Haug, J. L., Siegel, D. S., Greipp, P. R., Fonseca, R., & Rajkumar, S. V. (2011). Impact of gene expression profiling- based risk stratification in patients with myeloma receiving initial therapy with lenalidomide and dexamethasone. *Blood*, 118(16), 4359–4362. <https://doi.org/10.1182/blood-2011-03-342089>
- Lakshman A., Singh P.P., Rajkumar S.V., Lacy M.Q., Gertz M.A., Buadi F.K., Dingli D., Dispenzieri A., Hwa L., Fonder A., Hobbs M., Zeldenrust S., Lust J.A., Russell S.J., Leung N., Go R.S., Lin Y., Gonsalves W.I., Kapoor P., ... Kumar S.K. (2017). Efficacy of VDT pace-like regimens in treatment of relapsed/refractory multiple myeloma-a single center experience. *Blood*, 130((Lakshman A.; Rajkumar S.V.; Lacy M.Q.; Gertz M.A.; Buadi F.K.; Dingli D.; Dispenzieri A.; Hwa L.; Fonder A.; Hobbs M.; Zeldenrust S.; Lust J.A.; Russell S.J.; Leung N.; Go R.S.; Lin Y.; Gonsalves W.I.; Kapoor P.; Kourelis T.; Warsame R.; Kyle R.A.; Kumar S.K.) Division of Hematology, Mayo Clinic, Rochester,

- MN, United States). Embase.
<http://www.embase.com/search/results?subaction=viewrecord&from=export&id=L620335283>
- Landgren, O., Devlin, S., Boulad, M., & Mailankody, S. (2016). Role of MRD status in relation to clinical outcomes in newly diagnosed multiple myeloma patients: A meta-analysis. *Bone Marrow Transplantation*, 51(12), 1565–1568. <https://doi.org/10.1038/bmt.2016.222>
- Leone, P. E., Walker, B. A., Jenner, M. W., Chiecchio, L., Dagrada, G., Protheroe, R. K. M., Johnson, D. C., Dickens, N. J., Brito, J. L., Else, M., Gonzalez, D., Ross, F. M., Chen-Kiang, S., Davies, F. E., & Morgan, G. J. (2008). Deletions of CDKN2C in multiple myeloma: Biological and clinical implications. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*, 14(19), 6033–6041. <https://doi.org/10.1158/1078-0432.CCR-08-0347>
- Majithia, N., Rajkumar, S. V., Lacy, M. Q., Buadi, F. K., Dispenzieri, A., Gertz, M. A., Hayman, S. R., Dingli, D., Kapoor, P., Hwa, L., Lust, J. A., Russell, S. J., Go, R. S., Kyle, R. A., & Kumar, S. K. (2016). Early relapse following initial therapy for multiple myeloma predicts poor outcomes in the era of novel agents. *Leukemia*, 30(11), 2208–2213. <https://doi.org/10.1038/leu.2016.147>
- Moreau, P., Zweegman, S., Perrot, A., Hulin, C., Caillot, D., Facon, T., Leleu, X., Belhadj, K., Karlin, L., Benboubker, L., Levin, M.-D., Minnema, M. C., Jamet, B., Bodet-Milin, C., Sonneveld, P., Lambert, J., Pei, L., de Boer, C., Vermeulen, J., ... Kraeber-Bodere, F. (2019). Evaluation of the Prognostic Value of Positron Emission Tomography-Computed Tomography (PET-CT) at Diagnosis and Follow-up in Transplant-Eligible Newly Diagnosed Multiple Myeloma (TE NDMM) Patients Treated in the Phase 3 Cassiopeia Study: Results of the Cassiopet Companion Study. *Blood*, 134(Supplement_1), 692–692. <https://doi.org/10.1182/blood-2019-123143>
- National Cancer Institute Surveillance, Epidemiology and End Results Program (SEER). (n.d.). <https://seer.cancer.gov/statfacts/html/mulmy.html>
- Palumbo, A., Avet-Loiseau, H., Oliva, S., Lokhorst, H. M., Goldschmidt, H., Rosinol, L., Richardson, P., Caltagirone, S., Lahuerta, J. J., Facon, T., Bringhen, S., Gay, F., Attal, M., Passera, R., Spencer, A., Offidani, M., Kumar, S., Musto, P., Lonial, S., ... Moreau, P. (2015). Revised International Staging System for Multiple Myeloma: A Report From International Myeloma Working Group. *Journal of Clinical Oncology: Official Journal of the American Society of Clinical Oncology*, 33(26), 2863–2869. <https://doi.org/10.1200/JCO.2015.61.2267>
- Palumbo, A., Chanan-Khan, A., Weisel, K., Nooka, A. K., Masszi, T., Beksac, M., Spicka, I., Hungria, V., Munder, M., Mateos, M. V., Mark, T. M., Qi, M., Schecter, J., Amin, H., Qin, X., Deraedt, W., Ahmadi, T., Spencer, A., & Sonneveld, P. (2016). Daratumumab, Bortezomib, and Dexamethasone for Multiple Myeloma. *New England Journal of Medicine*, 375(8), 754–766. <https://doi.org/10.1056/NEJMoa1606038>
- Rajkumar, S. V., Dimopoulos, M. A., Palumbo, A., Blade, J., Merlini, G., Mateos, M.-V., Kumar, S., Hillengass, J., Kastiris, E., Richardson, P., Landgren, O., Paiva, B., Dispenzieri, A., Weiss, B., LeLeu, X., Zweegman, S., Lonial, S., Rosinol, L., Zamagni, E., ... Miguel, J. F. S. (2014). International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *The Lancet. Oncology*, 15(12), e538–548. [https://doi.org/10.1016/S1470-2045\(14\)70442-5](https://doi.org/10.1016/S1470-2045(14)70442-5)
- Rajkumar, S. V., Harousseau, J.-L., Durie, B., Anderson, K. C., Dimopoulos, M., Kyle, R., Blade, J., Richardson, P., Orlowski, R., Siegel, D., Jagannath, S., Facon, T., Avet-Loiseau, H., Lonial, S., Palumbo, A., Zonder, J., Ludwig, H., Vesole, D., Sezer, O., ... International Myeloma Workshop Consensus Panel 1. (2011). Consensus recommendations for the uniform reporting of clinical trials: Report of the International Myeloma Workshop Consensus Panel 1. *Blood*, 117(18), 4691–4695.

- <https://doi.org/10.1182/blood-2010-10-299487>
- Ravi, P., Kumar, S. K., Roeker, L., Gonsalves, W., Buadi, F., Lacy, M. Q., Go, R. S., Dispenzieri, A., Kapoor, P., Lust, J. A., Dingli, D., Lin, Y., Russell, S. J., Leung, N., Gertz, M. A., Kyle, R. A., Bergsagel, P. L., & Rajkumar, S. V. (2018). Revised diagnostic criteria for plasma cell leukemia: Results of a Mayo Clinic study with comparison of outcomes to multiple myeloma. *Blood Cancer Journal*, 8(12), 116. <https://doi.org/10.1038/s41408-018-0140-1>
- Rosebeck, S., Alonge, M., Jasielec, J., McCauley, D., Shacham, S., Kauffman, M., & Jakubowiak, A. (2014). Anti- Myeloma Activity of Combined Inhibition of the Proteasome with Carfilzomib (CFZ) and XPO1/CRM1- Dependent Nuclear Export By Selinexor (KPT-330) Via a Novel Mechanism of Intracellular Activation of Caspase 10- Dependent Apoptosis. *Blood*, 124(21), 3443–3443.
- Shaughnessy, J. D., Qu, P., Usmani, S., Heuck, C. J., Zhang, Q., Zhou, Y., Tian, E., Hanamura, I., van Rhee, F., Anaissie, E., Epstein, J., Nair, B., Stephens, O., Williams, R., Waheed, S., Alsayed, Y., Crowley, J., & Barlogie, B. (2011). Pharmacogenomics of bortezomib test-dosing identifies hyperexpression of proteasome genes, especially PSMD4, as novel high-risk feature in myeloma treated with Total Therapy 3. *Blood*, 118(13), 3512–3524. <https://doi.org/10.1182/blood-2010-12-328252>
- Shaughnessy, J. D., Zhan, F., Burington, B. E., Huang, Y., Colla, S., Hanamura, I., Stewart, J. P., Kordsmeier, B., Randolph, C., Williams, D. R., Xiao, Y., Xu, H., Epstein, J., Anaissie, E., Krishna, S. G., Cottler-Fox, M., Hollmig, K., Mohiuddin, A., Pineda-Roman, M., ... Barlogie, B. (2007). A validated gene expression model of high-risk multiple myeloma is defined by deregulated expression of genes mapping to chromosome 1. *Blood*, 109(6), 2276–2284. <https://doi.org/10.1182/blood-2006-07-038430>
- Sullivan, D. M., Dawson, J. L., & Turner, J. G. (2015). Overcoming Proteasome Inhibitor Resistance in Multiple Myeloma Using the XPO1: Inhibitor Selinexor. *Clinical Lymphoma, Myeloma and Leukemia*, 15, e290. <https://doi.org/10.1016/j.clml.2015.07.593>
- Terpos, E., Katodritou, E., Roussou, M., Pouli, A., Michalis, E., Delimpasi, S., Parcharidou, A., Kartasis, Z., Zomas, A., Symeonidis, A., Viniou, N.-A., Anagnostopoulos, N., Economopoulos, T., Zervas, K., Dimopoulos, M. A., & Greek Myeloma Study Group, Greece. (2010). High serum lactate dehydrogenase adds prognostic value to the international myeloma staging system even in the era of novel agents. *European Journal of Haematology*, 85(2), 114–119. <https://doi.org/10.1111/j.1600-0609.2010.01466.x>
- Turner, J. G., Kashyap, T., Dawson, J. L., Gomez, J., Bauer, A. A., Grant, S., Dai, Y., Shain, K. H., Meads, M., Landesman, Y., & Sullivan, D. M. (2016). XPO1 inhibitor combination therapy with bortezomib or carfilzomib induces nuclear localization of IκBα and overcomes acquired proteasome inhibitor resistance in human multiple myeloma. *Oncotarget*, 7(48), 78896–78909. <https://doi.org/10.18632/oncotarget.12969>
- Usmani, S. Z., Quach, H., Mateos, M.-V., Landgren, O., Leleu, X., Siegel, D. S., Weisel, K., Yang, H., Klippel, Z. K., Zahlten-Kumeli, A., & Dimopoulos, M. A. (2019). Carfilzomib, Dexamethasone, and Daratumumab Versus Carfilzomib and Dexamethasone for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma (RRMM): Primary Analysis Results from the Randomized, Open-Label, Phase 3 Study Candor (NCT03158688). *Blood*, 134(Supplement_2), LBA-6-LBA-6. <https://doi.org/10.1182/blood-2019-132629>
- Wisløff, F., Eika, S., Hippe, E., Hjorth, M., Holmberg, E., Kaasa, S., Palva, I., & Westin, J. (1996). Measurement of health-related quality of life in multiple myeloma. Nordic Myeloma Study Group. *British Journal of Haematology*, 92(3), 604–613. <https://doi.org/10.1046/j.1365-2141.1996.352889.x>
- Zamagni, E., Nanni, C., Mancuso, K., Tacchetti, P., Pezzi, A., Pantani, L., Zannetti, B., Rambaldi, I., Brioli, A., Rocchi, S., Terragna, C., Martello, M., Marzocchi, G., Borsi, E.,

Rizzello, I., Fanti, S., & Cavo, M. (2015). PET/CT Improves the Definition of Complete Response and Allows to Detect Otherwise Unidentifiable Skeletal Progression in Multiple Myeloma. *Clinical Cancer Research: An Official Journal of the American Association for Cancer Research*, 21(19), 4384–4390. <https://doi.org/10.1158/1078-0432.CCR-15-0396>

Appendix I: Multiple Myeloma Diagnostic Criteria

Clonal BMPC $\geq$ 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 percentage $\geq 60\%$
- ☐ Involved: uninvolved serum free light chain ratio ≥ 100
- ☐ > 1 focal lesion on MRI studies

Appendix II: ACCRU-ACCRU-MY-1901 SUBJECT MEDICATION DIARY

Name:	Subject ID Number:
Cycle:	
You will take:	

ORAL MEDICATION DIARY**Subject Instructions**

- ☐ Please bring your Medication Diary and any empty or unused medication container(s) with you to every appointment
- ☐ Please use an ink pen when completing the Medication Diary as these will be retained in our research record.
- ☐ Please contact your physician and study coordinator any time you go into the hospital. Your physician can advise if you should continue or stop taking your medication.
- ☐ To correct a mistake, please make a single line through that entry and write your initials and the date next to the mistake.
- ☐ Please indicate on the calendar on the next page that you took your study medication by recording the date and dose taken on the line under the date.
- ☐ If you miss a dose, place a "0" under the date, but remember to take your prescribed dose at the next regularly scheduled time.
- ☐ If you accidentally take more than you are instructed to, contact your doctor or the emergency room immediately.
- ☐ If you miss a dose, do not make up the dose and consult with your study team.

ACCRU-MY-1901 SUBJECT MEDICATION DIARY

Study Drug/Dose	Day 1
Date	
Dexamethasone/ mg	
Selinexor / mg	

Study Drug/Dose	Day 8
Date	
Dexamethasone / mg	
Selinexor / mg	

Study Drug/Dose	Day 15
Date	
Dexamethasone / mg	
Selinexor / mg	

Study Drug/Dose	Day 22
Date	
Dexamethasone / mg	

Date: _____
 Subject's Signature _____

Area Below Only To Be Completed by Coordinator

Week	1	2	3	4	Discrepancy (Yes or No)
Date of Pill Count					
Number of Pills Returned					
Study Coordinator Initials					

Appendix III: EORTC QLQ-C30

ENGLISH

**EORTC QLQ-C30 (version 3)**

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials:

--	--	--	--	--

Your birthdate (Day, Month, Year):

--	--	--	--	--	--	--	--	--	--

Today's date (Day, Month, Year):

31									
----	--	--	--	--	--	--	--	--	--

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a <u>long</u> walk?	1	2	3	4
3. Do you have any trouble taking a <u>short</u> walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:

	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your <u>family</u> life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your <u>social</u> activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1 2 3 4 5 6 7

Very poor

Excellent

30. How would you rate your overall quality of life during the past week?

1 2 3 4 5 6 7

Very poor

Excellent

Appendix IV: EORTC QLQ-MY20

ENGLISH

**EORTC QLQ – MY20**

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you had bone aches or pain?	1	2	3	4
32. Have you had pain in your back?	1	2	3	4
33. Have you had pain in your hip?	1	2	3	4
34. Have you had pain in your arm or shoulder?	1	2	3	4
35. Have you had pain in your chest?	1	2	3	4
36. If you had pain did it increase with activity?	1	2	3	4
37. Did you feel drowsy?	1	2	3	4
38. Did you feel thirsty?	1	2	3	4
39. Have you felt ill?	1	2	3	4
40. Have you had a dry mouth?	1	2	3	4
41. Have you lost any hair?	1	2	3	4
42. Answer this question only if you lost any hair: Were you upset by the loss of your hair?	1	2	3	4
43. Did you have tingling hands or feet?	1	2	3	4
44. Did you feel restless or agitated?	1	2	3	4
45. Have you had acid indigestion or heartburn?	1	2	3	4
46. Have you had burning or sore eyes?	1	2	3	4

Please turn to next page

ENGLISH

During the past week:		Not at All	A Little	Quite a Bit	Very Much
47.	Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
48.	Have you been thinking about your illness?	1	2	3	4
49.	Have you been worried about dying?	1	2	3	4
50.	Have you worried about your health in the future?	1	2	3	4