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TITLE: A Phase II Study of once weekly Carfilzomib, Lenalidomide, Dexamethasone, and Isatuximab in Newly Diagnosed, Transplant-Eligible Multiple Myeloma

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Agents
Carfilzomib: Amgen
Isatuximab: Sanofi
Lenalidomide: commercially available
Dexamethasone: commercially available

This is an investigator-initiated study with funding provided by Amgen and Sanofi.

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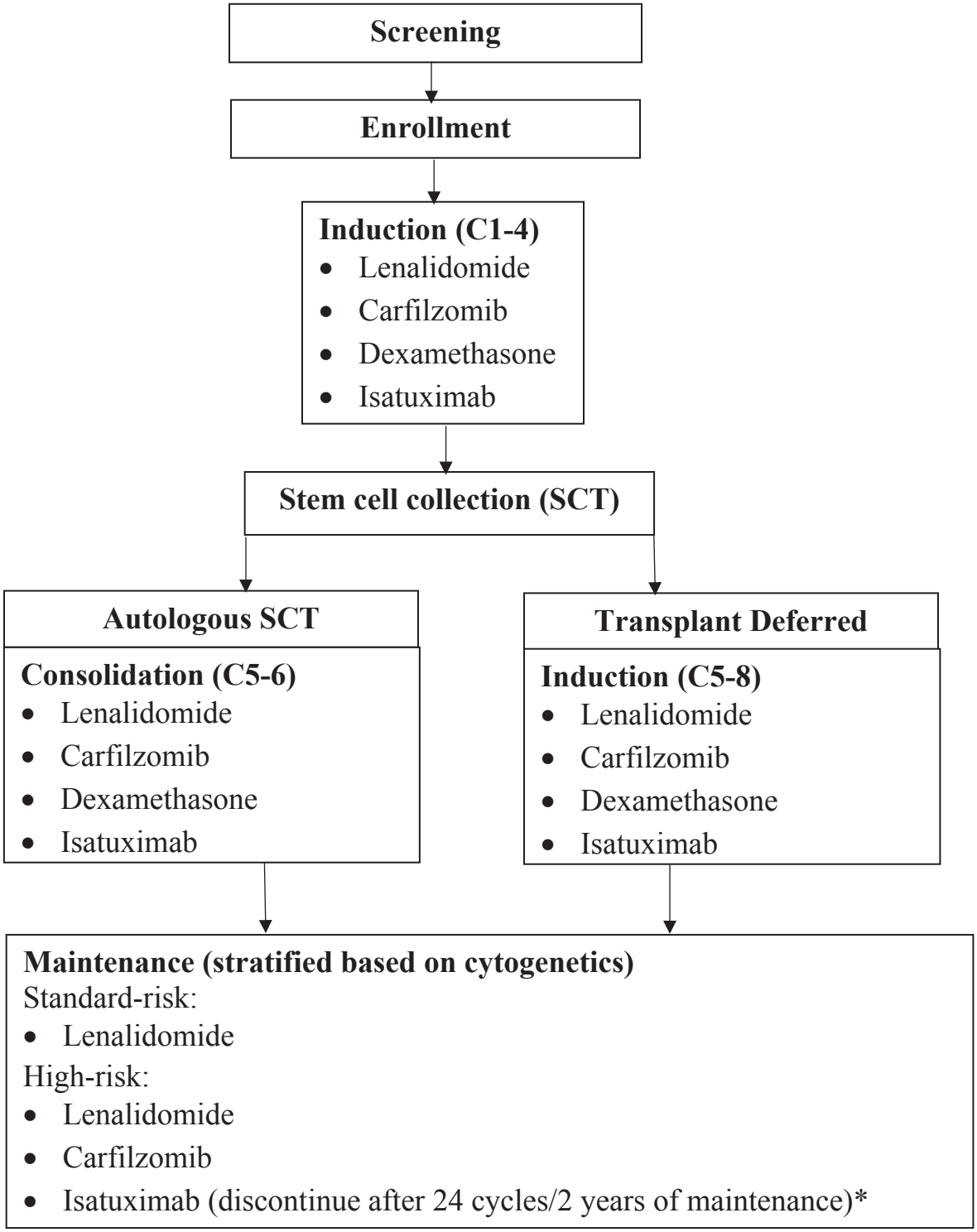
SCHEMA



* Dexamethasone will be given as a preinfusion medication for isatuximab when isatuximab is administered during maintenance

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Abbreviations	
Absolute Neutrophil Count	ANC
Adult Respiratory Distress Syndrome	ARDS
Adverse Events	AE
Adverse Event of Special Interest	AESI
Area Under the Drug Concentration-Time Curve	AUC
Aspartate Aminotransferase	AST
Alanine Aminotransferase	ALT
Beta2-Microglobulin	B2M
Blood Urea Nitrogen	BUN
Bone Marrow	BM
Case Report Form	CRF
Celsius	C
Chronic Obstructive Pulmonary Disease	COPD
Clinical Benefit Rate	CBR
Clinical Trials Management System	CTMS
Cluster of Differentiation	CD
Complete Blood Count	CBC
Complete Response	CR
Computerized Tomography	CT
Confidence Interval	CI
Creatinine Clearance	CrCl
Cyclophosphamide, Bortezomib, and Dexamethasone	CBd
Cytochrome P450	CYP
Dana-Farber/Harvard Cancer Center	DF/HCC
Data Safety Monitoring Committee	DSMB
Data Safety Monitoring Committee	DSMC
Deci-liter	dL
Deletion	del
Dissociation constant	Kd
Dose Escalation	DE
Dose-Limiting Toxicity	DLT
Dual-Energy X-Ray Absorptiometry	DXA
Duration of Response	DOR
Echocardiogram	ECG
Eastern Cooperative Oncology Group	ECOG
Efficacy Evaluable	EE
European Organisation for Research and Treatment of Cancer	EORTC

European Society for Blood and Marrow Transplantation	EBMT
Every	Q
Every Four Weeks	Q4W
Every Two Weeks	Q2W
Every Week	QW
Example Given	eg
Fahrenheit	F
Fluorescent in situ hybridization	FISH
Fibroblast Growth Factor	FGF
Food and Drug Administration	FDA
Forced Expiratory Volume	FEV
Glomerular Filtration Rate	GFR
Good Lab Practice	GLP
Gram	g
Granulocyte Colony Stimulating Factor	GCSF
Half-life	$t_{1/2}$
Highest Nonseverely Toxic Dose	HNSTD
Histamine	H
Human Immunodeficiency Virus	HIV
Immunofixation	IFE
Immunomodulatory Drug	IMiD
Immunoglobulin	Ig
Informed Consent Form	ICF
Infusion Reaction	IR
Infusion-Associated Reaction	IAR
Institutional Review Board	IRB
Intent-to-Treat	ITT
Interferon	IFN
Interleukin	ILBd
International Staging System	ISS
Intramuscular	IM
Intrauterine Device	IUD
Intravenous immunoglobulin	IVIG
Investigational Medical Product	IMP
Investigator's Brochure	IB
Kilogram	kg
KiloDalton	kDa
Lactate Dehydrogenase	LDH
Liter	L

Lenalidomide, Bortezomib, and Dexamethasone	LBd
Lenalidomide and Dexamethasone	Rd
Magnetic Resonance Image	MRI
Maximum Concentration	Cmax
Maximum Tolerated Dose	MTD
Melphalan, Prednisone, Thalidomide	MPT
Meter	m
Milligrams	mg
Milliliter	mL
Millimeter	mm
Millimol	mmol
Minimal Residual Disease	MRD
Minimal Response	MR
Minute	min
Monoclonal Antibody	mAb
Monoclonal Protein	M-protein
Multiple Myeloma	MM
National Cancer Institute Common Terminology Criteria for Adverse Events	NCI CTCAE
Near Complete Response	nCR
Newly Diagnosed Multiple Myeloma	NDMM
Nonsteroidal Anti-inflammatory Drug	NSAID
No-Observed Adverse Effect Level	NOAEL
Number	N
Oral	POEMS
Overall Response Rate	ORR
Partial Response	PR
Polyneuropathy,Organomegaly,Endocrinopathy, Monoclonal Protein, Skin Changes	POEMS
Positron Emission Tomography	PET
Posterior Reversible Encephalopathy Syndrome	PRES
Principal Investigator	PI
Progression Free Survival	PFS
Progressive Disease	PD
QT interval as corrected by Fridericia's formula	QTcF
Quality of Life	QOL
Red Blood Cell	RBC
Relapsed Refractory Multiple Myeloma	RRMM

Stable Disease	SD
Serious Adverse Event	SAE
Serum Protein Electrophoresis	SPEP
Severely Toxic Dose to 10%	STD10
Stem Cell Transplant	SCT
Stringent Complete Response	sCR
Subcutaneous	SC
System Organ Class	SOC
Thrombotic Microangiopathy	TMA
Time to Response	TTR
Translocation	t
Tumor Lysis Syndrome	TLS
Tumor Necrosis Factor	TNF
United States	US
Upper Limit of Normal	ULN
Urine Protein Electrophoresis	UPEP
Vascular Endothelial Growth Factor	VEGF
Very Good Partial Response	VGPR
Volume of Distribution at Steady State	Vss
World Health Organization	WHO

1. OBJECTIVES

1.1 Study Design

A phase II study to evaluate the efficacy of once weekly carfilzomib, lenalidomide, dexamethasone, and isatuximab (KRDI) in patients with newly diagnosed, transplant-eligible multiple myeloma.

1.1.1 Primary Objectives

To estimate the Complete Response (CR + stringent CR) rate to treatment after 4 cycles as assessed by site Investigators using the International Myeloma Working Group (IMWG) Uniform Response criteria after 4 cycles of KRDI.

1.1.2 Secondary Objectives

To describe the following in this study population:
- Safety and tolerability of once-weekly KRDI
- Minimal residual disease (MRD) after 4 cycles, at completion of consolidation (post-transplant) or induction (transplant-deferred) and at 24 months
- Complete response (CR + stringent CR) rate after 6 cycles in patients who undergo transplant, after 8 treatment cycles in transplant-deferred patients, and at 24 months for all patients- Overall response rate (ORR)
- Progression free survival (PFS)
- Overall survival (OS)
- Quality of life (QOL)

Exploratory
- Change in body composition
- PFS by MRD status

2. BACKGROUND

2.1 Multiple Myeloma

Multiple myeloma (MM) is a malignant proliferation of plasma cells. It is the second most common hematologic malignancy, accounting for an estimated 30,770 cases and 12,770 deaths in the United States (US) in 2018.[1] MM is a disease of older adults with the median age at diagnosis of 66 years.[2] Over the last 10 years, the reduced treatment-related morbidity and mortality associated with autologous stem cell transplantation (SCT) and the availability of effective new drugs with acceptable toxicity, such as the immunomodulatory drugs (IMiD) (thalidomide, lenalidomide, and pomalidomide) and the proteasome inhibitors (bortezomib,

carfilzomib, and ixazomib) have greatly modified the traditional treatment paradigms in patients with MM with an improvement in the quality and the duration of life for people with this disease. However, MM remains incurable with standard chemotherapy, despite the availability of multi-agent therapy. Strategies directed at improving and maintaining response for longer periods of time and new treatment options directed at alternative mechanisms are urgently needed for patients with MM.

2.2 Isatuximab

Isatuximab is a naked immunoglobulin (Ig) G1 monoclonal antibody (mAb) that selectively binds to the human cell surface antigen molecule classified as cluster of differentiation (CD) 38. CD38 is expressed in a number of hematological malignancies from B-lymphocyte, T-lymphocyte, and myeloid origin; therefore, isatuximab has the potential to treat a number of hematological malignancies.

Nonclinical studies

In vivo antitumor activity of isatuximab was demonstrated in several subcutaneous (SC) or intravenous (IV) implanted hematological tumor models. As a single agent, antitumor activity was observed in MM. In ex vivo primary patient tumor samples, isatuximab has demonstrated a direct proapoptotic effect in MM samples.

In Good Laboratory Practice (GLP) cross-reactivity studies with normal human tissues, isatuximab was bound specifically to lymphoid tissues (spleen, thymus, lymph node, and tonsil), bone marrow, pituitary gland (endothelial cells), prostate gland (glandular epithelial cells), and infiltrating or resident round cells (macrophages and/or lymphocytes) of the innate immune system including Kupffer cells in the liver. In preliminary non-GLP tissue cross-reactivity studies using a different isatuximab batch and different mAb concentrations, additional staining was also observed in the brain (astrocytes) and lung (bronchial epithelium). Staining of all nonlymphoid tissue elements was interpreted as evidence of cross-reactivity, indicating potential unintended off-target sites.

Isatuximab is specific for human CD38 protein. In the absence of a relevant animal species for toxicity testing, a repeat-dose IV (once weekly for 3 weeks) study was conducted in cynomolgus monkeys (a non-pharmacologically-reactive species) in order to evaluate potential non-targeted and nonspecific general toxicity. In this cynomolgus monkey toxicity study, no compound-related changes were noted in any parameters evaluated, and the no-observed adverse effect level (NOAEL) was 100 mg/kg/week (highest dose tested). In rabbits (a non-pharmacologically reactive species), isatuximab was well tolerated locally after IV (clinical route of administration), intramuscular (IM), intra-arterial, SC, or paravenous injection (routes by which it might be administered by accident or accidental extravasations) at concentrations up to 5 mg/mL. Plasma

compatibility and the hemolytic potential of isatuximab in human whole blood were tested in vitro at concentrations up to 2.5 mg/mL. No hemolytic effect or plasma incompatibility was observed.

Clinical Studies

Study TED10893 (Phase 1); Monotherapy in Relapsed Refractory MM (RRMM) and other hematological malignancies

From June 2010 to August 2016, a total of 89 patients with CD38+ hematological malignancies were treated with isatuximab. Overall, the median time on treatment was 10.1 weeks (range: 2 to 120 weeks) and the median age was 64.0 years (range: 40 to 85 years).

In patients with MM (n = 84), the median time from diagnosis to first isatuximab dosing was 5.84 years (range: 1.2 to 22.8 years). Median number of prior lines of therapies was 5.0 (range: 1 to 13 prior lines), with 94.0% receiving prior lenalidomide, 40.5% receiving prior pomalidomide, 98.8% receiving prior bortezomib, and 42.9% receiving prior carfilzomib. Overall response rate ([ORR] ≥ partial response [PR]) according to Investigator assessment by European Society for Blood and Marrow Transplantation (EBMT) criteria among the 84 MM treated-patients was 20.2% (1 complete response, 16 PRs). Clinical benefit response (≥minimal response [MR]) was 26.2% and best response was stable disease (SD) in 42.9% of the MM treated-patients. The MR or better occurred at all DLs ≥1 mg/kg. In patients treated at doses ≥10 mg/kg in dose escalation and expansion cohorts (n = 63), ORR was 23.8% (15/63), and the clinical benefit rate (CBR) was 30.2% (19/63). In patients treated at 10 mg/kg Q2W in the high-risk cohort (n = 18), ORR was 16.7% (n = 3/18) and CBR was 27.8% (5/18) (see Table 1).

Table 1 - TED10893 (Phase 1): Best overall response according to Investigator assessment (EBMT criteria) – All MM treated patients

	Isatuximab (dose level and schedule)								
	≤1mg/kg Q2W (N=13)	3mg/kg Q2W (N=5)	5mg/kg Q2W (N=3)	10mg/kg Q2W-DE+EC1 (N=25)	10mg/kg Q2W-HR (N=18)	10mg/kg QW (N=6)	20mg/kg Q2W (N=7)	20mg/kg QW (N=7)	All (N=84)
Overall response rate (≥PR)	1 (7.7%)	0	1 (33.3%)	7 (28.0%)	3 (16.7%)	2 (33.3%)	1 (14.3%)	2 (28.6%)	17 (20.2%)
- Complete response (CR)	0	0	0	0	0	1 (16.7%)	0	0	1 (1.2%)
- Partial response (PR)	1 (7.7%)	0	1 (33.3%)	7 (28.0%)	3 (16.7%)	1 (16.7%)	1 (14.3%)	2 (28.6%)	16 (19.0%)
Minimal response (MR)	0	1 (20.0%)	0	0	2 (11.1%)	0	1 (14.3%)	1 (14.3%)	5 (6.0%)
Stable disease (SD)	2 (15.4%)	3 (60.0%)	2 (66.7%)	12 (48.0%)	9 (50.0%)	3 (50.0%)	2 (28.6%)	3 (42.9%)	36 (42.9%)

Progressive disease (PD) 10 (76.9%)	1 (20.0%)	0	5 (20.0%)	4 (22.2%)	1 (16.7%)	2 (28.6%)	0	23 (27.4%)
Not evaluable 0	0	0	1 (4.0%)	0	0	1 (14.3%)	1 (14.3%)	3 (3.6%)
Clinical benefit rate (≥MR) 1 (7.7%)	1 (20.0%)	1 (33.3%)	7 (28.0%)	5 (27.8%)	2 (33.3%)	2 (28.6%)	3 (42.9%)	22 (26.2%)

Study TED10893 (Phase 2 Stage 1); monotherapy in RRMM

From July 2014 to December 2016, a total of 97 patients were treated in Phase 2 Stage 1 of TED10893 study at 4 different doses and/or schedules of administration. The median age of patients was 62 years (range: 38 to 85 years). The median time from diagnosis to first isatuximab dosing was 5.82 years (range: 1.2 to 24.1 years). As per inclusion criteria, patients were heavily pretreated as shown by a median number of prior lines of 5 (range: 2 to 14 lines) with 18 (18.6%) patients having received 8 or more prior lines of treatment. During the study, the median number of isatuximab cycles started was 3. The median duration of exposure was 13 weeks (range: 2 to 77 weeks). The median duration of exposure was the lowest in the 3 mg/kg Q2W (6.0 weeks) dose group and was consistently ≥14 weeks in the ≥10 mg/kg arms. Nine (9.3%) patients were still receiving treatment as of the analysis cutoff date (1 in the 3 mg/kg Q2W dose group, 4 in the 10 mg/kg Q2W dose group, and 2 each in the 10 mg/kg Q2W/Q4W and 20 mg/kg QW/Q2W dose groups).

The ORR was lowest in the 3 mg/kg Q2W dose group. At doses ≥10 mg/kg, ORR ranged from 20% to 29% (see Table 2). No CR was observed and more patients had VGPR in the 10 mg/kg arms (25.0% in Q2W and 12.0% in Q2W/Q4W) than in the 20 mg/kg arm (8.0%). However, the results of observed differences between the 20 mg/kg arm and the 3 other arms should be interpreted with caution because patients were not randomized to the 20 mg/kg QW/Q2W arm and the population could be different. Therefore, given the small sample size in each arm, and despite the efficacy data showing a dose response effect from the 3 mg/kg Q2W (ORR<10%) to the doses ≥10 mg/kg (ORR ≥20%), no conclusion can be drawn based on ORR at doses ≥10 mg/kg.

Table 2 - TED10893 (Phase 2 Stage 1) – overall response rate as per the independent adjudication committee– all treated population

	Isatuximab (dose level and schedule)				
	3mg/kg Q2W	**10mg/kg Q2W**	**10mg/kg Q2W/Q4W**	**20mg/kg QW/Q2W**	**All**
	(N=23)	**(N=24)**	**(N=25)**	**(N=25)**	**(N=97)**
Overall Response Rate (≥PR)	1 (4.3%)	7 (29.2%)	5 (20.0%)	6 (24.0%)	19 (19.6%)
- Very Good Partial Response (VGPR)	0	6 (25.0%)	3 (12.0%)	2 (8.0%)	11 (11.3%)
- Partial response (PR)	1 (4.3%)	1 (4.2%)	2 (8.0%)	4 (16.0%)	8 (8.2%)
95% CI[a]	(0.1% to 21.9%)	(12.6% to 51.1%)	(6.8% to 40.7%)	(9.4% to 45.1%)	(12.2% to 28.9%)
Minimal response (MR)	0	3 (12.5%)	3 (12.0%)	3 (12.0%)	9 (9.3%)
Stable disease (SD)	8 (34.8%)	5 (20.8%)	6 (24.0%)	12 (48.0%)	31 (32.0%)
Progressive disease (PD)	5 (21.7%)	3 (12.5%)	3 (12.0%)	3 (12.0%)	14 (14.4%)
Unconfirmed PD	4 (17.4%)	3 (12.5%)	2 (8.0%)	0	9 (9.3%)
Not evaluable	5 (21.7%)	3 (12.5%)	6 (24.0%)	1 (4.0%)	15 (15.5%)
Clinical benefit rate (≥MR)	1 (4.3%)	10 (41.7%)	8 (32.0%)	9 (36.0%)	28 (28.9%)
95% CI[a]	(0.1% to 21.9%)	(22.1% to 63.4%)	(14.9% to 53.5%)	(18.0% to 57.5%)	(20.1% to 39.0%)

Confidence Interval (CI) a estimated by Clopper-Pearson Exact method;

Study TED14154 (monotherapy in RRMM; Part A)

As of the cutoff date of 05 January 2018, Part A was completed. A total of 26 patients with RRMM were treated in Part A, 12 patients at 10 mg/kg QW/Q2W and 14 patients at 20 mg/kg QW/Q2W. The median age was 67.0 years (range: 53 to 81 years). The median time from initial MM diagnosis to first study treatment dose was 6 years (range: 1.6 to 13.5 years). The median number of lines was 5.0 (range: 2 to 13 lines). All patients received prior combined lenalidomide and bortezomib, 61.5% received prior pomalidomide, 57.7% received prior carfilzomib, and 38.5% received prior thalidomide. Overall, the median number of cycles was 4.5 (range: 1 to 22 cycles). The median number of cycles was 3.0 (range: 1 to 22 cycles) at 10 mg/kg QW/Q2W and 5.0 (range: 2 to 18 weeks) at 20 mg/kg QW/Q2W.

Overall, the ORR was 23.1%, including 3 (11.5%) patients with VGPR and 3 (11.5%) patients with PR (Table 3). The ORR was 25.0% and 21.4% at 10 and 20 mg/kg QW/Q2W, respectively. The CBR was 38.5% overall (33.3% and 42.9% at 10 and 20 mg/kg QW/Q2W, respectively).

Table 3 – TED14154 Part A – overall response rate – all treated population

	Isatuximab (dose level and schedule)		
	10 mg/kg QW/Q2W (N=12)	**20 mg/kg QW/Q2W (N=14)**	**All (N=26)**
Overall response rate (≥PR)	3 (25.0%)	3 (21.4%)	6 (23.1%)
- Very good partial response (VGPR)	2 (16.7%)	1 (7.1%)	3 (11.5%)
- Partial response (PR)	1 (8.3%)	2 (14.3%)	3 (11.5%)
95% CI[a]	(5.5% to 57.2%)	(4.7% to 50.8%)	(9.0% to 43.6%)
Minimal response (MR)	1 (8.3%)	3 (21.4%)	4 (15.4%)
Stable disease (SD)	6 (50.0%)	7 (50.0%)	13 (50.0%)
Progressive disease (PD)	2 (16.7%)	1 (7.1%)	3 (11.5%)
Clinical benefit rate (≥MR)	4 (33.3%)	6 (42.9%)	10 (38.5%)
95% CI[a]	(9.9% to 65.1%)	(17.7% to 71.1%)	(20.2% to 59.4%)

a estimated by Clopper-Pearson Exact method

Study TCD11863 (Len/Dex in RRMM)

This was a Phase 1b, open-label dose escalation study to determine the maximum tolerated dose of 2 schedules (Q2W and QW/Q2W) of administration of isatuximab in combination with lenalidomide and dexamethasone in patients with relapsed or refractory MM. A total of 57 patients with a median age of 61 years (range: 42 to 76 years) were enrolled. The median number of prior lines was 5 (range: 1 to 12 lines) with 15 (26.3%) patients having received 8 or more prior lines of treatment. Fifty-five (96.5%) patients were previously exposed to immunomodulatory drugs, including 54 (94.7%) patients with prior lenalidomide treatment. The efficacy evaluable population consists of 52 patients excluding 4 patients in the 20 mg/kg group who discontinued due to AE before completing treatment in Cycle 1 and 1 patient in the 3 mg/kg group who discontinued due to IR at the first infusion.

The first part of the trial evaluated 3 doses of isatuximab 3, 5 and 10 mg/kg using the Q2W schedule of administration; among the patients treated at 10 mg/kg (n = 24), the ORR was 62.5% with PR rate of 20.8%, very good PR (VGPR) rate of 33.3% and stringent complete response (sCR) rate of 8.3%. Among the patients treated in the second part of the trial (QW/Q2W schedule), the ORR was 50% for both 10 mg/kg (n = 12) and 20 mg/kg (n = 10) QW/Q2W. At 10 mg/kg QW/Q2W, best overall response was PR for 2 patients and VGPR for 4 patients, whereas at the 20 mg/kg QW/Q2W dose, all responses were VGPR (Table 4).

Table 4 - TCD11863 – overall response rate – evaluable population

	Isatuximab (dose level and schedule) + lenalidomide/dexamethasone					
	3 mg/kg Q2W (N=3)	**5 mg/kg Q2W (N=3)**	**10 mg/kg Q2W (N=24)**	**10 mg/kg QW/Q2W (N=12)**	**20 mg/kg QW/Q2W (N=10)**	**All (N=52)**
Overall response rate (≥PR)	1 (33.3%)	2 (66.7%)	15 (62.5%)	6 (50.0%)	5 (50.0%)	29 (55.8%)
- Stringent complete response (SCR)	0	0	2 (8.3%)	0	0	2 (3.8%)
- Very good partial response (VGPR)	0	0	8 (33.3%)	4 (33.3%)	5 (50.0%)	17 (32.7%)
- Partial response (PR)	1 (33.3%)	2 (66.7%)	5 (20.8%)	2 (16.7%)	0	10 (19.2%)
Minimal response (MR)	1 (33.3%)	0	2 (8.3%)	4 (33.3%)	1 (10.0%)	8 (15.4%)
Stable disease (SD)	1 (33.3%)	0	4 (16.7%)	2 (16.7%)	4 (40.0%)	11 (21.2%)
Progressive disease (PD)	0	1 (33.3%)	3 (12.5%)	0	0	4 (7.7%)
Clinical benefit rate (≥MR)	2 (66.7%)	2 (66.7%)	17 (70.8%)	10 (83.3%)	6 (60.0%)	37 (71.2%)

For this study, isatuximab will be dosed once weekly for 8 doses, every other week for 8 doses, and then monthly thereafter. This dosing is based on scheduling conventions for monoclonal antibodies, daratumumab (e.g. NCT02874742) and elotuzumab (e.g. NCT03030261). In NCT02874742, a phase 2 randomized study of daratumumab-RVD versus RVD, daratumumab is dosed once weekly for 8 doses, every other week for 8 doses, and then monthly thereafter. The goal is to provide continued, effective therapy but minimize patient burden. Ongoing clinical trials of isatuximab have incorporated this dosing schedule (e.g. NCT04270409).

2.3 Carfilzomib

Carfilzomib is a tetrapeptide epoxyketone proteasome inhibitor that irreversibly binds to N-terminal threonine-containing active sites of the 20S proteasome. Carfilzomib had antiproliferative and proapoptotic activities in vitro in solid and hematologic tumor cells. In animals, carfilzomib inhibited proteasome activity in blood and tissue and delayed tumor growth in models of multiple myeloma, hematologic, and solid tumors.

Non-clinical Studies

Nonclinical Pharmacology
Proteasome Inhibition After Intravenous Administration of Carfilzomib

The pharmacodynamics of carfilzomib has been determined by measurement of CT-L proteasome activity in tissue extracts after IV bolus administration in rats. Dose-dependent proteasome inhibition was observed 1 hour after dose administration in all tissues examined, with the exception of the brain [3]. Proteasome activity recovered in nucleated tissues with a t1/2 of approximately 24 hours. With a 12-mg/m2 (2-mg/kg) dose (the severely toxic dose to 10% of animals [STD10] once daily for 5 days), proteasome inhibition exceeded 80% in multiple tissues (blood, adrenal, heart, lung, and bone marrow). Equivalent levels of proteasome inhibition were seen in blood and tissues when carfilzomib was delivered as a bolus administration or as a 30-minute infusion indicating that the biodistribution and pharmacodynamics of carfilzomib are a function of the total dose administered and not the maximum observed drug concentration during a dosing interval (Cmax).

Efficacy of Carfilzomib in Mouse Tumor Studies

The antitumor efficacy of carfilzomib has been evaluated in immunocompromised mice implanted with a variety of human tumor cell lines[3, 4], including HT-29, a human colorectal adenocarcinoma cell line, and MM1.S, a multiple myeloma cell line. In both models, a statistically significant reduction in tumor size as compared with the control was seen when carfilzomib was administered on a weekly schedule of days 1 and 2.

Nonclinical Pharmacokinetics and Drug Metabolism

The pharmacokinetics of carfilzomib was examined after IV bolus administration to Sprague Dawley rats and cynomolgus monkeys. A dose-dependent increase in the area under the drug concentration-time curve (AUC) and a biphasic distribution profile after administration was observed. The t1/2 was calculated to be 5 to 17 minutes in rats and 7 minutes in monkeys. The plasma clearance of carfilzomib is 195 to 319 mL/min/kg in rats and 187 to 286 mL/min/kg in monkeys, which is higher than the liver blood flow for both species, indicating that clearance occurred largely extrahepatically in these species.

When carfilzomib was given as a 30-minute IV infusion at 8 mg/kg to rats, the concentration at steady state was approximately 28-fold lower than the Cmax with IV bolus at the equivalent doses. Other pharmacokinetic parameters (clearance, AUC, and $t_{1/2}$) were comparable between bolus and infusion dosing. Similar pharmacodynamics (proteasome inhibition in blood and tissues) between bolus and infusion dosing supported accessibility of carfilzomib to target tissues using a 30-minute infusion.

Metabolism

Carfilzomib is rapidly and extensively metabolized after IV administration to rats, monkeys, and humans. The predominant metabolites are peptide fragments and the diol of carfilzomib, with no unique metabolites identified in humans, suggesting that peptidase cleavage and epoxide hydrolysis are the principal pathways of metabolism in all these species. The metabolites do not

inhibit proteasome activity. Cytochrome P450 (CYP)-mediated pathways are not significant in the overall metabolism of carfilzomib.

Carfilzomib is also rapidly metabolized by peptidases and epoxide hydrolases in vitro upon incubation with rat blood and tissue homogenates derived from the lung, kidney, and liver, further corroborating the extrahepatic mechanisms of metabolism in vivo.

Distribution
The volume of distribution at steady state (Vss) was 0.3 to 2.0 L/kg and 0.3 to 1.1 L/kg for rats and monkeys, respectively. Because of metabolism in a variety of tissues and the irreversible covalent binding of carfilzomib to the 20S proteasome, the Vss values may underestimate the extent of tissue distribution of carfilzomib. Potent proteasome inhibitory effects in a variety of tissues after IV administration to rats at different dose levels, and detection of radioactivity in a variety of tissues with an IV administration of tritium-labeled carfilzomib ([3H-Phe]-carfilzomib) to rats at 2 mg/kg (12 mg/m2), indicated rapid and wide distribution of carfilzomib to tissues, except the brain. An in vitro protein-binding study using equilibrium dialysis demonstrated that approximately 97% of carfilzomib is bound to human plasma proteins, which is similar to rats and monkeys.

Elimination
Excretion of [3H-Phe]-carfilzomib was determined by quantitative whole-body autoradiography in rats receiving a single IV bolus administration of 2 mg/kg (12 mg/m^2). Urine and feces accounted for 14.1% and 18.0% of the dosed radioactivity, respectively, at 168 hours after the dose. Approximately 44% of the administered radioactivity remained in tissues, indicating slow elimination of drug-derived radioactivity, likely because of incorporation of tritium-labeled phenylalanine (3H-phenylalanine) into cellular proteins. Excretion was also determined in bile duct–cannulated rats after a single IV bolus administration of 2 mg/kg unlabeled carfilzomib. Carfilzomib was excreted mainly in the form of metabolites, with less than 1% of the dose excreted intact. About 57% of the dose was recovered within 24 hours of dosing in both bile and urine samples as major metabolites. The limited recovery was likely because of minor metabolites, target binding in cells unable to synthesize new proteasomes (eg, red blood cells (RBCs)), and peptidic metabolites that cannot be differentiated from endogenous components.

Toxicology
Unless otherwise noted, toxicology studies described below were GLP-compliant.

Acute Toxicity Studies in Monkeys
In a 2-dose, 7-day IV study in carfilzomib-naïve monkeys, carfilzomib was administered on 2 consecutive days at 2 mg/kg (24 mg/m^2), a dose that exceeds the established multidose highest nonseverely toxic dose (HNSTD) of 1 mg/kg (12 mg/m2) and 6 mg/m2 (0.5 mg/kg) in 28-day (TR-0017-171) and 9-month (TR-0073-171) repeated-dose studies, respectively. Carfilzomib

induced a prerenal azotemia 24 hours after the first dose, as manifested by elevated blood urea nitrogen (BUN) and creatinine, concomitant with an increase in urine specific gravity. The second dose of carfilzomib did not exacerbate these effects, and the renal function returned to baseline within 72 hours. Other findings included signs of an acute phase response (increased fibrinogen and C-reactive protein) and cardiotoxicity (increased troponin-I in 4 of 6 animals with myocardial degeneration/necrosis in 1 animal), and a drop in platelets of approximately 80% that resolved within 5 days of dosing and was not associated with a change in megakaryocyte number or morphology in bone marrow smears.

Clinical Studies

Carfilzomib entered clinical studies in September 2005. Study PX-171-006 was the first to explore the option of combination therapy using carfilzomib and lenalidomide, the IMiD most widely employed for the treatment of MM [5]. This investigation was the model for another Phase 2 study of the carfilzomib, lenalidomide, dexamethasone (KRd) combination conducted by the Multiple Myeloma Research Consortium, and it used a maximum planned dose of 36 mg/m2 twice weekly in patients with NDMM [6]. The Phase 3 ASPIRE study compared the efficacy of KRd versus lenalidomide and dexamethasone alone in a much larger trial that enrolled 792 RRMM subjects. ASPIRE showed an improved overall response rate and progression free survival PFS with KRd therapy and provides a strong incentive to optimize the KRd regimen[7].

The Phase 1/Phase 2 CHAMPION 1 trial of subjects with relapsed or progressing MM who had received 1 to 3 prior regimens evaluated the safety and efficacy of carfilzomib administered once weekly at doses higher than the 56 mg/m^2 maximum tolerated dose (MTD) previously established for the twice-weekly administration routine [8]. All subjects received carfilzomib (20 mg/m^2) on Cycle 1 Day 1 but received the cohort-assigned test dose on Cycle 1 Days 8 and 15. Testing started at 45 mg/m2 in the first cohort and was escalated to 56, 70, and 88 mg/m^2 in successive cohorts until the MTD was determined. Subjects received dexamethasone 40 mg (IV or orally) on Days 1, 8, 15, and 22 of Cycles 1 through 8 and on Days 1, 8, and 15 from Cycle 9 onward.

The ARROW study provided further support for the safety and efficacy of once weekly carfilzomib dosing.[9] 478 patients were randomly assigned and included in the efficacy analyses (240 to receive once weekly carfilzomib; 238 to receive twice weekly carfilzomib). Median progression-free survival was higher in the once weekly group than the twice weekly group (11·2 months [95% CI 8·6–13·0] *vs* 7·6 months [5·8–9·2]; hazard ratio [HR] 0·69, 95% CI 0·54–0·83; p=0·0029). The incidence of grade 3 or worse adverse events was higher in the once weekly group than the twice weekly group (68% [n=161] *vs* 62% [n=145]); the most common events were anemia, pneumonia, and thrombocytopenia (42 [18%] *vs* 42 [18%], 24 [10%] *vs* 16 [7%], and 17 [7%] *vs* 16 [7%], respectively for once weekly carfilzomib *vs* twice weekly carfilzomib). A lower proportion of patients had grade 3 or worse cardiac failure in the

once weekly group (7 [3%]) than in the twice weekly group (10 [4%]). Treatment-related deaths occurred in five (2%) of 238 patients in the once weekly group (sepsis [n=1], death [n=1], acute lung injury [n=1], acute respiratory distress syndrome [n=1], and tumor lysis syndrome [n=1]) and in two (1%) of 235 patients in the twice weekly group (plasma cell myeloma [n=1] and congestive heart failure [n=1]). There were 58 deaths in the once weekly group and 68 deaths in the twice weekly group at the time of data cutoff. The once weekly dosing demonstrated superior efficacy with comparable toxicity.

The combination of carfilzomib (twice-weekly), lenalidomide, and dexamethasone is a highly efficacious regimen in RRMM and NDMM subjects [6, 7]. Of specific note, 23 of 26 subjects who reached nCR/CR achieved negative minimal residual disease (MRD[-]) status in one study [6]. More recently, a phase 1b study evaluated weekly carfilzomib, lenalidomide, and dexamethasone in RRMM.[10] Patients received carfilzomib once weekly (30-minute IV infusion) on days 1, 8, and 15. In the dose-evaluation component of the study, patients received carfilzomib 20 mg/m^2 on cycle one, day one, and then 56 or 70 mg/m^2 starting on cycle one, day eight. In the dose-expansion component of the study, patients received KRd on the same schedule. All patients also received oral lenalidomide 25 mg once daily on days 1-21 and dexamethasone 40 mg (oral or IV) on days 1, 8, and 15. Dexamethasone was also given on day 22 for cycles 1-8. The ORRs were 90.0% in the 56-mg/m^2 group and 89.1% in the 70-mg/m^2 group. A VGPR or better was observed in 50.0% and 73.9% of patients in the two groups, respectively. A complete response (CR) or better in 20.0% and 30.4% of patients in the two groups, and a stringent CR in 10.0% and 17.4% of patients in the 2 groups was reported. Among all patients (n = 56), the ORR was 89.3%, the ≥VGPR rate was 69.6%, and the ≥CR rate was 28.6%. Median PFS was not reached in either the 56-mg/m^2 group (95% CI, 14.8 months-not evaluable [NE]) or the 70-mg/m^2 group (95% CI, 21.1 months-NE). As of the data cutoff date, 1 patient (10.0%) in the 56-mg/m^2 group and 7 patients (15.2%) in the 70-mg/m^2 group experienced disease progression. The incidence of grade ≥3 AEs observed with once-weekly KRd (56 mg/m^2, 70.0%; 70 mg/m^2, 69.6%) were lower than previously reported for the twice-weekly KRd regimen in the ASPIRE study (83.7%).[7] Overall, the safety profile observed with once-weekly KRd was consistent with the safety profile for twice-weekly KRd in the ASPIRE study. There were no patients who experienced cardiac arrest, cardiac disorder, or cardiac failure in the 56-mg/m^2 group; in the 70-mg/m^2 group, one patient had grade ≥3 cardiac failure, and two other patients had fatal cardiac events (cardiac arrest and cardiac disorder). Based on the results of this study, the 56-mg/m^2 dose was chosen to move forward with and is being evaluated further in the randomized phase 3 study of weekly versus twice weekly KRd (NCT03859427).

For this study, every other week carfilzomib dosing was chosen for maintenance based on the study design of the HOVON trial and recent data presented for every other week carfilzomib maintenance. In the HOVON study, patients received induction with either vincristine,

doxorubicin, and dexamethasone (VAD) or bortezomib, doxorubicin, and dexamethasone (PAD) followed by high-dose melphalan and autologous stem-cell transplantation. Maintenance consisted of thalidomide 50 mg (VAD) once per day or bortezomib 1.3 mg/m^2 (PAD) once every 2 weeks for 2 years. In high-risk patients presenting with increased creatinine more than 2 mg/dL, bortezomib significantly improved PFS from a median of 13 months to 30 months (HR, 0.45; 95% CI, 0.26 to 0.78; P = .004) and OS from a median of 21 months to 54 months (HR, 0.33; 95% CI, 0.16 to 0.65; P < .001). Bortezomib-based induction and maintenance showed an improved outcome for patients with del(17p) (median PFS 26 vs 12 months; 3-year OS 69% vs 17%)). At long-term follow-up, this advantage was still present. Based on this result, every other week has become the clinical convention for maintenance dosing of bortezomib. Further support of every other week maintenance for carfilzomib was derived from the Muk*five* trial. The MUK*five* phase 2 trial studied the safety and activity of carfilzomib, cyclophosphamide and dexamethasone (KCd) for patients at first relapse or refractory to one prior line, and compared activity and safety of maintenance K vs observation after fixed duration KCd. Participants with ≥SD after KCd were randomised (R2) 1:1 to receive maintenance K (36mg/m^2 days 1, 2, 15, 16 for 6m, then days 1, 2 for 12m) or no further treatment. Median PFS from randomization 2 (R2) for maintenance for K was 11.9 m vs 5.6 m obs (HR 0.59, p=0.009). At time of R2, 8/69 (11.6%) and 10/72 (13.9%) of patients were MRD- in the K and obs arms respectively. MRD- rate increased after 6m of K to 11/45 (24.4%), while in the obs group, only 1/30 (3.3%) remained MRD-. At 12m, 12.5% in the K arm were MRD- compared to only 4.5% in obs group. Of 8 patients who were MRD- at start of K, 5 remained MRD- at 6m (3 inadequate sample) and 2 at 12m, of 40 MRD+ patients, 4 became MRD- at 6m, 1 remaining so at 12m. In contrast, only 1 patient who was MRD- at start of observation remained so at 6m, remaining negative at 12m. Forty-four percent of patients completed 6 cycles of K, 18% completed 18 cycles. 82.1% of patients had a dose modification, but 88.7% of all cycles were received on time. Reasons for stopping K were completed treatment (18%), disease progression (65.6%), toxicity (4.9%), withdrew consent (6.6%). The results of this trial support both the use of carfilzomib as a potent maintenance drug band the safety and tolerability of an every other week dosing schedule as a maintenance strategy.

Carfilzomib in combination with isatuximab has also been explored in the RR setting with a favorable safety profile.[11] The median number of cycles given was 6. No DLT's or severe adverse drug reactions have been observed. No dose reduction for isatuximab or carfilzomib were needed. The most frequent occurring non-hematologic adverse events (occurring in ≥ 15%) at all dose levels were dyspnea (45%), fatigue (45%), nausea (45%), pain (back, chest wall and pelvis; 36%), peripheral neuropathy (36%), HTN (27%), cough (27%), anorexia (27%), gastroesophageal reflux disease (18%), constipation (18%), diarrhea (18%), nasal congestion (18%) and hypokalemia (18%); <5% of these adverse events were grade 3/4. Hematologic toxicity was mild; 9% grade 3/4 anemia, 9% grade 3/4 neutropenia, 64% grade 3/4 lymphopenia. The most frequent serious adverse event was grade 3 pneumonia (18%). Six patients (54%) had infusion reactions (grade 1 [n=4] or grade 2 [n=2]) but all completed therapy.

Building off these data, a favorable safety profile and promising preliminary efficacy for once-weekly carfilzomib in RRMM subjects was observed in the CHAMPION 1 study[8] and the ARROW [9] studies and more recently the phase 1b study of once weekly carfilzomib in combination with lenalidomide and dexamethasone, this study will explore the safety and tolerability of once-weekly carfilzomib administered with lenalidomide and dexamethasone with the addition of isatuximab in NDMM.

2.4 Lenalidomide

Lenalidomide is a second generation IMiD, with a chemical structure similar to thalidomide, and is widely used at all stages of illness. The specific mechanism of action of IMiDs has only recently been determined. Immunomodulatory drugs as a class bind to cereblon, a component of E3 ubiquitin ligase complexes. This then promotes the degradation of transcription factors critical to MM proliferation: IKZF1/3, MYC, and IRF4 [12-14]. Compared to thalidomide, lenalidomide is associated with significantly less peripheral neuropathy, sedation, and constipation but is associated with more myelosuppression. Two phase III trials, MM-009 [15] and MM-010 [16], showed that the combination of lenalidomide and dexamethasone was superior to dexamethasone alone and established the role for lenalidomide in treating relapsed disease. These trials shared a similar design: lenalidomide was given as 25 mg daily on days 1-21 on a 28-day cycle with dexamethasone 40 mg on days 1-4, 9-12, and 17-20 for the first four cycles and then on days 1-4. About two-thirds of patients had two or more prior lines of therapy. Pooling these trials together, the combination had a higher overall response rate (i.e. partial response or better; ORR), 60.6 vs. 21.9% [17]. The median time to progression and overall survival were also higher, 13.4 vs. 4.6 months and at least 38 months vs. 31.6 months, respectively. The benefit in survival was seen even when 47.6% of patients randomized to the dexamethasone alone arm crossed over after disease progression or study unblinding. Given these findings, lenalidomide was approved by the FDA for treating relapsed disease in June 2006.

A large, randomized Phase 3 study (FIRST Study) compared lenalidomide and dexamethasone (Rd) given until disease progression (Arm A) or for eighteen 28-day cycles (Arm B) with melphalan, prednisone, thalidomide (MPT) (Arm C) in subjects newly diagnosed with MM[18]. Continuous treatment with Rd (Arm A) significantly improved the primary endpoint of PFS compared with MPT (Arm C). Secondary endpoints (ORR, defined as PR or better, duration of response, and PFS2) consistently showed improvement in favor of Arm A over Arm C. The safety profile of Rd was manageable, with reduced hematologic second primary malignancies compared with MPT.

Motivated by *in vitro* data showing synergistic activity between bortezomib and lenalidomide,[19] a major step forward has been combining lenalidomide, bortezomib, and

dexamethasone (RVD).[20, 21] Among patients treated at the maximum tolerated dose of lenalidomide 25 mg days 1-14, bortezomib 1.3 mg/m^2 IV days 1, 4, 8, 11, dexamethasone 20 mg day of and day after bortezomib on a 21-day cycle, the ORR rate was 100% with rates of VGPR or better seen in 74% patients. The Southwest Oncology Group (SWOG) study S0777 validated this triplet regimen, showing superior PFS, OS, and ORR with the triplet combination of RVD versus the doublet combination of Rd alone in patients with NDMM without intention for immediate autologous stem cell transplant (SCT).[22]

Lenalidomide (REVLIMID®) in combination with dexamethasone was approved by both U.S. Food and Drug Administration (FDA) and the European Commission for the treatment of adult patients with previously untreated multiple myeloma who are not eligible for transplant, on 18 February 2015 and 20 February 2015, respectively.

Complete and updated adverse events AEs are available in IB.

2.5 Rationale

Clinical data support the combination of a proteasome inhibitor, an IMiD, and a glucocorticosteroid for the treatments of NDMM.[18] The combination of bortezomib, lenalidomide, and low-dose dexamethasone is very active and well-tolerated in the NDMM population. [20] Carfilzomib, another proteasome inhibitor was recently approved by the FDA in combination with dexamethasone or with lenalidomide plus dexamethasone for patients with relapsed or refractory disease who have received one to three lines of therapy. Given that carfilzomib has improved binding kinetics and pharmacologic profile compared with bortezomib, it is expected that these differences will translate into similar, if not improved, efficacy and safety profiles in the upfront setting. The data available with bortezomib forms the foundation for the proteasome inhibitor in this upfront combination in this study. The combination of carfilzomib (twice-weekly), lenalidomide, and dexamethasone is a highly efficacious regimen [6, 23]. Of specific note, 23 of 26 subjects who reached nCR/CR achieved negative minimal residual disease (MRD[-]) status in one study [6], while in another trial 27 of 27 subjects who reached nCR/CR achieved MRD[-] status [23], further emphasizing the efficacy of this combination. A favorable safety profile and promising preliminary efficacy for once-weekly carfilzomib has been observed in the phase 1b study of once weekly carfilzomib in combination with lenalidomide and dexamethasone.[10]

For maintenance, patients with standard-risk MM will be assigned to lenalidomide maintenance until disease progression, dose-limiting toxicity, patient withdrawal, or death. The rationale for continuous maintenance is based on the results of the FIRST trial that demonstrated improved PFS for patient receiving continuous lenalidomide and dexamethasone maintenance versus a defined 18-cycle course.[18] Patients with high-risk cytogenetic abnormalities (HR-CA) will receive ongoing maintenance with lenalidomide, carfilzomib, and isatuximab. The rationale for

multi-agent maintenance is based on the International Myeloma Working Group consensus statement of the treatment of multiple myeloma with high-risk (HR) cytogenetics that recommends the combination of a proteasome inhibitor with lenalidomide or pomalidomide and dexamethasone[24] and further supported by the prospective evaluation of consolidation and maintenance therapy with RVD in HRMM.[25] The recommendation from the IMWG is derived from several randomized trials have evaluated bortezomib for induction, consolidation, or maintenance treatment in cytogenetic subgroups. In IFM-2005-01, bortezomib/dexamethasone showed a superior response and OS compared with vincristine/doxorubicin/dexamethasone. This combination resulted in a better EFS and OS for patients with t(4;14), but did not improve outcome in del(17p) (4-year OS 50% vs 79%).[26] In HOVON65/GMMG-HD4, bortezomib-based induction and maintenance showed an improved outcome for patients with del(17p) (median PFS 26 vs 12 months; 3-year OS 69% vs 17%)). At long-term follow-up, this advantage was still present. However, OS remains inferior to patients without del(17p) (3-year OS 85%). In patients with t(4;14), PFS was not better with bortezomib (25 vs 22 months), whereas OS was improved (3-year OS 69% vs 44%) compared with 85% in patients without t(4;14).[27] In the GEM 2005 trial, bortezomib/thalidomide/dexamethasone (VTD) followed by ASCT and maintenance did not improve OS in HR CA (3-year OS 60% vs 88%).[28] The GIMEMA group compared VTD with thalidomide/dexamethasone (TD) for induction and consolidation with double ASCT. In the subgroup of 25% with t(4;14), OS was 69% vs 37% in favor of VTD compared with 74% vs 63% without t(4;14) and/or del(17p).[29] A meta-analysis of 4 randomized trials showed that the odds of post-transplantation complete response (CR) + near CR in bortezomib-treated patients were similar for HR (del(17p) + t(4;14)) and standard-risk (SR) cytogenetics (2.44 vs 1.67, n.s.).[30] These trials (1874 patients) showed that bortezomib plus ASCT was superior (PFS 41 vs 33 months) ($P < .0001$). In patients with HR FISH, this was 32 vs 22 months ($P < .0001$). PFS benefit was observed in patients with t(4;14) but lacking del(17p) (36 vs 24 months, $P = .001$) and in del(17p) lacking t(4;14) (27 vs 19 months, $P = .014$), but not in patients carrying both CA.[31] In TT3, OS was significantly shorter in patients with a HR profile (2-year OS 56% vs 88%) compared with SR GEP profile, with the exception of low TP53 expression.[32] Addition of bortezomib improved OS compared with TT2 in LR MM.[32, 33]

Data for lenalidomide in first-line therapy for HR-CA patients is limited. In HR-CA, PFS with lenalidomide was inferior compared with SR patients (18 vs 26 months).[34] In the GIMEMA trial comparing high-dose melphalan with MPR, there was a trend for better PFS with lenalidomide maintenance in SR compared with HR-CA (HR 0.38 [0.24-0.62] vs 0.73 [0.37-1.42]). However, there was no effect on OS.[35] In the IFM 2005-02 trial, lenalidomide maintenance did not overcome the poor prognosis of t(4;14) (27 vs 24 months) and only partly of del(17p) (29 vs 14 months vs 42 months in all patients).[36] Convincing data for continuous lenalidomide in CA groups are lacking.[37, 38] Subgroup analysis of the FIRST trial in NDMM did not demonstrate a benefit of continuous lenalidomide in HR CA.[18] In relapse MM, carfilzomib combined with lenalidomide and dexamethasone (K-RD) was effective across HR

and SR patients (23 vs 29 months, *P* = NS), whereas RD showed less activity (13 vs 19 months, *P* = .004).[7] Data of IFM did not show a benefit of RD in relapse/refractory multiple myeloma (RRMM) with del(13q) or t(4;14).[39] In the Eloquent 2 trial for RRMM, elotuzumab with RD (E-RD) improved outcome over RD in del(17p).[40] Recent data of the effect of pomalidomide with dexamethasone in patients with RRMM show that this combination does not abrogate overall adverse outcome in HR-CA, whereas OS may improve in del(17p).[41] In phase 2 trials, a response benefit of pomalidomide with dexamethasone was shown in patients with del(17p).[42]

Bortezomib combined with RD (VRD) in a phase 1/2 trial in 66 patients with NDMM showed 18-month PFS of 100% in 13 patients with del(17p) and/or t(4;14).[20] The EVOLUTION trial examined several schedules including VRD in NDMM. One-year PFS was similar in HR-CA (17% of all patients) and SR patients.[21] VRD in transplant-eligible patients with NDMM had similar 3-year PFS (86%) in patients with >60% del(17p) or t(4;14) or del(13q) compared with all patients.[43] In the phase 2 evaluation of consolidation and maintenance with RVD in HRMM, best responses with the current triplet maintenance strategy following melphalan high-dose therapy were stringent complete response among 51%, ⩾VGPR among 96%, with all patients achieving ⩾ PR. The median PFS for all patients was 32 months with a 3-year OS of 93%. A median PFS of 20 months was observed among patients achieving ⩾PR. The survival among all high-risk patients vs patients with del 17p was not different (median PFS of 32 months vs 28 months; *P*=0.86; 3-year OS of 93% vs 94%, *P*=0.51, respectively. No patient developed grade 3 or 4 neuropathy, and no patient discontinued maintenance therapy owing to adverse events.[25]

Carfilzomib monotherapy did not improve PFS/OS in t(4;14) or del(17p) in RRMM.[44] Carfilzomib combined with pomalidomide/dexamethasone had equivalent PFS and OS in HR vs SR RRMM.[45] In the Aspire trial, in RRMM, KRD was superior to RD for PFS across cytogenetic risk groups, suggesting that this combination (partly) abrogates the negative impact of t(4;14) and del(17p).[7] Similarly, in Tourmaline-MM1, ixazomib combined with RD showed identical PFS in patients with HR-CA or no CA (21.4 vs 20.6 months).[46] More recently, carfilzomib combined with lenalidomide (KRd) or thalidomide (KTd) and dexamethasone in NDMM showed similar CR rate (>60%) and PFS between HR and SR patients.[6, 47]

The anti-CD38 monoclonal antibody, isatuximab in combination with lenalidomide/dexamethasone and pomalidomide/dexamethasone demonstrated significant clinical responses, even in patients who were resistant to the combination partner. The addition of isatuximab to carfilzomib, lenalidomide, and dexamethasone is expected to increase response rates and depth of response with limited additional toxicity. The rationale for a 4-drug combination is to create a potentially curative upfront regimen where one does not currently exist.

3. PARTICIPANT SELECTION

Screening for eligible subjects will be performed within 28 days of study enrollment.

Eligibility Criteria

3.1 Inclusion Criteria

1. Subject must be at least 18 years of age.

2. Subject must have documented multiple myeloma satisfying the CRAB criteria and measurable disease defined as:

- Monoclonal plasma cells in the bone marrow ≥10% or presence of a biopsy-proven Plasmacytoma.
- Measurable disease as defined by any of the following:
  – IgG myeloma: Serum monoclonal paraprotein (M-protein) level ≥.5 g/dL or urine M-protein level ≥200 mg/24 hours; or
  – IgA, IgM, or IgD multiple myeloma: serum M-protein level ≥0.25 g/dL or urine M-protein level ≥200 mg/24 hours; or
  – Light chain multiple myeloma: Serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio.
- Sixty percent or greater clonal plasma cells on bone marrow examination.
- Serum involved / uninvolved free light chain ratio of 100 or greater, provided the absolute level of the involved free light chain is at least 100 mg/L (a patient's "involved" free light chain – either kappa or lambda – is the one that is above the normal reference range; the uninvolved light chain is the one that typically is in, or below, the normal range).
- More than one focal lesion on magnetic resonance image (MRI) that is at least 5 mm or greater in size.

3. Newly diagnosed and considered candidate for high-dose chemotherapy with stem cell transplant.
4. Subject must have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2.
5. Subject must have pretreatment clinical laboratory values meeting the following criteria during the Screening Phase:

a) hemoglobin ≥7.5 g/dL (≥5 mmol/L; prior RBC transfusion or recombinant human erythropoietin use is permitted);

b) absolute neutrophil count ≥1.0 x 10^9/L (granulocyte colony stimulating factor [GCSF] use is permitted);

c) platelet count ≥70 x 10^9/L for subjects in whom <50% of bone marrow nucleated cells are plasma cells; otherwise platelet count >50 × 10^9/L (transfusions are not permitted to achieve this minimum platelet count)
d) aspartate aminotransferase (AST) ≤2.5 x upper limit of normal (ULN);
e) alanine aminotransferase (ALT) ≤2.5 x ULN;
f) total bilirubin ≤2.0 x ULN, except in subjects with congenital bilirubinemia, such as Gilbert syndrome (direct bilirubin ≤2.0 x ULN)
g) creatinine clearance ≥30 mL/min
h) corrected serum calcium ≤14 mg/dL (≤3.5 mmol/L); or free ionized calcium <6.5 mg/dL (<1.6 mmol/L).

6. Women of childbearing potential must commit to either abstain continuously from heterosexual sexual intercourse or to use 2 methods of reliable birth control simultaneously. This includes one highly effective form of contraception (tubal ligation, intrauterine device [IUD], hormonal [birth control pills, injections, hormonal patches, vaginal rings or implants] or partner's vasectomy) and one additional effective contraceptive method (male latex or synthetic condom, diaphragm, or cervical cap). Contraception must begin 4 weeks prior to dosing. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy or bilateral oophorectomy.
7. A man who is sexually active with a woman of childbearing potential must agree to use a latex or synthetic condom, even if they had a successful vasectomy. All men must also not donate sperm during the study, for 4 weeks after the last dose of lenalidomide, for 90 days after the last dose of carfilzomib, and for 4 months after the last dose of isatuximab.
8. A woman of childbearing potential must have 2 negative serum or urine pregnancy tests at Screening, first within 10 to 14 days prior to dosing and the second within 24 hours prior to dosing.
9. Each subject (or their legally acceptable representative) must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol, as referenced in the ICF.

3.2 Exclusion Criteria

Any potential subject who meets any of the following criteria will be excluded from participating in the study.
1. Subject has a diagnosis of primary amyloidosis, monoclonal gammopathy of undetermined significance, or smoldering multiple myeloma. Monoclonal gammopathy of undetermined significance is defined by presence of serum M-protein <3 g/dL; absence of lytic bone lesions, anemia, hypercalcemia, and renal insufficiency related to the M-protein; and (if determined) proportion of plasma cells in the bone marrow of 10% or less. Smoldering multiple myeloma is defined as asymptomatic MM with absence of related organ or tissue impairment end organ

damage
2. Subject has a diagnosis of Waldenström's disease, or other conditions in which IgM M-protein is present in the absence of a clonal plasma cell infiltration with lytic bone lesions
3. Subject has prior or current systemic therapy or SCT for MM, with the exception of an emergency use of a short course (equivalent of dexamethasone 40 mg/day for a maximum 4 days) of corticosteroids before treatment.
4. Subject has a history of malignancy (other than MM) within 5 years before the date of enrollment (exceptions are squamous and basal cell carcinomas of the skin and carcinoma in situ of the cervix, or malignancy that in the opinion of the investigator, with concurrence with the sponsor's medical monitor, is considered cured with minimal risk of recurrence within 5 years).
5. Subject has had radiation therapy within 7 days of enrollment.
6. Subject has had plasmapheresis within 28 days of enrollment.
7. Subject is exhibiting clinical signs of meningeal involvement of MM.
8. Subject has known chronic obstructive pulmonary disease (COPD) (defined as a forced expiratory volume [FEV] in 1 second <60% of predicted normal), persistent asthma, or a history of asthma within the last 2 years (intermittent asthma is allowed). Subjects with known or suspected COPD or asthma must have a FEV1 test during screening.
9. Subject is known to be seropositive for history of human immunodeficiency virus (HIV) or known to have active hepatitis B or hepatitis C.
10. Subject has any concurrent medical or psychiatric condition or disease (eg, active systemic infection, uncontrolled diabetes, acute diffuse infiltrative pulmonary disease) that is likely to interfere with the study procedures or results, or that in the opinion of the investigator, would constitute a hazard for participating in this study.
11. Subject has clinically significant cardiac disease, including:

- myocardial infarction within 1 year before enrollment, or an unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, congestive heart failure, New York Heart Association Class III-IV;
- uncontrolled cardiac arrhythmia (National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 4 Grade ≥2) or clinically significant ECG abnormalities;
- screening 12-lead ECG showing a baseline QT interval as corrected by Fridericia's formula (QTcF) >470 msec.
- uncontrolled hypertension

12. Subject has known allergies, hypersensitivity, or intolerance to corticosteroids, monoclonal antibodies or human proteins, or their excipients (refer to respective package inserts or IB) or known sensitivity to mammalian-derived products.
13. Subject has plasma cell leukemia (according to World Health Organization [WHO] criterion: ≥20% of cells in the peripheral blood with an absolute plasma cell count of more than 2×10^9/L) or POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes).

14. Subject is known or suspected of not being able to comply with the study protocol (eg, because of alcoholism, drug dependency, or psychological disorder). Subject has any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments.
15. Subject is a woman who is pregnant, or breast-feeding, or planning to become pregnant while enrolled in this study within 30 days after the last dose of lenalidomide or carfilzomib, or within 4 months after the last dose of isatuximab. Or, subject is a man who plans to father a child while enrolled in this study, within 4 weeks after the last dose of lenalidomide, within 90 days of the last dose of carfilzomib, or within 4 months after the last dose of isatuximab.
16. Subject has had major surgery within 2 weeks before enrollment or has not fully recovered from surgery, or has surgery planned during the time the subject is expected to participate in the study. Kyphoplasty or vertebroplasty is not considered major surgery.
17. Subject has received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 4 weeks before enrollment or is currently enrolled in an interventional investigational study.
18. Subject has contraindications to required prophylaxis for deep vein thrombosis and pulmonary embolism.
19. Incidence of gastrointestinal disease that may significantly alter the absorption of oral drugs.
20. Peripheral neuropathy ≥ Grade 2 on clinical examination during the screening period.
21. Systemic treatment with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobartital), or use of Ginkgo biloba, St. John's wort within 14 days before the first dose of study treatment.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial.

4. REGISTRATION

4.1 General Guidelines for Dana-Farber/Harvard Cancer Center (DF/HCC) Institutions

Institutions will register eligible participants in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

An investigator will confirm eligibility criteria and a member of the study team will complete the protocol-specific eligibility checklist.

Following registration, participants may begin protocol-specific therapy and/or intervention. Issues that would cause treatment delays should be discussed with the Overall Principal Investigator (PI). If the subject does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

4.2 Registration Process for DF/HCC Institutions
Applicable DF/HCC policy (REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites
Not applicable

4.4 Registration Process for Other Investigative Sites
Not applicable

5. TREATMENT PLAN

5.1 Treatment Regimen

Carfilzomib, lenalidomide, dexamethasone, and isatuximab will be administered on a 28-day treatment cycle. All subjects will perform stem cell collection after 4 cycles of therapy.

For patient undergoing upfront stem cell transplant (SCT):
4 cycles of therapy followed by stem cell collection, high-dose chemotherapy, and autologous SCT followed by 2 additional cycles of therapy then maintenance.

For patients deferring SCT following collection:
4 cycles of therapy followed by stem cell collection followed by 4 additional cycles of therapy then maintenance.

Carfilzomib 56 mg/m^2 IV on Days 1, 8, 15
Lenalidomide 25 mg orally (po) on Days 1-21
Isatuximab 10 mg/kg IV Q1 week for 8 weeks, then Q2 weeks for 16 weeks, thereafter Q4 weeks
Dexamethasone 20 mg po will be administered day of and day after all doses of carfilzomib (Days 1, 2, 8, 9, 15, and 16) and isatuximab (Cycles 1 and 2 Days 22 and 23). The dexamethasone 20 mg oral or IV dose administered as a preinfusion medication on isatuximab infusion days (Days 1, 8, 15, 22) replaces the oral dexamethasone dose for that day.

*All subjects with receive carfilzomib 20 mg/m^2 on Day 1 Cycle 1

Maintenance:
Patients must achieve a PR or better to continue onto maintenance therapy on the study.

28-day Maintenance Cycle until progressive disease (PD) or unacceptable toxicity. Subjects will be stratified based on cytogenetics (deletion (del) 17, translocation (t)(4:14), t(14;16), t(14;20), 1q duplication).

Standard-risk:
Lenalidomide 10 mg po Days 1-21

High-risk:
Carfilzomib 56 mg/m^2 (or last tolerated dose) IV Days 1, 15
Lenalidomide 10 mg po Days 1-21
Isatuximab 10 mg/kg IV Day 1 for up to 24 cycles of maintenance (two years), then discontinue

In the maintenance phase, dexamethasone, 20 mg orally or IV will be administered to subjects as a preinfusion medication prior to isatuximab dosing. When dexamethasone is reduced to 20 mg/week and is given as preinfusion medication, subjects may receive low-dose methylprednisolone (≤20 mg) orally (or equivalent in accordance with local standards) for the prevention of delayed infusion-associated reactions (IARs), as clinically indicated.

Because lenalidomide is primarily excreted unchanged by the kidney, adjustments to the starting dose of lenalidomide are recommended to provide appropriate drug exposure in patients with renal impairment. Lenalidomide dose adjustment should be instituted for patients with a CrCl ≤50 mL/min. The recommended doses for patients with multiple myeloma and renal impairment are shown below in Table 9. If during treatment a patient's renal status changes, the dose should be adjusted as shown in Table 9. Similarly, adjustments to the starting and ongoing dosing of carfilzomib are recommended in the setting of hepatic impairment. The doses should be adjusted as shown in Table 10.

Stem cell collection and SCT should be done per institutional and FACT guidelines. The decision whether a patient will proceed to stem cell transplant will be made on the basis of treating physician recommendations and patient preference. Physician recommendations are typically based on disease response and on how well subjects are tolerating treatment. This kind of decision-making process related to stem cell transplant is considered standard of care in the multiple myeloma field. Subjects who do not proceed to stem cell transplant may receive a total of 8 cycles of therapy followed by maintenance. Those patients proceeding with stem cell transplant will receive an additional 2 cycles of therapy post-SCT followed by maintenance. Prior to continuing induction therapy, all stem cell harvest-related toxicity or stem cell

transplant-related toxicity must be improved such the patient meets criteria to treat outlined in section 5.2 of the protocol.

5.2 Pre-Treatment Criteria

A new cycle of treatment may begin on the scheduled Day 1 of a new cycle if the following criteria are met within 24 hours of Day 1:

- ANC ≥1,000/mm^3 (growth factor support is permitted during cycles with the exception of Cycle 1 Day 1 (C1D1); it is allowed on the same day as treatment administration).
- Platelet count ≥50,000/mm^3 (platelet support is permitted during cycles of treatment; it is allowed on the same day as treatment administration, including C1D1).
- Any lenalidomide-related allergic reaction/hypersensitivity or sinus bradycardia/other cardiac arrhythmia AE that may have occurred has resolved to < Grade 1.
- Any other lenalidomide, carfilzomib, or isatuximab-related adverse event that may have occurred has resolved to <Grade 2.
- Herpes zoster lesions, if present, are dry.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of therapy will not be initiated until the toxicity has resolved as described above. The maximum amount of time that treatment may be held for these toxicities to resolve is 3 weeks. If drug is held for more than 3 weeks due to toxicity, the patient is to discontinue all study treatment and enter the survival follow-up phase of the study.

For intra-cycle dosing on days where laboratory studies are scheduled, the following criteria must be met:

- Platelet count ≥ 30,000 (platelet transfusion support is permitted to meet criteria)
- Absolute neutrophil ≥ 500/mm^3 (growth factor support is permitted during cycles with the exception of Cycle 1 Day 1 (C1D1); it is allowed on the same day as treatment administration).

Intra-cycle dose modifications for all drugs will be allowed based on toxicity and according to dose modifications outline in Section 6.1, Table 9.

5.3 Agent Administration and Pharmaceutical Information

5.3.1 Isatuximab

5.3.1.1 Description

Isatuximab (SAR650984) is an IgG1 derived mAb binding selectively the human CD38 membrane protein. The protein structure is composed of 2 kappa light chains each with

molecular weight of approximately 23 kDa and 2 IgG1 heavy chains each with a molecular weight of approximately 49 kDa (deglycosylated form) linked through disulfide bridges. Each light chain consists of 214 amino acid residues and each heavy chain consists of 450 amino acid residues.

Appearance: Colorless to slightly yellow liquid which may contain visible particles.

Antigen binding: Isatuximab binds to CD38 with an apparent dissociation constant (Kd) of about 3 nM, determined by Surface Plasmon Resonance using monomeric CD38 protein.

5.3.1.2 Formulation

Isatuximab (SAR650984) drug product is supplied as concentrate for solution for infusion in the following formulations:

- 100 mg/5 mL (20 mg/mL) in single-dose vial
- 500 mg/25 mL (20 mg/mL) in single-dose vial

5.3.1.3 Storage and Stability

Storage of isatuximab should be in a secure area with restricted access. Isatuximab vials should be stored in a refrigerator at +2°C to +8°C in the original carton to protect from light. Do not freeze. Do not shake. Details of the stability for the diluted solution are provided below in the preparation section.

5.3.1.4 Preparation

Prepare the solution for infusion using aseptic technique as follows [49]:

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration.
- Remove the volume of diluent from a 250 mL bag of 0.9% Sodium Chloride Injection, USP, or 5% Dextrose Injection, USP that is equal to the required dose volume of Isatuximab plus manufacturer overfill in order to prepare a total volume of 250 mL.
- Withdraw the required dose volume of isatuximab based on a concentration of 20 mg/mL and dilute by adding to the infusion bag of 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP
- The infusion bag must be made of polyolefins (PO), polyethylene (PE), polypropylene (PP),polyvinyl chloride (PVC) with di-(2-ethylhexyl) phthalate (DEHP) or ethyl vinyl acetate (EVA).
- Gently homogenize the diluted solution by inverting the bag. Do not shake.
- The prepared isatuximab infusion solution should be administered by intravenous infusion using an intravenous tubing infusion set (in PE, PVC with or without DEHP, polybutadiene [PBD], or polyurethane [PU]) with a 0.22 micron in-line filter (polyethersulfone [PES], polysulfone, or nylon).

- The prepared isatuximab infusion solution should be used within 48 hours when stored refrigerated at 2°C to 8°C, followed by 8 hours (including infusion time) at room temperature.
- Do not administer isatuximab infusion solution concomitantly in the same intravenous line with other agents.
-

5.3.1.5 Administration

Do not administer isatuximab infusion solution concomitantly in the same intravenous line with other agents. On days when both isatuximab and carfilzomib are given, order of administration is per institutional preference. Administer the prepared isatuximab infusion solution according to the Infusion Rates in the table below. Incremental escalation of the infusion rate should be considered only in the absence of infusion-related reactions [49]

	Dilution Volume	**Initial Rate**	**Absence of Infusion-Related Reaction**	**Rate Increment**	**Maximum Rate**
First Infusion	250 mL	25 mL/hour	For 60 minutes	25 mL/hour every 30 minutes	150 mL/hour
Second Infusion	250 mL	50 mL/hour	For 30 minutes	50 mL/hour for 30 minutes then increase by 100 mL/hour every 30 minutes	200 mL/hour
Subsequent Infusions	250 mL	200 mL/hour	-	-	200 mL/hour

5.3.1.6 Treatment Schedule

Isatuximab (10 mg/kg) will be administered as an IV infusion. Each subject's dose will be calculated based on the subject's weight at C1D1. The dose of isatuximab will remain constant throughout the study, unless the subject's weight changes more than 10% (or per institutional standard policy) from C1D1. Isatuximab will be administered weekly during induction treatment in Cycle 1 to Cycle 2 (Days 1, 8, 15, and 22); every 2 weeks in Cycles 3-6 (Days 1 and 15), and every 4 weeks thereafter. For high-risk patients isatuximab will be administered every 4 weeks on Day 1 of each 28-day cycle during maintenance treatment until progressive disease (PD) or unacceptable toxicity for a maximum of 24 maintenance cycles (2 years) and then discontinued.

5.3.1.7 Premedications

To minimize the incidence and severity of infusion reactions, all the patients treated with isatuximab should routinely receive primary prophylactic treatment with diphenhydramine 25 to

50 mg IV (or equivalent), methylprednisolone 100 mg IV (or equivalent), montelukast 10mg orally (or equivalent), fexofenadine 60mg orally (or equivalent), and acetaminophen 650 to 1000 mg orally (or equivalent), approximately 15–60 minutes (but never >60 minutes) prior to the start of the isatuximab infusion.

Detailed guidelines for the management of infusion reactions (Table 5) are provided in each study protocol. In the event of an infusion reaction, the isatuximab infusion may be interrupted and can be subsequently resumed after recovery (if the reaction was mild-to-moderate), at a slower infusion rate, under close monitoring, and with supportive care as needed. Prior to restarting the infusion in case of moderate reactions, patients may receive additional medication based on the judgment of the Investigator; recommended medications consist of diphenhydramine 25 mg IV and methylprednisolone 100 mg IV (or equivalent). In the event of a severe hypersensitivity reaction, however, treatment with isatuximab is to be immediately and permanently discontinued. Patients who experience infusion reactions must also be informed of the potential risk of recurrent reactions at subsequent infusions. Patients who do not experience an infusion reaction during the first 4 isatuximab infusions may have their need for subsequent premedication reconsidered at the Investigator's discretion to avoid unnecessary sedation.

Table 5 - Management of Infusion Reactions (IR)

Symptom Severity (CTACAE ver 5.0)	**Recommended Intervention**
Mild (Grade 1) Infusion interruption or intervention not indicated	Continuation of isatuximab infusion per the judgement of the investigator following close direct monitoring of the patient's clinical status. Isatuximab infusion may be stopped at any time if deemed necessary. If stopped, IR will be classified as Grade 2 as per NCI-CTCAE
Moderate (Grade 2) Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, nonsteroidal anti-inflammatory drugs (NSAIDs), narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Stop isatuximab infusion. Give additional medication with IV diphenhydramine 25 mg IV (or equivalent) and/ or IV methylprednisolone 100 mg (or equivalent) as needed. Isatuximab may be resumed only after patient recovery, with slower infusion rate and with close monitoring.

Severe or life-threatening (Grade 3 or 4) Grade 3: prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae Grade 4: life-threatening consequences; urgent intervention indicated	Stop isatuximab infusion. Give additional medication with diphenhydramine 25 mg IV (or equivalent) and/ or IV methylprednisolone 100 mg (or equivalent) and/or epinephrine as needed. Definitive treatment discontinuation.

Patients who experience Grade 2 IAR may subsequently resume isatuximab infusion under close monitoring and supportive care as needed. Patients may receive additional premedication per the judgment of the Investigator. These patients must be informed of the potential risk of recurrent allergic reactions. The infusion must be completed within the time specified in the Package Insert.

Patients with Grade 3 or 4 isatuximab IAR must have isatuximab permanently discontinued and appropriate therapy should be administered. Should an isatuximab infusion reaction of Grade ≥2 occur, the infusion reaction and the therapy administered must be documented in the case report form (CRF).

All IARs must be reported as an adverse event of special interest (AESI). Study personnel should consult the Medical Monitor for further guidance regarding re treatment of patients with infusion reactions and regarding issues of premedication management (eg, alternative medications for patients allergic or intolerant to premedication agents) or to determine if locally used equivalent medications are acceptable.

5.3.1.8 Responsibilities

The Investigator, the Hospital Pharmacist, or other personnel allowed to store and dispense isatuximab will be responsible for ensuring that isatuximab is used in the clinical trial is securely maintained as specified by Sanofi and in accordance with the applicable regulatory requirements.

All isatuximab shall be dispensed in accordance with the Investigator's prescription and it is the Investigator's responsibility to ensure that an accurate record of Investigational Product issued and returned is maintained.

Any quality issue noticed with the receipt or use of isatuximab (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) should be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure.

A potential defect in the quality of isatuximab may be subject to initiation by Sanofi of a recall procedure. In this case, the Investigator will be responsible for promptly addressing any request made by Sanofi, in order to recall Investigational Product and eliminate potential hazards. Under no circumstances will the Investigator supply the isatuximab to a third party, allow the isatuximab to be used other than as directed by this Clinical Trial Protocol, or dispose of isatuximab in any other manner.

5.3.1.9 Retrieval of treatments and/or destruction

All used treatments vials of isatuximab will be destroyed at the study site after an accurate accountability has been performed and signed by the investigator (or the pharmacist). All partially-used and unused isatuximab may be retrieved by Sanofi or they will be destroyed on site, after final batch accountability has been validated by the Sponsor monitoring team representative, according to the standard practices of the site and /or to local regulations. The destruction is recommended to be performed at site depending on investigational medical product (IMP) specificities and local requirements, but IMP can be returned to the sponsor for destruction. A detailed treatment log form of the returned isatuximab will be established with the Investigator (or the pharmacist) and countersigned by the Investigator and the Monitoring Team.

The Investigator will not destroy the unused IMP unless Sanofi provides written authorization.

5.3.1.10 Availability and Ordering

Sanofi will supply isatuximab free-of-charge, shipped directly to the pharmacy at the study site. The investigator or designee will order isatuximab from Sanofi according to the ordering instructions provided by the company.

5.3.2 Carfilzomib

5.3.2.1 Description

Carfilzomib is a synthetic small molecule peptide bearing the chemical name (2S)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-ylcarbamoyl)-2-phenylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-4-methylpentanamide. The molecular formula is C40H57N5O7 and the molecular weight is 719.91. It specifically functions as an inhibitor of the chymotrypsin-like activity of the 20S proteasome which leads to the accumulation of protein substrates within the cell and induction of apoptosis. Carfilzomib for Injection will be provided as a lyophilized powder which, when reconstituted, contains a 2 mg/mL isotonic solution of carfilzomib Free Base in 10 mM sodium citrate buffer (pH 3.5) containing 10% (w/v) sulfobutylether-beta-cyclodextrin (SBE beta CD, Captisol).

5.3.2.2 Formulation

Carfilzomib for Injection is supplied as 60 mg lyophilized powder in single-use vials for reconstitution. Upon reconstitution with preservative-free sterile water for injection, USP, the reconstituted solution contains 2mg/mL carfilzomib. Additional information on carfilzomib may be found in the IB.

5.3.2.3 Storage and Stability

Study drugs should be stored in a securely locked area with access limited to appropriate study personnel. Lyophilized carfilzomib for Injection must be stored at 2°Celcius (C) to 8°C (36°Fahrenheit −46°F) in a refrigerator. Vials must be kept in cartons in order to protect from light until ready for reconstitution. Once a drug vial is reconstituted and inspected, the clear solution can be stored in a refrigerator (recommended) controlled temperature from 2°C to 8°C (36°F–46°F) for up to 24 hours. If kept at room temperature after reconstitution, it must be used within 4 hours. Once reconstituted, carfilzomib for Injection must be used by the time points outlined in Table 6 below.

Table 6 - Stability of Reconstituted Carfilzomib for Injection (60 mg/vial)

Storage Conditions of Reconstituted Carfilzomib	**Stability (in Hours) per Container**		
	Vial	**Syringe**	**IV Bag (D5W)**
Refrigerated (2°C to 8°C; 36°F to 46°F)	24	24	24
Room Temperature (15°C to 30°C; 59°F to 86°F)	4	4	4

5.3.2.4 Preparation

Carfilzomib will be prepared according to the provided Carfilzomib Investigator Sponsored Study (ISS) Pharmacy Information Guide.

5.3.2.5 Administration

On days when both isatuximab and carfilzomib are given, order of administration is per institutional preference. Administer the prepared carfilzomib infusion solution according to the Carfilzomib Investigator Sponsored Study (ISS) Pharmacy Information Guide and/or

Institutional Guidelines. Deliver the entire volume as a continuous infusion over a period of 10 minutes for carfilzomib doses ≤ 27 mg/m^2 or 30 minutes for carfilzomib doses > 27 mg/m^2.

5.3.2.6 Treatment Schedule

Carfilzomib will be administered once weekly during induction at a dose of 56 mg/m^2 IV on Days 1, 8, 15 of each 28-day cycle. All subjects with receive carfilzomib 20 mg/m^2 on Day 1 Cycle 1. For high-risk patients carfilzomib will be administered at a dose of 56mg/m^2 (or last tolerated dose) IV on Days 1 and 15 of each 28-day cycle during maintenance treatment until progressive disease (PD) or unacceptable toxicity. Subjects with a BSA > 2.2 m^2 will receive a dose based upon a BSA of 2.2 m^2, for all carfilzomib study treatment doses

5.3.2.7 Hydration

Adequate hydration is required prior to carfilzomib dosing in Cycle1, especially in patients at high-risk of tumor lysis syndrome (TLS) or renal toxicity. Consider hydration with both oral fluids (30mL per kg at least 48hours before Cycle1, Day1) and intravenous fluids (250mL to 500mL of appropriate intravenous fluid prior to each dose in Cycle1). If needed, give an additional 250mL to 500mL of intravenous fluids following carfilzomib administration. Continue oral and/or intravenous hydration, as needed, in subsequent cycles. Monitor patients for evidence of volume overload and adjust hydration to individual patient needs, especially in patients with or at risk for cardiac failure. [50]

5.3.2.8 Accountability, Handling and Destruction

Refer to provided Carfilzomib Investigator Sponsored Study (ISS) Pharmacy Information Guide.

5.3.2.9 Availability and Ordering

Amgen will supply carfilzomib free-of-charge, shipped directly to the pharmacy at the study site. The investigator or designee will order carfilzomib from Amgen according to the ordering instructions provided by the company.

5.3.3 Lenalidomide

5.3.3.1 Description

Lenalidomide (REVLIMID®), a thalidomide analogue, is an immunomodulatory agent with antiangiogenic properties. Lenalidomide is available for this study as 5 and 25 mg capsules for oral administration and does not require any other preparation. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

5.3.3.2 Storage and Stability

At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access. Lenalidomide should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

5.3.3.3 Handling

Females of childbearing potential should not handle or administer lenalidomide unless they are wearing gloves.

Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

5.3.3.4 Ordering

Lenalidomide will be obtained through commercial supply through the REMS® program. Per standard Revlimid REMS® program requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in, and must comply with, all requirements of the Revlimid REMS®program. Lenalidomide (Revlimid®) will be prescribed in accordance with Celgene Corporation's Revlimid REMS® program. Further information about the Revlimid REMS® program is available at: www.celgeneriskmanagement.com.

5.3.3.5 Treatment Schedule and Administration

During the induction phase of treatment, lenalidomide will be self-administered at a dose of 25 mg orally each day on Days 1 through 21 of each 28-day cycle for subjects with creatinine clearance (CrCl) >50 mL/min. During the maintenance phase for all patients, lenalidomide 10 mg will be administered daily on days 1-21 throughout each 28-day cycle until progressive disease (PD) or unacceptable toxicity.

Lenalidomide should be taken orally at about the same time each day. The capsules should not be opened, broken, or chewed. Lenalidomide capsules should be swallowed whole, preferably with water, either with or without food.

If less than 12 hours has elapsed since missing a dose, the patient can take the dose. If more than 12 hours has elapsed since missing a dose at the normal time, the patient should not take the dose, but take the next dose at the normal time on the following day. Do not take 2 doses at the same time.

5.3.4 Dexamethasone

5.3.4.1 Description

Dexamethasone is a synthetic adrenocortical steroid. Corticosteroids are naturally occurring chemicals produced by the adrenal glands located above the kidneys. Corticosteroids affect the

function of many cells within the body and suppress the immune system. Corticosteroids also block inflammation and are used in a wide variety of inflammatory diseases affecting many organs.
The molecular weight for dexamethasone is 392.47. It is designated chemically as 9-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione. Dexamethasone is stable in air and almost insoluble in water.

5.3.4.2 Formulation
Dexamethasone is a white to practically white, odorless, crystalline powder. It is available in 2- or 4-mg tablets (commercially) for oral administration. Each tablet contains dexamethasone as the active ingredient, and the following inactive ingredients: calcium phosphate, lactose, magnesium stearate, and starch. The tablet shell may contain the following: D&C Yellow 10, FD&C Yellow 6, and/or FD&C Blue 1.

5.3.4.3 Storage and Stability
Dexamethasone should be stored at controlled room temperature, 68-77◦F (20-25◦C) and not frozen, and according to label requirements.

5.3.4.4 Availability
Dexamethasone supply will be obtained through commercial supply.

5.3.4.5 Preparation
Dexamethasone is an oral drug and does not require specific preparation details.

5.3.4.6 Ordering
Dexamethasone will be ordered from retail pharmacy using commercial drug supply.

5.3.4.7 Accountability
As drug is from commercial supply, sites should keep records per their institutional policies.

5.3.4.8 Treatment Schedule and Administration
Dexamethasone will be self-administered orally at a dose of 20 mg on the day of and day after all doses of carfilzomib (Days 1, 2, 8, 9, 15, and 16) and isatuximab (Cycles 1 and 2 Days 22 and 23). The dexamethasone 20 mg oral or IV dose administered as a preinfusion medication on isatuximab infusion days (Days 1, 8, 15, 22) replaces the oral dexamethasone dose for that day.

For high-risk patients in the maintenance phase, dexamethasone, 20 mg orally or IV will be administered to subjects as a preinfusion medication prior to isatuximab dosing. After 24 cycles of maintenance (2 years) both dexamethasone and isatuximab should be discontinued. When dexamethasone is reduced to 20 mg/week and is given as preinfusion medication, subjects may receive low-dose methylprednisolone (≤20 mg) orally (or equivalent in accordance with local standards) for the prevention of delayed IARs, as clinically indicated.

Dexamethasone will be given according to institutional practice.

Each oral dexamethasone dose should be taken with food and at the same time each day. Dexamethasone should not be crushed, chewed, or dissolved, in water.

During the days when isatuximab is not given, if a dose is missed (more than 12 hours since the expected time) or vomited, the dose should not be made up and the participant should continue with regular scheduling of the drug.

On the days of isatuximab infusion, the investigator should be notified if the oral dose is missed to determine if it should be made up prior to the isatuximab infusion.

5.4 General Concomitant Medication and Supportive Care Guidelines

Supportive Care and Concomitant Medications

Prestudy and Concomitant Therapy
The following prestudy therapies given at any time before first dose of study treatment must be recorded at screening: steroids of any dose or duration given for MM.

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care. The sponsor must be notified in advance (or as soon as possible thereafter) of any instances in which prohibited therapies are administered.

Systemic use of the following concomitant medications will be collected in the CRF and recorded in the source documents beginning with signing of the ICF to 30 days after the last dose of the last study treatment or until the start of next-line anticancer treatment, if earlier: growth factors, transfusions, anti-infective medications (antibacterials, antivirals, and antimycotics), steroids, anti-arrhythmic medications and other cardiac supportive therapy, anti-epileptic medications, centrally acting psychiatric medications, anti-histamines and other medications targeting post-infusion systemic reactions, and any anticancer therapy (including radiation).

Recommended Therapy

Bone-Directed Therapy
For subjects who have not previously received bisphosphonates or denosumab, bone-directed therapy is recommended for all subjects with evidence of lytic destruction of bone or with osteopenia.

Commercially available IV bisphosphonates (pamidronate and zoledronic acid) or denosumab are preferred when available, and should be used according to the manufacturer's recommendations, as described in the prescribing information, for subjects with osteolytic or osteopenic myelomatous bone disease. Oral bisphosphonates may be used as alternatives if IV bisphosphonates are not available at the study site. Subjects who are currently using bone-

directed therapy when they enter the study should continue the same treatment. Subjects who are not using bone-directed therapy at the time of study entry should start bone-directed therapy as soon as possible.

Prophylaxis for Bacterial Infection
Prophylaxis for bacterial infections should be considered per institutional guidelines, especially for subjects with a history of recurrent bacterial infections or severe hypogammaglobulinemia.

Prophylaxis for Deep Vein Thrombosis (DVT)
Full-dose aspirin recommended. Therapeutic anticoagulation recommended for those at high-risk of thrombosis.

Prophylaxis for Herpes Zoster Reactivation
Prophylaxis for herpes zoster reactivation should be given unless contraindicated. Acceptable antiviral therapy includes acyclovir (eg, 400 mg given orally 2 times a day), famciclovir (eg, 125 mg given orally twice a day or per institutional standards), or valacyclovir (eg, 500 mg given orally, twice a day or per institutional standards), initiated within 1 week after the start of study treatment and continued at least throughout.

Therapy for Pneumocystis Carinii
Pneumocystis carinii pneumonia (PCP) prophylaxis should be considered, as per institutional guidelines.

Prevention of Steroid-Induced Gastritis
Dexamethasone and other steroids may induce gastritis. Medications to prevent gastritis are permitted per institutional guidelines, for example proton pump inhibitors (omeprazole or equivalent) or sucralfate, or histamine (H)2 blockers (ranitidine or equivalent).

Permitted Therapies
In addition, subjects are to receive full supportive care. The following medications and supportive therapies are examples of support therapies that may be used at any time during the study:

- Antiviral medications should be considered per institutional guidelines.
- Colony stimulating factors, erythropoietin, and transfusion of platelets and RBCs. If erythropoietin is given, then this should be given according to the US prescribing information for lenalidomide and epoetin alfa, as there is an increased risk of thrombosis with lenalidomide.
- It is important to prevent constipation (eg, adequate hydration, high-fiber diet, and stool softeners if needed).
- Adequate hydration is recommended for prevention of myeloma-related kidney disease.
- Intravenous immunoglobulin (IVIG) may be considered for subjects with recurrent infection related to hypogammaglobulinemia.

- Prophylactic antiemetics, with the exception of corticosteroids
- Loperamide is recommended for the treatment of diarrhea, starting at the time of the first watery stool. The loperamide dose and regimen is according to institutional guidelines. Prophylactic loperamide is not recommended.

Prohibited Therapies
Concomitant administration of any other antineoplastic therapy for the intention of treating MM is prohibited, including medications that target CD38, as well as medications used for other indications that have anti-myeloma properties (for example, interferon).

During Cycle 1, the prophylactic use of hematopoietic growth factors is prohibited. Concomitant administration of investigational agents is prohibited. Administration of commercially available agents with activity against or under investigation for MM, including systemic corticosteroids (>10 mg prednisone per day or equivalent) (other than those given for IARs as described for Management of Infusion-Associated Reactions) should be avoided. Nonsteroidal anti-inflammatory agents (NSAIDs) should be avoided to prevent myeloma-related kidney disease.

5.5 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of treatment delays due to adverse event(s), treatment may continue for until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the CRF. Alternative care options will be discussed with the participant.

When a participant is removed from protocol therapy and/or is off of the study, the relevant Off-Treatment/Off-Study information will be updated in OnCore.

5.6 Duration of Follow Up

Participants will be followed every three months after removal from protocol therapy for 2 years or until confirmation of progressive disease, initiation of subsequent myeloma therapy, death, withdrawal of consent, or loss of follow up, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event and then every three months until PD or initiating subsequent therapy.

The first follow up visit should occur three months after the end of treatment visit.

Following disease progression or initiation of subsequent myeloma therapy, participants may be followed-up for survival by telephone contact every three months or chart review for a period of five years from study enrollment.

5.7 Criteria for Taking a Participant Off Study

Participants will be removed from study when any of the following criteria apply:

- Lost to follow-up
- Withdrawal of consent for data submission
- Death

The reason for taking a participant off study, and the date the participant was removed, must be documented in the CRF. In addition, the study team will ensure Off Treatment/Off Study information is updated in OnCore in accordance with DF/HCC policy REGIST-101.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI CTCAE version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

6.1 Dose and Treatment Modifications

Isatuximab Modifications and Dose Delays

Dose Modification of Isatuximab

No isatuximab dose modification (increase or decrease) will be permitted.

Isatuximab Infusion-Associated Reactions

General guidelines for the management of the Infusion-Associated Reactions

Table 7 - Management of Infusion Reactions

Symptom Severity (CTACAE ver 5.0)	Recommended Intervention
Mild (Grade 1) Infusion interruption or intervention not indicated	Continuation of isatuximab infusion per the judgement of the investigator following close direct monitoring of the patient's clinical status. Isatuximab infusion may be stopped at any time if deemed necessary. If stopped, IR will be classified as Grade 2 as per NCI-CTCAE
Moderate (Grade 2) Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (eg, antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤24 hours	Stop isatuximab infusion. Give additional medication with IV diphenhydramine 25 mg IV (or equivalent) and/ or IV methylprednisolone 100 mg (or equivalent) as needed. Isatuximab may be resumed only after patient recovery, with slower infusion rate and with close monitoring.
Severe or life-threatening (Grade 3 or 4) Grade 3: prolonged (eg, not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae Grade 4: life-threatening consequences; urgent intervention indicated	Stop isatuximab infusion. Give additional medication with diphenhydramine 25 mg IV (or equivalent) and/ or IV methylprednisolone 100 mg (or equivalent) and/or epinephrine as needed. Definitive treatment discontinuation.

Patients who experience Grade 2 IAR may subsequently resume isatuximab infusion under close monitoring and supportive care as needed. Patients may receive additional premedication per the judgment of the Investigator. These patients must be informed of the potential risk of recurrent allergic reactions. The infusion must be completed within the time specified in the pharmacy manual.

Dose Delay and Toxicity Management

ONLY if any of the following criteria are met and the event cannot be ascribed to lenalidomide, carfilzomib, dexamethasone, or underlying MM, the isatuximab infusion must be held to allow for recovery from toxicity. The criteria for a dose delay are:

-Grade 4 hematologic toxicity (except for Grade 4 lymphopenia), or Grade 3 or higher thrombocytopenia with bleeding.
-Febrile neutropenia of any grade.
-Neutropenia with infection, of any grade.
-Grade 3 or higher nonhematologic toxicities with the following exceptions:
    -Grade 3 nausea or Grade 3 vomiting that responds to antiemetic treatment.
    -Grade 3 diarrhea that responds to antidiarrheal treatment.
    -Grade 3 fatigue or asthenia that was present at baseline and lasts for <7 days after the last administration of isatuximab.
    -Grade 3 or 4 electrolyte disturbances which can be managed with replacement therapy.

If isatuximab administration does not commence within the prespecified window (Table 8) of the scheduled administration date, then the dose will be considered a missed dose. Administration may resume at the next planned dosing date.

The maximum delay for toxicity before treatment is permanently discontinued will be 3 weeks; however, delays due to other circumstances should be discussed with the Principal Investigator. Delays of >3 weeks must be discussed with the Principal Investigator. Re-treatment will be at the discretion of the Principal Investigator.

Table 8: Isatuximab-Related Toxicity Management

Cycles	Frequency	Missed Dose	Dosing Resumption
1-2	Weekly (every 1 week)	>3 days	Next planned weekly dosing date
3-6	Every cycle (every 2 weeks)	>14 days	Next planned every 2 weeks dosing date
7 and beyond	Every cycle (every 4 weeks)	>28 days	Next planned every 4 weeks dosing date

A missed dose will not be made up. Any AE deemed to be related to isatuximab that requires a

dose hold of more than 28 days in the induction or consolidation phase will result in permanent discontinuation of isatuximab.

Interruption or Missed Doses

An isatuximab dose held for more than 8 days during induction or 14 days during maintenance from the per-protocol administration date for any reason other than toxicities suspected to be related to isatuximab should be brought to the attention of the sponsor at the earliest possible time. Subjects who miss ≥3 consecutive planned doses of isatuximab for reasons other than toxicity will be withdrawn from treatment, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

Carfilzomib and Lenalidomide Dose Modification Guidelines

Dose adjustments of lenalidomide will follow the approved labeling as follows:

- Starting dose: 25 mg
- Dose level -1: 15 mg
- Dose level -2: 10 mg
- Dose level -3: 5 mg

Dose adjustments should be based on the highest grade of toxicity that is ascribed to lenalidomide.

Dose adjustments of carfilzomib as follows:

- Starting dose: 56 mg/m^2 (Cycle 1 Day 1: 20 mg/m^2)
- Dose level -1: 45 mg/m^2
- Dose level -2: 36 mg/m^2
- Dose level -3: 27 mg/m^2

The maximum delay for toxicity before treatment is permanently discontinued will be 3 weeks; however, delays due to other circumstances should be discussed with the Principal Investigator. Delays of >3 weeks must be discussed with the Principal Investigator. Re-treatment will be at the discretion of the Principal Investigator.

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

Table 9 – Lenalidomide and Carfilzomib Dose Modifications

	Recommended Actions	
Thrombocytopenia	**Lenalidomide**	**Carfilzomib**

Return to ≥ 30 x 10^9/L	Resume lenalidomide at full dose	Resume carfilzomib at full dose.
Subsequently drop to < 30 x 10^9/L	Hold lenalidomide and follow CBC weekly	Hold carfilzomib and follow CBC weekly
Return to ≥ 30 x 10^9/L	Resume lenalidomide at 1 dose decrement	Resume carfilzomib at one dose decrement if cyclical thrombocytopenia is still below levels considered safe by the Treating Investigator at one dose decrement (i.e., dose decrease only if Treating Investigator judgment is that Carfilzomib contributed to thrombocytopenia)

Platelet transfusions should also be considered for the management of thrombocytopenia as clinically indicated

	Recommended Action	
Neutropenia : When ANC	**Lenalidomide**	**Carfilzomib**
Falls to < 0.5 x 10^9/L or to < 1.0 x 10^9/L with fever	Hold lenalidomide, add filgrastim if Grade 3 with fever or Grade 4, follow CBC weekly	Hold carfilzomib, add filgrastim if Grade 3 with fever or Grade 4, follow CBC weekly
Returns to 1.0 x 10^9/L (if neutropenia was the only toxicity noted)	Resume lenalidomide at full dose	Resume carfilzomib at full dose
Return to 1.0 x 10^9/L (if other toxicity noted)	Resume lenalidomide at 1 dose decrement	Resume carfilzomib at full dose unless marked cyclical thrombocytopenia is present, then reduce by 1 dose decrement
Subsequently drops to < 0.5 x 10^9/L or to < 1.0 x 10^9/L with fever	Hold lenalidomide treatments	Hold carfilzomib treatments
Returns to 1.0 x 10^9/L	Resume lenalidomide at 1 dose decrement	Resume carfilzomib previous dose at 1 dose decrement (dose decrease required only if treating investigator judgment is that Carfilzomib contributed to neutropenia)

Absolute neutrophil count (ANC); Complete blood count (CBC)

Toxicity	Recommended Action	
	Lenalidomide	**Carfilzomib**
Non-Blistering Rash		
Grade 3	Hold lenalidomide dose; follow weekly If the toxicity resolves to ≤ Grade 1 prior to Day 21 of the current cycle, restart at 1 dose decrement and continue the cycle until Day 21 of the current cycle.	Hold (if Treating Investigator's opinion is possibly related to Carfilzomib) until ≤ Grade 1, reinstitute at current dose
Grade 4	Discontinue lenalidomide study drug.	Hold until ≤ Grade 1, reinstitute at current dose.
Desquamating (blistering) rash – any grade	Discontinue lenalidomide study drug.	Hold until ≤ Grade 1, reinstitute at current dose.
Erythema multiforme ≥ Grade 3	Discontinue lenalidomide study drug.	Hold until ≤ Grade 1, reinstitute at current dose.
Sinus bradycardia/ other cardiac arrhythmia		
Grade 2	Hold lenalidomide dose. Follow at least weekly. If the toxicity resolves to ≤ Grade 1 prior to Day 21, restart at 1 dose decrement and continue the cycle until Day 21.	Hold until ≤ Grade 1, reinstitute at current dose.
≥ Grade 3	Discontinue lenalidomide study drug	Hold until ≤ Grade 1, reinstitute at current dose.
Allergic reaction/hypersensitivity		
Grade 2 – 3	Hold lenalidomide dose. Follow at least weekly. If the toxicity resolves to ≤ Grade 1 prior to Day 21, restart at 1 dose decrement and continue the cycle until Day 21.	Hold until ≤ Grade 1, reinstitute at current dose.
Grade 4	Discontinue	Discontinue

Toxicity	Recommended Action	
	Lenalidomide	**Carfilzomib**
Tumor lysis syndrome (≥ 3 of the following: ≥ 50% increase in creatinine, uric acid, or phosphate;≥ 30% increase in potassium;≥ 20% decrease in calcium; or ≥ 2-fold increase in LDH	Hold lenalidomide until all abnormalities in serum chemistries have resolved. Reinstitute at full doses.	Hold carfilzomib until all abnormalities in serum chemistries have resolved. Reinstitute at full doses.
Infection Grade 3 or 4	Hold lenalidomide until systemic treatment for infection is completed. If no neutropenia, restart both drugs at full dose. If neutropenic, follow neutropenic instructions.	Hold carfilzomib until systemic treatment for infection is completed If no neutropenia, restart both drugs at full dose. If neutropenic, follow neutropenic instructions.
Herpes zoster or simplex of any grade	Hold lenalidomide until lesions are dry. Reinstitute at full doses.	Hold carfilzomib until lesions are dry. Reinstitute at full doses.
Grade 2 neuropathy with pain or any Grade 3 neuropathy	Hold until ≤ Grade 2. Then restart lenalidomide at 1 dose decrement	Hold until resolved to ≤ Grade 2. Then restart carfilzomib at 1 dose decrement
Grade 4 neuropathy	Discontinue	Discontinue
Toxicity	**Recommended Action**	
	Lenalidomide	**Carfilzomib**
Renal dysfunction		
Serum creatinine > 2 mg/dL	Base dose reduction on calculated GFR (below)	Base dose reduction on calculated GFR (below)
CrCl>50 mL/min	Full dose	Full dose
CrCl <50 mL/min > 30 mL/min	Reduce lenalidomide to 10 mg every 24 h; may reinstate prior dose if, after 2 cycles, CrCl normalizes	Full dose

CrCl< 30 mL/min	Reduce lenalidomide to 15 mg every 48 h	Hold carfilzomib until CrCl> 30 mL/min; restart at 1 dose decrement
CrCl< 30 mL/min requiring dialysis	5 mg. Once daily. On dialysis days the dose should be administered following dialysis.	Hold until resolved to ≤ Grade 2. Then restart carfilzomib at 1 dose decrement
Venous thrombosis/embolism ≥ Grade 3	Hold lenalidomide dose and adjust anticoagulation regimen; re-start at Treating Investigator's discretion at full dose	No adjustment required
Hyperthyroidism or hypothyroidism	Omit lenalidomide for remainder of cycle, evaluate, and initiate appropriate therapy. Restart lenalidomide next cycle at 1 dose decrement	No adjustment required
Congestive heart failure (CHF)	Any subject with symptoms of CHF, whether or not lenalidomide related, must have the dose held until resolution or return to baseline. If CHF was felt to be lenalidomide related, reinstate by one dose decrement after return to baseline. If no resolution of CHF after 2 weeks, the subject will be withdrawn from the study.	Any subject with symptoms of CHF, whether or not carfilzomib related, must have the dose held until resolution or return to baseline. If CHF was felt to be carfilzomib related, reinstate by one dose decrement after return to baseline. If no resolution of CHF after 2 weeks, the subject will be withdrawn from the study.
Hypertension including Hypertensive Crises	NA	≥ Grade 3: Carfilzomib attribution, hold drug until resolved to ≤ Grade 2. Resume at one level dose reduction
Toxicity	**Recommended Action**	
	Lenalidomide	**Carfilzomib**

Heart problems, including rapid, strong, or irregular heartbeat **Heart attack, reduced blood flow to the heart, abnormal amount of fluid between the heart and lining around the heart, and swelling/irritation of the lining around the heart**	NA	≥ Grade 3: Carfilzomib attribution, hold drug until resolved to ≤ Grade 1. Resume at one level dose reduction
Pericardial Effusion	NA	≥ Grade 3: Carfilzomib attribution, hold drug until resolved to Grade 1. Resume at one level dose reduction
Pericarditis	NA	≥ Grade 3: Carfilzomib attribution, hold drug until resolved to Grade 1. Resume at one level dose reduction
Toxicity	**Recommended Action**	
	Lenalidomide	**Carfilzomib**
Pulmonary Hypertension	NA	= Grade 2: Carfilzomib attribution, Reduce drug: one level dose reduction ≥ Grade 3: Carfilzomib attribution, hold drug until resolved to ≤Grade 2. Resume at one level dose reduction
Pulmonary Toxicities: Interstitial Lung Disease (inc. pneumonitis), Acute Respiratory Failure, and Adult Respiratory Distress Syndrome (ARDS), cough and cough with phlegm	NA	≥ Grade 2 for Pneumonitis ≥ Grade 3 for ARDS ≥ Grade 4 for Respiratory Failure Carfilzomib attribution, hold drug until resolved to ≤Grade 1. Resume at one level dose reduction
Blood clot in the lungs, fluid in the lungs, bleeding in the lungs	NA	≥ Grade 3: Carfilzomib attribution, hold drug until resolved to ≤ Grade 1. Resume at one level dose reduction
Gastrointestinal Perforation	NA	≥ Grade 3: Carfilzomib attribution, hold drug until resolved to Grade 1. Resume at one level dose reduction

Hepatic Toxicities (≥ Grade 3 elevation of AST or ALT, Bilirubin, or other ≥ Grade 3 liver abnormalities)	Hold drug until resolved to ≤Grade 1 or baseline. Resume at the same dose or reduced dose as appropriate. If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician. Frequent monitoring of liver function should then be implemented.	Hold drug until resolved to ≤Grade 1 or baseline. Resume at the same dose or reduced dose as appropriate. If tolerated, the reduced dose may be escalated to the previous dose at the discretion of the physician. Frequent monitoring of liver function should then be implemented. Please see additional information on hepatic impairment in Table 9
Other non-hematologic toxicity assessed as lenalidomide-related ≥ Grade 3	Hold lenalidomide dose. Follow at least weekly. If the toxicity ≤ Grade 1 before Day 21 of the current cycle, restart at 1 dose decrement and continue until Day 21 of the current cycle	Full dose
Other non-hematologic toxicity assessed as carfilzomib-related	Full dose	Hold carfilzomib dose until toxicity resolves to ≤ Grade 1 or baseline. Restart at 1 dose decrement
Other non-hematologic toxicity assessed as drug-related ≥ Grade 3	Hold treatment and restart at 1 dose decrement when toxicity has resolved to ≤ Grade 1 or baseline	Hold treatment and restart at 1 dose decrement when toxicity has resolved to ≤ Grade 1 or baseline

Table 10. Additional Carfilzomib Dose modifications and Safety Measures:

Hepatic Impairment Mild to moderate liver dysfunction defined as 2 consecutive values at least 28 days apart, of: -Total bilirubin (>33%) > 1x ULN or <3x ULN OR -An elevation of AST and/or ALT with normal bilirubin	-25% dose reduction. Dose may be re-escalated if liver function tests return to normal and drug-induced hepatoxoticity is excluded. -Hold carfilzomib until resolution to baseline. Resume with a 25% dose reduction if drug-induced hepatoxicity is excluded. Monitor bilirubin and direct

-Grade 3 elevation in total bilirubin -Drug-induced hepatoxocity (attributable to carfilzomib)	bilirubin weekly. -Upon resolution of total bilirubin to normal, resume carfilzomib doing with 25% dose reduction if drug-induced hepatoxicity is excluded. -Discontinue carfilzomib
Posterior Reversible Encephalopathy Syndrome (PRES)	If PRES is suspected, hold carfilzomib, Consider MRI for onset of visual or neurological symptoms suggestive of PRES. If PRES confirmed, permanently discontinue carfilzomib. If PRES excluded, carfilzomib administration may resume at same dose if clinically appropriate.
Thrombotic Microangiopathy (TMA)	If the diagnosis is suspected, hold carfilzomib and manage per standard of care including plasma exchange as clinically appropriate. If TMA confirmed, permanently discontinue carfilzomib. If TMS excluded, carfilzomib can be restarted.
Contraception/Female	Females of child-bearing potential and/or their male partners should use effective contraception methods or abstain from sexual activity during and for 30 days after treatment with carfilzomib.
Contraception/Male	Males and/or their female partners should use effective contraceptive methods or abstain from sexual activity while treated with carfilzomib and for 90 days after treatment.
Breastfeeding/Lactation	Breastfeeding women and women planning on breastfeeding may not participate in the clinical trial
Hepatitis B reactivation	Carriers of HBV who require treatment with Kyprolis should be closely monitored for signs and symptoms of active HBV infection throughout treatment. Any subject who becomes HBV DNA positive or develops reactivation of HBV should have carfilzomib treatment interrupted and receive appropriate anti-viral treatment as per a specialist in Hepatitis B.
Progressive Multifocal Leukoencephalopathy	Patients should be monitored for any new or worsening neurologic, cognitive or behavioral signs or symptoms that may be suggestive of PML as part of the differential diagnosis of CNS disorders. If PML is suspected, patients should be promptly referred to a specialist and appropriate diagnostic testing should be initiated. Discontinue Kyprolis if PML diagnosis is confirmed.

Tumor Lysis Syndrome

Tumor lysis syndrome (TLS), which may be associated with multi-organ failure, has been observed in Cycles 1 and 2 of some subjects with multiple myeloma treated with carfilzomib. In addition, MM subjects with high tumor burden (e.g., Durie-Salmon or International Staging System (ISS) Stage II/III) or rapidly increasing M-protein or light chains or compromised renal function glomerular filtration rate (GFR) < 50 mL/min) should be considered to be at particularly high risk. All such subjects should be identified at screening.

During Cycles 1 and 2, serum electrolytes and chemistries are closely monitored. Subjects with laboratory abnormalities consistent with lysis of tumor cells (e.g., serum creatinine ≥ 50% increase, lactate dehydrogenase (LDH) ≥ 2-fold increase, uric acid ≥ 50% increase, phosphate ≥ 50% increase, potassium ≥ 30% increase, calcium ≥ 20% decrease) prior to dosing should not receive the scheduled dose. Subjects with such abnormalities should be re-evaluated as clinically indicated. The Lead Principal Investigator should be consulted if there are further delays. Subjects should be informed of signs and symptoms that may be indicative of TLS such as fevers, chills/rigors, nausea, vomiting, muscle tetany, weakness, or cramping, seizures, and decreased urine output; subjects should be instructed to report such symptoms immediately and seek medical attention.

Grade 3 or 4 Adverse Events

For other Grade 3 or 4 toxicities judged by the investigator to be related to lenalidomide alone, treatment with lenalidomide should be interrupted and restarted at the next lower dose level once the toxicity has resolved to Grade 2 or less. If a Grade 3 toxicity can be controlled (eg, a Grade 3 electrolyte disturbance that can be controlled with repletion within 24 hours), the investigator should discuss the toxicity with the sponsor's medical monitor before interrupting or lowering the lenalidomide dose. Treatment with isatuximab, carfilzomib, and dexamethasone may continue, as applicable depending on the study phase.

Dexamethasone Toxicity

For management of dexamethasone toxicity, see Table 11.

Table 11. If dexamethasone is permanently discontinued due to toxicity, pre- and post-infusion doses administered on the day of isatuximab dosing may be given at the investigator's discretion.

Table 11 represents suggested dose modifications of dexamethasone, but physician discretion and clinical judgment should prevail.

The maximum delay for toxicity before treatment is permanently discontinued will be 3 weeks; however, delays due to other circumstances should be discussed with the Principal Investigator.

Delays of >3 weeks must be discussed with the Principal Investigator. Re-treatment will be at the discretion of the Principal Investigator.

Table 11: Dexamethasone Dose Modification Based on Toxicity (NCI-CTCAE v.5.0)

SOC	Toxicity	Dose
Gastrointestinal	Grade 1-2 dyspepsia, gastric, or duodenal ulcer, gastritis requiring medical management	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measure, decrease dexamethasone dose by 50%.
	Grade 3 requiring hospitalization or surgery	Omit dexamethasone until symptoms adequately controlled Restart at 50% of current dose along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measure, discontinue dexamethasone and do not resume.
	Acute pancreatitis	Discontinue therapeutic dose of dexamethasone and do not resume
Cardiovascular	≥Grade 3 edema limiting function and unresponsive to therapy or anasarca	Diuretics as needed and decrease dexamethasone dose by 25%. If edema persists despite above measures, decrease dose to 50% of initial dose. Discontinue dexamethasone and do not resume if symptoms persist despite 50% reduction.
Neurology/Psychiatric	≥Grade 2 interfering with function but not interfering with activities of daily living	Omit dexamethasone until symptoms adequately controlled. Restart at 50% of current dose. If symptoms persist How long is too long? despite above measure, discontinue dexamethasone and do not resume.
Musculoskeletal	≥Grade 2 muscle weakness symptomatic and interfering with function but not interfering with activities of daily living	Decrease dexamethasone dose by 25%. If weakness persists despite above measures, decrease dose to 50% of initial dose. Discontinue dexamethasone and do not resume if symptoms persist despite 50% reduction.
Metabolic	≥Grade 3	≥Grade 3 hyperglycemia. Treat with insulin

	hyperglycemia	or oral hypoglycemic agents as needed. If uncontrolled despite above measures, decrease dose by 25% decrements until levels are satisfactory.

Abbreviations: NCI-CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; SOC=system

Treatment Discontinuation

Administration of isatuximab, carfilzomib, lenalidomide and dexamethasone can be discontinued permanently in the event of a treatment-related toxicity at the Treating Investigator's discretion.

If a delay of starting a new cycle is greater than 21 days, the subject should be discontinued from treatment, unless continuing treatment is mutually agreed upon by the Treating Investigator and the Lead Principal Investigator.

If isatuximab, carfilzomib, or lenalidomide requires permanent discontinuation before Cycle 4 induction, the subject's treatment will be discontinued at the end of Cycle 4 induction. If isatuximab, carfilzomib or lenalidomide requires permanent discontinuation during maintenance cycles, the subject may remain on study with the remaining drug(s). Dexamethasone may be discontinued without the subject discontinuing study treatment.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. Pretreatment symptoms/conditions to be graded at baseline and AEs to be graded at each evaluation per NCI-CTCAE v 5.0 grading.

Adverse Event List for Investigational Agent, Isatuximab*:*

Possible risks

Beside hematological malignancies, the CD38 antigen is expressed on normal immune cells and despite the lack of significant depletion in the in vitro studies, isatuximab could modulate cell survival and differentiation of both lymphoid and myeloid cells in cancer patients. This modulation could increase the risk for infections. In addition, while no association between transient cytokine increases and the occurrence of IRs has been demonstrated in patients, administration of isatuximab in the clinical setting has been correlated with a single occurrence of nonserious Grade 2 cytokine release syndrome at Cycle 1, reported as a medical diagnosis in a patient who subsequently received further administrations of single agent isatuximab without recurrence of symptoms suggestive of cytokine release syndrome.

The CD38 antigen is also expressed in several normal nonlymphoid human tissues:
• Strong specific staining was observed in the glandular epithelial cells of prostate tissues.
• Moderate to strong specific staining was observed in the endothelial cells lining the pituitary gland.
• Moderate focal staining of round cells compatible with Kupffer cells was observed in the liver.
• Staining of astrocytes in the brain and bronchial epithelium cells in the lungs was observed in a non-GLP study, though this finding was not observed in the definitive GLP tissue cross-reactivity study.

Evaluation of prostate specific antigen and pituitary hormone values were systematically assessed
before each isatuximab treatment cycle in the first-in-human Phase 1 single agent trial TED10893.

Among the 89 patients treated in Study TED10893 Phase 1, the reported laboratory abnormalities
and AE do not suggest an effect of the study treatment on these organ functions. Therefore, those systematic laboratory assessments during study treatment have no longer been considered necessary in the subsequent clinical studies.

Close monitoring of safety is required during the clinical studies and clinical exams are systematically recorded in the case report forms. Beside any tests to be performed when clinically indicated, parameters analyzed routinely until the end of treatment visit in the study protocols include: physical examination, vital signs, all AEs/Serious AEs (SAE), echocardiogram (ECG), and laboratory findings. These analyses required in all the patients during the clinical studies provide an adequate method to detect specific organ function abnormalities.

Possible adverse drug reactions
Within the context of IARs, anaphylactic reaction, cytokine release syndrome, and pyrexia are among the adverse reactions observed in patients treated with isatuximab; these reactions may involve immunogenicity mechanisms (human antihuman antigen) and hypersensitivity reactions, and are well-known to occur in association with other therapeutic mAb proteins. These adverse reactions, whether acute or delayed, may be serious and systemic.

Drug interactions
No drug-drug interaction has been observed between isatuximab other drugs used in combination (lenalidomide, pomalidomide).

Contraindications
Contraindications include:

• Known intolerance or hypersensitivity to infused proteins products, sucrose, histidine, and polysorbate 80.
• Pregnant or lactating women.

Adverse Event List(s) for Commercial Agent(s): carfilzomib, lenalidomide, dexamethasone

For each commercial agent, please refer to the package insert(s) for the comprehensive list of adverse events.

Adverse Events

7.1 Definitions

Adverse Event (AE)

An AE is any undesirable sign, symptom or medical condition or experience that develops or worsens in severity after starting the first dose of study treatment or any procedure specified in the protocol, even if the event is not considered to be related to the study.

An adverse event is any change in health occurring in a person who is a participant in biomedical research, whether this change is related or not to the research or to the product that the research is being conducted on. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of drug.

For this protocol, an abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

Serious adverse event (SAE) and events requiring expedited reporting

A serious adverse event is an undesirable sign, symptom, or medical condition, regardless of causality that:

- Results in death;
- Is life-threatening. Life-threatening means that the participant was at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction which hypothetically might have caused death had it occurred in a more severe form;
- Requires hospitalization or prolongation of existing hospitalization (i.e., the event required at least a 24-hour hospitalization or prolonged a hospitalization beyond the expected length of stay). Hospitalization admissions and/or surgical operations scheduled to occur during the study period, but planned prior to study entry are not considered SAEs if the illness or disease existed before the participant was enrolled in the trial, provided that it did not

deteriorate in an unexpected manner during the trial (e.g., surgery performed earlier than planned);

- Results in persistent or significant disability/incapacity. Disability is defined as a substantial disruption of a person's ability to conduct normal life functions;
- Is a congenital abnormality or birth defect;
- Is an important medical event. An important medical event is an event that, when based upon appropriate medical judgment may jeopardize the participant and require medical or surgical intervention to prevent one of the outcomes listed above. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, the development of drug dependency or drug abuse, or suspected transmission of infectious agents by medicinal product.

The following event must also be reported in an expedited manner:

- Results in pregnancy.
- Any adverse event arising after study treatment discontinuation/study termination that is possibly related to study treatments/procedures must be reported regardless of the delay between event onset and study treatment discontinuation/study termination.
- Secondary malignancies must be reported as serious adverse events regardless of when they occur and regardless of their relationship to the study treatments/procedures.

Events **not** considered to be serious adverse events are hospitalizations for:

- Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition, or for elective procedures of a condition unrelated to the studied indication or its treatment.
- Elective or pre-planned treatment for a pre-existing condition that did not worsen.
- Emergency outpatient treatment for an event not fulfilling the serious criteria outlined above and not resulting in inpatient admission.
- Respite care.

Please note the distinction between seriousness and severity of an AE. Severity is a measure of intensity of an event (mild, moderate, severe). However, the event itself may be of relatively minor medical significance; thus, a severe reaction may not necessarily be classified as a serious reaction. This differs from seriousness, which is based on patient/event outcome or action criteria described above and are usually associated with events that pose a threat to a patient's life or functioning. A severe adverse event does not necessarily need to be considered serious. **Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.**

Adverse Events of Special Interest

Adverse events of special interest (AESIs): An AE of special interest (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which

ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial sponsor to other parties (eg, regulators) might also be warranted. The AEs for this study are:

- Infusion reactions: ≥Grade 3
- Infections: ≥Grade 4
- Cytopenias: ≥Grade 4
- Tumor Lysis Syndrome (if present, qualifies as Grade 3 or higher per CTCAE V5.0 guidelines)
- Intervascular Hemolysis – all grades
- New primary malignancies (if present, qualifies as Grade 3 or higher per CTCAE V 5.0 guidelines), regardless of causal relationship to study drug(s), occurring at any time for the duration of the study, from the time of signing informed consent for at least 3 years, after the last dose of investigational product.

Adverse Events of Special Interest are only reported by sites in an expedited manner if the event meets the criteria for an SAE (as per Section). All other AESIs will be collected in the SDC, but do not require immediate submission.

Pregnancy

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female participant occurring while the participant is on study drug or within 28 days of the participant's last dose of study drug are to be reported immediately to Massachusetts General Hospital. If the participant is on study drug, the study drug is to be discontinued immediately and the participant is to be instructed to return any unused portion of the study drug to the Investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported immediately of the investigator's knowledge of the pregnancy by phone and e-mail/facsimile to the lead site using the Pregnancy Reporting Form. Immediately upon receipt of this report, the lead site will inform study pharmaceutical partners using the Pregnancy Reporting Form.

The female should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

The investigator will follow the female participant until completion of the pregnancy and must notify the lead site of the outcome of the pregnancy (including notification of false-positive tests) within 24 hours of having knowledge of the event by email/facsimile using the Follow-Up Pregnancy Reporting Form.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e.,

spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly [including that in an aborted fetus]), the investigator should follow the procedures for reporting SAEs (i.e., report the event to the lead site, within 24 hours of the investigator's knowledge of the event by e-mail or facsimile).

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the investigator suspects is related to the *in utero* exposure to the study drug should also be reported to the lead site, within 24 hours of the investigator's knowledge of the event by e-mail or facsimile.

In the case of a live "normal" birth, the lead site should be advised as soon as the information is available.

If the female is found not to be pregnant, any determination regarding the participant's continued participation in the study will be determined by the investigator.

Female partners of a male taking investigational product should be advised to call their healthcare provider immediately if they get pregnant. The male participant should notify the investigator of his partner's pregnancy and her healthcare provider information. The investigator will then provide this information to the lead site for follow-up as necessary.
The pharmaceutical partner may in accordance with local data privacy laws request the subject's physicians' contact information in order to follow-up the pregnancy until birth outcome. The lead site shall provide the pharmaceutical company with all reasonably requested information (within the timeframe requested by company) to enable company to evaluate and submit complete single case and aggregate safety reports to regulatory agencies according to regulatory reporting requirements, and otherwise comply with applicable law.

Expectedness

Adverse events can be "Expected" or "'Unexpected."

Expected adverse event

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered **expected** when it appears in the current Investigator's Brochure or is included in the informed consent document as a potential risk. Scheduled hospitalizations for the study treatment, participant follow-up and medical conditions related to the progression of the disease are considered to be expected SAEs.

The investigator must evaluate all abnormal lab results to determine the clinical significance. If an abnormal result appears to be clinically significant, it must be considered to be an AE.

Unexpected adverse event

For the purposes of this study, an adverse event is considered **unexpected** when it varies in nature, intensity or frequency from information provided in the current Investigator's Brochure, section 6 of the protocol, or when it is not included in the informed consent document as a potential risk.

Attribution (Causality)

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. It will be assigned by using the WHO causality method assessment linked to CTCAE grading system (as follows):

Term	Description
Certain/Definite	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory re-challenge procedure if necessary. The AE **is clearly related** to the study treatment.
Likely/Probable	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition. The AE **is likely related** to the study treatment.
Possible	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear. The AE **may be related** to the study treatment.
Unlikely	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations. The AE **is doubtfully related** to the study treatment.
Unrelated	The AE **is clearly NOT related** to the study treatment.

An event will be considered possibly study-related if causality criteria will be "certain/definite," "likely/probable," and "possible."

The causality criteria "unlikely" and "unrelated" is intended to be used when the exclusion of drug causality of a clinical event seems most plausible. It will be used to define "not study-related" events.

An event will also be considered as "concomitant drug-related," "disease progression-related" or "other cause related."

Causality will be assessed for each investigational treatment used in the trial (bortezomib, lenalidomide and dexamethasone).

If a reported SAE is considered an unexpected and suspected serious adverse reaction (SUSAR), reporting/notification rules described below must be followed.

7.2 Adverse Event Recording and Reporting

Reporting participating investigators will assess the occurrence of AEs and SAEs at all participant evaluation time points during the study. All AEs and SAEs whether reported by the participant, discovered during questioning, directly observed, or detected by physical examination, laboratory test or other means, will be recorded in the participant's medical record and on the appropriate study-specific case report forms. All AEs must be recorded in the participant's medical record, stating the duration and intensity of the event, action taken by the investigator and outcome of the event. The investigator must evaluate the causal relationship between the study drug(s) and the adverse event.

The investigator must evaluate all abnormal laboratory results to determine the clinical significance.

All AEs detected by the investigator or by the participant must be recorded on the appropriate study-specific CRFs, stating the duration and intensity of the event, action taken by the investigator and outcome of the event. The investigator must evaluate the causal relationship for each AE.

The descriptions and grading scales found in the CTEP Version 5.0 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. The CTEP Version 5.0 of the CTCAE is identified and located on the CTEP website at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Each adverse event will be assessed to determine if it meets the criteria for SAE reporting. If an SAE occurs, expedited reporting will follow local policies and regulations as appropriate.
Hematologic adverse events will be recorded/reported only if >grade 2 or if an action on study drug was required. These events should be captured on the adverse event pages of the CRF only.

7.3 Reporting Requirements

For multi-site trials where a DF/HCC investigator is serving as the sponsor, each participating investigator is required to abide by the reporting requirements set by the DF/HCC. The study must

be conducted in compliance with FDA regulations, local safety reporting requirements, and reporting requirements of the Principal Investigator/Sponsor.

Each investigative site will be responsible to report SAEs that occur at that institution to their respective IRB. It is the responsibility of each participating investigator to report serious adverse events to the Principal Investigator/Sponsor, the participating site's IRB, and others as described below.

7.4 Reporting to the Study Sponsor

Serious Adverse Event Reporting

The lead site will be responsible for SAE reporting to the pharmaceutical partners (including SUSAR events). The lead site will report all reports/outcomes associated to pregnancy or lactation exposure to the pharmaceutical partners.

If a patient experiences an SAE after signing informed consent, but prior to receiving study drug, the event will NOT be collected unless the investigator feels the event may have been caused by a protocol procedure. All serious adverse events that are related to study drug and occur \ during treatment or within 30 days of the last dose of treatment, with the exception of participants who withdraw from treatment, in whom adverse events will be collected until 60 days following the last treatment administration. All DF/HCC Reportable Adverse Events must be reported to the study sponsors within 1 working day. This includes the following:

- Grade 2 (moderate) and Grade 3 (severe) events that are unexpected and at least possibly related/associated with the intervention.

  Note: Grade 2 and Grade 3 lab abnormalities that are considered by the investigator to be clinically insignificant and do not require therapy, or adjustment in prior therapy, do not need to be reported.

- All Grade 4 (life-threatening or disabling) events that are unexpected or not specifically listed in the protocol as not requiring reporting.
- All Grade 5 (fatal) events while the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention.

Note, if the participant is in long term follow up, report the death at the time of continuing review.

Due to the additional expedited reporting criteria, the table below is a tool to summarize the reporting requirements and timelines for SAEs and DF/HCC reportable adverse events.

Attribution	SAEs	DF/HCC Reportable AEs				
	All SAEs (section 7.1)	Gr. 2 & 3 AE Expected#	Gr. 2 & 3 AE Unexpected#	Gr. 4 AE Expected#	Gr. 4 AE Unexpected#	Gr. 5 AE Expected or Unexpected
Unrelated Unlikely	24 hours	Not required	Not required	5 calendar days*	5 calendar days	24 hours
Possible Probable Definite	24 hours	Not required	5 calendar days	5 calendar days*	5 calendar days	24 hours

If event meets SAE criteria listed in section 7.1 in addition to grade, attribution and expectedness, event must be reported within 24 hours.

* If listed in protocol as expected and not requiring reporting, event does not need to be reported.

Participating investigators must report each serious and/or DF/HCC reportable adverse event in accordance with the table above using the MEDWATCH FDA Form 3500A form or local IRB report form. In the event that the participating investigator does not become aware of the serious adverse event immediately (e.g., participant sought treatment elsewhere) or within the time frames listed in the table above, the participating investigator is to report the event within 24 hours after learning of it and document the time of his or her first awareness of the adverse event.

The Overall PI will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

Non-Serious Adverse Event Reporting

Non-serious adverse events will be reported on the adverse event Case Report Form.

7.5 Reporting to the Food and Drug Administration (FDA)

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.6 Reporting to Hospital Risk Management

Participating investigators will report to their local Risk Management office any participant safety reports, sentinel events or unanticipated problems that require reporting per institutional policy.

7.7 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the Institutional Review Board (IRB), FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

8. STUDY CALENDAR

Baseline evaluations are to be conducted within 28 days prior to start of protocol therapy. Scans and x-rays must be done ≤4 weeks prior to the start of therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

Assessments must be performed prior to administration of any study agent. Study assessments and agents should be administered within ± 8 days of the protocol-specified date, unless otherwise noted.

Table 12 Treatment Schedule-Representative Cycle for Induction Phase

Study treatment	Days																												
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Lenalidomide	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Carfilzomib	X							X							X													
Isatuximab[a]	X							X							X							X						
Dexamethasone	X	X						X	X						X	X						X	X					

a - IV every week (Q1W) for 8 weeks, then every 2 weeks (Q2W) for 16 weeks, thereafter, every 4 weeks (Q4W). Note that this table is a representative cycle for the induction phase in the first 8 weeks.

Table 13 Treatment Schedule-Representative Cycle for Maintenance Phase

Study treatment	Days																												
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28
Lenalidomide	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X							
Carfilzomib[a]	X														X													
Isatuximab[a]	X																											

a – Carfilzomib and isatuximab for high-risk patients only; lenalidomide alone for standard-risk. Isatuximab will discontinue after completing two years of maintenance.

In the maintenance phase, dexamethasone 20mg PO or IV will be administered to patients as a pre-infusion medication prior to isatuximab dosing.

Table 14: Schedule of Assessments

Table 14A: KRDI with Autologous Stem Cell Transplant

	Screening (Within 28 days prior to registration)[1]	Induction Phase				Maintenance Phase (Cycles 7+)	At treatment discontinuation (30 [d ± 7] days after last dose)	Follow up[18] (Every 12 ± 3 weeks)
		Treatment Phase (Cycles 1-2)	Treatment Phase (Cycles 3-4)	Auto-SCT	Consolidation Phase (Cycles 5-6)			
Procedures (± 8-day window for obtaining all assessments)								
Informed consent[2]								
Demographics/Medical History	X							X
ECOG Performance Status	X	X	X		X	X	X	X
12 lead ECG	X							
Physical Examination including height and weight[3]	X	X	X		X	X	X	X
Vital Signs (temperature, heart rate, blood pressure)[4]	X	X	X		X	X	X	X
AE evaluation		X	X		X	X	X	
Blood type/indirect antiglobulin test	X							
Pulmonary Function Test FEV1[5]	X							
Bone Marrow Biopsy[6]	X	After 4 cycles, at the completion of consolidation, and after 24 cycles (± 3 weeks) if sCR or CR maintained (including subjects with VGPR or better and suspected isatuximab interference)					X[7]	
Laboratory Assessments								
CBC with diff[8]	X	D1, 8, 15, 22	D1, 15		D1, 15	X	X	X
Serum Chemistries[9]	X	D1, 8, 15, 22	D1, 15		D1, 15	X	X	X
Creatinine Clearance[10]	X	D1, 8, 15, 22	D1, 15		D1, 15	X	X	
SPEP, IFE, B2M	X	X	X		X	X	X	X
Free light chain testing	X	X	X		X	X	X	X
UPEP [17]	X	X	X[17]		X[17]	X[17]	X[17]	X[17]
24-hour urine, protein, creatinine [17]	X	X	X[17]		X[17]	X[17]	X[17]	
Pregnancy Test[11]	X	X	X		X	X	X	
Interference Testing[12]	X	X	X		X	X	X	
MRD (aspirate)[13]		After 4 cycles, at completion of consolidation, and after 24 cycles (± 3 weeks) if sCR or CR maintained (including subjects with VGPR or better and suspected isatuximab interference)						
Imaging Assessments								

Skeletal Survey[14]	X							
Extramedullary Plasmacytoma [15]	X							
DXA[16]	X					X		
Quality of Life Assessments								
EORTC-QLQ-C30		X	X		X	X	X	
EORTC-QLQ-MY20		X	X		X	X	X	

Table 14B: KRDI with Transplant-Deferred

	Screening (Within 28 days prior to registration)[1]	Induction Phase		Maintenance Phase (Cycles 9+)	At treatment discontinuation (30 [d ± 7] days after last dose)	Follow up[18] (Every 12 ± 3 weeks)
		Treatment Phase (Cycles 1-2)	Treatment Phase (Cycles 3-8)			
		Procedures (± 8-day window for obtaining all assessments)				
Informed consent[2]						
Demographics/Medical History	X					X
ECOG Performance Status	X	X	X	X	X	X
12 lead ECG	X					
Physical Examination including height and weight[3]	X	X	X	X	X	X
Vital Signs (temperature, heart rate, blood pressure)[4]	X	X	X	X	X	X
AE evaluation		X	X	X	X	
Blood type/indirect antiglobulin test	X					
Pulmonary Function Test FEV1[5]	X					
Bone Marrow Biopsy[6]	X	After 4 cycles, at the completion of induction, and after 24 cycles (± 3 weeks) if sCR or CR maintained (including subjects with VGPR or better and suspected isatuximab interference)			X[7]	
Laboratory Assessments						
CBC with diff[8]	X	D1, 8, 15, 22	D1, 15	X	X	X
Serum Chemistries[9]	X	D1, 8, 15, 22	D1, 15	X	X	X
Creatinine Clearance[10]	X	D1, 8, 15, 22	D1, 15	X	X	
SPEP, IFE, B2M	X	X	X	X	X	X

Free light chain testing	X	X	X	X	X	X
UPEP [17]	X	X	X[17]	X[17]	X[17]	X[17]
24-hour urine, protein, creatinine[17]	X	X	X[17]	X[17]	X[17]	
Pregnancy Test[11]	X	X	X	X	X	
Interference Testing[12]	X	X	X	X	X	
MRD (aspirate)[13]	X	After 4 cycles, at the completion of induction, and after 24 cycles (± 3 weeks) if sCR or CR maintained (including subjects with VGPR or better and suspected isatuximab interference)			X[7]	
Imaging Assessments						
Skeletal Survey[14]	X					
Extramedullary Plasmacytoma [15]	X					
DXA[16]	X			X		
Quality of Life Assessments						
EORTC-QLQ-C30		X	X	X	X	
EORTC-QLQ-MY20		X	X	X	X	

Abbreviations: AE= adverse events; ANC= absolute neutrophil count; B2M=Beta2-Microglobulin; Cycle= each cycle is 28 Days.; DXA = dual-energy x-ray absorptiometry; IFE=Immunofixation; MRD = Minimal Residual Disease; SPEP= Serum protein electrophoresis, UPEP=Urine protein electrophoresis.

[1] ≤28 days prior to patient enrollment. Some pretreatment clinical laboratory values should be tested ≤14 days of registration.

[2] Informed consent must be obtained before any study assessments are performed unless it is standard of care.

[3] Physical examination: A routine physical examination by the investigator (or the designated physician will include height (screening only) and weight. Height will be measured only once at screening. Weight will be measured on every visit day. Actual weight on C1D1 should be used for initial dose calculation. If a subject's weight changes by more than 10% from C1D1, the dose of all study treatments should be re-calculated.

[4] Vital signs (temperature, pulse/heart rate, respiratory rate, and blood pressure) will be measured in sitting position. For all infusions except C1D1 (see note below), these should be measured immediately before the start of isatuximab infusion, prior to each infusion rate increase, and at the end of isatuximab infusion.

[5] Pulmonary function testing (spirometry) is required only for subjects with chronic obstructive pulmonary disease or asthma. FEV1 should be measured.

[6] Bone marrow biopsy and aspirate for morphology, immunohistochemistry, or immunofluorescence, cytogenetics- Fluorescent in situ hybridization (FISH), and karyotype. FISH testing to include del(17p), t(4;14), t(14;16), t(14;20), and 1q duplication. Bone marrow biopsy is recommended at the time of best response for confirmation of complete response.

[7] Bone marrow biopsy recommended at time of progression.

[8] CBC with differential: Complete blood count with differential (includes white blood cells, red blood cells, platelets, ANC, lymphocyte and hemoglobin).

[9] Serum chemistries: To include sodium, potassium, chloride, bicarbonate, calcium, magnesium, phosphorus, blood urea, nitrogen, creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, and uric acid.

[10] Creatinine clearance: Estimated glomerular filtration rate will be calculated using Cockcroft-Gault equation.

[11] Pregnancy test will be done at screening and once every cycle. Urine or serum HCG may be tested based on institutional preference.

[12] For all patients with VGPR, a positive serum IFE, and a negative SPEP and/or patients with an M-protein of ≤.02 g/dL on SPEP and IgG kappa MM

[13] At all visits, during the bone marrow aspirate procedure, the first aspirate sample that is drawn will be sent to the central laboratory to determine MRD. All bone marrow aspirates to be sent to the central laboratory should be at least 5 mL. Any patient with a residual IgG kappa M-protein obtaining a VGPR be tested. There should also be a note that patient with a non-IgG kappa myeloma who have a measurable IgG kappa M-protein after treatment be tested as well. Additional bone marrow aspirate samples may be taken and used for local laboratory testing. MRD will be tested after 4 cycles, at the completion of induction, and after 24 cycles if CR maintained

[14] Skeletal Survey: Radiograph of skull, spine, chest, pelvis, upper extremities shoulder to elbow, lower extremities hip to knee.

[15] Clinical examination or MRI may be used (subjects with history; physical or radiologic examination, as applicable).

[16] DXA to be performed at baseline and at the completion of induction (transplant-deferred) or consolidation (post-SCT)

[17]24 hour urine & UPEP may be omitted after Cycle 2 if subjects disease is not followed by Urine M Protein. Except at time of suspected CR and sCR.

[18] The first follow up visit should occur three months after the end of treatment visit.

9.0 MEASUREMENT OF EFFECT

9.1 International Myeloma Working Group (IMWG) Response Categories

Disease evaluations will be performed at the completion of each cycle of treatment during the induction phase and then at the completion of every even cycle (14, 16, 20, etc.) during maintenance phase until disease progression.

Isatuximab detection on serum immunofixation electrophoresis (IFE) has been demonstrated in patients treated and may interfere with the traditional IMWG criteria of negative serum IFE for CR or sCR. To mitigate this interference, serum M-protein interference sampling will be performed.

For all patients with VGPR, a positive serum IFE, and a negative M-protein by serum protein electrophoresis (SPEP), reflex IFE testing will be performed to confirm the presence of isatuximab on IFE. In addition, patients who have an SPEP of ≤0.2 g/dL and IgG kappa MM, reflex testing will also be performed to determine whether the para-protein identified on SPEP/IFE is monoclonal isatuximab or the patient's endogenous myeloma protein.

IMWG Uniform Response Criteria + Definition of Minimal Response as Adopted from the EBMT Criteria

The IMWG uniform response criteria will be used for determining response to therapy and progression of disease (Table 15). Source documentation for all biochemical and radiographic evaluations of disease will be collected for confirmation of response and disease progression.

Table 15: IMWG Uniform Response Criteria

Response Category	Response Criteria	Response Criteria for Disease Measurable by Serum FLC Testing Only
Complete Response (CR)	Negative serum immunofixation and 24-hour urine immunofixation, disappearance of all extramedullary plasmacytomas (if present at baseline) and <5% plasma cells on repeat bone marrow examination.	All other criteria for CR met + normal serum free light chain ratio.
Stringent Complete Response (sCR)	All criteria for CR must be met + normal serum free light chain ratio + absence of clonal plasma cells on bone marrow examination by immunohistochemistry or 2- to 4-color flow cytometry.	All other criteria for sCR met + normal serum free light chain ratio.
Very Good Partial Response (VGPR)	Serum and urine M-protein detectable on immunofixation testing but not on electrophoresis OR ≥90% reduction in serum M-protein plus urine M-protein <100 mg/24 hours.	≥90% reduction in the difference between the involved and uninvolved serum free light chain level.
Partial Response (PR)	≥50% decrease in the serum M-protein + ≥90% reduction in the urine M-protein OR to <200 mg/24 hours + ≥50% reduction in the size of extramedullary plasmacytomas (if present at baseline).	≥50% reduction in the difference between the involved and uninvolved serum free light chain level.
Minimal Response (MR)	25% - 49% decrease in the serum M-protein + 50 – 89% reduction in the urine M-protein + 25% – 49% reduction in the size of extramedullary plasmacytomas (if present at baseline) + no increase in size or number of lytic bone lesions (development of compression fracture does not exclude response).[a]	
Stable Disease (SD)	Not meeting criteria for CR, sCR, VGPR, PR, MR, or PD	

Progressive Disease (PD)	Increase of ≥25% from lowest response value (nadir)[b] in any of the following: 1) Serum M-protein (absolute increase must be ≥0.5 g/dL) AND/OR: 2) Urine M-protein (absolute increase must be ≥200 mg/24 hours) AND/OR: 3) For patients without a measurable serum or urine M-protein but measurable disease by serum free light chain testing: Difference between the involved and uninvolved serum free light chain level (absolute increase must be ≥10 mg/dL) AND/OR: 4) For patients without a measurable serum or urine M-component or serum free light chain level: % marrow involvement with myeloma (absolute increase must be ≥10%). Definite development of new bone lesions or extramedullary plasmacytomas or definite increase in the size of existing bone lesions or extramedullary plasmacytomas.

[a] For patients who do not have measurable disease by M-protein measurement or serum free light chain levels but ≥30% involvement of the marrow at baseline, a ≥50% reduction of bone marrow involvement is required to meet criteria for a PR.

[b] The lowest response value (nadir) does not have to be a value that has been confirmed by repeat measurement.

9.2 Minimal Residual Disease Assessment

Minimal residual disease (MRD) assessment will be assessed by next generation sequencing in both blood and bone marrow aspirate whenever a bone marrow (BM) sample is obtained as described in (Table 16) at the time points mentioned in and the Schedule of Assessments. Please see the Appendix F for details of MRD collection and processing.

Table 16: Bone Marrow Testing Requirements

Sample	Local Laboratory Testing	Central Laboratory Testing
Screening aspirate and biopsy	Cytogenetics (FISH[a]), morphology, immunohistochemistry, immunofluorescence, or flow cytometry	MRD: a portion of the BM aspirates (at least 5 mL) collected at screening will be sent to a central laboratory. If a fresh BM aspirate will not be performed at screening because a sample is available within 28 days prior to enrollment, then non-decalcified diagnostic tissue (BM aspirate smear or clot slides) should be collected for MRD assessment
Follow-up aspirate and/or biopsy	Morphology, immunohistochemistry, immunofluorescence, or flow cytometry	MRD: a portion of the BM aspirates (at least 5 mL) collected at screening will be sent to a central laboratory.
For response confirmation, additional BM aspirates or biopsies will be performed locally to confirm CR or sCR		
To confirm CR or sCR at any time (including patients with VGPR or better and suspected istuximab interference) immunohistochemistry, immunofluorescence (requires kappa/lambda ration from analysis of ≥ 100 cells) or 2- to 4- color flow cytometry		

[a]FISH- testing to include del(17p), t(4;14), t(14;16), t(14;20), and 1q duplication

9.3 Assessment of Lytic Bone Disease

A complete skeletal survey (including skull, entire vertebral column, pelvis, chest, humeri, femora, and any other bones for which the investigator suspects involvement by disease) is to be performed and evaluated by the local roentgenography during the screening phase. Magnetic resonance imaging and/or low dose computerized tomography (CT)-scan, and/or positron

emission tomography (PET)/CT fusion studies are acceptable methods for evaluation of bone disease and may be included at the discretion of the investigator. If an alternative imaging modality (MRI, CT, or PET/CT) was used prior to registration in addition to the complete skeletal survey, then both methods must be used to document disease status.

Sometimes subjects present with disease progression manifested by symptoms of pain due to bone changes. Therefore, disease progression may be documented, in these cases, by skeletal survey or other imaging studies, depending on the symptoms that the subject experiences. If the diagnosis of disease progression is obvious by radiographic investigations, then no repeat confirmatory x-rays are necessary. In instances where changes may be more subtle, a repeat x-ray may be needed in 1 to 3 weeks.

9.4 Documentation of Extramedullary Plasmacytomas

Sites of known extramedullary plasmacytomas must be documented prior to registration. Clinical examination or MRI may be used to document extramedullary sites of disease. Computed tomography scan evaluations are an acceptable alternative if there is no contraindication to the use of IV contrast. Positron emission tomography scan or ultrasound tests are not acceptable to document the size of extramedullary plasmacytomas. However, PET/CT fusion studies are acceptable.

Extramedullary plasmacytomas should be assessed for all subjects with a history of plasmacytomas, or if clinically indicated prior to registration, by clinical examination or radiologic imaging. Assessment of measurable sites of extramedullary disease will be performed and evaluated locally for subjects with a history of plasmacytomas or as clinically indicated during treatment until development of confirmed CR or confirmed disease progression. If assessment can only be performed radiologically, then evaluation of extramedullary plasmacytomas must be performed according to the Schedule of Assessments. For every subject, the methodology used for evaluation of each disease site should be consistent across all visits. Irradiated or excised lesions will be considered not measurable and will be monitored only for disease progression.

To qualify for PR, the sum of products of the perpendicular diameters of the existing extramedullary plasmacytomas must have decreased by at least 50%, and new plasmacytomas must not have developed. To qualify for disease progression, either the sum of products of the perpendicular diameters of the existing extramedullary plasmacytomas must have increased by at least 50% or a new plasmacytoma must have developed. In the cases where not all existing extramedullary plasmacytomas are reported, but the sum of products of the perpendicular diameters of the reported plasmacytomas have increased by at least 50%, this will also qualify as disease progression.

9.5 Isatuximab Interference with Indirect Antiglobulin Test Results

Based on information published in relation to a drug of the same class as isatuximab, daratumumab[48], the CD38 protein is weakly expressed on the surface of red blood cells. Because of this, anti-CD38 antibodies in patients' plasma can lead to pan-reactivity and thus interfere with various blood bank serologic tests. For example, plasma samples from daratumumab-treated patients showed positive reactions in indirect antiglobulin tests, antibody detection (screening) tests, antibody identification panels, and antihuman globulin crossmatches. ABO/RhD typing is not affected by anti-CD38 antibody.

To avoid potential problems with blood transfusion, the American Association of Blood Banks recommends that patients being treated with anti-CD38 antibodies have blood type and screen tests performed at baseline. After treatment, and each time before blood transfusion, the antibody screen test (indirect Coombs test) should be performed.

9.6 Evaluation of Body Composition

Fat and lean mass will be measured using DXA (Hologic QDR 4500, Hologic Inc., Waltham, MA) at the three pre-specified time points. Total lean mass, extremity lean mass, total fat and trunk fat mass, as well as visceral adipose tissue mass will be quantified using Hologic APEX 3.1 software (Hologic).

9.7 Patient-Reported Outcomes

The European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 includes 30 items resulting in 5 functional scales (physical functioning, role functioning, emotional functioning, cognitive functioning, and social functioning), 1 global health status scale, 3 symptom scales (fatigue, nausea and vomiting, and pain), and 6 single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties. Administration time is approximately 11 minutes.

The EORTC QLQ-MY20 is a disease-specific validated instrument, that contains 20 questions that measures 4 myeloma-specific PRO domains: disease symptoms, side effects of treatment, future perspective, and body image.

10. DATA REPORTING

10.1.1 Method

The DF/HCC Office of Data Quality (ODQ) will collect, manage, and perform quality checks on the data for this study.

10.1.2 Responsibility for Data Submission

All participating sites are responsible for submitting data and/or data forms to the ODQ according to the schedule set by the ODQ.

11.0 DATA SAFETY MONITORING

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of medical oncologists, research nurses, pharmacists and biostatisticians with direct experience in cancer clinical research. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

The DSMC will review each protocol up to four times a year with the frequency determined by the outcome of previous reviews. Information to be provided to the committee may include: up-to-date participant accrual; current dose level information; dose-limiting toxicity (DLT) information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 30 days of intervention for Phase I or II protocols; for gene therapy protocols, summary of all deaths while being treated and during active follow-up; any response information; audit results, and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12.0 STATISTICAL CONSIDERATIONS

12.1 Study Design/Endpoints

50 patients will be enrolled.

Statistical Power Calculations:
The reference CR rate after 4 cycles of treatment is assumed to be 0.27. A study with a sample size of 50 achieves 80% power to detect a difference (P1-P0) of 0.16 using a one-sided, one sample exact binomial test at a significance level of 0.10, assuming that the CR rate (P1) in the study population is at least 0.43. If 19 or more patients experience a CR, the study will reject the reference rate of 0.27 in favor of a higher CR rate. If 10% of patients do not complete 4 cycles of treatment, the sample size of 45 evaluable patients still achieves 80% power to detect a difference of 0.16 based on the above assumptions. With 45 evaluable patients, the study will reject the reference CR rate of 0.27 in favor of a higher rate if 17 or more patients experience a CR.

Primary Analysis: Efficacy analysis will be performed both the Intent-to-Treat (ITT) Population and Efficacy Evaluable (EE) Population. The ITT Population will include all treated patients, and the EE Population will include all patients who meet eligibility criteria, receive at least 1 cycle of study drug, and have at least 1 post-baseline efficacy assessment. The primary analysis will be based on the EE population, and will use the Investigator-assessed response data

evaluated according to consensus recommendations based on the IMWG criteria. CR (CR+sCR) rate to treatment after 4 cycles of KRDI as assessed by site Investigators using the International Myeloma Working Group (IMWG) Uniform Response criteria will be reported with 90% confidence interval. Secondary analyses will evaluate CR rate at other pre-determined time-points.
Secondary Analysis: Secondary analyses will evaluate overall response rate, MRD rate, PFS and OS. Overall response rate will be percent of patients who achieve at least partial response (PR). Percent of patients achieving MR or better will also be collected as clinical benefit response. MRD rate after 4 cycles, at completion of induction, and at 24 months will be determined by deep sequencing of genomic deoxyribonucleic acid from bone marrow samples using rearranged Ig locus-specific primers (Adaptive, Seattle, WA). PFS will be defined as the time from first dose of study treatment to the first documentation of PD or death from any cause during study. OS will be defined as the time from first dose of study treatment to death from any cause. For responders, time to response (TTR) and duration of response (DOR) will be analyzed. TTR will be defined as the time from first dose of study treatment to the first documentation of response (either PR, very good partial response (VGPR) or CR, nCR, and sCR). DOR will be defined as the time from the first PR, VGPR, or CR to the first documentation of PD or death, whichever occurs earlier.

Response rates together with confidence intervals (CIs) will be provided. Kaplan-Meier curves will be used to characterize the time-to-event outcomes(PFS, OS, response duration) when there is censoring; univariate summary statistics will be provided for TTR. In addition, outcomes including median PFS and median OS will be calculated within sub-groups based on risk status (standard vs high) and MRD status (positive vs negative).

A 90% CI for the response rate will be constructed for evaluating the efficacy of KRDI. Kaplan-Meier curves will be constructed to characterize PFS, OS, and DOR. One sample standard inferences for PFS, OS, and DOR will be made accordingly.

Demographic, Disposition, Study Medication:
The baseline (C1D1) characteristics of patients enrolled in the study will be summarized. An accounting will be made of the study course for all patients who received study drug and, in particular, the number of patients who died or withdrew during treatment will be specified and reasons for withdrawal categorized. Study drug administration and information on dose reductions will be summarized.

Safety Analysis:
Safety data will be summarized when all patients have completed the first 28-day cycle (C1). Safety data for patients undergoing SCT, as well as for patients who continued treatment without SCT, will be analyzed when all patients have completed consolidation therapy. All patients who received at least one dose of study drug will be included in the safety analyses. SAEs, treatment-

emergent AEs, vital sign measurements, clinical laboratory information, and concomitant medications will be tabulated and summarized when appropriate. Patient incidence rates of all AEs (including serious, Grade 3/4, treatment-related, and events requiring the discontinuation of investigational product), will be tabulated by system organ class (SOC), preferred term, and severity using Medical Dictionary for Regulatory Activities (MedDRA) terms and NCI CTCAE Version 5.0 severity grades. Death, SAEs, and AEs resulting in study discontinuation will also be summarized. AEs leading to dose reduction or interruption will also be tabulated. All other measurements will be summarized using means, standard deviations, medians, minimum, and maximum. Graphical displays will be provided where useful in the interpretation of results.

Safety Stopping Rule:

If 3 or more of the first 10 treated patients develop a Grade >= 4 adverse event (AE) that is possibly, probably or definitely related to treatment, enrollment to the trial will be temporarily suspended so that all AE data can be examined. Additionally, once the number of treated patients exceeds 10, if at any point during treatment 30% or more of patients develop a Grade >= 4 adverse event (AE) possibly/probably/definitely related to treatment, enrollment will be temporarily suspended for review of AE data. These stopping rules apply to the cumulative number of Grade >=4 AEs and patients treated across study arms, not within arms separately.

If 3 or more of the first 10 treated are unable to collect adequate stem cells for autologous stem cell transplant, enrollment to the trial will be temporarily suspended so that the stem cell collection data can be examined. Additionally, once the number of treated patients exceeds 10, if at any point during treatment 30% or more of patients are unable to collect adequate stem cells for autologous stem cell transplant, enrollment will be temporarily suspended for review of the stem cell collection data.

12.2 Analysis of Secondary Endpoints

QOL Evaluations
The QOL will be measured using the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life (QOL) Questionnaire - Core (QLQ-30), the MY20 questionnaire. Descriptive statistics will be presented for change from baseline in QOL over time. Analyses will be performed on summary scores as well as individual items.

Body Composition
The endpoints for body composition will include changes in lean and fat mass from baseline to the final study assessment.

11.3 Evaluation of toxicity

All participants will be evaluable for toxicity from the time of their first treatment.

13. PUBLICATION PLAN

The results should be made public within 24 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than three (3) years after the end of the study.

14. REFERENCES

1. Siegel, R.L., K.D. Miller, and A. Jemal, *Cancer statistics, 2018.* CA Cancer J Clin, 2018. **68**(1): p. 7-30.
2. Kyle, R.A., et al., *Review of 1027 patients with newly diagnosed multiple myeloma.* Mayo Clin Proc, 2003. **78**(1): p. 21-33.
3. Demo, S.D., et al., *Antitumor activity of PR-171, a novel irreversible inhibitor of the proteasome.* Cancer Res, 2007. **67**(13): p. 6383-91.
4. Chauhan, D., et al., *A novel orally active proteasome inhibitor ONX 0912 triggers in vitro and in vivo cytotoxicity in multiple myeloma.* Blood, 2010. **116**(23): p. 4906-15.
5. Wang, M., et al., *Phase 2 dose-expansion study (PX-171-006) of carfilzomib, lenalidomide, and low-dose dexamethasone in relapsed or progressive multiple myeloma.* Blood, 2013. **122**(18): p. 3122-8.
6. Jakubowiak, A.J., et al., *A phase 1/2 study of carfilzomib in combination with lenalidomide and low-dose dexamethasone as a frontline treatment for multiple myeloma.* Blood, 2012. **120**(9): p. 1801-9.
7. Stewart, A.K., et al., *Carfilzomib, lenalidomide, and dexamethasone for relapsed multiple myeloma.* N Engl J Med, 2015. **372**(2): p. 142-52.
8. Berenson, J.R., et al., *CHAMPION-1: a phase 1/2 study of once-weekly carfilzomib and dexamethasone for relapsed or refractory multiple myeloma.* Blood, 2016. **127**(26): p. 3360-8.
9. Moreau, P., et al., *Once weekly versus twice weekly carfilzomib dosing in patients with relapsed and refractory multiple myeloma (A.R.R.O.W.): interim analysis results of a randomised, phase 3 study.* Lancet Oncol, 2018. **19**(7): p. 953-964.
10. Biran, N., et al., *Weekly carfilzomib, lenalidomide, and dexamethasone in relapsed or refractory multiple myeloma: A phase 1b study.* Am J Hematol, 2019. **94**(7): p. 794-802.
11. Martin, T., et al., *A phase 1b study of isatuximab plus lenalidomide and dexamethasone for relapsed/refractory multiple myeloma.* Blood, 2017. **129**(25): p. 3294-3303.
12. Kronke, J., et al., *Lenalidomide causes selective degradation of IKZF1 and IKZF3 in multiple myeloma cells.* Science, 2014. **343**(6168): p. 301-5.
13. Lopez-Girona, A., et al., *Cereblon is a direct protein target for immunomodulatory and antiproliferative activities of lenalidomide and pomalidomide.* Leukemia, 2012. **26**(11): p. 2326-35.
14. Lu, G., et al., *The myeloma drug lenalidomide promotes the cereblon-dependent destruction of Ikaros proteins.* Science, 2014. **343**(6168): p. 305-9.
15. Weber, D.M., et al., *Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America.* N Engl J Med, 2007. **357**(21): p. 2133-42.
16. Dimopoulos, M., et al., *Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma.* N Engl J Med, 2007. **357**(21): p. 2123-32.
17. Dimopoulos, M.A., et al., *Long-term follow-up on overall survival from the MM-009 and MM-010 phase III trials of lenalidomide plus dexamethasone in patients with relapsed or refractory multiple myeloma.* Leukemia, 2009. **23**(11): p. 2147-52.
18. Benboubker, L., et al., *Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma.* N Engl J Med, 2014. **371**(10): p. 906-17.

19. Mitsiades, N., et al., *Apoptotic signaling induced by immunomodulatory thalidomide analogs in human multiple myeloma cells: therapeutic implications.* Blood, 2002. **99**(12): p. 4525-30.
20. Richardson, P.G., et al., *Lenalidomide, bortezomib, and dexamethasone combination therapy in patients with newly diagnosed multiple myeloma.* Blood, 2010. **116**(5): p. 679-86.
21. Kumar, S., et al., *Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma.* Blood, 2012. **119**(19): p. 4375-82.
22. Durie, B.G., et al., *Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): a randomised, open-label, phase 3 trial.* Lancet, 2017. **389**(10068): p. 519-527.
23. Korde, N., et al., *Treatment With Carfilzomib-Lenalidomide-Dexamethasone With Lenalidomide Extension in Patients With Smoldering or Newly Diagnosed Multiple Myeloma.* JAMA Oncol, 2015. **1**(6): p. 746-54.
24. Sonneveld, P., et al., *Treatment of multiple myeloma with high-risk cytogenetics: a consensus of the International Myeloma Working Group.* Blood, 2016. **127**(24): p. 2955-62.
25. Nooka, A.K., et al., *Consolidation and maintenance therapy with lenalidomide, bortezomib and dexamethasone (RVD) in high-risk myeloma patients.* Leukemia, 2014. **28**(3): p. 690-3.
26. Avet-Loiseau, H., et al., *Bortezomib plus dexamethasone induction improves outcome of patients with t(4;14) myeloma but not outcome of patients with del(17p).* J Clin Oncol, 2010. **28**(30): p. 4630-4.
27. Neben, K., et al., *Administration of bortezomib before and after autologous stem cell transplantation improves outcome in multiple myeloma patients with deletion 17p.* Blood, 2012. **119**(4): p. 940-8.
28. Rosinol, L., et al., *Superiority of bortezomib, thalidomide, and dexamethasone (VTD) as induction pretransplantation therapy in multiple myeloma: a randomized phase 3 PETHEMA/GEM study.* Blood, 2012. **120**(8): p. 1589-96.
29. Cavo, M., et al., *Bortezomib with thalidomide plus dexamethasone compared with thalidomide plus dexamethasone as induction therapy before, and consolidation therapy after, double autologous stem-cell transplantation in newly diagnosed multiple myeloma: a randomised phase 3 study.* Lancet, 2010. **376**(9758): p. 2075-85.
30. Sonneveld, P., et al., *Bortezomib-based versus nonbortezomib-based induction treatment before autologous stem-cell transplantation in patients with previously untreated multiple myeloma: a meta-analysis of phase III randomized, controlled trials.* J Clin Oncol, 2013. **31**(26): p. 3279-87.
31. Cavo M, S.H., Rosinol L, et al. , *Double vs single autologous stem cell transplantation after bortezomib-based induction regimens for multiple myeloma: an integrated analysis of patient-level data from phase European III studies [abstract].* Blood 2013;122(21) Abstract 767.
32. van Rhee, F., et al., *Total Therapy 3 for multiple myeloma: prognostic implications of cumulative dosing and premature discontinuation of VTD maintenance components, bortezomib, thalidomide, and dexamethasone, relevant to all phases of therapy.* Blood, 2010. **116**(8): p. 1220-7.

33. Pineda-Roman, M., et al., *Sustained complete remissions in multiple myeloma linked to bortezomib in total therapy 3: comparison with total therapy 2.* Br J Haematol, 2008. **140**(6): p. 625-34.
34. Kapoor, P., et al., *Impact of risk stratification on outcome among patients with multiple myeloma receiving initial therapy with lenalidomide and dexamethasone.* Blood, 2009. **114**(3): p. 518-21.
35. Palumbo, A., et al., *Autologous transplantation and maintenance therapy in multiple myeloma.* N Engl J Med, 2014. **371**(10): p. 895-905.
36. Attal, M., et al., *Lenalidomide maintenance after stem-cell transplantation for multiple myeloma.* N Engl J Med, 2012. **366**(19): p. 1782-91.
37. Palumbo, A., et al., *Continuous lenalidomide treatment for newly diagnosed multiple myeloma.* N Engl J Med, 2012. **366**(19): p. 1759-69.
38. McCarthy, P.L., et al., *Lenalidomide after stem-cell transplantation for multiple myeloma.* N Engl J Med, 2012. **366**(19): p. 1770-81.
39. Avet-Loiseau, H., et al., *Impact of high-risk cytogenetics and prior therapy on outcomes in patients with advanced relapsed or refractory multiple myeloma treated with lenalidomide plus dexamethasone.* Leukemia, 2010. **24**(3): p. 623-8.
40. Lonial, S., et al., *Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma.* N Engl J Med, 2015. **373**(7): p. 621-31.
41. Dimopoulos, M.A., et al., *Cytogenetics and long-term survival of patients with refractory or relapsed and refractory multiple myeloma treated with pomalidomide and low-dose dexamethasone.* Haematologica, 2015. **100**(10): p. 1327-33.
42. Leleu, X., et al., *Pomalidomide plus low-dose dexamethasone in multiple myeloma with deletion 17p and/or translocation (4;14): IFM 2010-02 trial results.* Blood, 2015. **125**(9): p. 1411-7.
43. Roussel, M., et al., *Front-line transplantation program with lenalidomide, bortezomib, and dexamethasone combination as induction and consolidation followed by lenalidomide maintenance in patients with multiple myeloma: a phase II study by the Intergroupe Francophone du Myelome.* J Clin Oncol, 2014. **32**(25): p. 2712-7.
44. Jakubowiak, A.J., et al., *Treatment outcomes in patients with relapsed and refractory multiple myeloma and high-risk cytogenetics receiving single-agent carfilzomib in the PX-171-003-A1 study.* Leukemia, 2013. **27**(12): p. 2351-6.
45. Shah, J.J., et al., *Carfilzomib, pomalidomide, and dexamethasone for relapsed or refractory myeloma.* Blood, 2015. **126**(20): p. 2284-90.
46. Mateos, M.V., et al., *Impact of prior therapy on the efficacy and safety of oral ixazomib-lenalidomide-dexamethasone vs. placebo-lenalidomide-dexamethasone in patients with relapsed/refractory multiple myeloma in TOURMALINE-MM1.* Haematologica, 2017. **102**(10): p. 1767-1775.
47. Sonneveld, P., et al., *Phase 2 study of carfilzomib, thalidomide, and dexamethasone as induction/consolidation therapy for newly diagnosed multiple myeloma.* Blood, 2015. **125**(3): p. 449-56.
48. Giralt, S., et al., *American Society of Blood and Marrow Transplantation, European Society of Blood and Marrow Transplantation, Blood and Marrow Transplant Clinical Trials Network, and International Myeloma Working Group Consensus Conference on Salvage Hematopoietic Cell Transplantation in Patients with Relapsed Multiple Myeloma.* Biol Blood Marrow Transplant, 2015. **21**(12): p. 2039-2051.

49. *Sarclisa (isatuximab-irfc.* Package insert. Sanofi; updated 3/2020.

50. *Kyprolis (carfilzomib).* Package insert. Amgen; udpated 8/2020.

15.0 APPENDICES

16. APPENDIX A

PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

17. APPENDIX B

SERUM M-PROTEIN INTERFERERENCE sampling

Supplies stored labeled in kit box:
Collection Tube: 1 x Tube, 2.5 mL, SST w/gel [RD25; 8T3B in Japan]
Transfer Tube: 2 x Tube.Falsebottom,5mL,Clear,PP,For Serum[SS5C; 8SSC in Japan]

1. Fill tube completely with peripheral blood.
2. Gently invert 5 times.
3. Allow blood to clot for 45 minutes in an upright position.
4. Centrifuge at 1800 x g for 15 minutes.
5. Aliquot serum into 2 labeled 5 mL cryovial.
6. Freeze within 1 hour of collection at -80°C until shipment.
7. Discard cells.
8. Samples should be stored at ≤-80C until assay is available

18. APPENDIX C

Quality of Life Assessments

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 long walk?	1	2	3	4
3. Do you have any trouble taking a short 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

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 family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social 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

EORTC Multiple Myeloma Module (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

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

APPENDIX F: MINIMAL RESIDUAL DISEASE COLLECTION AND PROCESSING

1. COLLECTION SCHEMA

After 4 cycles, at the completion of consolidation, and after 24 months (± 3 weeks) if sCR or CR maintained (including patients with VGPR or better and suspected isatuximab interference).

Sample	Screening	After C4	After C6 or C8***	C24*
MRD (Aspirate)	X**	X	X	X

* ± 3 weeks

** A portion of the BM aspirates collected at screening (during the BM Biopsy) will be sent to the central laboratory along with the post-sample collected at the completion of cycle 4 sample. If a fresh BM aspirate will not be performed at screening because a sample is available within 28 days prior to randomization, then non-decalcified diagnostic tissue (BM aspirate smear or FFPE clot slides) should be collected for MRD assessment.

*** Specimen will be collected after 6 cycles in those receiving a transplant after 8 cycles in those deferring a transplant

2. COLLECTION MATERIALS

2.1 NGS-MRD stored specimen kit (provided by Adaptive) – contains:

2.1.1 Two (2) slide case containers (holds up to 5 slides per case)

2.1.2 Ambient gel pack, specimen bag, absorbent pad, FedEx next day return shipping label and packing instructions.

2.2 NGS-MRD fresh specimen kit (provided by Adaptive) – contains:

2.2.1 Two (2) K2EDTA tubes, one (1) 3ml and one (1) 10ml

2.2.2 Ambient gel pack, specimen bag, absorbent pad, FedEx next day return shipping label and packing instructions.

3. METHODS FOR COLLECTION AND PROCESSING

3.1 Bone Marrow Aspirates

3.1.1 Collection

Bone marrow aspirates are collected following the schedule outlined above (section 1), at least one 3 mL tube should be filled with aspirate. BM aspirate smear slides or FFPE clot slides specimen will be stored per institutional practice.

3.1.2 Sample Preparation and Shipping

Label each specimen tube with the Subject ID and date the sample was collected.

Immediately after collection, package the sample in the NGS-MRD fresh specimen kit

following the directions provided in the kit.

- If nearing a holiday, please contact Chelsea Mullins with the anticipated arrival dates. Each shipper contains two K2EDTA tubes (one (1) 3mL and one (1) 10mL), ambient gel pack, specimen bag, absorbent pad, FedEx next day return shipping label and packing instructions.
- Retain one copy of the Clinical Trial Sample Submission Form for your records.

4. SHIPPING

4.1 If possible, please avoid shipping samples for receipt on Saturday. If there is a delay in shipping, the samples will not be received until Monday and there could be lysing of cells and degradation. Also, please note that shipments cannot be received on holidays. No samples should be shipped the day before a federal holiday. Please plan the biopsy time accordingly.

4.2 The first shipment (C5D1) to Adaptive Biotechnologies will include both stored and fresh samples.

4.2.1 When you are ready to ship the BM aspirate smear slides or FFPE clot slides, complete the Clinical Trial Sample Submission Form (editable PDF) (Appendix 1) and print a hard copy to include in the NGS-MRD stored specimen kit.

4.2.1.1 Prepare the shipment by following the instructions included in the packaging kit provided.

4.2.2 When you are ready to ship the fresh BMA vacutainers, complete the Clinical Trial Sample Submission Form (Appendix 1) and print a hard copy to include in the NGS-MRD fresh specimen kit.

4.2.2.1 Prepare the shipment by following the instructions included in the packaging kit provided.

4.3 The second (C6/C8) and third shipments shipment (C24) to Adaptive Biotechnologies will include ONLY fresh samples.

4.3.1 When you are ready to ship the fresh BMA vacutainers, complete the Clinical Trial Sample Submission Form (Appendix 1) and print a hard copy to include in the NGS-MRD fresh specimen kit.

4.3.1.1 Prepare the shipment by following the instructions included in the packaging kit provided.

4.4 Ship by FedEx using the FedEx return label provided by Adaptive. Adaptive address is on the FedEx return label.

Please ensure the following address is listed on the return label:

Adaptive Biotechnologies
1551 Eastlake Ave. East, Suite 200
Seattle, WA 98102

Shipping Contact:

Chelsea Mullins, Project Manager at cmullins@adaptivebiotech.com.

4.5 After shipment arrival and review, Adaptive may reach out to the site contact listed in the "Submitting Site Information" section of the "Clinical Trial Sample Submission Form" to resolve

any discrepancies between the specimen tube label and the Clinical Trial Sample Submission Form.