SUMMARY OF CHANGES

Protocol Amendment # 2

LCCC 2119: Phase 2 study of isatuximab plus pomalidomide and dexamethasone in highly toxicity-vulnerable subjects with relapsed or refractory multiple myeloma

AMENDMENT INCORPORATES:
X__ Editorial, administrative changes
_X_ Eligibility Changes
X__ Scientific changes
__ Therapy changes
Rationale for amendment: Eligibility criteria modified for clarity and to allow inclusion of the following groups which had previously been excluded: subjects without measurable disease who have at least 30% baseline bone marrow involvement with multiple myeloma, subjects with disease progression on or after the last line of therapy who have M-spike 0.5-0.9 g/dL without other criteria for measurable disease, subjects with prior pomalidomide exposure who remain pomalidomide-sensitive, subjects with anti-CD38 exposure within the past 6 months who remain sensitive to anti-CD38 therapy, and subjects with relapsed (but not refractory) disease after one prior line of therapy that contains an IMiD and/or PI. Also included language to clarify that requirements for response to prior anti-CD38 therapy only apply to those patients who are refractory to prior treatment with anti-CD38 therapy. Also modified eligibility language surrounding diagnosis of prior malignancy.

Eligibility:

Sections 4.1.5

Eligibility criteria updated to state that if previously treated with at least 2 consecutive cycles of an anti-CD38 containing regimen, and if refractory to that regimen, the subject must have achieved at least a PR to that line of therapy and must not have received an anti-CD38 mAb for at least 6 months prior to enrollment.

Section 4.1.3

Language added to define refractory disease and relapsed disease

Section 4.1.4

Criteria updated to state that Subjects must have received at least 1

	prior line of therapy that includes an IMiD and/or a PI and should have received at least 2 cycles of that regimen
Section 4.1.7	Eligibility criteria updated to state that high risk may be defined as subjects not meeting criteria A and B of 4.1.7 but felt by treating clinician to not be candidate for a standard full-dose regiment on a account of one of the following: i) History of clinically significant non-hematologic grade ≥3 (NCI CTCAE, version 5.0) toxicity attributed to prior anticancer therapy ii) History of requiring dose-reduction of at least two separate anticancer drugs during prior therapy for multiple myeloma.
Section 4.2.2	Exclusion criteria updated to state that subject is not eligible if refractory to pomalidomide and/or known to be intolerant to pomalidomide at a dose of 3mg or less.
Section 4.1.8	Measurable disease definition updated to allow for monoclonal protein (M-protein) present in serum and/or urine, defined as serum M-protein of ≥ 0.5 g/dL. Language also added to state that Subjects without measurable disease (including non-secretory multiple myeloma) will also be eligible to participate if the baseline marrow burden of myeloma is at least 30%.
Section 4.2.4	Section 4.2.4 deleted; exclusion criteria stated that subject was not eligible to be on study if they had received anti-CD38 monoclonal antibody therapy within the previous 6 months. Criteria numbering updated.
Section 4.2.3	Exclusion criteria updated to state that subject cannot be on study if they have received any monoclonal antibody therapy within the previous 28 days.
Section 4.2.11	Language added: Diagnosis of other prior malignancy within 2 years of enrollment also permissible if no evidence of disease, previously treated with curative intent, and if felt to be unlikely to impact survival during the duration of the study. Other low-risk malignancies also permissible if natural history or treatment is unlikely to interfere with efficacy or safety endpoints.
Section 4.2.12	Language updated to state that Concurrent use of other anti-cancer agents or treatments (with the exception of adjuvant/maintenance hormonal therapy for participants with a history of breast or prostate cancer and other similar agents deemed to have a low likelihood of affecting the outcome of this study (per discretion of treating physician)).

Editorial/Administrative changes:

Table 4 ___ Language corrected, should refer to pomalidomide and not lenalidomide.

Scientific changes:

Section 8.1 Time and events table change: Medical History, Physical Exam, Performance Status removed from C1D15 assessments.

Section 8.1
1. Footnote 3 updated to add: If screening medical history and physical exam are performed within 3-days of C1D1, these do not need to be repeated on C1D1.
2. Footnote 7 updated to add: BM biopsy should be repeated every 12 weeks in subjects with non-secretory disease.

THE ATTACHED VERSION DATED August 2, 2024 INCORPORATES THE ABOVE REVISIONS

SUMMARY OF CHANGES

Protocol Amendment #1

LCCC 2119: Phase 2 study of isatuximab plus pomalidomide and dexamethasone in highly toxicity-vulnerable subjects with relapsed or refractory multiple myeloma

AMENDMENT INCORPORATES:
_X_ Editorial, administrative changes
X__ Scientific changes
__ Therapy changes
_X_ Eligibility Changes

Rationale for amendment: The purpose of this amendment is to update inclusion criteria that applies to the initial diagnosis so that the subjects would not necessarily have to meet the criteria at the time of screening. The reason for this change is that inclusion criteria 4.1.8 as written requires the presence of multiple myeloma-related organ disfunction (i.e. CRAB criteria) or myeloma-related biomarker of malignancy (i.e. ≥60% bone marrow plasmacytosis, serum involved/uninvolved free light chain ratio >100, or ≥1 focal lesion on MRI ≥ 5 mm in size). This was not intended to be a requirement at the time of screening.

Additionally, this amendment serves to clarify changes to the Lawson and Katz assessments to ensure that the questionnaires match those included in the IMWG Frailty Assessment instrument. As such, language in each of the questionnaires was updated and the corresponding scoring documents were added to the appendices.

Editorial, administrative changes:
___Mechanical edits made throughout; typos corrected.
Section 10.3.1: Language updated and corrected for consistency throughout the protocol.

Eligibility changes:

Section 4.1.8___	Sections 4.1.8 A, C and D removed, and inclusion criteria reworded to state: Measurable disease as defined by one or more of the following: A. Monoclonal protein (M-protein) present in serum and/or urine, defined as serum M-protein of ≥ 1 g/dL (0.5 g/dL for IgA MM) B. Urine M-protein of ≥ 200 mg/24 hours

	C. Involved light chain ≥ 10 mg/dL (100 mg/L) AND abnormal serum free light chain ratio.
Section 4.1.4	Inclusion criteria reworded for clarity.
Section 4.1.5	Inclusion criteria removed for clarity as it was redundant.
Section 4.2.14	Clarified that patients with positive anti-HCV are eligible

Scientific changes:

Section 13.3	Appendix C updated to include instructions for scoring IMWG Frailty Assessment Tool as well as Lawson IADL and Katz ADL assessments
Section 8.1	Row added for Pill Diary assessment at D1 for every cycle.
Section 8.1	Assessments updated for C2D15, removing medical history, physical exam, karnofsky performance status and concomitant medication review. Concomitant medication review also removed from C3D15 and C4+D15.
Section 8.1	Clock-in-the-box assessment removed
Section 8.1	CARG-GA and IMWG Assessments changed from C1D1 to screening with footnote 8 updated.
Section 8.1	Footnote 13 added to clarify Gait speed test, PROMIS-cog and Mini-cog assessments and timepoints
Section 13.3	Appendix C IMWG Frailty Assessment Scoring Table updated to change > 80 to ≥ 81.
Section 13.10	Appendix J CARG Global Assessment questionnaire questions updated specific to IADL and ADL
Section 13.11	Appendix K CARG Global Assessment: Subsequent Assessment questions updated relative to IADL and ADL

THE ATTACHED VERSION DATED February 14, 2023 INCORPORATES THE ABOVE REVISIONS

LCCC 2119: Phase 2 study of isatuximab plus pomalidomide and dexamethasone in highly toxicity-vulnerable subjects with relapsed or refractory multiple myeloma

Short Title: Isa-Pom-Dex in elderly/frail subjects with RRMM

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Version #: 3.0
Version Date: August 2, 2024

LCCC 2119: Phase 2 study of isatuximab plus pomalidomide and dexamethasone in highly toxicity-vulnerable subjects with relapsed or refractory multiple myeloma

Principal Investigator

[redacted]

Signature Page

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name: _____

PI Signature: _____

Date: _____

Version #: 3.0
Version Date: August 2, 2024

LIST OF ABBREVIATIONS

ADCC	Antibody dependent cellular cytotoxicity
AE	Adverse event
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BID	*Bis in die* (twice daily)
BSA	Body surface area
CAP	College of American Pathologists
CBCD	Complete blood count with differential
CBR	Clinical benefit rate
cfDNA	Circulating free deoxyribonucleic acid
CL	Clearance
Cmax	Maximum plasma drug concentration
CMP	Comprehensive metabolic panel
CPO	Clinical Protocol Office
CR	Complete response
CT	Computer tomography
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DSMC	Data safety monitoring committee
EC50	Concentration associated with 50% maximal effect
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EOI	End of infusion
FDA	Food and Drug Administration
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
HBs-Ag	Hepatitis B surface antigen
HBc	Hepatitis B core
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
IC50	Concentration associated with 50% inhibition of maximal effect
IDS	Investigational drug service
Ig	Immunoglobulin
IHC	Immunohistochemistry
IMIDs	Immunomodulators
INR	International normalized ratio
IP	Intraperitoneal
IV	Intravenous
LCCC	Lineberger Comprehensive Cancer Center
LDH	Lactate dehydrogenase
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
MRI	Magnetic resonance Imaging
MTD	Maximum Tolerated Dose
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NF-κB	Nuclear factor kappa light-chain enhancer of activated B cells
NK	Natural killer
OAT	Organic anion transporter

OATP	Organic anion transporter polypeptide
ORR	Objective response rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Progressive disease
PET	Positron Emission Tomography
PFS	Progression free survival
PFT	Pulmonary function test
Pgp	P-glycoprotein
PI	Principal investigator
PK	Pharmacokinetic(s)
PR	Partial response
PRC	Protocol review committee
PT	Prothrombin time
PTT	Partial thromboplastin time
QD	*Quaque die* (once daily)
RBC	Red blood cell
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic acid
RP2D	Recommended Phase 2 dose
SAE	Serious adverse event
s.c.	Subcutaneous
SD	Stable disease
SOI	Start of infusion
SAR	Serious adverse reaction
t½	Half-life
TBNK	T or B-cell natural killer
TLS	Tumor lysis syndrome
Tmax	Time to maximum drug concentration
ULN	Upper limit of normal
UNC	University of North Carolina
USP	United States Pharmacopeia

1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

Among patients with relapsed/refractory multiple myeloma (RRMM), selection of appropriate therapy is often challenging for the subset of patients who are especially toxicity-vulnerable on account of advanced age, comorbid medical conditions, or other factors. Traditional clinical trials typically use conservative eligibility criteria that exclude such patients in favor of young, fit patients with few comorbidities. This limits the generalizability of available trial data to more toxicity-vulnerable patients. This phase II trial of isatuximab, pomalidomide, and dexamethasone (Isa-Pom-Dex) seeks to address these challenges by selectively enrolling 49 much older and/or otherwise highly toxicity-vulnerable patients.

The starting doses of pomalidomide and dexamethasone will be 3 mg and 20 mg, respectively. Isatuximab will be administered at the standard dose of 10 mg/kg. Subjects will be treated with all three medications until progression, unacceptable toxicity, or subject withdrawal from the study.

The primary objective of this phase II study is to estimate the overall response rate (ORR) of subjects treated with the proposed regimen. Secondary objectives will include estimation of the median progression-free survival (PFS), median overall survival (OS), treatment failure-free survival (TFFS), depth of response (including achievement of bone marrow minimal residual disease [MRD]-negativity), clinical benefit rate, time to response, duration of response, and the toxicity and tolerability of therapy. All subjects on the trial will also be evaluated by Cancer and Aging Research Group-Geriatric Assessments (CARG-GA) and patient-reported outcome (PRO) measures of quality of life (QOL). Correlative blood samples (mandatory at UNC site, opt-in for other sites) will be collected with the aim of studying biomarkers of aging and frailty with a focus on both the relation to isatuximab specifically, as well as treatment response and risk for intolerability.

We hypothesize that isatuximab, pomalidomide, and dexamethasone, at the doses proposed above, will be a well-tolerated and highly effective regimen for treating frail and very elderly adults with RRMM. The ORR and other outcome measures will be descriptively compared to historical controls, primarily the randomized phase 3 ICARIA-MM trial and a subgroup analysis of elderly patients enrolled on this trial. We hypothesize that the ORR will be approximately 48% among subjects treated with Isa-Pom-Dex at the proposed dosing.

1.2 Multiple Myeloma

Multiple Myeloma (MM) is an incurable malignancy of plasma cells that accounts for 1% of all cancers and approximately 10% of all hematologic malignancies [1]. The American Cancer Society estimated that 34,920 new cases of MM and 12,410 deaths due to MM would occur in the United States in 2021 (https://seer.cancer.gov/statfacts/html/mulmy.html). MM can cause osteolytic bone

lesions, which may result on fractures and are the primary cause of morbidity. Other manifestations can include renal failure, cytopenias, and immune suppression [1]. Overall survival (OS) has improved significantly over the past 20 years with the advent of high-dose chemotherapy and autologous stem cell transplantation (ASCT) along with the development of therapies such as thalidomide, lenalidomide, pomalidomide, bortezomib, and carfilzomib. The inclusion of these therapies in treatment regimens for both newly diagnosed and relapsed MM increased the median 5-year survival for MM from just 27% in the period of 1987-1989 to 49% in the period of 2005-2011 [2-4]. Newer immunotherapies, monoclonal antibodies, and most recently chimeric antigen-receptor (CAR)-T cell therapies include isatuximab, daratumumab, elotuzumab, belantamab mafodotin, and idecabtagene vicleucel; the development of such therapies has had additional positive impacts the continually evolving treatment landscape for MM [5, 6].

Nonetheless despite these recent advances, MM remains a challenge to treat for several reasons. First and foremost, MM is primarily a cancer of older adults: the median age at diagnosis is 70, and approximately 37% of patients are older than 75 when diagnosed [7]. Consequently, many MM patients may have significant age-related comorbidities and functional decline at the time of diagnosis that are unrelated to MM, in addition to what may be substantial and new MM-induced problems. The resultant increased susceptibility to chemotherapy toxicity can make treating many MM patients difficult and, in many cases, entirely precludes certain effective options such as high-dose chemotherapy with autologous stem cell transplantation or even full-dose, non-transplant-based chemotherapy induction regimens. It is clear that approved drugs for MM have their own toxicities that manifest with greater severity in this patient population. Some of the most frequent toxicities include cytopenias, infections, peripheral neuropathy, nausea, constipation, and fatigue, all of which can limit tolerability and compromise efficacy in older patients who are more susceptible to these side effects [8]

Second, MM remains incurable and so all MM patients, regardless of their age or ability to receive various therapy, will eventually relapse if they live long enough [1]. As MM evolves throughout an individual's lifespan with the disease it generally becomes more refractory to chemotherapy, and in most patients, both the rate and duration of response progressively decline with subsequent lines of therapy, resulting in a continual need for novel therapeutic approaches for this disease. Based on all of these factors, novel drugs and novel approaches for using existing drugs in older and/or otherwise toxicity-vulnerable patients are necessary.

1.3 Current Standard of Care for Highly Toxicity-Vulnerable Subjects with Multiple Myeloma in Early Relapse

Initial therapy for NDMM depends in part on eligibility for ASCT, which requires patients to have a good performance status, minimal comorbidities, and adequate cardiac, pulmonary, liver and renal function [9]. As noted above, many patients with MM will not be eligible for this approach because of their age, functional

status and/or comorbidities. Therefore, individualizing therapy is critical in the non-transplant setting, aiming to achieve the best response possible while minimizing toxicity [7].

A variety of regimens are commonly used in non-transplant-eligible, newly diagnosed MM patients. Rd is a recommended and approved regimen based on data from Phase III trials [10]. The bortezomib, cyclophosphamide and dexamethasone combination (VCD / CyBorD) is widely used and induces high response rates and PFS [11]. Recently, Rd was compared prospectively with Rd plus bortezomib (VRd), and the addition of the proteasome inhibitor bortezomib (VRd) resulted in significantly improved PFS and overall survival (OS) and was considered to have an acceptable risk-benefit profile, although that study was conducted in transplant candidates [12]. The VRd regimen has been further tested in the IFM-2009 study [13] resulting in VRd arguably being the standard of care for treating newly diagnosed MM in the US. That said, VRd is an intensive regimen, the toxicity of which is not negligible [12]. Consequently, most older/frail patients are not candidates for the regimen as published. Modifications to VRd have been tested in older/frail patients, such as "RVD-Lite" [14]. RVD-Lite in a cohort enrolling older/frail patients was efficacious and less toxic than standard RVD, but significant adverse events were still common and 26% of patients discontinued therapy for reasons that largely centered around toxicity [12]. RVD-Lite hence represents an important step maintaining efficacy while reducing toxicity, but there is still an unmet need for relatively non-toxic yet effective regimens for these patients. More recently, the MAIA study examined Rd with or without daratumumab in non-ASCT candidates with NDMM. 30-month PFS was superior in subjects who received daratumumab, at 70.6% vs 55.6% in those who did not. The regimen was also promisingly tolerable. This result provided the basis for FDA approval of the Rd+daratumumab combination in this patient population [15].

In the setting of relapsed or refractory disease, optimal therapy for toxicity-vulnerable adults with MM is even less well defined. There is a lack of prospective clinical trial data that specifically addresses this population, and therapy for such patients typically involves empiric dose-reduction of standard triplet regimens. There is thus an ongoing need for studies that prospectively evaluate the efficacy and tolerability of treatment regimens for toxicity-vulnerable adults with RRMM. Ideally, all patients should be assessed for risk of toxicity based on their age, level of frailty, comorbidities, and other factors as part of choosing therapy for both NDMM and RRMM [16]. One initial attempt at this has been formulated in the International Myeloma Working Group (IMWG) frailty score that predicts mortality and the risk of toxicity in MM [17]. Our group and others have piloted other geriatric assessment instruments and methods with promising initial results [17, 18].

1.4 Isatuximab

1.4.1 Isatuximab Mechanism of Action (MOA) and general information

Isatuximab is an immunoglobulin (Ig) G1 monoclonal antibody (mAb) that selectively binds to the human cell surface antigen molecule classified as cluster of differentiation 38 (CD38). Isatuximab targets CD38 expressed in hematological malignancies and is able to destroy CD38 expressing tumor cells *in vitro* through several mechanisms, including: Antibody-dependent cellular cytotoxicity (ADCC), Antibody-Dependent Cellular Phagocytosis (ADCP), Complement- dependent cytotoxicity (CDC), and direct apoptosis. Isatuximab binding to CD38 expressed on immune cells triggers immunomodulatory functions. For instance, isatuximab can activate NK cells and increase their lytic activity. Isatuximab can also induce the polarization of monocytes to an M1 phenotype and restore the proliferative potential of conventional T cells repressed by regulatory T cells (Tregs).

1.4.2 Summary of Preclinical Data

Single-agent isatuximab has shown antitumor activity in MM, non-Hodgkin's lymphoma (NHL), and acute lymphocytic leukemia (ALL) tumor models. In *ex vivo* models isatuximab has shown proapoptotic effects in MM and acute myeloid leukemia (AML) samples.

Isatuximab binds lymphoid tissues, bone marrow, pituitary gland, prostate gland cells, and infiltrating or resident round cells (macrophages and/or lymphocytes) of the innate immune system including Kupffer cells in the liver.

1.4.3 Clinical Development

As of the cutoff date of 01 March 2021, overall, 2208 patients have been exposed to isatuximab or comparator. For additional information refer to the Investigator's Brochure.

Table 1 Summary of Clinical Studies

Study	Indication	Design
TED10893	CD38+ Hematological Malignancies	Phase 1 dose escalation study of single agent isatuximab
TED10893 Phase 2 Stage 1	RRMM	Activity of single agent isatuximab at different doses/schedules
TED10893 Phase 2 Stage 2	RRMM	Activity of isatuximab single agent or in combination with dexamethasone
TED14154 (Part A & B)	RRMM	Phase 1b dose escalation study of single agent isatuximab

Study	**Indication**	**Design**
TCD11863	RRMM	Phase 1b dose-escalation study of isatuximab in combination with lenalidomide/dexamethasone
TCD14079 Part A	RRMM	Phase 1b dose-escalation study of isatuximab in combination with pomalidomide/dexamethasone
TCD14079 Part B	RRMM	Phase 1b study of isatuximab in combination with pomalidomide/dexamethasone, administered from a fixed infusion volume
TCD14906	RRMM	Phase 1/2 study of isatuximab in combination with cemiplimab
TCD13983	NDMM	Phase 1b dose escalation study of isatuximab in combination with bortezomib-based regimen in two cohorts (ICBd and VRDI)
TCD15484	RRMM	Phase 1b multi-center open label study of subcutaneous and intravenous isatuximab in combination with pomalidomide and dexamethasone
TED14095	RRMM	Phase 1 dose escalation study of single agent isatuximab in Japanese subjects
TED15085	RRMM	Open-label multicenter study of single agent isatuximab in Chinese patients
EFC14335	RRMM	Phase 3 multicenter randomized study of pomalidomide/dexamethasone with or without isatuximab
EFC15246	RRMM	Phase 3 multicenter randomized study of carfilzomib/dexamethasone with or without isatuximab
EFC12522	NDMM	Phase 3 multicenter randomized study of bortezomib, lenalidomide, and dexamethasone with or without isatuximab
ACT14596	ALL	Phase 2 single arm multicenter study of single agent isatuximab
ACT15319	mCRPC, NSCLC	Phase 1/2 open-label study of isatuximab in combination with cemiplimab
ACT15320	HL, DLBCL, PTCL	Phase 1/2 open-label study of isatuximab in combination with cemiplimab

Study	Indication	Design
ACT15377	HCC, SCCHN, EOC, GBM	Phase 1/2 open-label study of isatuximab in combination with atezolizumab
ACT15378	R/R B-ALL or T-ALL or AML	Phase 2 open-label, single-arm study of isatuximab in combination with chemotherapy
EFC15992	HR-SMM	Phase 3 randomized, open-label, multicenter study of isatuximab in combination with lenalidomide and dexamethasone
TED16414	Patients awaiting kidney transplant	Phase 1b/2 open-label, non-randomized, multicenter study of isatuximab

1.4.4 Pharmacokinetics: Study TCD14079

The PK of isatuximab in presence of pomalidomide/dexamethasone were assessed in TCD14079 Part A when isatuximab was given at 5 to 20 mg/kg QW/Q2W and pomalidomide at 4 mg. Pomalidomide dose could have been reduced to 3, 2, or 1 mg based on criteria defined in the study protocol. The PK analysis of isatuximab in combination with pomalidomide was performed by NCA and by modeling.

Isatuximab exposure when administered in combination with pomalidomide/dexamethasone (study TCD14079 Part A) was comparable to that after single agent therapy (study TED10893), with the geometric mean ratio of TCD14079/TED10893 AUC1week being 0.93.

1.4.5 Summary of Clinical Safety: Study TCD14079

In part A, treatment-emergent AEs of any grade and regardless of relationship with study treatment were most frequently reported in the SOCs of general disorders and administration site conditions (84.4%), followed by respiratory, thoracic and mediastinal disorders (77.8%), gastrointestinal disorders (75.6%), infections and infestations (73.3%), blood and lymphatic system disorders (73.3%), musculoskeletal and connective tissue disorders (71.1%), injury, poisoning and procedural complications (71.1%), nervous system disorders (66.7%), and psychiatric disorders (53.3%).

For part B, all patients (100.0%) had at least 1 TEAE (any grade), 35 (74.5%) patients had Grade ≥3 TEAEs, and 27 (57.4%) patients had at least 1 serious TEAE. There were 6 (12.8%) patients who experienced TEAEs leading to death during the study. At the time of this analysis, 5 (10.6%) patients experienced TEAEs leading to definitive treatment discontinuation (i.e., discontinuation of all study treatment), and 1 (2.1%) patient who experienced TEAEs leading to premature discontinuation of pomalidomide.

The most frequently reported non-hematological TEAEs of any grade and regardless of relationship with study treatment (in >25% of patients) were fatigue (30 patients, 63.8%), infusion reaction (IR), cough, and upper respiratory infection (19 patients, 40.4% each), dyspnea, diarrhea, and nausea (16 patients, 34.0% each), insomnia (15 patients, 31.9%), constipation and back pain (14 patients each, 29.8%), and arthralgia (13 patients, 27.7%).

1.4.5.1 Dose Limiting Toxicities: TCD14079

Dose limiting toxicities in this study included Grade 4 neutropenia, Grade 4 neutropenic infection, and Grade 3 Confusional state.

1.4.5.2 Serious Adverse Events: TCD14079

In part A, the most common (in Grade ≥3 of 45 patients) serious TEAEs consisted of pneumonia (17.8%; Grade ≥3: 17.8%), neutropenia (13.3%; Grade ≥3: 13.3%), disease progression (8.9%; Grade ≥3: 8.9%), and traumatic fracture (6.7%; Grade ≥3: 6.7%).

In part B, the most frequently reported serious TEAEs (any grade) regardless of relationship with study treatment (in >2 patients) were pneumonia (5 patients, 10.6%), atrial fibrillation, and spinal cord compression (3 patients each, 6.4%), dehydration, disease progression, dyspnea, neutropenia, sepsis, transient ischemic attack, and traumatic fracture (2 patients each, 4.3%). The majority of these serious TEAEs were Grade ≥3 with the exception of 1 AE each of atrial fibrillation, pneumonia, spinal cord compression, and both events of transient ischemic attack.

1.4.5.3 Infusion Reactions: TCD14079

The most frequent symptoms of IRs in Study TCD14079 Part A (N = 45) are listed below by all grades (N and % of population):

- Any event: 19 (42%)
- Infusion related reaction: 19 (42%)
- Chills: 3 (6.7%)
- Dyspnea: 3 (6.7%)
- Nasal congestion: 3 (6.7%)

For Part B, Overall, IRs of any grade were reported in 19/47 (40.4%) patients and occurred in 19/490 (3.9%) of the infusions. There was no Grade 3 or 4 IRs, all the IRs were Grade 2. Nineteen (40.4%) patients had the first onset of an IR at their first infusion. All the infusion reactions occurred on the same day as the infusion and resolved within 24 hours.

1.5 Pomalidomide

The following information is from the package insert. For additional information please refer to the full prescribing information:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/204026s019lbl.pdf

For adverse events see section 6.2.

1.5.1 Background

Pomalidomaide is a thalidomide analogue indicated, in combination with dexamethasone, for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy.

1.5.2 Clinical Experience

Trial 1 was a phase 2, multicenter, randomized open-label study in patients with relapsed multiple myeloma who were refractory to their last myeloma therapy and had received lenalidomide and bortezomib. Patients were considered relapsed if they had achieved at least stable disease for at least 1 cycle of treatment to at least 1 prior regimen and then developed progressive disease. Patients were considered refractory if they experienced disease progression on or within 60 days of their last therapy. A total of 221 patients were randomized to receive pomalidomide alone or pomalidomide with Low-dose Dex. The results are presented below.

Table 2 Trial 1 Results

	POMALYST[a] (n=108)	**POMALYST + Low-dose Dex (n=113)**
Response		
Overall Response Rate (ORR),[b] n (%)	8 (7.4)	33 (29.2)
95% CI for ORR (%)	(3.3, 14.1)	(21.0, 38.5)
Complete Response (CR), n (%)	0 (0.0)	1 (0.9)
Partial Response (PR), n (%)	8 (7.4)	32 (28.3)
Duration of Response (DOR)		
Median, months	NE	7.4
95% CI for DOR (months)	NE	(5.1, 9.2)

a Results are prior to the addition of dexamethasone.
b ORR = PR + CR per EBMT criteria.
CI, confidence interval; NE, not established (the median has not yet been reached).
Data cutoff: 01 April 2011

Trial 2 was a Phase 3 multi-center, randomized, open-label study, where pomalidomide + Low-dose Dex therapy was compared to High-dose Dex in adult patients with relapsed and refractory multiple myeloma, who had received at least two prior treatment regimens, including lenalidomide and bortezomib, and demonstrated disease progression on or within 60 days of the last therapy. Patients with creatinine clearance ≥ 45mL/min qualified for the trial. A total of 455 patients were enrolled in the trial: 302 in the pomalidomide + Low-dose Dex arm and 153 in the High-dose Dex arm. Patients in the pomalidomide + Low-dose Dex arm were

administered 4 mg pomalidomide orally on Days 1 to 21 of each 28-day cycle. PFS was significantly longer with pomalidomide + Low-dose Dex than High-dose Dex: HR 0.45 (95% CI: 0.35-0.59 $p < 0.001$). OS was also significantly longer with pomalidomide + Low-dose Dex than High-dose Dex: HR 0.70 (95% CI: 0.54-0.92 $p = 0.009$).

1.6 Dexamethasone

1.6.1 Background

Corticosteroids – first prednisone and now also dexamethasone – have been recognized as potent contributors to MM therapy since the 1960's [19]. This class of agent appears to be directly cytotoxic to MM cells and furthermore appears to potentiate the effect of other MM therapies, such as bortezomib. As a result, many clinical trials, including those mentioned above, either include corticosteroids as part of experimental regimens, or corticosteroids are added to initial therapy for patients with inadequate responses [20].

1.6.2 Clinical Experience

Dexamethasone is FDA-approved for therapy of MM. It is also used widely as an anti-inflammatory and anti-neoplastic agent, particularly in lymphoid malignancies including non-Hodgkin's lymphoma and MM. Dexamethasone has a long clinical history in MM therapy as monotherapy [21] but is nowadays far more commonly as part of combination regimens inlcuding lenalidomide and isatuximab as discussed above. Dexamethasone is a core component of many MM regimens.

Dexamethasone causes toxicity that is dependent on both dose and frequency of administration. At doses administered with the current protocol side effects are usually mild and can include mood changes, hyperglycemia, tremors, infections, insomnia, or stomach ulcers. The lower, weekly dose of dexamethasone planned for this protocol is well established thanks to a trial by Rajkumar et al. [10], in which lenalidomide was tested with either low- or high-dose dexamethasone (40 mg weekly versus 40 mg on four subsequent days, three times per month). ORR was superior in subjects on high-dose dexamethasone, although toxicity was significantly greater, with 65% versus 48% experiencing any grade 3 or worse, non-hematological toxicity at any point during protocol therapy. Furthermore, excess toxicity induced excess mortality, and an OS benefit was noted in the low-dose dexamethasone arm. In the latter group, infections, venous thromoboembolic events, and fatigue were the most common toxicities.[10]

1.7 Rationale for Clinical Study

The incidence of multiple myeloma increases significantly with age with about 70% of diagnoses occurring in patients older than 65 and 40% occurring in those older than 75.[22] Older patients with multiple myeloma are particularly heterogeneous with regard to their comorbidities and general fitness levels. Determining optimal treatment regimens for very elderly and/or otherwise toxicity-vulnerable patients

who are not candidates for intensive therapy is challenging because traditional clinical trial eligibility criteria are commonly quite conservative and largely result in the exclusion of these patients in favor of enrolling young, fit patients with limited comorbidities. This exclusion limits the generalizability of available trial data to more toxicity-vulnerable patients. Several trials in the newly diagnosed setting have evaluated less intense induction regimens for toxicity-vulnerable patients (e.g. "RVD-Lite" [14], UPFRONT [23], and "VCD-Lite" [24]), although there is a need for further studies to evaluate monoclonal antibody-based combinations such populations. However, in the relapsed/refractory setting, there even less available clinical trial data to guide treatment decisions for toxicity-vulnerable patients. Therefore, this phase II trial of isatuximab, dose-reduced pomalidomide, and dexamethasone (Isa-Pom-Dex) seeks to address these challenges by selectively enrolling much older and/or otherwise highly toxicity-vulnerable patients.

Isatuximab is an immunoglobulin (Ig) G1 monoclonal antibody (mAb) that selectively binds to the human cell surface antigen CD38 expressed in hematological malignancies and is able to destroy CD38-expressing tumor cells *in vitro* through several mechanisms, including antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis (ADCP), complement-dependent cytotoxicity (CDC), and direct apoptosis. Isatuximab binding to CD38 expressed on immune cells also triggers immunomodulatory functions, including activation of NK cells and targeting of CD38-expressing regulatory T cells (Tregs), resulting in increased effector cell responses. Importantly, although isatuximab targets the same CD38 surface antigen that is targeted by daratumumab, the exact epitope and mechanism of myeloma cell kill are different. The clinical significance of this has not been fully elucidated, i.e., whether daratumumab and isatuximab have similar clinical efficacy despite these pharmacodynamic and mechanistic differences. Consequently, exploring isatuximab in this particular clinical niche is warranted despite daratumumab's established role.

The combination of pomalidomide and dexamethasone was previously evaluated in the phase 3b STRATUS (MM-010)[25] study, which included 682 patients with RRMM. Patients had received a median of 5 prior lines of therapy, and most were refractory to lenalidomide and bortezomib. The median progression free survival (PFS) was 4.6 months, and the median overall response rate (ORR) was 32.6%. The addition of a CD38-directed agent to this regimen was first evaluated in the phase 1b EQUULEUS (MMY1001)[26], in which 103 patients with RRMM were treated with daratumumab, pomalidomide, and dexamethasone. Patients in this study had received a median of 4 prior lines of therapy, and 71% were refractory to a proteasome inhibitor and an immunomodulatory drug. The median progression free survival (PFS) was 8.8 months and overall response rate (ORR) was 60%.

The addition isatuximab to pomalidomide and dexamethasone (Isa-Pom-Dex) was previously evaluated in the randomized phase 3 ICARIA-MM trial [27], in which 154 patients were assigned to treatment with isatuximab, pomalidomide, and dexamethasone, and 153 patients were assigned to receive pomalidomide and dexamethasone alone. Patients on the isatuximab arm had a median age of 68 (range 60-74) and had received a median of 3 prior lines of therapy, with 72% refractory to both lenalidomide and a proteasome inhibitor. The median PFS on the isatuximab-containing arm was 11.5 months (versus 6.5 months on the pomalidomide-dexamethasone arm) and the ORR was 63% (versus 32% on the pomalidomide-dexamethasone arm). This combination was also well tolerated with no increase in treatment discontinuations or fatal events on the isatuximab-containing arm.

In a subgroup analysis of elderly patients enrolled on the ICARIA-MM trial,[28] outcomes were compared for patients ≥75, 65-74, and <65 years old. Compared with Pd alone, median PFS was shown to be significantly prolonged with Isa-Pom-Dex, and was similar in all three age groups, with patients ≥75 years old having a median PFS of 11.4 months compared to 4.47 months on Pd. Health related quality of life (QoL) parameters were also better maintained in the Isa-Pom-Dex arm among patients ≥75 years as compared to the other age groups. Importantly, the incidence of grade ≥3 treatment-emergent adverse events (TEAE), serious TEAEs, and discontinuations due to TEAEs were higher in patients ≥75 years, although there was no increase in fatal TEAEs in this group. Infections were the most common TEAEs leading to treatment discontinuation in patients ≥75, occurring in 9.4% of patients ≥75 in the Isa-Pom-Dex arm.

Although ICARIA-MM and the above-referenced subgroup analysis provide important data on the use Isa-Pom-Dex in elderly patients, ICARIA-MM did not assess frailty, thus limiting the conclusions that can be drawn regarding safety and efficacy of Isa-Pom-Dex in frail and very elderly myeloma patients. However, the ICARIA-MM results, including the results of this subgroup analysis, support the evaluation of Isa-Pom-Dex in this population.

1.7.1 Dose Rationale

While there is a lack of prospective clinical trial data supporting a starting pomalidomide dose of 3 mg, expert opinion supports empiric initial dose-reduction of pomalidomide to 3 mg when treating older and unfit patients with multiple myeloma, and this approach is commonly followed in routine clinical practice.[29] Reduction of the starting dose of pomalidomide to 3 mg is further supported by the high rates of dose-reductions in prior phase 2 and phase 3 clinical trials of pomalidomide-based combinations. For example, in the phase 3 MM-003 trial,[30] pomalidomide plus low-dose dexamethasone was compared to high-dose dexamethasone alone among patients with RRMM. Of the 302 patients on the pomalidomide-containing arm, 135 (45%) were >65 years old and 24 (8%) were >75 years old. In this arm, 48% of patients developed grade 3/4 neutropenia and

27% of patients required pomalidomide dose reductions. In the ICARIA study,[27] 21% of patients on the Isa-Pom-Dex arm and 19% of patients on the pom-dex arm were ≥75 years old. On the Isa-Pom-Dex arm, 65 (43%) patients required pomalidomide dose-reductions compared with 36 (24%) requiring dose reductions on the pom-dex arm. Dose reductions were primarily due to neutropenia and infections. On the isa-pom-dex arm, grade 3/4 neutropenia occurred in 85% of patients and grade 3/4 pneumonia occurred in 16% of patients. Finally, in a systematic review and meta-analysis of phase 2 and 3 clinical trials evaluating pomalidomide-based regimens for the treatment of RRMM, the mean incidence of grade ≥3 neutropenia was 47.6%.[31] While neutropenia is only one of many potential reasons for dose-reduction of pomalidomide, this data suggests relatively high rates of pomalidomide dose-reductions across trials despite the inclusion of relatively small numbers of elderly/frail patients in these trials.

Thus, we hypothesize that isatuximab, low-dose pomalidomide (with a proposed starting dose of 3 mg), and low-dose dexamethasone will be a well-tolerated and highly effective regimen for treating frail and very elderly adults with RRMM.

1.8 Correlative Studies

1.8.1 Biomarkers of frailty and aging, including $p16^{INK4a}$

Expression of the cyclin dependent kinase inhibitor $p16^{INK4a}$ tumor suppressor gene is one molecular biomarker of aging. The *INK4a/ARF* tumor suppressor locus is critical to the senescence or aging pathway within cells. This locus encodes two tumor suppressors, p16 and ARF, both of which are capable of initiating senescence. Expression of $p16^{INK4a}$ has been shown to markedly increase with aging in most tissues of many different mammalian species including humans.[32-34] Sharpless and colleagues determined *p16* expression in cellular fractions of human whole blood, and found the highest expression in peripheral blood T-lymphocytes (PBTL).[35] They then measured *INK4/ARF* transcript expression in PBTL from two independent cohorts of healthy humans (170 donors total, aged 18-80), and analyzed their relationship with donor characteristics. Expression of $p16^{INK4a}$, but not other *INK4/ARF* transcripts, appeared to exponentially increase with donor chronologic age. $p16^{INK4a}$ expression did not independently correlate with gender or body-mass index but was significantly associated with tobacco use and physical inactivity, two factors positively associated with an increased risk of age-related diseases. These data suggest that $p16^{INK4a}$ in PBTL is an easily measured, peripheral blood biomarker of molecular age. In addition, the large changes seen in $p16^{INK4a}$ expression are of practical importance, as the highly dynamic nature of the biomarker assures that it is relatively easy to quantify reliably.[36, 37]

Expression of $p16^{INK4a}$ is also potently induced by DNA damaging agents, such as certain chemotherapy agents and total body irradiation therapy. In mice, a nearly 10-fold increase in expression of $p16^{INK4a}$ is observed within weeks of myelotoxic

exposures to ionizing radiation or alkylating agents. These data suggest that the benefits of chemotherapy and/or myelotoxic doses of radiation therapy may be partially offset by age-promoting ('gerontogenic') effects and shortened survival. Recent data from breast cancer patients treated with adjuvant chemotherapy suggests that standard adjuvant chemotherapy regimens substantially age the immune system rapidly and irreversibly.[38]

p16^{INK4a} has also been shown in one small study to have relevance to MM.[39] Rosko et al., performed studies similar to Sharpless to examine *p16^{INK4a}* as a marker of a patients' physiological age before and after treatment for MM. *p16^{INK4a}* levels interestingly were similar between normal controls, patients with untreated MM, and in patients treated with lenalidomide (which kills MM via mechanisms that do not include DNA damage). These data suggest that neither MM itself nor non-genotoxic therapies drive higher *p16^{INK4a}* levels. Conversely, *p16^{INK4a}* rose between 2- and 32-fold after ASCT. ASCT in MM is achieved with high doses of alkylators, which primarily act by damaging DNA. Although preliminary, these data suggest that genotoxic drugs used to treat MM may drive cellular senescence, i.e., certain MM therapies may accelerate aging. Other published markers of aging have been studied in plasma cell disorders (PCD) biology as well, such as interleukin-6 and TNF-α, but they have never been looked at specifically through the lens of aging in the MM patient.[40]

As a result, we will prospectively examine peripheral blood T-cell *p16^{INK4a}* mRNA expression and to bank other samples for future research aimed at MM in older adults. An emerging body of work increasingly portrays the importance of p16, telomere length, and microRNA expression, among others, as markers of aging and frailty. Using Pallis et al.,[41] as a foundation for proposing future analyses, samples will be banked with aim of studying these markers and others, with a focus on aging, treatment response and toxicity more broadly.

1.8.2 Study of the tumor microenvironment with a specific focus on T regulatory cells and T cell senescence

Dysfunctional cellular immunity is likely to play an important role in the development of multiple myeloma.[42] Progression from monoclonal gammopathy of undetermined significance (MGUS) to MM has been associated with a loss of tumor-specific CD4+ and CD8+ effector T-cell function in the bone marrow, suggesting that cytotoxic T-cell dysfunction correlates with disease progression.[43] T cell senescence and exhaustion are likely important in this process and represent the two dominant dysfunctional states in cancer.[44] T cell exhaustion may result from chronic antigen stimulation (e.g. cancer, chronic infections, and autoimmune disorders) whereas T cell senescence typically results from DNA damage through replicative erosion of telomeres or via other mechanisms. Ageing is clearly associated with a progressive accumulation of senescent T cells [44]. T cell expression of *p16^{INK4a}* is a marker of senescence and likely explains the utility of *p16^{INK4a}* as a biomarker of molecular age as discussed above.

Effector T cell senescence may also be induced by regulatory T cell (Treg) populations [45]. In myeloma, increases in the numbers and the immunosuppressive functions of Tregs are thought to be important mediators of disease progression (e.g. several studies have demonstrated increased CD4+CD25+FoxP3+ Treg populations in the peripheral blood of MM patients [42]).

Anti-CD38-directed monoclonal antibodies, in addition to directly targeting CD38 on the surface of MM cells, have broad immunomodulatory functions which are not yet fully elucidated, but are likely to be critical to their activity in myeloma. Daratumumab is known to produce rapid declines in CD38-expressing immunosuppressive regulatory B- and T-cells (Bregs and Tregs).[46, 47] CD38-expressing Tregs were shown to have increased immunosuppressive activity in vitro compared with CD38-negative regulatory T-cells.[47] Daratumumab was also reported to trigger clonal expansion of both $CD4^+$ T-helper cells and $CD8^+$ cytotoxic T-cells and was shown to increase $CD8^+$:$CD4^+$ and $CD8^+$Treg ratios, findings which were significantly more pronounced in patients who respond to therapy.[47] *In vitro* studies have also demonstrated a significant decline in CD38+ myeloid-derived suppressor cells (MDSCs) after exposure to daratumumab.[47]

Although IMiDs have a wide range of effects on the immune system, the synergistic activity seen with IMiD/daratumumab combinations may be partially explained by the finding that IMiDs increase CD38-expression on both Tregs[48] and MM cells.[49] In addition, IMiDs may directly promote immune cell activation via disruption of the cereblon-CD147-MCT1 axis, thereby abrogating a potential negative regulatory role of CD147 in T-cell function.[50]

We therefore aim to use mass cytometry and RNA seq to perform a comprehensive assessment of T cell, myeloid cell, and B cell populations in the bone marrow and peripheral blood of elderly/frail patients with myeloma, with a specific focus on evaluating T cell exhaustion and senescence, regulatory B and T cell populations, and $p16^{INK4a}$ expression in T cell subsets. We aim to correlate this data with the clinical assessments of frailty included in this study and with measures of treatment response in patients receiving isatuximab, pomalidomide, and dexamethasone.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

2.1.1 To assess the clinical efficacy of isatuximab/pomalidomide and dexamethasone (Isa-Pom-Dex) in elderly/frail subjects with relapsed or refractory multiple myeloma (RRMM), as determined by the overall response rate (ORR).

2.2 Secondary Objectives

2.2.1 To assess the safety profile of Isa-Pom-Dex in elderly/frail subjects with RRMM, as determined by the rate of treatment related adverse events.

2.2.2 To estimate the rate of treatment failure-free survival (TFFS) Isa-Pom-Dex in elderly/frail subjects with RRMM.

2.2.3 To determine the maximum depth of response: including minimal response (MR), partial response (PR), very good partial response (VGPR), complete response (CR), and stringent complete response (sCR) in elderly/frail subjects with RRMM treated with Isa-Pom-Dex

2.2.4 To assess clinical benefit rate (CBR) in elderly/frail subjects with RRMM treated with Isa-Pom-Dex.

2.2.5 To assess the rate of achievement of bone marrow minimal residual disease (MRD) negativity in elderly/frail subjects with RRMM treated with Isa-Pom-Dex.

2.2.6 To assess the median time to first response in elderly/frail subjects with RRMM treated with Isa-Pom-Dex.

2.2.7 To assess the median time to best response in elderly/frail subjects with RRMM treated with Isa-Pom-Dex.

2.2.8 To assess the median duration of response (DOR) in elderly/frail subjects with RRMM treated with Isa-Pom-Dex.

2.2.9 To assess the median progression free survival (PFS) in elderly/frail subjects with RRMM treated with Isa-Pom-Dex.

2.2.10 To assess the median time to next treatment (TTNT) in elderly/frail subjects with RRMM treated with Isa-Pom-Dex.

2.2.11 To estimate the median overall survival (OS) in elderly/frail subjects with RRMM treated with Isa-Pom-Dex.

2.3 Exploratory Objectives

2.3.1 [redacted]

[redacted]

[redacted]

[redacted]

3.0 Criteria for Evaluation / Study Endpoints

3.1 Primary Endpoint

3.1.1 Overall response (OR), defined as partial response or better (≥PR) to study therapy at any time, based on IMWG criteria provided in **Appendix O. Response Criteria for Multiple Myeloma**.

3.2 Secondary Endpoints

3.2.1 All treatment related adverse events as defined by changes from baseline via NCI-CTCAE criteria (version 5.0).

3.2.2 Treatment failure-free survival (TFFS), defined as the time the start of study therapy until discontinuation for any reason, including disease progression, toxicity, or death. TFFS captures a regimen's capacity to control MM without inducing adverse events that cause disability or loss of functional independence, resulting in therapy discontinuation.

3.2.3 Maximum depth of response: including minimal response (MR), partial response (PR), very good partial response (VGPR), complete response (CR), and stringent complete response (sCR) as defined by IMWG criteria provided in **Appendix O. Response Criteria for Multiple Myeloma**.

3.2.4 Clinical benefit rate (CBR), defined as the ORR plus the MR rate as defined by IMWG criteria provided in **Appendix O. Response Criteria for Multiple Myeloma**.

3.2.5 Bone marrow MRD negativity as assessed by next-generation sequencing with minimum sensitivity of 1×10^{-5}.

3.2.6 Time to first response, defined as the time from first study treatment to achievement of PR or better as defined by IMWG criteria provided in **Appendix O. Response Criteria for Multiple Myeloma**.

3.2.7 Time to best response, defined as the time from first study treatment to achievement of best response (PR, VGPR, CR, or sCR) based on IMWG criteria provided in **Appendix O. Response Criteria for Multiple Myeloma**.

3.2.8 Duration of response, defined as the time from achievement of PR or better until progressive disease (PD) based on IMWG criteria provided in **Appendix O. Response Criteria for Multiple Myeloma**. Patients will be censored if they die of anything other than myeloma.

3.2.9 Progression-free survival (PFS), defined as the time from first study treatment until confirmed PD based IMWG criteria provided in **Appendix O. Response Criteria for Multiple Myeloma** or death from any cause, whichever comes first.

3.2.10 Median time to next treatment (TTNT) is defined as time from start of study treatment to next MM treatment or death from any cause, whichever occurs first.

3.2.11 Overall survival, defined as the time from first study treatment to death from any cause.

3.3 Exploratory Endpoints

3.3.1 [redacted]

4.0 SUBJECT ELIGIBILITY

In order to participate in this study a subject must meet ALL of the eligibility criteria outlined below.

4.1 Inclusion Criteria

4.1.1 Written informed consent obtained to participate in the study and Health Insurance Portability and Accountability Act (HIPAA) authorization for release of personal health information (PHI). Consent must be obtained before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.

4.1.2 Age ≥ 18 years at the time of consent.

4.1.3 Documented symptomatic multiple myeloma that has previously responded to therapy (partial response or better) and is relapsed or relapsed and refractory to the last line of therapy. Refractory disease is defined as less than a minimal response or confirmed progressive disease per IMWG criteria within 60 days (measured from the end of the last cycle) after cessation of treatment. Relapsed disease is defined as previously treated disease that progresses and requires initiation of therapy but does not meet criteria for refractory disease.

4.1.4 Subjects must have received at least 1 prior line of therapy that includes an IMiD and/or a PI and should have received at least 2 cycles of that regimen.

4.1.5 If previously treated with at least 2 consecutive cycles of an anti-CD38 containing regimen, and if refractory to that regimen, the subject must have achieved at least a PR to that line of therapy and must not have received an anti-CD38 mAb for at least 6 months prior to enrollment.

4.1.6 Willing and able to adhere to the study visit schedule and other protocol requirements based on the judgement of the investigator.

4.1.7 Predicted high risk for severe toxicity from intensive regimens for RRMM, such as standard (full-dose) DPD, DVD, KPD, KRD, Ixa-PD, or Elo-PD as each regimen was published (such regimens often use, for example, twice-weekly bortezomib at 1.3 mg/m^2, lenalidomide at 25 mg, or pomalidomide 4 mg). High-risk is defined as one of the following:

A. Score ≥ 2 (indicating "frail") on the International Myeloma Working Group instrument (IMWG; Palumbo et al. [Blood 2015]) in Appendix C [17]

B. KPS ≤ 70

C. Not meeting criteria A or B above but felt by treating clinician to not be candidate for a standard full-dose regimen on account of one of the following:

i) History of clinically significant non-hematologic grade ≥3 (NCI CTCAE, version 5.0) toxicity attributed to prior anticancer therapy

ii) History of requiring dose-reduction of at least two separate anticancer drugs during prior therapy for multiple myeloma.

Subjects qualifying for enrollment by criteria (C) should be discussed with study PI before enrollment, to ensure uniform application of this criterion across participating sites.

4.1.8 Measurable disease as defined by one or more of the following:

A. Monoclonal protein (M-protein) present in serum and/or urine, defined as serum M-protein of ≥ 0.5 g/dL
B. Urine M-protein of ≥ 200 mg/24 hours
C. Involved light chain ≥ 10 mg/dL (100 mg/L) AND abnormal serum free light chain ratio.

Subjects without measurable disease (including non-secretory multiple myeloma) will also be eligible to participate if the baseline marrow burden of myeloma is at least 30%.

4.1.9 Subjects who require radiotherapy (which must be localized in its field size) may be enrolled but initiation of study therapy should be deferred until the radiotherapy is completed and 14 days have elapsed since the last date of radiotherapy.

4.1.10 Demonstrate adequate organ function as defined in the table below; all screening labs to be obtained within 72 hours prior to initiating study treatment.

System	Laboratory Value
Hematological*	
Hemoglobin (Hgb)	≥ 8 g/dL *Transfusion of packed red blood cells or use of erythropoietin or analogs is permitted, if clinically appropriate, to achieve this threshold.*
Absolute Neutrophil Count (ANC)	≥ 1.0 x 10^9/L *Use of growth factors is permitted to fulfill this criterion if neutropenia is felt to be due to MM or due to prior therapy for MM.*
Platelets	≥ 50 × 10^9/L if < 50% of bone marrow nucleated cells are plasma cells ≥ 30 × 10^9/L if ≥ 50% of BM nucleated cells are plasma cells. *Platelet transfusions are permitted to reach entry criteria if thrombocytopenia is felt to be due to MM or due to prior therapy for MM.*
Renal*	
Calculated creatinine clearance	Any GFR as long as not currently dialysis-dependent
Hepatic*	
Bilirubin	≤ 2 × upper limit of normal (ULN). Subjects with Gilbert's syndrome may be enrolled despite a total bilirubin level > 2 × ULN if their conjugated bilirubin is < 2 × ULN)
Aspartate aminotransferase (AST)	≤ 3 × ULN
Alanine aminotransferase (ALT)	≤ 3 × ULN

*Note: Hematology and other lab parameters that are ≥ grade 2 BUT still meet criteria for study entry are allowed. Furthermore, changes in laboratory parameters during the study should not be considered adverse events unless they meet criteria for dose modification(s) of study medication outlined by the protocol and/or worsen from baseline during therapy.

4.1.11 Male or Female Contraceptive Requirements

a) Male participants

Men must agree to use a latex or synthetic condom during sexual contact with a FCBP even if they have had a vasectomy from the time of signing the informed consent form through 90 days after the last dose of pomalidomide and 5 months after the last dose of isatuximab. These same patients must not donate sperm.

b) Female participants

A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:

Not a Female of childbearing potential (FCBP)*,

OR

If an FCBP, participant must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days prior to and again within 24 hours of starting pomalidomide and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME (Male or Female Contraceptive Requirements), at least 28 days before she starts taking pomalidomide through 90 days after the last dose of pomalidomide and 5 months after the last dose of isatuximab. FCBP must also agree to ongoing pregnancy testing during the entire duration of treatment and monthly for 5 months after the last dose of isatuximab. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. All patients enrolled into this trial, must be registered in and must comply with all requirements of the POMALYST REMS program.

*A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

4.1.12 Subject may be HIV+ if the following criterion are met:

1. CD4+ T-cell counts ≥ 350 cells/μL
2. No history of AIDS-defining opportunistic infections
3. Subject is on an established antiretroviral therapy (ART) for at least 4 weeks prior to initiation of study treatment.
4. Absence of known, clinically significant drug-drug interactions with isatuximab, pomalidomide, and dexamethasone.

4.1.13 Subjects is willing and able to comply with study procedures based on the judgement of the investigator or protocol designee.

4.2 Exclusion Criteria

All subjects meeting any of the listed exclusion criteria at baseline with be excluded from study participation.

4.2.1 Anti-myeloma treatment within 2 weeks of cycle 1 day 1

4.2.2 Subject is refractory to pomalidomide and/or known to be intolerant of pomalidomide at a dose of 3 mg or less.

4.2.3 Any monoclonal antibody therapy within the previous 28-days

4.2.4 Autologous stem cell transplantation within 12 weeks of day 1 of cycle 1

4.2.5 Subjects felt to not be candidates by treating physician for ANY systemic therapy due to excessive comorbidities, frailty, impaired performance status, or other severe limitations. Such limitations can be conceptualized generally as making subjects exceedingly high-risk for ANY systemic treatment. These limitations often stem from medical comorbidities unrelated to MM and they are hence unlikely to improve with MM therapy.

4.2.6 Light-chain (AL) amyloidosis. Subjects with secondary amyloidosis due to MM are eligible, providing amyloidosis is not felt to be a clinically significant issue (e.g., amyloid found incidentally on bone marrow core biopsy without evidence of amyloid-mediated organ compromise).

4.2.7 Myocardial infarction within 3 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure (**Appendix N. New York Heart Association Classification of Cardiac Disease**), uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities.

4.2.8 Evidence of active bleeding requiring intervention within the last four weeks.

4.2.9 Current unstable liver or biliary disease per investigator assessment defined by the presence of ascites, encephalopathy, coagulopathy, hypoalbuminemia, esophageal or gastric varices, persistent jaundice, or cirrhosis. Note: Stable chronic liver disease (including Gilbert's syndrome or asymptomatic gallstones) or hepatobiliary involvement of malignancy is acceptable if patient otherwise meets entry criteria.

4.2.10 Any major surgery within the last four weeks

4.2.11 Diagnosed or treated for another malignancy within 2 years of enrollment, with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, an in-situ malignancy, or low-risk prostate cancer after curative therapy. Diagnosis of other prior malignancy within 2 years of enrollment also permissible if no evidence of disease, previously treated with curative intent, and if felt to be unlikely to impact survival during the duration of the study. Other low-risk

malignancies also permissible if natural history or treatment is unlikely to interfere with efficacy or safety endpoints.

4.2.12 Concurrent use of other anti-cancer agents or treatments (with the exception of adjuvant/maintenance hormonal therapy for participants with a history of breast or prostate cancer and other similar agents deemed to have a low likelihood of affecting the outcome of this study (per discretion of treating physician)).

4.2.13 Known to have hepatitis A, B, or C active infection.

Uncontrolled or active HBV infection: Patients with positive HBsAg and/or HBV DNA. Of note:

- Patient can be eligible if anti-HBc IgG positive (with or without positive anti- HBs) but HBsAg and HBV DNA are negative.
    - If anti-HBV therapy in relation with prior infection was started before initiation of IMP, the anti-HBV therapy and monitoring should continue throughout the study treatment period.
- Patients with negative HBsAg and positive HBV DNA observed during screening period will be evaluated by a specialist for start of anti-viral treatment. If HBV DNA becomes negative and all the other study criteria are still met the subject will be eligible.

Active HCV infection: positive HCV RNA and negative anti-HCV. Of note:

- Patients with antiviral therapy for HCV started before initiation of IMP and positive anti-HCV are eligible. The antiviral therapy for HCV should continue throughout the treatment period until seroconversion.
- Patients with positive anti-HCV and undetectable HCV RNA without antiviral therapy for HCV are eligible.

4.2.14 Active systemic infection and severe infections requiring treatment with a parenteral administration of antibiotics.

4.2.15 Any clinically significant, uncontrolled medical or psychiatric conditions that, in the Investigator's opinion, would expose the patient to excessive risk or may interfere with compliance or interpretation of the study results.

4.2.16 Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent. Hypersensitivity or history of intolerance to steroids, mannitol, pregelatinized starch, sodium stearyl fumarate, histidine (as base and hydrochloride salt), arginine hydrochloride, poloxamer 188, sucrose or any of the other components of study intervention that are not amenable to

premedication with steroids and H2 blockers or would prohibit further treatment with these agents.

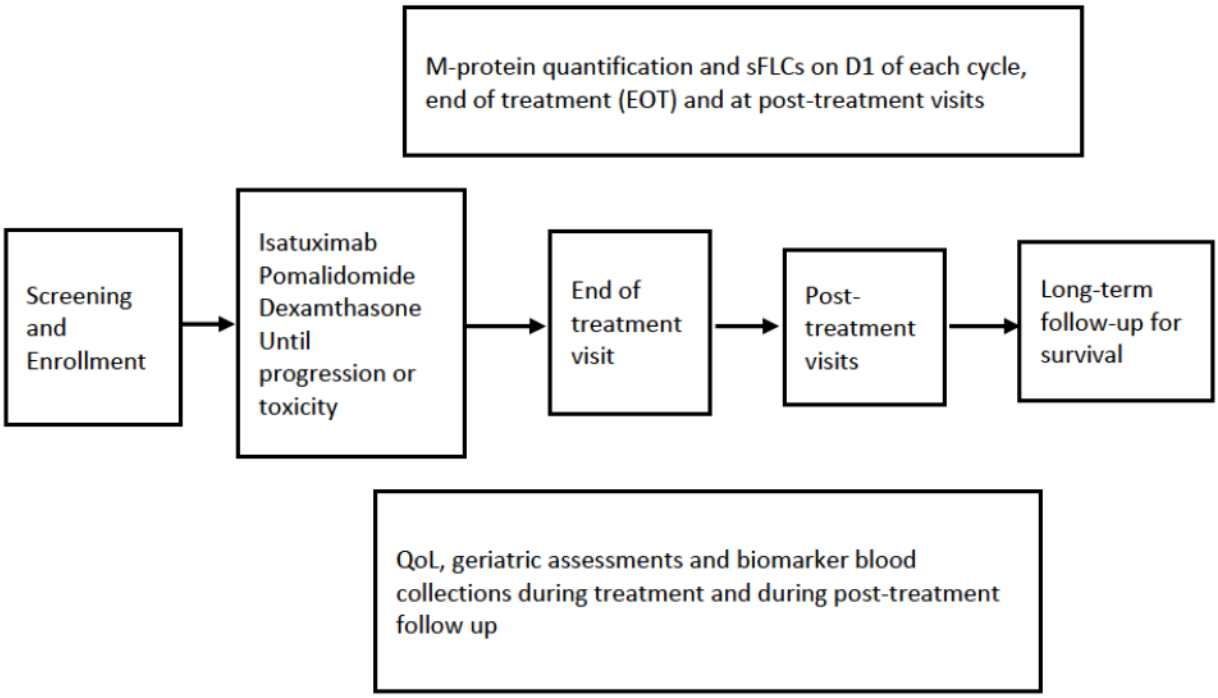
4.2.17 Received any investigational drug within 14 days or 5 half-lives of the investigational drug prior to initiation of study intervention, whichever is longer.

4.2.18 Subject is receiving prohibited medications or treatments as listed in section 5.7 and **Appendix A. Prohibited Medications or Those to be Used with Caution** of the protocol that cannot be discontinued/replaced by an alternative therapy.

4.2.19 Subject does not currently use tobacco products including cigarettes, chew, or smokeless tobacco.

5.0 TREATMENT PLAN

5.1 Schema



5.2 Treatment Dosage and Administration

REGIMEN DESCRIPTION					
Agent	**Premedications; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Isatuximab	Montelukast 10 mg orally (C1 only) Dexamethasone 20 mg orally Acetaminophen/paracetamol 650 to 1000 mg orally. Diphenhydramine 50 mg orally (or equivalent: e.g., cetirizine, promethazine, dexchlorpheniramine, according to the approval availability) or diphenhydramine 25 50 mg IV (or equivalent). Intravenous route is preferred for at least the first four IV infusions.	10 mg/kg	IV	days 1,8,15 and 22 of cycle 1, then days 1 and 15 of cycles 2+	4 weeks (28 days)
Pomalidomide		3 mg	PO	days 1-21 of each cycle	
Dexamethasone		20 mg	PO	days 1, 8, 15, and 22 of each cycle	

5.3 Criteria for Initiating a New Cycle of Treatment

Subject must meet the following criteria to start a cycle of treatment:

- ANC $\geq 1.0 \times 10^9$/L.*
- Platelets $\geq 50 \times 10^9$/L if < 50% of BM nucleated cells are plasma cells.*
- Platelets $\geq 30 \times 10^9$/L if $\geq$ 50% of BM nucleated cells are plasma cells (cycles 1-3 only)*
- All other treatment-related, non-hematologic toxicity (except for alopecia) must have resolved to $\leq$ Grade 1 or to the subject's baseline condition. Treatment-emergent AEs that remain above Grade 1 but are NOT felt to be related to study treatment do not require delay in study therapy, but clinician should use his/her judgment in nonetheless delaying therapy if it is in the subject's best interest clinically.

*Supportive care interventions (growth factors, transfusions, etc.) as outlined in eligibility criteria may also be employed to achieve required cell counts prior to starting a cycle of therapy.

If the subject fails to meet the above start criteria for initiation of a next cycle of treatment, dosing should be delayed for 1 week. The subject should then be re-evaluated. If the subject continues to fail to meet the above-cited criteria, delay therapy again and continue to re-evaluate weekly. For delays of >2 weeks due to cytopenias felt to be due to therapy, see Table 3 in Section 5.4.2 below.

The maximum delay before study treatment should be permanently discontinued will be 6 weeks, unless a longer delay is clinically appropriate and approved by the study PI.

See section 5.4 for dose modifications and further guidance related to dose delays.

5.4 Toxicities and Dosing Delays/Dose Modifications

Mid-cycle missed doses should not be made up. Missed doses should be skipped.

5.4.1 Isatuximab Dose Modifications/Delays

Dose modifications are not allowed with the exception of recalculating dose to account for weight changes of > 10% from cycle 1 day 1 weight.

For information on management of infusion reactions see Managing Infusion Reactions.

5.4.2 Pomalidomide Dose Modifications/Delays

Allowable dose adjustments/reductions are outlined in **Table** 3 If 1 mg is not tolerated despite maximal supportive care, then pomalidomide should be permanently discontinued and other study drugs may be continued if felt to be appropriate by the treating clinician.

Table 3 Pomalidomide Dose Levels/Modifications

Dose Level	Dose (mg)
+1*	4 mg
0	3 mg
-1	2 mg
-2	1 mg
-3	Discontinue

**If after 3-cycles, the patient has SD (<MR) and has not experienced any grade ≥3 hematologic toxicities or treatment-related grade ≥2 non-hematologic toxicities, at the investigator's discretion, the dose of pomalidomide may be increased to 4 mg beginning*

with cycle 4. Pomalidomide dose increases to 4 mg may also be considered in other situations on a case-by-case basis after discussion with the PI.

5.4.2.1 Mid-cycle pomalidomide dose reductions

Per modification rules in **Table 4** and **Table 5**, subjects may warrant pomalidomide dose reduction mid-cycle. Insurance and/or pharmacy delivery limitations may prevent receipt of a new bottle of pomalidomide at the reduced dose until the next cycle, and pomalidomide capsules cannot be cut in half. If this occurs, the treating clinician may do one of the following:

A) Have the subject take one pill **EVERY OTHER DAY** of their current dose of pomalidomide, to complete the usual three weeks of pomalidomide for the current cycle and then switch to the new daily dose for next cycle

OR

B) Remain off pomalidomide until the subject receives a new supply at the lower dose and is due to start the next cycle.

Decisions should be made at the discretion of the treating clinician based on the urgency of continuing pomalidomide and other relevant considerations such as subject's ability to comply with every other day dosing strategy.

As an example, a hypothetical subject is on 3 mg pomalidomide and on day 10 of the current cycle of Isa-Pom-Dex, the subject experiences a toxicity requiring pomalidomide dose reduction to 2 mg. The treating clinician has the following options: A) instruct the subject to take pomalidomide 3 mg every **OTHER** day until day 21 of the current cycle, followed by the standard 7-day break; or B) instruct the subject to remain off pomalidomide for the remainder of the current cycle. In either case, the subject would begin a pomalidomide dose of 2 mg on day 1 of the next cycle.

5.4.2.2 Pomalidomide Dose Modifications for Specific Toxicities

Table 4 Pomalidomide Dose Modification for Hematologic Toxicity

Toxicity	Action / Considerations
Delay of >2 weeks due to cytopenias, per Criteria for Initiating a New Cycle of Treatment.	• If event is solely neutropenia, consider adding G-CSF and resuming at prior dose of pomalidomide. • For all other events, upon count recovery, reduce pomalidomide by one dose level.
Mid-cycle grade 4 thrombocytopenia (platelets $< 25 \times 10^9$/L)	• Hold pomalidomide and continue other study therapies if clinically appropriate. • Consider holding VTE prophylaxis (aspirin or anticoagulation) if subject is currently taking it.

	• Resume pomalidomide with one dose level reduction only when the subject's platelets recover to ≥ 50 × 10^9/L
Mid-cycle grade 4 neutropenia (ANC < 0.5 × 10^9/L) OR any grade febrile neutropenia	• Hold pomalidomide and continue other study therapies if event is not febrile neutropenia and continuing is felt to be clinically appropriate. • Resume pomalidomide when ANC recovers to ≥ 1 × 10^9/L and fever and/or infections, if present, have resolved. • If investigator plans on adding G-CSF and no other indication for reducing study therapies exists, may resume pomalidomide at same dose. • If subject was already on short-acting G-CSF ≥ 3 times weekly (e.g., Neupogen or Granix) or long-acting G-CSF at any frequency (e.g., Neulasta), OR investigator does not feel G-CSF is clinically appropriate, reduce pomalidomide one dose level. • For each subsequent drop of ANC less than 0.5x10^9 . pomalidomide will be held and other study therapies will continue if continuation is felt to be clinically appropriate. Pomalidomide will then resume with one dose-level reduction when ANC recovers to ≥0.5× 10^9/L.

Table 5. Other Treatment Modifications/Delays for Non-Hematologic Toxicity

Adverse Event (Severity)	Action on Study Drugs	Further Considerations
GI Grade ≥ 2 diarrhea	• Ensure supportive care (anti-motility agents, bile acid sequestrants, etc.) are maximized. • If diarrhea is attributed to pomalidomide, hold pomalidomide until resolution to Grade ≤ 1. • If event occurred without maximal supportive care (per discretion of the treating clinician), resume pomalidomide at prior dose with maximized supportive care. If event occurred despite maximal supportive care, reduce pomalidomide one dose level.	
Peripheral Neuropathy: *Consider workup for alternative causes such as amyloidosis, diabetic neuropathy, and also neurology evaluation, since study agents uncommonly cause neuropathy. Attributing progressive neuropathy to study therapy should be done very cautiously. Study treatment should not be held for worsening peripheral neuropathy that is not due to direct neurotoxicity of therapy, especially neuropathy that precedes study participation.*		
Worsening grade 2 peripheral neuropathy with pain or new grade 2-3 peripheral neuropathy	• Hold pomalidomide until resolution to grade ≤ 1 or to prior baseline • Reduce pomalidomide to next lower dose upon recovery	Grade 2 signs and symptoms: Moderate symptoms; limiting instrumental activities of daily living (ADL)
New or worsening grade 4 peripheral neuropathy	• Discontinue pomalidomide permanently	
Skin Rash		
Grade 2-3 non-blistering rash	• If offending drug is felt to be pomalidomide, hold pomalidomide and reduce to next lower dose upon return to Grade ≤ 1 or baseline.	Maximize supportive care such as H1 and H2 blockers and/or topical corticosteroid preparations. May use short-course (< 2 weeks) oral corticosteroids if felt to be warranted.
Grade 4 non-blistering rash	• Discontinue offending drug permanently.	
Grade ≥3 blistering / desquamating skin rash or erythema multiforme	• Discontinue offending drug permanently.	

Adverse Event (Severity)	Action on Study Drugs	Further Considerations
Other grade 3 non-hematologic toxicity judged to be related to isatuximab, pomalidomide, or dexamethasone with exceptions of alopecia, electrolyte abnormalities, hyperglycemia, diarrhea, or nausea and vomiting that can be managed with supportive care and do not persist as Grade 3 toxicities for > 72 hours.	• Hold offending drug until resolution to Grade ≤ 1 or baseline. • If offending drug is pomalidomide or dexamethasone, resume at next lower dose upon return to Grade ≤1 or baseline. • If offending drug is isatuximab, discuss resumption with study PI.	
Other grade 4 non-hematologic toxicity	• Permanent discontinuation of offending agent	

5.4.3 Dose Modifications for Dexamethasone

For participants with contraindications to the starting dose of dexamethasone, or participants who are intolerant of the starting dose of dexamethasone due to specific toxicities attributed to dexamethasone, the dose of dexamethasone may be reduced as outlined in **Table 6**. If dose level -2 (8 mg) is not tolerated, dexamethasone should be permanently discontinued but can remain on the study with the other treatment therapies.

Table 6 Dexamethasone Dose Levels/Modifications

Dose Level	Dose (mg)
0	20 mg
-1	12 mg
-2	8 mg

5.5 Concomitant Medications/Treatments/Supportive Care Allowed, Including Required Supportive Care

The following medications and procedures are permitted during the study:

- Antiemetics, including 5-HT3 serotonin receptor antagonists, may be used at the discretion of the investigator.
- Loperamide or other antidiarrheal agents should be used for symptomatic diarrhea at discretion of the investigator. The dose and regimen will be according to institutional guidelines. Preemptive antidiarrheals are encouraged for subjects experiencing frequent diarrhea as a result of study treatment (there is no need to wait for diarrhea to begin before initiating therapy if clinician and subject know it will occur when subject is taking,

for example, pomalidomide). Intravenous fluids should be given in cases of volume depletion.

- Growth factors (e.g., granulocyte colony stimulating factor [G-CSF], granulocyte macrophage-colony stimulating factor [GM-CSF], recombinant erythropoietin) are permitted as noted elsewhere in this protocol. Their use should follow published guidelines and/or institutional practice.
- Subjects should be transfused with red blood cells and platelets as clinically indicated and according to institutional guidelines.
- Prophylactic antiviral therapy with acyclovir, valacyclovir, or similar agent is required unless a compelling contraindication exists.
- Prophylactic antibiotics are permitted per local institutional guidance, especially among participants with Grade 3-4 neutropenia.
- Concomitant treatment with bisphosphonates or denosumab is allowed if the patient has previously received dental clearance to minimize risk of osteonecrosis of the jaw.
- Venous thromboembolic event (VTE) prophylaxis is strongly encouraged with aspirin (dose determined by treating clinician) or any form of anticoagulation, depending on VTE risk as assessed by treating clinician.
- HBV vaccination may be considered, following the investigator's discretion, for patients with negative HBsAg, total anti-HBc, anti-HBs and HBV-DNA. In case of viral reactivation during study treatment, study treatment should be held, and specialist may be consulted for initiation of anti-viral treatment and monitoring of the patient. Re-initiation of study treatment may be considered at the discretion of the treating clinician only if specialist (hepatologist) is in agreement (if consulted) and only if infection is acceptably controlled. Close monitoring of ALT and AST should then be continued up until study treatment discontinuation and HBV DNA to be monitored as per specialist advice.

5.6 Contraceptive Requirements

FCBP or male subjects with female partners of childbearing potential shall be required agree to practice true abstinence, when this is in line with the preferred and usual lifestyle of the subject or to use contraception as outlined below.

- FCBP must agree to initiate and practice contraception (using 2 effective methods – 1 highly effective method (Section 5.6.1.1) and 1 additionally effective method (Section 5.6.1.2) at the same time) at least 28 days before starting pomalidomide treatment through 90 days after the last dose of pomalidomide or 5 months after the last dose of isatuximab.

- Male subjects with female partners of childbearing potential, even if surgically sterilized (i.e., status post vasectomy) must agree to use barrier contraception (latex or synthetic condom) 2 weeks prior to study drug administration, during

the entire study treatment period and through 90 days or 5 months after the last dose of pomalidomide or isatuximab, respectively.

5.6.1 Methods of contraception

5.6.1.1 The following highly effective methods of contraception are accepted:

- Established use of oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation
- Established use of oral, injectable, or implantable progestogen-only hormonal contraception associated with inhibition of ovulation
- Placement of an intrauterine device or intrauterine hormone-releasing system
- Tubal ligation
- Male sterilization (vasectomy: provided that the partner is the sole sexual partner of the patient and that the sterilized partner has received medical assessment of the surgical success)
- Sexual abstinence during the entire period of risk associated with study treatments.

5.6.1.2 The following are additional effective methods of contraception

- Male latex or synthetic condom
- Diaphragm
- Cervical cap

5.6.1.3 UNACCEPTABLE methods of contraception

- Progesterone-only "mini-pills"
- IUD Progesterone T
- Female Condoms
- Cervical shield
- Fertility awareness
- Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods for the female partner) and withdrawal

5.7 Absolutely or Relatively Contraindicated Medications/Treatments

The following products and procedures are prohibited during the study:

- Any antineoplastic treatment with activity against MM, other than study drugs
- Radiation therapy except as approved by the study PI for symptom palliation.
- Short-course additional corticosteroids are permitted for the treatment of other medical problems. Longer-term additional steroids (> 2 weeks) should be discussed with study PI.
- Subjects taking concomitant therapies such as erythropoietin-stimulating agents or estrogen containing therapies may have an increased risk for thrombosis with concomitant administration of pomalidomide.

See Appendix A

5.8 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue until:

- Disease progression
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Pregnancy
- Subject decides to withdraw from study treatment
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator, or
- Subject is lost to follow up

5.9 Duration of Follow Up

All subjects will be followed for up to 3 years, or until death, whichever occurs first after removal from study treatment for determination of study endpoints.

5.10 Study Withdrawal

If a subject decides to withdraw from the study (and not just from protocol therapy) an effort should be made to complete and report study assessments as thoroughly as possible. At the time of withdrawal, the investigator should attempt to establish as completely as possible the reason for the study withdrawal.

- The subject should be asked if they are willing to allow for the abstraction of relevant information from their medical record in order to meet the long term follow up (e.g., survival) objectives outlined in the protocol.
- A complete final evaluation at the time of the subject's study withdrawal should be obtained with an explanation of why the subject is withdrawing from the study.
- If the subject is noncompliant and does not return for an end of study follow up assessment, this should be documented in the eCRF.
- If the reason for removal of a subject from the study is an adverse event, the principal specific event will be recorded on the eCRF.

Excessive subject withdrawals from protocol therapy or from the study can render the study un-interpretable; therefore, unnecessary withdrawal of subjects should be avoided.

5.11 Off Study Criteria

Subjects will be considered off study by any of the following criteria:

- Death
- The subject completely withdraws from the study including any further data collection.
- The subject completes all study activities and follow up and no further data is to be collected.
- The subject is removed because of change of condition or other instance in which the investigator feels the subject is no longer able to complete the study.

6.0 DRUG INFORMATION

6.1 Isatuximab

6.1.1 How Supplied

Commercial supply of isatuximab will be provided by the funding source at no cost to the subject.

6.1.1.1 Isatuximab concentrate for solution for infusion at 20 mg/mL

Isatuximab is available for parenteral administration as a sterile, non-pyrogenic, injectable, colorless to slightly yellow, 20 mg/mL concentrate for solution for infusion, essentially free of visible particles.

It is supplied as two presentations:

- 30 mL Type I colorless clear glass vials fitted with elastomeric closures. Each vial contains a nominal content of 500 mg of isatuximab. The fill volume has been established to ensure removal of 25 mL.
- 6 mL Type I colorless clear glass vials fitted with elastomeric closures. Each vial contains a nominal content of 100 mg of isatuximab. The fill volume has been established to ensure removal of 5 mL.

The concentrated solution is diluted in 0.9% sodium chloride solution or dextrose 5% solution before use.

Table 7. Isatuximab Information

Study intervention name	**Isatuximab**
Dosage formulation	Concentrate for solution for intravenous infusion
Unit dose strength(s)/Dosage level(s)	Concentration: 20 mg/mL Dosage presentation: 500 mg/25 mL and 100 mg/5 mL
Route of administration	Intravenous infusion
Dosing instructions	10 mg/Kg weekly cycle 1, 10mg/kg every two weeks thereafter (combination therapy)
Packaging and labeling	Isatuximab will be provided in 1 glass vial per box (30 mL vial for 500 mg and 6 mL vial for 100 mg). The label contents will be in accordance with the local regulatory specifications and requirements.

For details of isatuximab preparation and administration, refer to pharmacy manual.

6.1.2 Isatuximab Dosing and Administration

Premedication should be used prior to isatuximab infusion with the following medications to reduce the risk and severity of infusion reactions (IRs). At least 15 to 30 minutes (but no longer than 60 minutes) prior to isatuximab administration:

- Montelukast 10 mg orally (C1 only)
- Dexamethasone 20 mg orally
- Acetaminophen/paracetamol 650 to 1000 mg orally.
- Diphenhydramine 50 mg orally (or equivalent: e.g., cetirizine, promethazine, dexchlorpheniramine, according to the approval availability) or diphenhydramine 25-50 mg IV (or equivalent). Intravenous route is preferred for at least the first four IV infusions.

The order of premedication administration is the following: Montelukast, dexamethasone, acetaminophen/paracetamol, and then diphenhydramine.

Participants who do not experience IRs after four consecutive administrations of isatuximab may, at the Investigator's discretion, have their need for subsequent premedication reconsidered.

On days of co-administration with isatuximab, dexamethasone is used for the double purpose of premedication for IRs and therapeutic effect and should be given prior to isatuximab as part of premedication.

6.1.3 Stability, Storage conditions and shelf life

Vials of isatuximab concentrate for solution for infusion should be stored between 2°C and 8°C (36°F to 46°F) and protected from light. Do not freeze. Do not shake. The shelf life of unopened vial is 36-months.

6.1.3.1 Concentrate for solution for infusion at 20 mg/mL:

Storage Condition: between +2°C and +8°C, protected from light
Precautions for handling: Isatuximab should never be frozen
Shelf life: 36 months

6.1.4 General Precautions

Infusion reactions have been reported as the most common adverse reactions consequent to the administration of isatuximab (either as single agent or in combination with other anticancer agents); this is consistent with the results from clinical studies and from the post-marketing experience observed with other therapeutic mAb proteins. Extensive clinical experience with approved mAbs, in fact, indicates that mild to moderate IRs (either allergic, or consisting of cytokine release, which mimics hypersensitivity reactions) are very common, particularly during the first infusion; the cytokine release syndrome associated with mAbs consists of a pseudo-allergic Type B (non-IgE mediated) reaction.

The IRs associated with isatuximab have occurred most commonly at the first administration, are not dose-dependent, and subjects do not appear to sustain permanent sequelae. Infusion reactions generally do not cause therapy discontinuation and tend not to recur at subsequent administrations of isatuximab. Occasionally, these adverse reactions may be serious and systemic (as with anaphylactic reactions, which have been reported in 5 subjects throughout the isatuximab program, corresponding to an incidence of 0.3%). Infusion reactions, however, are most frequently of Grade 1–2 severity and are manageable.

6.1.5 Managing Infusion Reactions

Table 8 Infusion Reaction Management

Severity (CTCAE version 5.0)	**Recommendation intervention**
Mild (Grade 1) Infusion interruption or intervention not indicated	Continuation of isatuximab infusion per the judgment 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 and infusion will be restarted at half of the initial infusion rate.
Moderate (Grade 2) Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., 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, at half the infusion rate and with close monitoring.

Severe or life-threatening (Grade 3 or 4) Grade 3: prolonged (e.g., 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 the 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 until the resolution of the AE or until the AE improves to Grade 1. Only then, if previous Grade 3 the infusion may be restarted at the Investigator's discretion; if so, the infusion rate should be half of the infusion rate before the interruption, and it may be increased subsequently, at the Investigator's discretion. If the severity of an infusion-related AE returns to Grade 3 after the restart of the infusion, the same procedure described above may be repeated at the Investigator's discretion. If a Grade 3 infusion-related AE occurs for a 3rd time, treatment with isatuximab will be definitively discontinued for that participant. In case of Grade 4, isatuximab will be permanently discontinued.

6.1.6 Contraindications

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

6.1.7 Drug Interactions

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

The contraindications for isatuximab include the following:

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

6.1.8 Method of Administration

IV Infusion

To minimize the incidence and severity of infusion reactions, all the subjects treated with isatuximab should routinely receive primary prophylactic treatment as detailed in Section 6.1.2.

6.1.8.1 Infusion instructions

Rate and duration of infusion:

First infusion: Initiate infusion at 25 mL/hour. In the absence of IRs after 1 hour of infusion, increase infusion rate by 25 mL/hour increments every 30 minutes, to a maximum of 150 mL/hour. In case of grade 2 IR during first infusion, infusion could be restarted at one-half (12.5 mL/hour) of the initial infusion rate when the IR improves to Grade ≤1. If symptoms do not recur after 30 minutes, the infusion rate may be increased by 25 mL/hour increments every 30 minutes, until the total volume is infused.

Infusion duration, minutes	Infusion rate increment*, mL/hour	Infusion rate to be administered, mL/hour	Cumulative infused volume, mL
0 – 60 (60 minutes)	-	25	25
61 – 90 (30 minutes)	+ 25	50	50
91 – 120 (30 minutes)	+ 25	75	87,5
121 – 150 (30 minutes)	+ 25	100	137,5
151 – 180 (30 minutes)	+ 25	125	200
181 – 200 (20 minutes)	+ 25	150	250

Second infusion: Initiate infusion at 50 mL/hour. In the absence of grade 2 IR after 30 minutes of infusion, increase rate to 100 mL/hour for 30 minutes, then, to 200 mL/hour until the total volume is infused.

Infusion duration, minutes	**Infusion rate increment, mL/hour**	**Infusion rate to be administered, mL/hour**	**Cumulative infused volume, mL**
0 – 30 (30 minutes)	-	50	25
31 – 60 (30 minutes)	+50	100	75
61 – 113 (53 minutes)	+100	200	250

In case of grade 2 IR during second infusion, infusion could be restarted at one-half (25 mL/hour) of the initial infusion rate when the IR improves to Grade ≤1. If symptoms do not recur after 30 minutes, the infusion rate may be increased by 50 mL/hour increments every 30 minutes, until the total volume is infused.

Third and subsequent infusions: Initiate infusion at a fixed infusion rate of 200 mL/hour, until the total volume is infused. In case of grade 2 IR during third infusion and subsequent infusions, infusion could be restarted at one-half (100 mL/hour) of the infusion rate when the IR improves to Grade ≤1. If symptoms do not recur after 30 minutes, the infusion rate may be increased by 50 mL/hour increments every 30 minutes, until the total volume is infused.

6.1.9 Drug Ordering and Accountability

The investigator or designee is responsible for keeping accurate records of the clinical supplies received from the company or designee, the amount dispensed to the subjects and the amount remaining at the conclusion of the trial. An accurate and current accounting of the dispensing and return of study drug for each subject will be maintained on an ongoing basis by a member of the study site staff. The amount of study drug dispensed and returned by the subject will be recorded in the Drug Accountability Record.

6.1.10 Return and Retention of Study Drug

Upon completion or termination of the study, all unused and/or partially used product will be destroyed at the site per the UNC IDS drug destruction policy. It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

6.1.11 Disposal

Local requirements for disposal of hazardous drugs should be followed at each participating clinical site.

Please see UNC policy on hazardous drugs:
https://unchealthcare-uncmc.policystat.com/policy/4734545/latest/

6.1.12 Isatuximab Adverse Events

6.1.12.1 Possible Risks

As of 05 January 2020, a total of 1643 patients were treated with isatuximab IV in studies sponsored by Sanofi with isatuximab given alone (as single agent, or monotherapy, in 458 patients), or in combination with other anti-cancer drugs (in 1185 patients).

A pooled safety analysis of completed monotherapy studies (TED10893 [Phase1 and Phase2 Stage1] and TED14154 [PartA]) has been performed.

Treatment emergent AEs of any grade and regardless of relationship with study treatment were most frequently reported in the SOCs of general disorders and administration site conditions (72.2%), followed by respiratory, thoracic and mediastinal disorders (61.8%), injury, poisoning and procedural complications (61.8%), gastrointestinal disorders (61.3%), infections and infestations (56.6%), musculoskeletal and connective tissue disorders (50.5%), nervous system disorders (43.9%), metabolism and nutrition disorders (32.5%), and blood and lymphatic system disorders (32.1%).

For more details regarding TEAEs incidence please refer to current IB.

6.1.12.2 Infusion reactions that may be caused by isatuximab

Isatuximab IV may cause infusion reactions, which typically occur within 24 hours from the start of an infusion, and most commonly during the first infusion. The most frequent symptoms of infusion reactions associated with isatuximab include chills, shortness of breath, nausea, chest discomfort, flushing, cough, and headache. Although usually mild-to-moderate and always reversible either spontaneously or with treatment, infusion reactions can also be severe or even life threatening. Serious infusion reactions (such as throat tightness, difficulty in breathing, lowered blood pressure, or severely increased blood pressure) are known to occur at any time during the administration of monoclonal antibodies, including isatuximab.

In addition to infusion reactions, isatuximab might also cause the following condition(s):

- Cytokine release syndrome: this condition is reversible, but it could be severe or even life threatening.
- Tumor lysis syndrome.

6.1.12.3 Reproductive toxicity, pregnancy and breast feeding

The effects of isatuximab on reproductive toxicity, pregnancy and lactation have not been investigated in formal toxicity studies. Therefore, the effects of isatuximab on reproductive organs in males and females are unknown.

Females of childbearing potential or male subjects with female partners of childbearing potential shall be required to use highly effective contraceptive methods (a failure of <1% per year when used consistently and correctly) starting 28 days before first isatuximab administration, while on therapy and for 5 months following the last dose of isatuximab. A woman is considered of childbearing potential, i.e., fertile, following menarche and until becoming post-

menopausal unless permanently sterile. The following highly effective methods of contraception are accepted:

- Established use of oral, intravaginal, or transdermal combined (estrogen and progestogen
- containing) hormonal contraception associated with inhibition of ovulation
- Established use of oral, injectable, or implantable progestogen-only hormonal
- contraception associated with inhibition of ovulation
- Placement of an intrauterine device or intrauterine hormone-releasing system
- Bilateral tubal occlusion
- Male sterilization (provided that the partner is the sole sexual partner of the patient and
- that the sterilized partner has received medical assessment of the surgical success)
    - Sexual abstinence during the entire period of risk associated with study treatments. If a woman becomes pregnant while taking isatuximab, treatment with isatuximab should be discontinued and the pregnancy should be followed until its outcome.

For complete guidance, please refer to the Guidance on Pregnancy and Contraception in the study protocols.

6.1.12.4 Potential interference with blood bank serologic tests

Isatuximab, an anti-CD38 antibody, may interfere with blood bank serologic tests with false positive reactions in indirect antiglobulin tests (indirect Coombs tests), antibody detection (screening) tests, antibody identification panels, and antihuman globulin crossmatches in patients treated with isatuximab. To avoid potential problems with blood transfusion, the American Association of Blood Banks recommends that participants being treated with anti-CD38 antibodies have blood type and screen tests performed at baseline. After treatment, each time before a blood infusion, the antibody screen test (indirect Coombs test) should be done. In all isatuximab studies, patient blood will be typed and screened before (if not already done) the first administration of the drug and a card with blood type will be carried by the patient throughout the study.

More detailed information about the known and expected benefits and risks and reasonably expected AEs of isatuximab may be found in the IB.

6.1.12.5 Potential interference of isatuximab with serum M protein tests

Isatuximab is an IgG kappa monoclonal antibody that can be incidentally detected on both serum protein electrophoresis (SPE) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein of patients with multiple myeloma. This interference can impact the accuracy of the determination of complete response in some patients with IgG kappa myeloma protein.

6.1.12.6 Secondary Primary Malignancies

In a Phase 3 trial (ICARIA-MM), second primary malignancies (SPMs) were reported in 6 patients (3.9%) treated with isatuximab and in 1 patient (0.7%) treated with pomalidomide and dexamethasone and included skin squamous cell carcinoma in 4 patients treated with isatuximab and in 1 patient treated with pomalidomide and dexamethasone. Patients continued treatment after resection of the skin squamous cell carcinoma. The overall incidence of SPMs in all the isatuximab -exposed patients is 3%. Physicians should carefully evaluate patients before and during treatment as per International Myeloma Working Group (IMWG) guidelines for occurrence of SPM and initiate treatment as indicated.

6.1.12.7 Possible Adverse Drug Reactions (ADRs)

Within the context of IRs, anaphylactic reaction, cytokine release syndrome, and pyrexia are among the adverse reactions observed in subjects 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.

6.1.12.8 AESIs

An adverse event of special interest is an adverse event (serious or non-serious) of scientific and medical concern specific to the Sponsor's product

AESIs for isatuximab include infusion reactions (IRs), symptomatic overdose, secondary primary malignancies, viral reactivation, and pregnancy.

6.1.12.9 Severe Adverse Reactions for Isatuximab in Combination with pomalidomide and dexamethasone

The following information is from Table 111 in the May 19, 2021 Investigator's Brochure. Please refer to the Investigator's Brochure for a more complete listing of severe adverse reactions for isatuximab.

Table 9 Severe Adverse Reactions for Isatuximab

Expected Severe Adverse Reactions for isatuximab in combination with pomalidomide and dexamethasone occurring in ≥1% of exposed subjects		
		Number of subjects = 266
System Organ Class (SOC)	**Severe Adverse Reactions**	**All Severe Adverse Reactions** **N (%)**
Blood and lymphatic system disorders	Febrile neutropenia	12 (4.5)
	Neutropenia	12 (4.5)

	Thrombocytopenia	6 (2.3)
General disorders and administration site conditions	Pyrexia	4 (1.5)
Infections and infestations	Bronchitis	3 (1.1)
	Pneumonia	32 (12.0)
	Sepsis	3 (1.1)
	Urinary tract infection	3 (1.1)
Injury, poisoning and procedural complications	Infusion-related reaction	8 (3.0)
Nervous system disorders	Transient ischemic attack	3 (1.1)
Respiratory, thoracic and mediastinal disorders	Dyspnea	3 (1.1)
	Pulmonary embolism	5 (1.9)

6.2 Commercial Drug Description and Management

6.2.1 Pomalidomide

6.2.1.1 Brief Description:

Pomalidomide, an analogue of thalidomide, is an immunomodulatory agent with antineoplastic activity. In *in vitro* cellular assays, pomalidomide inhibited proliferation and induced apoptosis of hematopoietic tumor cells. Additionally, pomalidomide inhibited the proliferation of lenalidomide-resistant multiple myeloma cell lines and synergized with dexamethasone in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumor cell apoptosis. Pomalidomide enhanced T cell- and natural killer (NK) cell-mediated immunity and inhibited production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes. Pomalidomide demonstrated anti-angiogenic activity in a mouse tumor model and in the *in vitro* umbilical cord model.

Full prescribing information for pomalidomide is available at:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/204026s019lbl.pdf

6.2.1.2 Supplier/How Supplied

Dark blue opaque cap and yellow opaque body, imprinted "POML" on the cap in white ink and "1 mg" on the body in black ink
1 mg bottles of 21 (NDC 59572-501-21)
1 mg bottles of 100 (NDC 59572-501-00)

Dark blue opaque cap and orange opaque body, imprinted "POML" on the cap and "2 mg" on the body in white ink
2 mg bottles of 21 (NDC 59572-502-21)
2 mg bottles of 100 (NDC 59572-502-00)

Dark blue opaque cap and green opaque body, imprinted "POML" on the cap and "3 mg" on the body in white ink

3 mg bottles of 21 (NDC 59572-503-21)
3 mg bottles of 100 (NDC 59572-503-00)
Dark blue opaque cap and blue opaque body, imprinted "POML" on the cap and "4 mg" on the body in white ink
4 mg bottles of 21 (NDC 59572-504-21)
4 mg bottles of 100 (NDC 59572-504-00)

6.2.1.3 Dosage and Administration

See

Treatment Dosage and Administration

6.2.1.4 Storage and Stability

Store at 20°C-25°C (68°F-77°F); excursions permitted to 15°C-30°C (59°F-86°F). [see USP Controlled Room Temperature].

6.2.1.5 Handling and Disposal

Care should be exercised in handling of pomalidomide. Pomalidomide capsules should not be opened or crushed. If powder from pomalidomide contacts the skin, wash the skin immediately and thoroughly with soap and water. If pomalidomide contacts the mucous membranes, flush thoroughly with water.

Local requirements for disposal of hazardous drugs should be followed at each participating clinical site.

Please see UNC policy on hazardous drugs:
https://unchealthcare-uncmc.policystat.com/policy/4734545/latest/

6.2.1.6 Adverse Events Associated with Commercial Drug

Most common adverse reactions (≥30%) included fatigue and asthenia, neutropenia, anemia, constipation, nausea, diarrhea, dyspnea, upper- respiratory tract infections, back pain, and pyrexia.

6.2.2 Contraindications

Concomitant therapy with strong CYP1A2 inhibitors should be avoided if possible. If concomitant use of a strong CYP1A2 inhibitor is unavoidable, the pomalidomide dose should be reduced to 1 mg until the strong CYP1A2 inhibitor is discontinued.

6.2.3 Commercial Drug Description and Management: Dexamethasone

6.2.3.1 Brief Description

Dexamethasone is a practically white or white, odorless, crystalline powder that is a synthetic glucocorticoid. Glucocorticoids produce varied metabolic effects.

6.2.3.2 Supplier/How Supplied

Dexamethasone is commercially available and therefore is to be purchased by a third party. Dexamethasone is available in seven potencies (0.5 mg, 0.75 mg, 1mg, 1.5 mg, 2 mg, 4 mg, and 6 mg) in tablet form.

6.2.3.3 Dosage and Administration

See

Treatment Dosage and Administration

Note: Dexamethasone is to be given with a snack/light meal to reduce gastric irritation.

Refer to package insert for complete dispensing instructions available at: http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Roxane/Dexamethasone/Dexamethasone%20Tablets%20Solution%20and%20Intensol.pdf

6.2.3.4 Storage and Stability

Store dexamethasone at 20°C-25°C (68°F-77°F).

6.2.3.5 Handling and Disposal

Local requirements for disposal of hazardous drugs should be followed at each participating clinical site.

Please see UNC policy on hazardous drugs: https://unchealthcare-uncmc.policystat.com/policy/4734545/latest/

6.2.3.6 Adverse Events Associated with Dexamethasone

Gastrointestinal: Nausea, vomiting, anorexia, increased appetite, weight gain; aggravation of peptic ulcers.

Dermatologic: Rash, skin atrophy, facial hair growth, acne, facial erythema, ecchymoses. Genitourinary: Menstrual changes (amenorrhea, menstrual irregularities).

Neurologic: Insomnia, euphoria, headache, vertigo, psychosis, depression, seizures, muscle weakness.

Cardiovascular: Fluid retention and edema, hypertension; rarely, thrombophlebitis. Ocular: Cataracts, increased intraocular pressure, exophthalmos.

Metabolic: Hyperglycemia, decreased glucose tolerance, aggravation or precipitation of diabetes mellitus, adrenal suppression (with Cushingoid features), hypokalemia.

Hematologic: Leukocytosis.

Other: Osteoporosis (and resulting back pain), appearance of serious infections including herpes zoster, varicella zoster, fungal infections, Pneumocystis carinii, tuberculosis; muscle wasting; delayed wound healing; suppression of reactions to skin tests.

6.2.3.7 Contraindications

Contraindicated in systemic fungal infections.

Use in Pregnancy
Pregnancy Category C: Corticosteroids have been shown to be teratogenic in many species when given in doses equivalent to the human dose.

Use in Nursing Women
Systemically administered corticosteroids appear in human milk and could suppress growth, interfere with endogenous corticosteroid production, or cause other adverse effects on the nursing infant.

Overdose
Treatment of overdosage is by supportive and symptomatic therapy. In the case of acute overdosage, according to the subject's condition, supportive therapy may include gastric lavage or emesis.

7.0 CLINICAL ASSESSMENTS

Clinical assessments will be performed as outlined in the **Time and Events Table** in EVALUATIONS AND ASSESSMENTS

7.1 Evaluations and Assessment

7.1.1 Concomitant Medications

All concomitant medication and concurrent therapies will be documented at screening, within 7 days prior to Day 1 of the study treatment and throughout the study at each treatment visit and at the end of treatment. Dose, route, unit frequency of administration, and indication for administration and dates of medication will be captured.

7.1.2 Demographics

Demographic information (date of birth, gender, race) will be recorded at Screening.

7.1.3 Medical History

Relevant medical history, including history of current disease, other pertinent history, and information regarding underlying diseases will be recorded at time of screening. within 21 days prior to Day 1 of the study treatment and a focused medical history on symptoms/toxicity will be performed thereafter throughout the study.

7.1.4 Physical Examination/Vital Signs/Performance Status

A complete physical examination including height (at screening only), weight, Karnofsky Performance status (Appendix B. Karnofsky Performance Status Scale) and vital signs (i.e., temperature and blood pressure).

Qualified staff (MD, DO, NP, or PA) will complete the exams.

New abnormal physical exam findings must be documented and will be followed by a physician or other qualified staff at the next scheduled visit.

7.1.5 Adverse Events

Any patient who receives treatment on this protocol will be evaluable for toxicity. Events should be assessed per NCI-CTCAE criteria v5.0. Information regarding occurrence of adverse events will be captured throughout the study, including as outlined in the time and events table (see section 8.1). Duration (start and stop dates), severity/grade, outcome, treatment and relation to study drug will be recorded in the case report form (CRF).

7.2 MM Disease Assessment

7.2.1 Beta-2-Microglobulin and Lactate Dehydrogenase (LDH)

Only required at D1 of cycle 1, prior to starting maintenance, and at the end of study treatment.

7.2.2 Monoclonal protein (M-protein) assessments

1) Serum protein electrophoresis (SPEP) with immunofixation electrophoresis (IFE),
2) Serum free light chain assay,
3) Serum immunoglobulin (Ig) quantification
4) 24-hour urine protein electrophoresis (UPEP) with IFE

7.2.3 Bone marrow (BM) Aspirate and Biopsy

BM aspirate and biopsy for morphology, flow cytometry, cytogenetics, and fluorescence *in situ* hybridization (FISH), and correlative research, will be collected per the Time and Events Table at screening and at EOT timepoints. BM aspirate and biopsy for morphology and flow cytometry (plus cytogenetics and FISH if clinically warranted) will also be collected as needed to assess response status, such as CR or PD. Commercially available minimal residual disease (MRD) assessments by next-generation sequencing with a minimum sensitivity of 1×10^{-5} should be performed if possible on bone marrow, in subjects who are in serological CR. Results will be reported on the eCRF with other bone marrow results.

7.3 Clinical Laboratory Assessments

Timing of clinical assessments should follow the schedule presented in the Time and Events Table.

All clinical laboratory testing should be performed locally. There are no central laboratory tests with the sole exception of correlative studies.

7.3.1 Hematology

Complete blood count should be accompanied by a white blood cell differential.

7.3.2 Serum Chemistry Profile

Serum chemistries must include sodium, potassium, chloride, CO_2, BUN, creatinine, glucose, and calcium. Albumin, total protein, total bilirubin, AST, ALT, alkaline phosphatase should be included on specific dates as outlined in the Time and Events Table.

7.3.3 Pregnancy Test

Frequent pregnancy testing is required for females of childbearing potential who receive pomalidomide. See the **Time and Events Table**.

Because of the embryo-fetal risk, POMALYST is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called "**POMALYST REMS**."

Required components of the **POMALYST REMS** program include the following:

- Prescribers must be certified with the **POMALYST REMS** program by enrolling and complying with the REMS requirements.
- Patients must sign a Patient-Physician Agreement Form and comply with the REMS requirements. In particular, female patients of reproductive potential who are not pregnant must comply with the pregnancy testing and contraception requirements and males must comply with contraception requirements.
- Pharmacies must be certified with the **POMALYST REMS** program, must only dispense to patients who are authorized to receive POMALYST, and comply with REMS requirements.

Further information about the **POMALYST REMS** program is available at www.CelgeneRiskManagement.com or by telephone at 1-888-423-5436.

If a woman becomes pregnant while taking isatuximab, treatment with isatuximab should be discontinued and the pregnancy should be followed until its outcome.

7.3.4 Type and Screen, Red Blood Cell Phenotyping

Should be obtained prior to starting isatuximab.

7.4 Clinical Imaging

7.4.1 CT / MRI / PET-CT

Computerized Tomography (CT), magnetic resonance imaging (MRI) or PET-CT should be performed with screening if a subject is known to have an extramedullary plasmacytoma. If done, the same technique should be employed as clinically indicated during the study treatment (including if relevant to confirm response), and again at the end of study treatment.

7.4.2 Skeletal Survey or WBLT-CT

X-ray skeletal survey or whole-body low-dose CT (WBLD-CT) is required for screening and thereafter as per the Time and Events Table.

7.5 Patient Reported Outcomes/Quality of Life

7.5.1 CARG Global Assessment

The CARG-GA assesses various domains including functional status, social determinants of health, and falls, among others. The GA will be administered either in person or online. Information on how subjects will complete the assessment will be provided to sites.

Note that there is a coordinator-completed component and a subject-completed component to the GA. Coordinators complete the same form with each assessment (Appendix I. CARG Global Assessment: Healthcare Team). For subjects, the first time they complete the GA they should complete the **baseline** assessment (Appendix J. CARG Global Assessment: Subject-Completed Baseline Questionnaire). Subsequent assessments should be completed using the **subsequent** assessment form (Appendix K. CARG Global Assessment: Subsequent Assessment).

7.5.2 IMWG Frailty

The IMWG Frailty assessment tool requires the following assessments:

- Charlson Comorbidity Index
- Katz Activities of Daily Living (ADL)
- Lawton Instrumental Activities of Daily Living (iADL)

Appendix C. Instructions for Scoring IMWG Frailty Assessment Tool, Including Lawton IADL and Katz ADL Assessments and Charlson Comorbidity Index provides additional information.

7.5.3 Q-TWiST

Quality-adjusted Time Without Symptoms of disease progression or Toxicity of treatment (Q-TwiST) assesses the time without symptoms or toxicity. Toxicity, time without toxicity and relapse will be captured throughout the study.

7.5.4 EORTC QLQ-C30

The tool assesses the quality of life in individuals with cancer. This will be provided to sites as a PDF and/or electronically (Appendix D. EORTC QLQ-C30).

7.5.5 EORTC QLQ-MY20

The tool assesses the quality of life in individuals with multiple myeloma. This will be provided to sites as a PDF and/or electronically (Appendix E. EORTC-MY20).

7.5.6 Mini-Cog and PROMIS-cog

Mini-Cog and PROMIS-cog (Appendix H. Mini-Cog and Appendix G. PROMIS Cognitive Function-Short Form 8a) are validated instruments for assessing cognitive and subjective cognitive impairment, respectively. Coordinators administering Mini-Cog will be trained in how to administer the test. Forms will be provided to sites.

7.5.7 Gait Speed

Gait speed will be evaluated as part of the CARG-GA and is found in Appendix L. Gait Speed.

7.5.8 Financial Toxicity

Financial toxicity will be evaluated using the COST-FACIT questionnaire, which will be provided to sites (Appendix F. COST-FACIT).

7.6 Correlative Studies

Bone marrow biopsy/aspirate should be obtained per the Time and Events Table in section 8.1. Specimens will be collected for correlative research (non-UNC multicenter sites may opt-out of this component of the study) only at the screening and EOT timepoints.

Blood draws will be performed per the Time and Events Table in section 8.1. Blood biomarker sample collection (non-UNC multicenter sites may opt-out of this portion of the study) is performed at C1D1, C4D1, and at end-of-treatment.

For UNC subjects (mandatory) and non-UNC multicenter sites (unless opted-out of this component of the study) we will evaluate immune cell populations in the bone marrow and peripheral blood as justified in 1.8.2. We will also study peripheral blood T-cell $p16^{INK4}$ levels as discussed in section 1.8.1.

Please refer to the laboratory manual for details on sample collection.

8.0 EVALUATIONS AND ASSESSMENTS

8.1 Time and Events Table

Assessment	Screening[1c]	C1 D1[2]	C1 D8[2]	C1 D15[2]	C1 D22[2]	C2 D1[2]	C2 D15[2]	C3 D1[2]	C3 D15[2]	C4+ D1[2]	C4+ D15[2]	EOT[3]	Post-Treatment Visits[3] (Study)	Long-term Follow-up[3]
Informed Consent	X													
Eligibility Verification	X													
Medical history	X[1a]	X				X		X		X		X	X	X
Physical exam	X[1a]	X				X		X		X		X	X	
Vital signs	X[1a]	X	X	X	X	X	X	X		X		X	X	
Karnofsky Performance Status	X	X				X		X		X		X	X	
Serum Pregnancy Test and Contraception Screening[1d, 1e]	X	X	X	X	X	X	X[1d]	X	X[1d]	X	X[1d]	X[1d]		
Skeletal Survey *or* WBLD-CT	X[1a]	As clinically indicated										X		
Plasmacytoma evaluation[10]	X[1a]	As clinically indicated										X		
Bone marrow aspiration/biopsy[7]	X[1b]	As clinically indicated										X		
Hematology[4]	X[1c]	X	X	X	X	X	X	X				X	X	
Type and screen, red blood cell phenotyping (prior to isatuximab)		X												
Serum Chemistry[5]	X[1c]	X	X	X	X	X	X	X		X		X	X	

Assessment	Screening[1c]	C1 D1[2]	C1 D8[2]	C1 D15[2]	C1 D22[2]	C2 D1[2]	C2 D15[2]	C3 D1[2]	C3 D15[2]	C4+ D1[2]	C4+ D15[2]	EOT[3]	Post-Treatment Visits[3] (Study)	Long-term Follow-up[3]
β-2-microglobulin and LDH	x	x										x		
M-protein quantification[6] and serum free light chain assay	x	x				x		x		x		x	x	
Blood biomarker collection[8]		x[8]								x[8]		x[8]	x[8]	
Isatuximab IV		x	x	x	x	x	x	x	x	x	x			
Pomalidomide PO[12]		x[12]												
Dexamethasone PO[9]		x	x	x	x	x[9]								
Subject Pill Diary[14]		x				x		x		x				
Clinical toxicity assessment (CTCAE v5.0)[11]	x	x	x	x	x	x	x	x	x[11]	x[11]	x[11]	x	x	
Concomitant medications review	x	x	x	x	x	x		x		x		x		
CARG-Global Assessment	x[8]									x[8]		x[8]	x[8]	
Gait speed test, PROMIS-cog, Mini-cog, [13]	x[13]									x[13]		x[13]	x[13]	
IMWG Frailty assessment	x[8]													
EORTC QLQ-C30, EORTC QLQ-MY20 QOL assessments[8]		x[8]								x[8]		x[8]	x[8]	
Survival														x

Footnotes to Time and Events Table

1. Screening Windows for assessments are as follows:
    a. Complete history, physical exam and all imaging assessments should be performed within 21 days prior to day 1 of study treatment in cycle 1 except x-ray skeletal survey or WBLD-CT scan, which may be performed up to 4 weeks prior to cycle 1 day 1.
    b. Baseline bone marrow biopsy/aspirate should be obtained within 4 weeks prior starting treatment on cycle 1 day 1.
    c. All screening evaluations (except for pregnancy test) must be performed within 21 days prior to cycle 1 day 1 unless otherwise stipulated. Screening hematology and chemistry labs must be completed within 72 hours prior to start of treatment on Day 1, Cycle 1. All lab testing and study visits may be performed up to 24 hours prior to isatuximab infusion if clinically appropriate, for subject convenience.
    d. Serum β-HCG pregnancy test must be performed within 10-14 days of cycle 1 day 1 and then again within 24 hours of cycle 1 day 1 for women of child-bearing potential. Additional pregnancy tests are required weekly during first 4 weeks of therapy and then on a monthly basis thereafter in subjects with regular menstrual cycles or every two weeks if the menstrual cycle is irregular. Additional pregnancy tests will be required if a menstrual cycle is missed or there is unusual menstrual bleeding, or if pomalidomide is not dispensed within 7 days of taking the pregnancy test.
    e. Men must agree to use a latex or synthetic condom during sexual contact with a FCBP even if they have had a vasectomy from the time of signing the informed consent form through 90 days after the last dose of pomalidomide and 5 months after the last dose of isatuximab. These same patients must not donate sperm. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. All patients enrolled into this trial, must be registered in and must comply with all requirements of the POMALYST REMS program.

2. A window of ±3 days applies to all study visits unless otherwise specified. Study visit including all lab testing may be performed up to 1-day prior to isatuximab infusion, if clinically appropriate, for subject and clinic convenience. If screening medical history and physical exam are performed within 3-days of C1D1, these do not need to be repeated on C1D1.

3. The end of treatment visit should only occur when subjects permanently stop study treatment and should be performed within 30 days (±7 days) after the last dose of study medication. Subjects will be followed for adverse events during this 30-day period.

Post-treatment visits will be conducted for subjects who have an ongoing ≥ grade 3 or serious AE (SAE) at the end of treatment visit and will be continued until the event is resolved or deemed irreversible by the investigator. These visits will occur at least once every 4 weeks (±1 week) for the first 6 visits and then once every 12 weeks (±2 weeks) thereafter. However, follow-up every 12 weeks by telephone or any other modality is permissible if a less frequent monitoring schedule is clinically appropriate, and if the subject would otherwise require removal from the study.

In addition, post-treatment visits will be conducted for subjects who remain progression free at their end of treatment visit and will occur once every 4 weeks (±1 week) for the first 6 visits and then once every 12 weeks (±2 weeks) thereafter until disease progression or the start of a new MM treatment. If follow up of ≥grade 3 or serious adverse events (as outlined above) has also concluded, patients will then enter the long-term follow-up phase. If possible, during the post-treatment phase, subjects should complete the Karnofsky performance status, CARG global assessment, quality of life assessment, cognitive testing, and blood correlatives every six months until they enter the long-term follow up phase.

The Long-Term Follow-up period will begin (except in the case of withdrawal of consent) after the end of treatment and post-treatment (if applicable as outlined above) visits and will take place every 3 months

(±2 weeks) for a maximum of 3-years from the end-of-treatment visit. Long-Term Follow-up visits will be limited to history of any subsequent cancer treatments, diagnosis of another cancer and survival status. Long-term follow up assessments may be conducted either in person, by telephone, via audio/video, medical record abstraction, or by other modality deemed appropriate for this purpose by the investigator.

After documented progression of MM and/or initiation of other, non-study therapy, follow-up should be every three months by any modality (telephone, via audio/video, or by other modality deemed appropriate for this purpose by the investigator).

4. Hematology: CBC with white blood cell differential

5. Serum chemistries must include the following:

    - Every chemistry assessment: sodium, potassium, chloride, CO_2, BUN, creatinine, glucose, and calcium.
    - Day 1 of each cycle only: also include albumin, total protein, total bilirubin, AST, ALT, alkaline phosphatase.

6. SPEP, serum IFE, serum immunoglobulin quantification (IgG, IgA, IgM, plus IgD and/or IgE if clinically indicated for IgD or IgE myeloma) and 24h UPEP/IFE. Sebia Hydrashift ISA assay (Labcorp) is recommended for patients with IgG-kappa multiple myeloma in VGPR or better.

7. For morphology, flow cytometry, conventional cytogenetics, FISH, and correlative assessment (unless non-UNC multicenter site that has opted-out of the correlative portion of the study). MRD testing by next generation sequencing with minimum sensitivity of 1×10^{-5} by next generation sequencing should be performed if subject appears to be in complete response by serum and/or urine MM markers.

    BM biopsy should be repeated every 12 weeks in subjects with non-secretory disease.

8. IMWG Frailty Assessment is only performed at screening, using CARG-GA administered at screening. CARG-GA is then again assessed at C4D1, at D1 of every 3rd cycle thereafter (C7, C10, etc.), at EOT, and every six months (during post-treatment visits) until progression of MM and/or initiation of other MM therapy.

Regarding CARG-GA, there is a coordinator-completed component and a subject-completed component to the GA. Coordinators complete the same form with each assessment (Appendix I). For subjects, the first time they complete the GA they should complete the **baseline** assessment (Appendix J). Subsequent assessments should be completed using the **subsequent** assessment form (Appendix K).

IMWG frailty assessment should be completed using the scoring instructions in Appendix C.

EORTC QLQ-C30, EORTC QLQ-MY20 QOL assessments are performed at C1D1 (or during screening), C4D1, at D1 of every 3rd cycle thereafter (C7, C10, etc.), at EOT, and every six months (during post-treatment visits) until progression of MM and/or initiation of other MM therapy.

Blood biomarker sample collection (non-UNC multicenter sites may opt-out of this portion of the study) is performed at C1D1, C4D1, and at end-of-treatment.

9. Dexamethasone is given on days 1, 8, 15 and 22 of each cycle. On days that both dexamethasone and isatuximab are given, dexamethasone should be administered prior to isatuximab infusion on days patient receives isatuximab. Note: Dexamethasone should be given with a snack/light meal to reduce gastric irritation.

10. CT, MRI or PET-CT should be performed with screening if a subject is known to have an extramedullary plasmacytoma. If done, the same technique should be employed as clinically indicated during the study treatment (including if relevant to confirm response), and again at the end of study treatment.

11. From Cycle 3 and beyond, assess toxicity at D1 of each cycle and as needed.

12. Administered daily on Days 1-21 of a 28-day cycle

13. Gait speed (Appendix L), PROMIS-cog (Appendix G) and Mini-Cog (Appendix H) testing cannot be performed virtually, rather must be performed in-person. Prior to starting study treatment, subject may complete these items either up to 21 days prior to cycle 1 day 1 OR on cycle 1 day 1 itself, whichever is more convenient for an in-person encounter with a study coordinator. For subsequent assessments, if subject is scheduled for these tests but conducting a virtual visit that day, then these assessments should be postponed until next in-person visit. It has been <2 months since these tests were last conducted, these items can be skipped to avoid redundancy.
14. Pill diary should be checked for subject adherence at the beginning of every cycle.

8.2 Handling of Biospecimens Collected for Correlative Research

Biospecimens collected for this study will be stored in the Lineberger Comprehensive Cancer Center (LCCC) Tissue Procurement Facility (TPF), or if needed, in a secure off-site storage facility. All biospecimen samples will be obtained in accordance with procedures outlined in the LCCC 2119 Study Laboratory Manual and stored in containers with controlled access. Each sample will be assigned a unique code number and no identifiable personal health information (PHI) will be on the specimen label. Information about the subject's disease will be linked to the specimens stored in the repository database. TPF-associated research staff, LCCC Bioinformatics staff who support the TPF database and the LCCC Data Warehouse, and researchers with IRB-approval for access to PHI for each subject in this study will be able to link specimens to relevant medical information. Some results from laboratory analyses that occurred during the subject's participation in the clinical study may also be included. This information may be important for understanding how the subject's cancer developed and responded to treatment.

Storage Time:

- The biospecimen will be used first and foremost for research purposes outlined within the confines of this protocol. Samples will be discarded/destroyed after relevant data are collected for this study, unless consent was obtained from the subject to use tissue for other research purposes (e.g., TPF consent form was signed by the subject). In this circumstance, there is a 15-year limit on use and storage of the biospecimens. If storage is anticipated to be indefinite, there will be an opt-out on the informed consent form allowing subjects to choose not to allow their specimens to be used for such future research.
    - The investigator must agree to abide by policies and procedures of the TPF facility and sign a letter of research agreement for ethical and appropriate conduct of their research that utilizes specimens obtained from the TPF facility (e.g., Use of leftover specimens will require a protocol outlining the research plan for biospecimen use).

Compliance Statement

Biospecimen collection for this study will be conducted in full accordance with all applicable University of North Carolina (UNC) Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, and the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. Any episode of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent, and will report unexpected problems in accordance with The UNC IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

Provision of Data to Correlative Scientists

Identification and Role of the Study Coordinator (or other named role) as the Honest Broker

The study coordinator (or other named role) will be in charge of collecting and maintaining all data points and data management. The study coordinator should have adequate training to enter, manage, and deidentify data. The study coordinator will provide a unique study number to each enrolled subject. All documentation and samples will be labeled with the unique study number. The correlative teams will only be provided this unique study ID number as opposed to any other patient identifiers. The clinical team will be the only people able to access identifiable data and the study coordinator will be a conduit to provide the de-identified data to the correlative team.

Requests for a data

Identifiable data will not be given out to any correlative investigators at any time. Multicenter and UNC correlative Investigators may ask the study coordinator for a specific data set, and the study coordinator will return a deidentified data set. This data may only be used for purposes of the study. Any use other than directly related to the study must be approved by the IRB of record. If there is a need for an investigator to access identifiable data during the study, then a new IRB application will need to be submitted from that investigator detailing the reasons needed to access that data. The study coordinator will also ensure that correlative results are not returned from the correlative team to the clinical team to dictate treatment or follow-up decisions unless this is specifically approved by the IRB of record and delineated in the clinical protocol.

8.3 Assessment of Safety

Any subject who receives at least one dose of study therapy on this protocol will be evaluable for toxicity. Each subject will be assessed periodically for the development of any toxicity according to the Time and Events Table. Toxicity will be assessed according to the NCI CTCAEv5.0.

8.4 Assessment of Efficacy

Any subject who receives treatment on this protocol will be evaluable for efficacy. Subjects who are withdrawn from the protocol before receiving any study treatment will not be evaluated for efficacy and will be replaced.

To assess disease status, MM labs will be performed as a baseline prior to treatment and then as outlined in the Time and Events Table.

This study will use the Consensus Criteria for Response by the International Myeloma Working Group (IMWG) Appendix O. Response Criteria for Multiple Myeloma [51].

The primary endpoint of the study is overall response rate as defined as the percentage of subjects achieving a partial response or better (≥ PR) to study therapy at any time (per IMWG criteria provided in Appendix O. Response Criteria for Multiple Myeloma).

9.0 ADVERSE EVENTS

9.1 Definitions

9.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence (e.g., an abnormal laboratory finding, symptom, or disease temporally associated with the use of a drug) in a subject or clinical investigation subject administered an investigational product and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not related to the medicinal product.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of a central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable by the investigator to the study therapy.

9.1.2 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the investigational product is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by an investigational product.

Causality assessment to a study drug is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study investigational product exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering drug as the cause of the AE:

- Single occurrence of an uncommon event known to be strongly associated with investigational product exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event not commonly associated with investigational product exposure, but otherwise uncommon in the population (e.g., tendon rupture); often more than once occurrence from one or multiple studies would be needed before the sponsor could determine that there is *reasonable possibility* that the investigational product caused the event.

- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the investigational product treatment group than in a concurrent or historical control group

9.1.3 Unexpected AE or SAR

An AE or SAR is considered unexpected if the specificity or severity of it is not consistent with the applicable product information (e.g., Investigator's Brochure (IB) for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the IB as occurring with a class of investigational product or as anticipated from the pharmacological properties of the investigational product but are not specifically mentioned as occurring with the particular investigational product under investigation.

9.1.4 Serious AE or SAR

An AE or SAR is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization (>24 hours) or prolongation of existing hospitalization; *
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse study treatment-related experience when, based upon appropriate medical judgment, they may jeopardize the subject or subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

Pregnancy that occurs during the study must also be reported as an SAE.

9.2 Documentation of non-serious AEs or SARs

For non-serious AEs or SARs, documentation must begin from day 1 of study treatment and continue through the 30-day follow-up period after treatment is discontinued.

Collected information should be recorded in the Case Report Forms (CRF) for that subject. Please include a description of the event, its severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug. Documentation should occur at least monthly.

9.3 SAEs or Serious SARs

9.3.1 Timing

After informed consent but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g., SAEs related to invasive procedures such as biopsies, medication washout).

For any other experience or condition that meets the definition of an SAE or a serious SAR, recording of the event must begin from day 1 of study treatment and continue through the 30-day follow-up period after treatment is discontinued. NOTE: For drug(s) with long half-lives, it may be appropriate to extend the 30-day follow-up period.

9.3.2 Documentation and Notification

SAEs or Serious SARs must be recorded in the SAE console within OnCore® for that subject within 24 hours of learning of its occurrence. Additionally, the UNC Multicenter Project Manager must also be notified via email of all SAEs within 24 hours of learning of its occurrence.

9.4 Adverse Event Reporting

9.4.1 IRB Reporting Requirements

UNC:

- The UNC-IRB will be notified of all SAEs that qualify as an Unanticipated Problem as per the UNC IRB Policies using the IRB's web-based reporting system within 7 days of the Investigator becoming aware of the problem.

Multicenter sites:

- The IRB will be notified of all SAEs that qualify as an Unanticipated Problem in accordance with their SOPs. These events must be reported to the sponsor within 24 hours of learning of the occurrence and entered into OnCore® by the multicenter site.

Pregnancy

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study, or within 30 days of the subject's last dose of study should be recorded as SAEs. The subject is to be discontinued immediately from the study.

For Affiliate sites, the pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Multicenter Project Manager immediately (within 24 hours) via email (preferred) or facsimile to 919-966-4300. The Multicenter Project Manager will then report the event to the Funding Source (see requirements below). The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy and must document the outcome of the pregnancy (either normal or abnormal outcome) and report the condition of the fetus or newborn to the UNC Project Manager. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE.

9.4.2 Funding Source (e.g., Manufacturer) Reporting Requirements

9.4.2.1 Sanofi

The reference safety information (RSI) in section 8 of the isatuximab Investigator's Brochure provides listings of those serious adverse reactions (SARs) that are to be considered expected for regulatory purposes. Monitoring of AEs at any time during the study period starts when the patient signs the informed consent form.

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to isatuximab, for which ongoing monitoring and rapid communication by the Sponsor to Sanofi is appropriate. Such an adverse event might require further investigation to be characterized and understood.

To be reported as an AE, a laboratory test abnormality must cause an action to be taken with the IMPs or must meet a criterion for the definition of serious adverse event.

The External Sponsor warrants that the study will be performed in compliance with all applicable local and international laws and regulations, including without limitation ICH E6 guidelines for Good Clinical Practices.

The External Sponsor shall be responsible for the respect of all obligations required by applicable local and international laws and regulations.

The External Sponsor shall be responsible for ensuring submission of required expedited and periodic reports to the appropriate Regulatory Authority (RA), the Ethics Committee and investigators of each country participating in the ISS/ESC (based on applicable regulations).

The study reports of any ISS/ESC must contain a section describing safety review and conclusion and must be reviewed by Sanofi before finalization.

The External Sponsor must provide to Sanofi upon request results of any relevant complementary exams performed to obtain the final diagnosis of any SAE (e.g., hospital discharge summary, autopsy, consultation).

The External Sponsor is responsible for providing new safety finding of Sanofi Product received from Sanofi to the investigators and Ethics Committee in each country participating in the study.

Specific country regulations may be more stringent in terms of requirements than the present document. In those cases, all provisions must be applied in accordance with local regulatory requirements.

The reference safety information to be used by the External Sponsor for evaluation of expectedness of adverse events shall be the current approved product label available in the country (for an approved indication)/ the Investigator Brochure (for an unapproved indication).

The External Sponsor must transmit the following information in English to the Sanofi Pharmacovigilance contact (Email: CL-CPV-Receipt@sanofi.com or Fax: to +33 1 60 49 70 70):

- For interventional Studies, the External Sponsor must transmit to Sanofi all SAEs and AESIs regardless of Investigator's assessment of causality, within 24h

9.4.3 FDA Expedited Reporting requirements for studies conducted under an IND

A sponsor must report any suspected adverse reaction that is both serious and unexpected to the FDA (refer to Section 9.1.4 and 9.1.3, respectively for the definition of serious and unexpected). The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event as defined in Section 9.1.2.

The sponsor must submit each IND safety report on FDA Form 3500A form. Each notification to FDA must bear prominent identification of its contents, i.e., "IND Safety Report," and must be transmitted to the review division that has the responsibility for review of the IND. In each IND safety report, the sponsor must identify all IND safety reports previously submitted to FDA concerning a similar suspected adverse reaction and must analyze the significance of the

suspected adverse reaction in light of previous, similar reports or any other relevant information.

Timing

FDA must be notified of potential serious risks within 15 calendar days after the sponsor determines the event requires reporting. FDA must be notified of unexpected fatal or life-threatening suspected adverse reactions as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information. The sponsor must be notified of the SAE by the investigator within 24 hours of the event. For Multicenter trials, Lineberger is the sponsor, therefore, the UNC Multicenter Project Manager must be notified of the SAE within 24 hours of the event. If the results of a sponsor's investigation show that an adverse event not initially determined to be reportable is reportable, the sponsor must report such suspected adverse reaction in an IND safety report as soon as possible, but in no case later than 15 calendar days after the determination is made.

Follow-up

The sponsor must promptly investigate all safety information it receives. Relevant follow-up information to an IND safety report must be submitted as soon as the information is available and must be identified as such, i.e., "Follow-up IND Safety Report." Additionally, upon request from FDA, the sponsor must submit to FDA any additional data or information that the agency deems necessary, as soon as possible, but in no case later than 15 calendar days after receiving the request.

Notification of Investigators

The sponsor must notify all participating investigators (i.e., all investigators to whom the sponsor is providing investigational product under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

Process

If the sponsor deems that an event is both a serious adverse reaction (SAR) AND unexpected, it must also (in addition to OnCore®) be recorded on the MedWatch Form 3500A as per 21 CFR 312.32. Unexpected adverse events or adverse reaction refers to an event or reaction that is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed; or if an Investigator's Brochure is not required or available, is not consistent with the risk information described in the general investigation plan or elsewhere in the current IND application.

The MedWatch form and supporting documents defining the event and causality should be sent to the electronic mailbox (CPOMultiCenter@med.unc.edu) of the Multicenter Project Manager along with supporting documentation defining the event and causality. The UNC Multicenter Project Manager will then send the report to the

Funding Source and notify the Multicenter and CPO Regulatory Associate of the event. The MedWatch 3500a form can be accessed at: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm.

(Please be sure and access form 3500A, and not form 3500).

Once the UNC Principal Investigator determines an event is a serious SAR AND unexpected, the MedWatch 3500A form will be submitted to the FDA. If the event is serious, unexpected and considered to be possibly-, probably- or definitely-related to the study treatment, the UNC Project Manager will inform the Regulatory Associate at UNC and IND Specialist. The MedWatch form will be submitted according to LCCC SOP for safety reporting for a multi-site study.

All IND safety reports must be submitted on Form 3500A and be accompanied by Form 1571. The FDA must be notified of any unexpected or life-threatening suspected adverse reactions as soon as possible, but no later than 7 calendar days of learning of the event.

The UNC Multicenter Project Manager will also be responsible for informing each multicenter site of all serious and unexpected SARs reported to the FDA as soon as possible.

Additional Reporting Requirements

The following additional items must be reported via IND safety report:

- *Findings from other studies.* The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk to humans exposed to the drug/investigational product.
- *Findings from animal or in vitro testing.* The sponsor must report any findings from animal or *in vitro* testing, whether or not conducted by the sponsor, that suggest a significant risk in humans exposed to the drug/investigational product, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure.
- *Increased rate of occurrence of serious suspected adverse reactions.*

Additional Guidance

Please refer to 21CFR312.32 and "Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies" for additional information and reporting requirements. All IND Safety Reports will be submitted in accordance with these regulations/guidances.

9.5 Data and Safety Monitoring Plan

The Principal Investigator will provide continuous monitoring of subject safety in this trial with periodic reporting to the Data and Safety Monitoring Committee (DSMC).

Meetings/teleconferences will be held at a frequency dependent on study accrual. These meetings will include the investigators as well as protocol nurses, clinical research associates, regulatory associates, data managers, biostatisticians, and any other relevant personnel the principal investigators may deem appropriate. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory, data collection, etc.

The team will produce summaries or minutes of these meetings. These summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the oversight of Office of Human Research Ethics (OHRE) Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute Data and Safety Monitoring Board (DSMB).

The UNC LCCC Data and Safety Monitoring Committee (DSMC) will review the study on a regular (quarterly to annually) basis, with the frequency of review based on risk and complexity as determined by the UNC Protocol Review Committee. The UNC PI will be responsible for submitting the following information for review: 1) safety and accrual data including the number of subjects treated; 2) significant developments reported in the literature that may affect the safety of participants or the ethics of the study; 3) preliminary response data; and 4) summaries of team meetings that have occurred since the last report. Findings of the DSMC review will be disseminated by memo to the UNC PI, PRC, the UNC IRB and DSMB.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

This study is designed as a single arm, open label, multi-center phase II study which will estimate the overall response rate (defined as partial response or better to study therapy at any time, based on IMWG criteria provided in Appendix O. Response Criteria for Multiple Myeloma) of highly toxicity-vulnerable patients with relapsed and/or refractory multiple myeloma who are treated with isatuximab, pomalidomide, and dexamethasone. Secondary endpoints (as defined in section 3.2) include TFFS, CR, VGPR, PR, PFS, OR, time to initial response, time to best response, duration of response, and measures of the toxicity and tolerability of therapy.

10.2 Sample Size and Accrual

Simon's two-stage design will be used with a total of 49 patients to test the response rate to isatuximab, low-dose pomalidomide, and dexamethasone among very elderly and/or otherwise highly toxicity-vulnerable patients. The null hypothesis that the response rate is 31% will be tested against a one-sided alternative. In the first stage, 25 patients will be accrued. If there are 7 or fewer responses in these 25 patients, the study will be stopped. Otherwise, 24 additional patients will be accrued for a total of 49. The null hypothesis will be rejected if 21 or more patients respond to the combination. This test has the type I error rate of 0.052 and power of 0.80 when the true response rate is 48%.

The predicted ORR is based on a subgroup analysis of elderly patients included in the randomized phase 3 ICARIA-MM trial, which demonstrated an ORR of 53.1% among patients on the Isa-Pom-Dex arm who were ≥75 years of age.[28] The ORR of patients ≥75 years treated on the control (Pd) arm was 31%. The population included in the current study is likely to be frailer overall than the ≥75-year-old cohort included in ICARIA-MM. Furthermore, the response rates to may be somewhat lower given the starting pomalidomide dose of 3 mg.

Of note, the ORR among all patients treated with Isa-Pom-Dex on the ICARIA-MM trial was 60%, however the patients included in the current study will again be significantly older and more toxicity-vulnerable than the overall population of ICARIA-MM, which is expected to correlate with a lower ORR.

Based on accrual data from prior trials in refractory multiple myeloma at our institution, we estimate an accrual rate of approximately 2 eligible patients per month across all sites. We estimate that the enrollment period will be approximately 25 months and that the average duration on study will be approximately 10 months.

Sequential boundaries will be used to monitor unacceptable toxicity rate. Unacceptable toxicity is defined as a Grade 4 or higher non-hematological adverse

event attributed to study treatments except for Grade 4 infusion related reaction (IRR) occurring within 48 hours of the infusion of isatuximab. The accrual will be halted if excessive numbers of dose-limiting toxicities are seen, that is, if the number of unacceptable toxicities is equal to or exceeds b_n out of n patients with full follow-up (see table). This is a Pocock-type stopping boundary that yields the probability of crossing the boundary at most 0.15 when the rate of unacceptable toxicity is equal to the acceptable rate 0.2.

The trial will be stopped if the number of dose limiting toxicities is equal to or exceeds b_n out of n patients with completed follow-up.

Table 10: Toxicity-Related Stopping Boundaries

Number of Patients, n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary, b_n	-	2	3	3	4	4	4	5	5	5	6	6	6	7	7	7	7	8	8	8
Number of Patients, n	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Boundary, b_n	8	9	9	9	10	10	10	10	11	11	11	11	12	12	12	12	13	13	13	14
Number of Patients, n	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
Boundary, b_n	14	14	14	15	15	15	15	16	16											

Additionally, sequential boundaries will be used to monitor the rate of treatment related death. The accrual will be halted if excessive numbers of treatment related deaths are seen, that is, if the number of treatment related deaths is equal to or exceeds b_n out of n patients with full follow-up (see table). This is a Pocock-type stopping boundary that yields the probability of crossing the boundary at most 0.15 when the rate of treatment related death is equal to the acceptable rate 0.05.

The trial will be stopped if the number of treatment related deaths is equal to or exceeds b_n out of n patients with completed follow-up.

Table 11: Treatment-Related Death Stopping Boundaries

Number of Patients, n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary, b_n	1	2	2	2	2	2	2	3	3	3	3	3	3	3	3	3	3	4	4	4
Number of Patients, n	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Boundary, b_n	4	4	4	4	4	4	4	4	4	5	5	5	5	5	5	5	5	5	5	5
Number of Patients, n	41	42	43	44	45	46	47	48	49	50	51	52	53	54	55	56	57	58	59	60
Boundary, b_n	5	6	6	6	6	6	6	6	6											

10.3 Data Analysis Plans

10.3.1 Primary and Secondary Endpoints

The ORR and clinical benefit rates will be estimated as a proportion with corresponding 95% confidence intervals. Maximum depth of response (PR, VGPR, CR, or sCR) and bone marrow MRD status will be tabulated. PFS, TFFS, OS, time to response, duration of response, and time to next treatment will be estimated using the Kaplan-Meier method and 95% confidence intervals will be computed. Safety will be assessed per NCI-CTCAE criteria v5.0 based on changes in relevant clinical parameter measurements compared to baseline. Formal statistical comparisons of PFS or other outcomes will not be performed, but findings for this study will be put in descriptive context with non-statistical comparisons to prior studies such as ALCYONE, MAIA and RVD-Lite as mentioned above.

The primary analysis for the primary endpoint will be performed after all enrolled patients have completed tumor response assessment after 10 cycles of treatment or have disease progression, have died, or have been discontinued/withdrawn from study treatment. Afterwards, we will periodically evaluate secondary endpoints and safety.

10.3.2 Exploratory and Correlative Endpoints

[redacted].

11.0 STUDY MANAGEMENT

11.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s) and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the subject will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a subject's participation in the trial, the written informed consent form should be signed and personally dated by the subject and by the person who conducted the informed consent discussion.

11.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Protocol Office (CPO) at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list or Federalwide Assurance (FWA) number
- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation
- Financial Disclosures
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

11.3 Registration Procedures

All study subjects must be registered with the Lineberger Comprehensive Cancer Center (LCCC) CPO Multicenter Office at the University of North Carolina. Multicenter site staff must email a copy of the signed informed consent documentation and completed New Subject Patient Registration Form to the assigned UNC Multicenter Project Manager (contact e-mail provided at Site Initiation Meeting (SIM)) and to CPOMulticenter@med.unc.edu (M-F 8:30AM – 5:00PM eastern standard time (EST)) or call 919-966-7359 to alert the UNC LCCC Multicenter Office of a potential patient. Upon verification of the Informed Consent documentation by the assigned Project Manager, a unique subject sequence number will be provided to the site study staff. Multicenter site staff must submit complete eligibility packets (institutionally-signed eligibility checklist and full source documentation confirming eligibility) via email to the assigned UNC Multicenter Project Manager and CPOMulticenter@med.unc.edu to begin review. All subjects must have final eligibility verified by the UNC Multicenter Project Manager on behalf of the UNC PI prior to starting treatment. Please allow a minimum of 24 hours for source to be reviewed and notification of subject eligibility released. A patient registration email will be sent to the site's study staff to officially confirm registration of the patient 'On-Study'. All subjects must maintain eligibility from the time of this notification through the beginning of treatment.

11.4 Data Management and Monitoring/Auditing

UNC LCCC will serve as the coordinating center for this trial. Data will be collected through a web based electronic data capture system, Advarra EDC. Other study institutions will be given a password to directly enter their own data onto the web site via electronic case report forms (eCRFs). Multicenter personnel will coordinate and manage data for quality control assurance and integrity.

All data will be collected and entered into Advarra EDC by the multicenter study teams at participating institutions. The investigators at each site will allow monitors to review all source documents supporting data entered into Advarra EDC.

The site will provide direct access to source data/documents for trial-related monitoring, audits, IRB/IEC review, and regulatory inspection. As an investigator-initiated study, this trial will be audited at least every 12 months. Any corrective and preventive action plans (CAPAs) resulting from the audit will be reviewed by the LCCC compliance committee for acceptability. The study will also be monitored in accordance with the LCCC Monitoring Plan. The Clinical Data Management Associate (CDMA) will review the clinical trial data in accordance with the study's clinical data management plan. The CDMA can be reached at LCCC_OnCore@med.unc.edu or LCCC_EDC@med.unc.edu. All data will be monitored, and source data will be verified on selected subjects. Database queries will be issued on an ongoing basis on all subjects. The site should respond to data queries within 14 days of receipt.

11.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study subject requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.5.1 Emergency Modifications

UNC may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB/IEC approval/favorable opinion.

For any such emergency modification implemented, the IRB/IEC should be notified by UNC Research Personnel within five (5) business days of making the change.

For Institutions Relying on UNC's IRB:
For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

For Institutions Relying on Their Own IRB:
For Affiliate investigators relying on their own institution's IRB, as soon as possible after the modification has been made, the implemented deviation or change and the reasons for it should be submitted to:

- To UNC Principal Investigator for agreement
- The Affiliate institution's IRB for review and approval. (Once IRB's response is received, this should be forwarded to the Multicenter Regulatory Associate).

11.5.2 Single Subject Exceptions

Eligibility single subject exceptions are not permitted for Lineberger Comprehensive Cancer Center Investigator Initiated Trials under any circumstances. Other types of single subject exceptions may be allowed if proper regulatory review has been completed in accordance with Lineberger Comprehensive Cancer Center's Single Subject Exceptions Policy.

11.5.3 Other Protocol Deviations/Violations

A protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants

- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs, please follow the guidelines below:

Protocol Deviations: UNC or multicenter sites will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies.
Protocol Violations: Any protocol violation that occurs must be reported to the local IRB per institutional policies, recorded in OnCore®, and reported to the UNC Multicenter Regulatory Associate and Multicenter Project Manager within 5 days. UNC-CH will determine if the violation affects the safety of the subject and integrity of the data. Once your institution's IRB response is received, please forward to the UNC Multicenter Regulatory Associate.

Any events that meet the criteria for "Unanticipated Problems (UPs)" must be reported to the Multicenter Project Manager in addition to the IRB. Examples of such UPs include a lost or stolen laptop computer that contains sensitive study information. If the UP is the result of a protocol deviation, then the deviation must also be recorded in OnCore®.

11.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the subject, a revised consent form might be required.

For Institutions Relying on UNC's IRB:
The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

For Institutions Relying on Their Own IRB:
Investigators must submit the amendment to their institution's IRB for approval. For multicenter studies, any multicenter site must submit their informed consent revisions to the Multicenter Regulatory Associate for review and approval prior to submission to their IRB.

11.7 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor correspondence to Investigators, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed subject consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug/investigational product seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

11.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study subjects. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the eCRFs. Periodically, auditing and monitoring of trials will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all eCRFs will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

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13.0 APPENDICES

13.1 Appendix A. Prohibited Medications or Those to be Used with Caution

Isatuximab

No drug-drug interaction has been observed between isatuximab and other drugs used in combination.

Pomalidomide

The following information is from Section 7 (Drug Interactions) of the package insert. Additional information may be found here:
https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/204026s019lbl.pdf

Co-administration of pomalidomide with the following drugs did not increase pomalidomide exposure to a clinically significant extent: ketoconazole (a strong CYP3A4 and P-gp inhibitor), carbamazepine (a strong CYP3A4 inducer) and dexamethasone (a weak to moderate inducer of CYP3A4). Co-administration of pomalidomide with drugs that are CYP1A2 inducers has not been studied.

CYP1A2 Inhibitors: Co-administration of fluvoxamine (a strong CYP1A2 inhibitor) with pomalidomide increased mean [90% confidence interval] pomalidomide exposure by 125% [98% to 157%] compared to pomalidomide alone in healthy subjects. Co-administration of fluvoxamine in the presence of ketoconazole (a strong CYP3A4 and P-gp inhibitor) with pomalidomide increased mean pomalidomide exposure by 146% [126% to 167%] compared to pomalidomide administered alone in healthy subjects, indicating the predominant effect of CYP1A2 inhibition in the increase of pomalidomide exposure [*see Dosage and Administration (2.2) and Drug Interactions (7.1)*].

Strong CYP3A4 and P-gp Inhibitors: Co-administration of ketoconazole (a strong CYP3A4 and P-gp inhibitor) in 16 healthy male subjects increased AUC of pomalidomide by 19% compared to pomalidomide administered alone.

Drugs that Induce Pomalidomide Metabolism

Strong CYP1A2 Inducers: Co-administration of pomalidomide with drugs that are CYP1A2 inducers has not been studied and may reduce pomalidomide exposure.

Strong CYP3A4 Inducers: Co-administration of carbamazepine to 16 healthy male subjects decreased AUC of pomalidomide by 20% with a 90% confidence interval [13% to 27%] compared to when pomalidomide was administered alone.

Dexamethasone: Co-administration of multiple doses of 4 mg pomalidomide with 20 mg to 40 mg dexamethasone (a weak to moderate inducer of CYP3A4) to patients with multiple myeloma had no effect on the pharmacokinetics of pomalidomide compared to when pomalidomide was administered alone.

Smoking: In 14 healthy male subjects who smoked 25 cigarettes per day for a total of 10 days, after single oral dose of 4 mg pomalidomide, C_{max} of pomalidomide increased 14% while AUC of pomalidomide decreased 32%, compared to that in 13 healthy male volunteers who were non-smokers.

In Vitro Studies
Pomalidomide does not inhibit or induce CYP450 enzymes or transporters *in vitro.*

Dexamethasone
Below is a partial description of drugs or drug classes that may interact with dexamethasone. Further information can be found at:
https://medlibrary.org/lib/rx/meds/dexamethasone/page/3/

Aminoglutethimide
Amphotericin B injection and potassium-depleting agents
Antibiotics
Anticholinesterases
Anticoagulants, Oral
Antidiabetics
Antitubercular Drugs
Cholestyramine
Cyclosporine
Dexamethasone Suppression Test (DST)
Digitalis Glycosides
Ephedrine
Estrogens, including Oral Contraceptives
Hepatic Enzyme Inducers, Inhibitors and Substrates
Ketoconazole
Nonsteroidal Anti-Inflammatory Agents (NSAIDS)
Phenytoin
Thalidomide
Vaccines

13.2 Appendix B. Karnofsky Performance Status Scale

Condition	Percentage	Comments
A. Able to carry on normal activity and to work. No special care is needed.	100	Normal, no complaints, no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease
	80	Normal activity with effort; some signs or symptoms of disease
B. Unable to work. Able to live at home, care for most personal needs. A varying degree of assistance is needed.	70	Cares for self; unable to carry on normal activity or do active work
	60	Requires occasional assistance, but is able to care for most personal needs
	50	Requires considerable assistance and frequent medical care
C. Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing.	40	Disabled, requires special care and assistance (In bed more than 50% of the time)
	30	Severely disabled, hospitalization is indicated although death not imminent. (Almost completely bedfast)
	20	Hospitalization necessary, very sick, active supportive treatment necessary. (Totally bedfast and requiring extensive nursing care by professionals and/or family)
	10	Moribund, fatal processes progressing rapidly. (Comatose or barely arousable)
	0	Dead

Adapted from Peus, et al. [52]

13.3 Appendix C. Instructions for Scoring IMWG Frailty Assessment Tool, Including Lawton IADL and Katz ADL Assessments and Charlson Comorbidity Index

Lawton IADL, Katz ADL and Charlson Comorbidity Index used for IMWG Frailty Assessment are all built into the study's CARG global assessment (appendix J in section 13.10) and none needs to be administered separately. Scoring below should be performed using patient responses to the assessment questionnaires.

The Lawton IADL and Katz ADL questionnaires are administered as part of both the baseline and subsequent CARG global assessments.

IMWG Frailty Score should only be calculated at screening.

To complete IMWG Frailty Scoring, enter data in the table on the next page, using the instructions that follow.

1. Enter the score for the subject's age in the Subject's Score column. This score should be 0, 1 or 2.

2. **Lawton IADL**: Count the number of times the subject selects answers in their Lawton IADL questionnaire that are marked as **red/underlined** below (questions 1 through 8). Enter that number here _____. Find the corresponding "Assigned Score" for Lawton IADL in the IMWG frailty assessment scoring table below and enter that score in the "Subject's Score" column for Lawton IADL. That score should be either 0 or 1.

3. **Katz ADL**: Count the number of times the subject selects answers in their Katz ADL questionnaire that are marked as **red/underlined** below (questions 9 through 14). Enter that number here _____. Find the corresponding "Assigned Score" for Katz ADL in the IMWG frailty assessment scoring table below and enter that score in the "Subject's Score" column for Katz ADL. That score should be either 0 or 1.

4. **Charlson Comorbidity Index**: See "Charlson Comorbidity Index Scoring" key below. Enter "**patient point total**" from that key here_____. Find the corresponding "Assigned Score" for Charlson Comorbidity Index in the IMWG frailty assessment scoring table below and enter that score in the "Subject's Score" column for Charlson Comorbidity Index. That score should be either 0 or 1.

5. **IMWG Frailty Score**: Add up points from the items above in the IMWG frailty assessment scoring table and enter that number in the bottom right "Subject's Total Score" box. That score should range from 0-5. Find the corresponding IMWG frailty category (fit, intermediate fit or frail) in the key that follows.

IMWG Frailty Assessment Scoring Table

CALCULATE ONLY AT SCREENING

CIRCLE SCORES FOR EACH COMPONENT PER INSTRUCTIONS ABOVE

CALCULATE TOTAL SCORE AND ASSOCIATED FITNESS LEVEL

Age, Years	Assigned Score	Subject Score
≤75	0	
76-80	1	
>80	2	
Lawton IADL		
0-2	0	
3 or more	1	
Katz ADL		
0-1	0	
2 or more	1	
Charlson Index		
0-1	0	
2 or more	1	
TOTAL SUBJECT SCORE		
IMWG Frailty Assessment Total Score Interpretation (circle one)		**0 = Fit** **1 = Intermediate fitness** **≥2 = Frail**

Lawton Physical Instrumental Activities of Daily Living (IADLs):

Lawton IADL: Lawton MP, et al., 1969

FOR SCORING ONLY – NOT TO BE USED WITH PATIENTS DIRECTLY.

FOR EACH QUESTION, ONLY ONE ANSWER SHOULD BE SELECTED

1. Can you use the telephone . . .
○ without help, including looking up and dialing numbers;
○ you can only dial a few well-known numbers or call numbers on speed dial;
○ you can answer the telephone but not make any calls on your own; or
○ you don't use the telephone at all.

2. Can you manage transportation . . .
○ without help (you drive your own car, or you travel alone on buses or taxis);
○ you can arrange your own travel by taxi but you do not otherwise use public transportation (like bus or train);
○ you can use public transportation but only with help from someone else;
○ you can only travel in a car or taxi, and only do that with help from someone else; or
○ you don't travel at all.

3. Can you go shopping . . .
○ without help for any kind of shopping;
○ with help for big shopping trips, but you can do small purchases or trips without any help;
○ you need help from someone else for any kind of shopping; or
○ you are unable to do any shopping.

4. Can you prepare your own meals . . .
○ without help (you plan, cook, and serve full meals yourself);
○ you can prepare meals if you are supplied the ingredients;
○ you can heat, serve, and prepare meals, or you prepare meals but you do not maintain an adequate diet; or
○ you need to have all meals prepared and served to you.

5. Can you do your housework . . .
○ without any help or with occasional assistance with heavier work only;
○ you can only perform light daily tasks such as dish washing and making your bed;
○ you can perform light daily tasks but you cannot keep your home acceptably clean on your own;
○ you need help with all home maintenance tasks; or
○ you do not participate in any housekeeping tasks.

6. Can you take your own medicines . . .
○ without any help (you take the right doses at the right time completely on your own);
○ with some help (you are able to take medicines correctly if someone prepares them for you, like putting your pills in a pillbox); or
○ you are completely unable to take your medicines on your own.

7. Can you handle your own money . . .
○ without help (including writing checks and paying bills);
○ with some help (you manage day-to-day buying but need help with managing your checkbook and paying your bills); or
○ you are completely unable to handle money.

8. Can you do your laundry. . .
○ without help;
○ you can do laundry if it is just small items such as rinsing socks; or
○ you are completely unable to do your own laundry.

Katz Physical Activities of Daily Living (ADLs):

FOR SCORING ONLY – NOT TO BE USED WITH PATIENTS DIRECTLY.

FOR EACH QUESTION, ONLY ONE ANSWER SHOULD BE SELECTED

9. Can you eat . . .
○ without any help (able to feed yourself completely, including cutting and getting food from the plate to your mouth); or
○ only with help

10. Can you dress and undress yourself . . .
○ without any help (able to pick out clothes, and dress and undress yourself); or
○ only with help

11. Can you get in and out of bed . . .
○ without any help from people (using devices such as walkers don't count as help for this); or
○ only with help from people.

12. Can you take a bath or shower . . .
○ without any help, or with just very limited help like washing your back or genital area; or
○ you need help with most washing, or with getting in and out of the shower or tub.

13. Do you need help going to the toilet?

○ No, you are able to use it completely on your own, including getting to the bathoom, getting on and off the toilet, and cleaning yourself.

○ Yes, you need help using the toilet or you use a bedpan.

14. Do you ever have trouble getting to the bathroom on time . . .

○ No, you have complete control over urination and bowel movements.

○ Yes, you sometimes have accidents (lose control of your bowels or bladder).

Charlson Comorbidity Index Scoring:

FOR SCORING ONLY – NOT TO BE USED WITH PATIENTS DIRECTLY

Review this table with the "your medical history" section of the patient-completed questionnaire from their baseline CARG global assessment (section 13.10, appendix J).

Items in the table below correspond to patient's answers to individual questions.

Question summary	Points For all questions do not give additional points for multiple checked answers. If multiple answers are checked, still give only the specific number of points indicated below.	Point tally Enter points as instructed in the center column
a. Heart attack?	If yes, give 1 point	
b. Heart failure?	If yes, give 1 point	
c. Unclog or bypass arteries?	If yes, give 1 point	
d. Stroke or TIA?	If yes, give 1 point	
d1. Trouble moving arm or leg due to prior stroke?	If yes, give 2 points (in addition to the point already given in row above)	
e1 and f1. Medicine for asthma or other lung disease?	If yes to either, give 1 point	
g. Ulcer disease?	If yes, give 1 point regardless of answer to g1	
h. Diabetes?	If yes to any, give 1 point	
h1. Diabetes causing kidney or eye problems?	If yes to either, give 1 point (in addition to the point already given in the row above)	
i. Kidney problems from any cause?	If yes to any, give 2 points	

j and j2. Rheumatoid arthritis / lupus / polymyalgia?	If patient indicates yes to any of these conditions, give 1 point regardless of answer to question j1 about medications	
k. Dementia?	If yes, give 1 point	
k. Cirrhosis / liver disease?	If yes, give 2 points	
k. Leukemia / polycythemia?	If yes, give 2 points	
k. Lymphoma?	If yes, give 2 points	
k. AIDS?	If yes, give 6 points	
k. Cancer other than myeloma or those mentioned above?	If yes, give 2 points	
k1. Metastatic cancer other than myeloma or those mentioned above?	If yes, give 4 points (in addition to 2 points already given in row above)	
TOTAL POINTS (Possible range is 0-32)		**Patient point total:**

13.4 Appendix D. EORTC QLQ-C30

Assessment forms will be provided as PDFs and/or electronically to sites.

Study coordinators administering the Mini-Cog will be trained in how to do so.

ENGLISH

EORTC QLQ-C30 (version 3)

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

Please fill in your initials:
Your birthdate (Day, Month, Year):
Today's date (Day, Month, Year): 31

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a 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

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your 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

13.5 Appendix E. EORTC-MY20

ENGLISH

EORTC QLQ – MY20

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

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

Please turn to next page

ENGLISH

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

13.6 Appendix F. COST-FACIT

COST – FACIT (Version 1)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

		Not at all	A little bit	Some-what	Quite a bit	Very much
FT1	I know that I have enough money in savings, retirement, or assets to cover the costs of my treatment	0	1	2	3	4
FT2	My out-of-pocket medical expenses are more than I thought they would be	0	1	2	3	4
FT3	I worry about the financial problems I will have in the future as a result of my illness or treatment	0	1	2	3	4
FT4	I feel I have no choice about the amount of money I spend on care	0	1	2	3	4
FT5	I am frustrated that I cannot work or contribute as much as I usually do	0	1	2	3	4
FT6	I am satisfied with my current financial situation	0	1	2	3	4
FT7	I am able to meet my monthly expenses	0	1	2	3	4
FT8	I feel financially stressed	0	1	2	3	4
FT9	I am concerned about keeping my job and income, including work at home	0	1	2	3	4
FT10	My cancer or treatment has reduced my satisfaction with my present financial situation	0	1	2	3	4
FT11	I feel in control of my financial situation	0	1	2	3	4

From deSouza, Cancer, 2017.

13.7 Appendix G. PROMIS Cognitive Function-Short Form 8a

PROMIS® Item Bank v2.0 – Cognitive Function- Short Form 8a

Cognitive Function- Short Form 8a

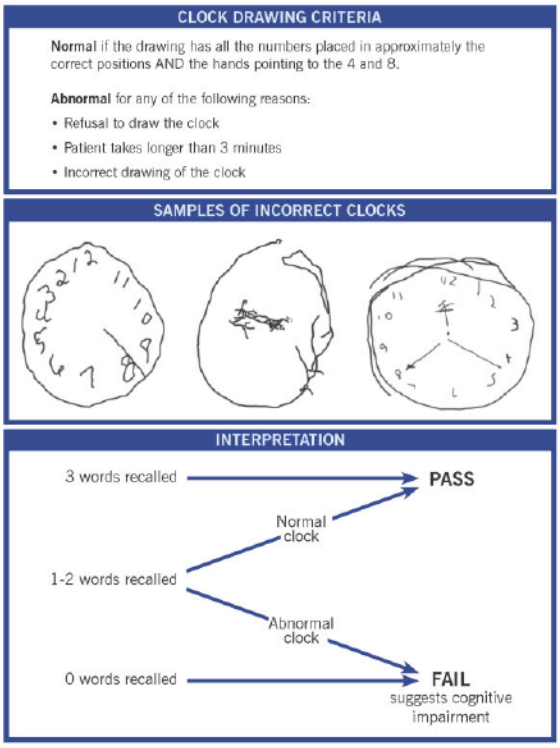
Please respond to each question or statement by marking one box per row.

	In the past 7 days...	**Never**	**Rarely (Once)**	**Sometimes (Two or three times)**	**Often (About once a day)**	**Very often (Several times a day)**
PC2r	My thinking has been slow.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC35r	It has seemed like my brain was not working as well as usual.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC36r	I have had to work harder than usual to keep track of what I was doing.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC42r	I have had trouble shifting back and forth between different activities that require thinking	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC8r	I have had trouble concentrating.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC25r	I have had to work really hard to pay attention or I would make a mistake	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC1r	I have had trouble forming thoughts	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PC5r	I have had trouble adding or subtracting numbers in my head	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

23 January 2020
 Page 1 of 1

13.8 Appendix H. Mini-Cog

Mini-Cog Graphic



Mini-Cog©

Instructions for Administration & Scoring

ID:_____ Date: _____

Step 1: Three Word Registration

Look directly at person and say, "Please listen carefully. I am going to say three words that I want you to repeat back to me now and try to remember. The words are [select a list of words from the versions below]. Please say them for me now." If the person is unable to repeat the words after three attempts, move on to Step 2 (clock drawing).

The following and other word lists have been used in one or more clinical studies.[1-3] For repeated administrations, use of an alternative word list is recommended.

Version 1	Version 2	Version 3	Version 4	Version 5	Version 6
Banana	Leader	Village	River	Captain	Daughter
Sunrise	Season	Kitchen	Nation	Garden	Heaven
Chair	Table	Baby	Finger	Picture	Mountain

Step 2: Clock Drawing

Say: "Next, I want you to draw a clock for me. First, put in all of the numbers where they go." When that is completed, say: "Now, set the hands to 10 past 11."

Use preprinted circle (see next page) for this exercise. Repeat instructions as needed as this is not a memory test. Move to Step 3 if the clock is not complete within three minutes.

Step 3: Three Word Recall

Ask the person to recall the three words you stated in Step 1. Say: "What were the three words I asked you to remember?" Record the word list version number and the person's answers below.

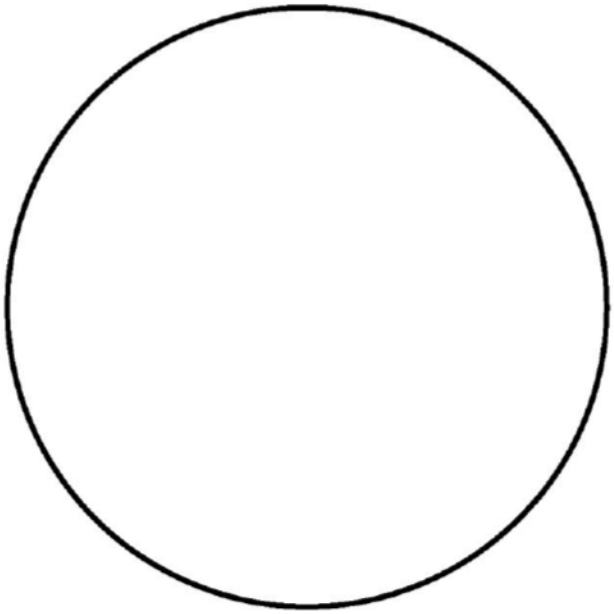
Word List Version:_____ Person's Answers: _____ _____ _____

Scoring

Word Recall: _____ (0-3 points)	1 point for each word spontaneously recalled without cueing.
Clock Draw: _____ (0 or 2 points)	Normal clock = 2 points. A normal clock has all numbers placed in the correct sequence and approximately correct position (e.g., 12, 3, 6 and 9 are in anchor positions) with no missing or duplicate numbers. Hands are pointing to the 11 and 2 (11:10). Hand length is not scored. Inability or refusal to draw a clock (abnormal) = 0 points.
Total Score: _____ (0-5 points)	Total score = Word Recall score + Clock Draw score. A cut point of <3 on the Mini-Cog™ has been validated for dementia screening, but many individuals with clinically meaningful cognitive impairment will score higher. When greater sensitivity is desired, a cut point of <4 is recommended as it may indicate a need for further evaluation of cognitive status.

Clock Drawing

ID:_____ Date:_____



References

1. Borson S, Scanlan JM, Chen PJ et al. The Mini-Cog as a screen for dementia: Validation in a population based sample. J Am Geriatr Soc 2003;51:1451–1454.
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3. Lessig M, Scanlan J et al. Time that tells: Critical clock-drawing errors for dementia screening. Int Psychogeriatr. 2008 June; 20(3): 459–470.
4. Tsoi K, Chan J et al. Cognitive tests to detect dementia: A systematic review and meta-analysis. JAMA Intern Med. 2015; E1-E9.
5. McCarten J, Anderson P et al. Screening for cognitive impairment in an elderly veteran population: Acceptability and results using different versions of the Mini-Cog. J Am Geriatr Soc 2011; 59: 309-213.
6. McCarten J, Anderson P et al. Finding dementia in primary care: The results of a clinical demonstration project. J Am Geriatr Soc 2012; 60: 210-217.
7. Scanlan J & Borson S. The Mini-Cog: Receiver operating characteristics with the expert and naive raters. Int J Geriatr Psychiatry 2001; 16: 216-222.

13.9 Appendix I. CARG Global Assessment: Healthcare Team

Assessment instruments will be provided as PDFs or otherwise electronically to sites.

Traditionally called the "geriatric assessment," this assessment will be implemented with study participants regardless of age, so avoiding the use of the term "geriatric" is warranted and the assessment will be referred to as "global assessment."

LCCC 2119 Provider / Coordinator Assessment
Data to be Gathered by the Healthcare Team - V1 (9/29/20)

Office use only

Study Site

Subject Study ID

Date Completed (MM/DD/YR)

I) Karnofsky Performance Status: ___ %

DEFINITION	%	CRITERIA
Able to carry on normal activity and able to work. No special care is needed.	100	Normal: no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal Activity with effort; some signs or symptoms of disease.
Unable to work. Able to live at home, and for most personal needs, a varying amount of assistance is needed.	70	Cares for self. Unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his needs
	50	Requires considerable assistance and frequent medical care
Unable to care for self. Requires equivalent of institutional or hospital care. Disease may be progressing rapidly.	40	Disabled; requires special care and assistance
	30	Severely disabled; hospitalization is indicated although death is not imminent.
	20	Very sick; hospitalization necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly
	0	Dead

Karnofsky Physician-rated Performance Rating Scale: Karnofsky, D.A., et al., 1948

II) Nutrition:

a) What is the patient's height?

☐ feet ☐☐ inches (Please round to the nearest whole number.)

b) What is the patient's current weight?

☐☐☐.☐ pounds

c) What is the patient's weight approximately 6 months ago?

☐☐☐.☐ pounds

d) Calculated Body Mass Index: ☐☐.☐

$$\text{Body Mass Index} = \frac{weight\ (kg)}{height^2\ (m^2)}\ or\ \frac{weight\ (lb)\times 703}{height^2\ (in^2)}$$

e) Percent Unintentional Weight Loss: ☐☐☐.☐%

$$\%\ \text{unintentional weight loss} = \left(\frac{unintentional\ weight\ lost\ in\ last\ 6\ months}{baseline\ body\ weight}\right) \times 100$$

III) Did the patient require assistance with the patient-completed component of the assessment?

○ No
○ Yes

Name of person completing this document:

_____

Signature: _____ Date: ☐☐/☐☐/☐☐☐☐

13.10 Appendix J. CARG Global Assessment: Subject-Completed Baseline Questionnaire

LCCC 2119 PATIENT QUESTIONNAIRE - BASELINE ASSESSMENT

V1 (9/12/2020)

Instructions: Please answer the following questions. While this information will be helpful to us, you do not have to answer any questions if you do not wish to. If you have any questions or need help in filling out this form, ask the person who gave you the form for help or your physician.

I. Your Background:

1. What is the highest grade you finished in school? (*Fill in one oval completely.*)
○ 1-8 grades
○ 9-11 grades
○ High school graduate
○ Some college
○ Junior college degree
○ College degree (B.A./B.S.)
○ Some post-college work
○ Advanced degree

Office use only

Study Site

Subject Study ID

Date Completed (MM/DD/YR)

2. What is your marital status? (*Fill in one oval completely.*)
○ Single, never married
○ Married
○ Separated
○ Divorced
○ Widowed

3. With whom do you live? (*Mark an X in all that apply.*)
□ Spouse/Partner
□ Parent(s)/Parent(s)-In-Law
□ Live alone
□ Other relative, specify:

□ Children aged 18 years or younger
□ Children aged 19 years or older
□ Other, specify:

4. What is your current employment status? (*Mark an X in all that apply.*)
□ Employed more than 32 hours per week
□ Employed less than 32 hours per week
□ Full-time student
□ Part-time student
□ Homemaker
□ On medical leave

□ Disabled
□ Unemployed
□ Retired
□ Other, specify:

5. How old are you? ☐☐ years old

6. What is your race? (*Fill in one oval completely.*)

○ White
○ Black or African American
○ Native Indian or Alaskan Native
○ Prefer Not to Answer
○ Other

○ Asian
○ Native Hawaiian or Other Pacific Islander
○ Unknown

7. What is your ethnicity? (*Fill in one oval completely.*)
○ Hispanic or Latino
○ Non-Hispanic
○ Unknown
○ Prefer not to answer

II. Your Medical History:

For the following items please choose the health status that best describes you: (*Fill in one box completely for each question.*)

a. Have you ever had a heart attack?
☐No
☐Yes

b. Have you ever been treated for heart failure? (You may have been short of breath and the doctor may have told you that you had fluid in your lungs or that your heart was not pumping well.)
☐No
☐Yes

c. Have you had an operation to unclog or bypass the arteries in your legs?
☐No
☐Yes

d. Have you had a stroke, cerebrovascular accident, blood clot or bleeding in the brain, or transient ischemic attack (TIA)?
☐No
☐Yes

d.1. If Yes, do you have difficulty moving an arm or leg as a result of the stroke or cerebrovascular accident?
☐ No
☐ Yes

e. Do you have asthma?
☐No
☐Yes

e.1. If Yes, do you take medicines for your asthma?
☐ No
☐ Yes

f. Do you have emphysema, chronic bronchitis, or chronic obstructive lung disease?
☐No
☐Yes

f.1. If Yes, do you take medicines for your lung disease?
☐ No

☐ Yes

g. Do you have stomach ulcers, or peptic ulcer disease?

☐No
☐Yes

g.1. If Yes, has this condition been diagnosed by endoscopy (where a doctor looks into your stomach through a scope) or an upper gi or barium swallow study (where you swallow chalky dye and then xrays are taken)?

☐ No
☐ Yes

h. Do you have diabetes (high blood sugar)?

☐No
☐Yes, treated by modifying my diet
☐Yes, treated by medications taken by mouth
☐Yes, treated by insulin injections

h.1. If Yes, has the diabetes caused any of the following problems? (Select all that apply)

☐ Problems with your kidneys
☐ Problems with your eyes, treated by an ophthalmologist

i. Have you ever had the following problems with your kidneys? (select all that apply)

☐Poor kidney function (blood tests show high creatinine)
☐Have used hemodialysis or peritoneal dialysis
☐Have received kidney transplantation

j. Do you have rheumatoid arthritis?

☐No
☐Yes

j.1. If Yes, Do you take medications for it regularly?

☐ No
☐ Yes

j.2. Do you have (select all that apply):

☐ Lupus (systemic lupus erythematosus)
☐ Polymalgia rheumatica

k. Do you have any of the following conditions? (select all that apply)

☐Alzheimer's Disease, or another form of dementia
☐Cirrhosis, or serious liver damage

☐Leukemia or polycythemia vera
☐Lymphoma
☐AIDS
☐Cancer, other than multiple myeloma, skin cancer, leukemia or lymphoma?

k.1. If yes, has the cancer spread, or metastasized to other parts of your body?

☐ No
☐ Yes

Self-reported Charlson Comorbidity Index: Katz JN et al., Medical Care 1996

III. Your Daily Activities:

Instructions: Please fill in one oval for each question.

Instrumental activities of daily living (IADL)

1. Can you use the telephone . . .
○ without help, including looking up and dialing numbers;
○ you can only dial a few well-known numbers or call numbers on speed dial;
○ you can answer the telephone but not make any calls on your own; or
○ you don't use the telephone at all.

2. Can you manage transportation . . .
○ without help (you drive your own car, or you travel alone on buses or taxis);
○ you can arrange your own travel by taxi but you do not otherwise use public transportation (like bus or train);
○ you can use public transportation but only with help from someone else;
○ you can only travel in a car or taxi, and only do that with help from someone else; or
○ you don't travel at all.

3. Can you go shopping . . .
○ without help for any kind of shopping;
○ with help for big shopping trips, but you can do small purchases or trips without any help;
○ you need help from someone else for any kind of shopping; or
○ you are unable to do any shopping.

4. Can you prepare your own meals . . .
○ without help (you plan, cook and serve full meals yourself);
○ you can prepare meals if you are supplied the ingredients;
○ you can heat, serve, and prepare meals, or you prepare meals but you do not maintain an adequate diet; or
○ you need to have all meals prepared and served to you.

5. Can you do your housework . . .
○ without any help or with occasional assistance with heavier work only;
○ you can only perform light daily tasks such as dish washing and making your bed;
○ you can perform light daily tasks but you cannot keep your home acceptably clean on your own;
○ you need help with all home maintenance tasks; or
○ you do not participate in any housekeeping tasks.

6. Can you take your own medicines . . .
○ without any help (you take the right doses at the right time completely on your own);
○ with some help (you are able to take medicines correctly if someone prepares them for you like putting your pills in a pillbox); or
○ you are completely unable to take your medicines on your own.

7. Can you handle your own money . . .
○ without help (including writing checks and paying bills);
○ with some help (you manage day-to-day buying but need help with managing your checkbook and paying your bills); or
○ you are completely unable to handle money.

8. Can you do your laundry. . .
○ without help;
○ you can do laundry if it is just small items such as rinsing socks; or
○ you are completely unable to do your own laundry.

Lawton IADL: Lawton MP, et al., 1969

Physical activities of daily living (ADL):

9. Can you eat . . .
○ without any help (able to feed yourself completely, including cutting and getting food from the plate to your mouth); or
○ only with help.

10. Can you dress and undress yourself . . .
○ without any help (able to pick out clothes, and dress and undress yourself); or
○ only with help.

11. Can you get in and out of bed . . .
○ without any help from people (using devices such as walkers don't count as help for this); or

○ only with help from people.

12. Can you take a bath or shower . . .
○ without any help, or with just very limited help like washing your back or genital area; or
○ you need help with most washing, or with getting in and out of the shower or tub.

13. Do you need help going to the toilet?
○ No, you are able to use it completely on your own, including getting to the bathoom, getting on and off the toilet, and cleaning yourself.
○ Yes, you need help using the toilet or you use a bedpan.

14. Do you ever have trouble getting to the bathroom on time . . .
○ No, you have complete control over urination and bowel movements.
○ Yes, you sometimes have accidents (lose control of your bowels or bladder).

Katz ADL: Katz S., et al., 1970

Performance Status:

Which of the following phrases best characterizes you at this time? *(Please mark only one response.)*
○ Normal, no complaints, no symptoms of disease
○ Able to carry on normal activity, minor symptoms of disease
○ Normal activity with effort, some symptoms of disease
○ Care for self, unable to carry on normal activity or to do active work
○ Require occasional assistance but able to care for most of personal needs
○ Require considerable assistance for personal care
○ Disabled, require special care and assistance
○ Severely disabled, require continuous nursing care

Karnofsky Self-Reported Performance Rating Scale: Loprinzi, C.L., et al., 1994

IV. Your Health:

Please fill in the appropriate oval.

Does your health limit you …

Activities	Limited a lot	Limited a little	Not limited at all
Walking one block	○	○	○

How is your eyesight (with glasses or contacts)?
- ○Excellent
- ○Good
- ○Fair
- ○Poor
- ○Totally blind

If fair, poor, or totally blind:

How much does it interfere with your activities?
- ○ Not at all
- ○ Somewhat
- ○ A great deal

How is your hearing (with a hearing aid, if needed)?
- ○Excellent
- ○Good
- ○Fair
- ○Poor
- ○Totally deaf

If fair, poor, or totally deaf:

How much does it interfere with your activities?
- ○ Not at all
- ○ Somewhat
- ○ A great deal

Medical Outcomes Study (MOS) Physical Health: Stewart AL., et al., 1992
CARG Toxicity Score

How many times have you fallen in the last 6 months?
(A **fall** is an unexpected event in which you come to rest on the ground, floor, or lower level.)

☐☐☐ times

Your Medications

How many medications do you take on a daily basis? Please count all of your medications, prescribed medications, over-the-counter medications, herbs, or vitamins.

☐☐ Number of medications

V. Your Social Activities:

Instructions: Please fill in the appropriate oval completely.

1. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

○ All of the time
○ Most of the time
○ Some of the time
○ A little of the time
○ None of the time

Medical Outcomes Study (MOS) Social Activity Limitations Measure: Sherbourne, C.D., et al., 1991

VI. Your Mood:

These questions are about how you feel, and how things have been with you mostly within the *past two weeks*. Please fill in the bubble with the answer that best corresponds to how you felt for each statement.

How much of the time during the past two weeks:	All of the Time	Most of the Time	A Good Bit of the Time	Some of the Time	A Little of the Time	None of the Time
1. has your daily life been full of things that were interesting to you?	○	○	○	○	○	○
2. did you feel depressed?	○	○	○	○	○	○
3. have you been in firm control of your behavior, thoughts, emotions, feelings?	○	○	○	○	○	○
4. have you felt downhearted and blue?	○	○	○	○	○	○
5. have you been moody, or brooded about things?	○	○	○	○	○	○
6. have you felt cheerful, light-hearted?	○	○	○	○	○	○
7. have you been in low or very low spirits?	○	○	○	○	○	○
8. did you feel you had nothing to look forward to?	○	○	○	○	○	○

9. have you felt so down in the dumps that nothing could cheer you up?	○	○	○	○	○	○
10. have you been a very nervous person?	○	○	○	○	○	○
11. have you felt tense or high-strung?	○	○	○	○	○	○
12. have you felt calm or peaceful?	○	○	○	○	○	○
13. have you been anxious or worried?	○	○	○	○	○	○
14. have you felt restless, fidgety, or impatient?	○	○	○	○	○	○
15. were you a happy person?	○	○	○	○	○	○
16. have you felt loved and wanted?	○	○	○	○	○	○
17. have you felt emotionally stable?	○	○	○	○	○	○

MHI-17: Stewart and Ware, 1992 [questions 1-9 are depression and 10-14 for anxiety and 15-17 other]

VII. Your Social Support:

1. Instrumental Support

Please respond to each item by marking one box per row.

	Never	Rarely	Sometimes	Usually	Always
Do you have someone to help you if you are confined to bed?	○ 1	○ 2	○ 3	○ 4	○ 5
Do you have someone to take you to the doctor if you need it?	○ 1	○ 2	○ 3	○ 4	○ 5
Do you have someone to help with your daily chores if you are sick?	○ 1	○ 2	○ 3	○ 4	○ 5
Do you have someone to help run errands if you need it?	○ 1	○ 2	○ 3	○ 4	○ 5

PROMIS Instrumental Support

2. Social Isolation

Please respond to each item by marking one box per row.

	Never	Rarely	Sometimes	Usually	Always
I feel left out.	○ 1	○ 2	○ 3	○ 4	○ 5
I feel that people barely know me.	○ 1	○ 2	○ 3	○ 4	○ 5
I feel isolated from others.	○ 1	○ 2	○ 3	○ 4	○ 5
I feel that people are around me but not with me.	○ 1	○ 2	○ 3	○ 4	○ 5

PROMIS Social Isolation

VIII. PROMIS Global Health Measures:

	Excellent	Very good	Good	Fair	Poor
1. In general, would you say your health is:	○	○	○	○	○
2. In general, would you say your quality of life is:	○	○	○	○	○
3. In general, how would you rate your physical health?	○	○	○	○	○
4. In general, how would you rate your mental health, including your mood and your ability to think?	○	○	○	○	○
5. In general, how would you rate your satisfaction with your social activities and relationships?	○	○	○	○	○
6. In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc).	○	○	○	○	○

	Never	**Rarely**	**Sometimes**	**Often**	**Always**
8. How often have you been bothered by emotional problems such as feeling anxious, depressed, or irritable?	○	○	○	○	○

	None	**Mild**	**Moderate**	**Severe**	**Very Severe**
9.How would you rate your fatigue on average?	○	○	○	○	○

	No Pain 1	2	3	4	5	6	7	8	9	Worst Pain Imaginable 10
10. How would you rate your pain on average?	○	○	○	○	○	○	○	○	○	○

IX. Health Behaviors Questionnaire

1. Which of the following describes your smoking habits?

○ I have never smoked (skip to #4)
○ I used to smoke
○ I smoke

2. How many years have you/did you smoke?

☐☐☐ years

3. How many packs a day did you/do you smoke?

☐☐.☐ packs

4. How often do you do vigorous physical activities for at least 10 minutes that cause heavy sweating or large increases in heart rate or breathing?

○ Never (skip to #6)
○ A few times a month
○ 1-2 times per week
○ 3-4 times per week
○ 5 or more times per week

5. How long do you do these vigorous physical activities each time?

☐☐☐ minutes

6. Do you drink alcohol?

○ Yes
○ Almost never
○ No (skip to #9)

7. If you drink alcohol, about how many drinks do you have each week?

☐☐☐ drinks

8. What do you drink most often?

○ Beer
○ Red Wine
○ White and red wine
○ Hard liquor (such as bourbon, gin, vodka)
○ All of the above

9. If your parents are still living, how old are they? Or, if either one has passed away, how old was he or she when they died?

Mother ☐☐☐	☐ Alive ☐ Deceased	(Current age, or if deceased age of death)
Father ☐☐☐	☐ Alive ☐ Deceased	(Current age, or if deceased age of death)

NHANES Health Behavior Questionnaire

X. Final Questions:

Did you require assistance with the questionnaire?
○ No
○ Yes

Date you completed questionnaire:
☐☐ ☐☐ ☐☐☐☐

THANK YOU VERY MUCH!

13.11 Appendix K. CARG Global Assessment: Subsequent Assessment

LCCC 2119 PATIENT QUESTIONNAIRE - SUBSEQUENT ASSESSMENT

V1 (9/12/2020)

Instructions: Please answer the following questions. While this information will be helpful to us, you do not have to answer any questions if you do not wish to. If you have any questions or need help in filling out this form, ask the person who gave you the form for help or your physician.

I. **Your Daily Activities:**
Instructions: Please fill in one oval for each question.

Instrumental activities of daily living (IADL)

1. Can you use the telephone . . .
○ without help, including looking up and dialing numbers;
○ you can only dial a few well-known numbers or call numbers on speed dial;
○ you can answer the telephone but not make any calls on your own; or
○ you don't use the telephone at all.

2. Can you manage transportation . . .
○ without help (you drive your own car, or you travel alone on buses or taxis);
○ you can arrange your own travel by taxi but you do not otherwise use public transportation (like bus or train);
○ you can use public transportation but only with help from someone else;
○ you can only travel in a car or taxi, and only do that with help from someone else; or
○ you don't travel at all.

Office use only

Study Site

Subject Study ID

Date Completed (MM/DD/YR)

Treatment Cycle Number

3. Can you go shopping . . .
○ without help for any kind of shopping;
○ with help for big shopping trips, but you can do small purchases or trips without any help;
○ you need help from someone else for any kind of shopping; or
○ you are unable to do any shopping.

4. Can you prepare your own meals . . .
○ without help (you plan, cook, and serve full meals yourself);
○ you can prepare meals if you are supplied the ingredients;
○ you can heat, serve, and prepare meals, or you prepare meals but you do not maintain an adequate diet; or
○ you need to have all meals prepared and served to you.

5. Can you do your housework . . .
○ without any help or with occasional assistance with heavier work only;
○ you can only perform light daily tasks such as dish washing and making your bed;
○ you can perform light daily tasks but you cannot keep your home acceptably clean on your own;
○ you need help with all home maintenance tasks; or
○ you do not participate in any housekeeping tasks.

6. Can you take your own medicines . . .
○ without any help (you take the right doses at the right time completely on your own);
○ with some help (you are able to take medicines correctly if someone prepares them for you, like putting your pills in a pillbox); or
○ you are completely unable to take your medicines on your own.

7. Can you handle your own money . . .
○ without help (including writing checks and paying bills);
○ with some help (you manage day-to-day buying but need help with managing your checkbook and paying your bills); or
○ you are completely unable to handle money.

8. Can you do your laundry. . .
○ without help;
○ you can do laundry if it is just small items such as rinsing socks; or
○ you are completely unable to do your own laundry.

Lawton IADL: Lawton MP, et al., 1969

Physical activities of daily living (ADL):

9. Can you eat . . .
○ without any help (able to feed yourself completely, including cutting and getting food from the plate to your mouth); or
○ only with help

10. Can you dress and undress yourself . . .
○ without any help (able to pick out clothes, and dress and undress yourself); or
○ only with help

11. Can you get in and out of bed . . .
○ without any help from people (using devices such as walkers don't count as help for this); or
○ only with help from people.

12. Can you take a bath or shower . . .
○ without any help, or with just very limited help like washing your back or genital area; or
○ you need help with most washing, or with getting in and out of the shower or tub.

13. Do you need help going to the toilet?
○ No, you are able to use it completely on your own, including getting to the bathoom, getting on and off the toilet, and cleaning yourself.
○ Yes, you need help using the toilet or you use a bedpan.

14. Do you ever have trouble getting to the bathroom on time . . .
○ No, you have complete control over urination and bowel movements.
○ Yes, you sometimes have accidents (lose control of your bowels or bladder).

Katz ADL: Katz S., et al., 1970

Performance Status:

Which of the following phrases best characterizes you at this time? *(Please mark only one response.)*

○ Normal, no complaints, no symptoms of disease
○ Able to carry on normal activity, minor symptoms of disease
○ Normal activity with effort, some symptoms of disease
○ Care for self, unable to carry on normal activity or to do active work
○ Require occasional assistance but able to care for most of personal needs
○ Require considerable assistance for personal care
○ Disabled, require special care and assistance
○ Severely disabled, require continuous nursing care

Karnofsky Self-Reported Performance Rating Scale: Loprinzi, C.L., et al., 1994

II. Your Health:

Please fill in the appropriate oval.

Does your health limit you …

Activities	Limited a lot	Limited a little	Not limited at all
Walking one block	○	○	○

Medical Outcomes Study (MOS) Physical Health: Stewart AL., et al., 1992
CARG Toxicity Score

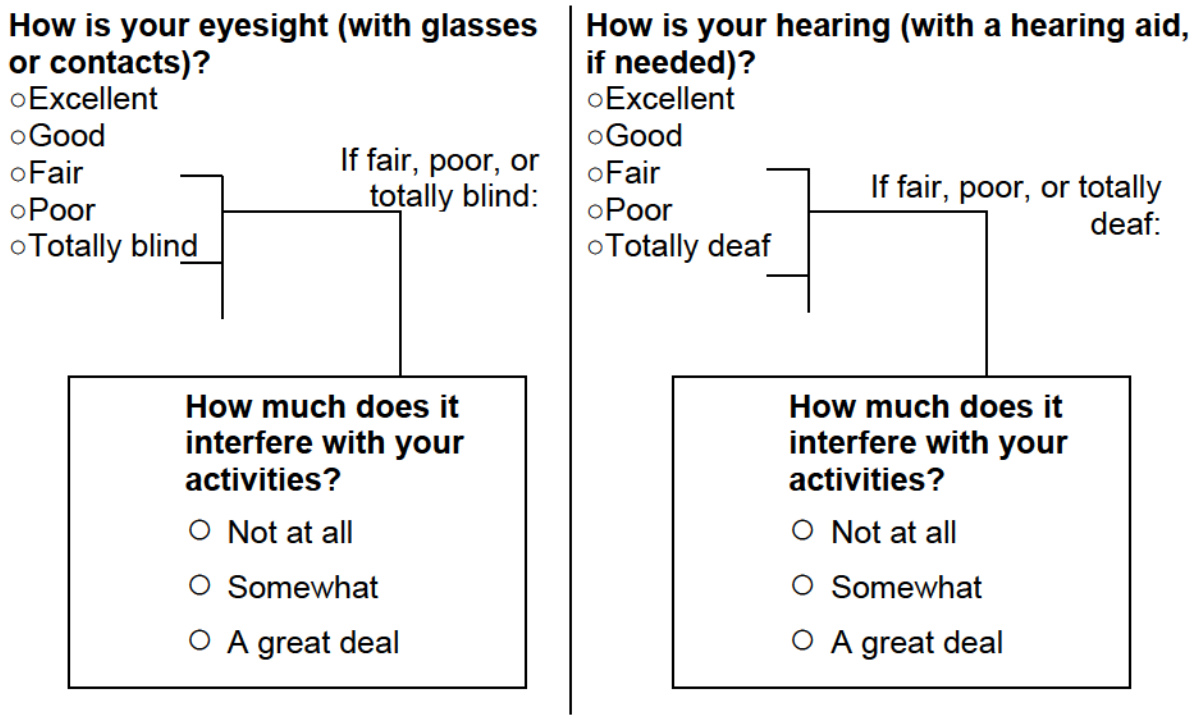
How many times have you fallen in the last 6 months?
(A **fall** is an unexpected event in which you come to rest on the ground, floor, or lower level.)

☐☐☐ times

Your Medications

How many medications do you take on a daily basis? Please count all of your medications, prescribed medications, over-the-counter medications, herbs, or vitamins.

☐☐ Number of medications



III. Your Social Activities:

Instructions: Please fill in the appropriate oval completely.

1. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives, etc.)?

○ All of the time
○ Most of the time
○ Some of the time
○ A little of the time
○ None of the time

Medical Outcomes Study (MOS) Social Activity Limitations Measure: Sherbourne, C.D., et al., 1991

IV. Your Mood:

These questions are about how you feel, and how things have been with you mostly within the *past two weeks*. Please fill in the bubble with the answer that best corresponds to how you felt for each statement.

How much of the time during the past two weeks:	None of the Time	A Little of the Time	Some of the Time	A Good Bit of the Time	Most of the Time	All of the Time
1. has your daily life been full of things that were interesting to you?	○	○	○	○	○	○
2. did you feel depressed?	○	○	○	○	○	○
3. have you been in firm control of your behavior, thoughts, emotions, feelings?	○	○	○	○	○	○
4. have you felt downhearted and blue?	○	○	○	○	○	○
5. have you been moody, or brooded about things?	○	○	○	○	○	○
6. have you felt cheerful, light-hearted?	○	○	○	○	○	○
7. have you been in low or very low spirits?	○	○	○	○	○	○
8. did you feel you had nothing to look forward to?	○	○	○	○	○	○
9. have you felt so down in the dumps that nothing could cheer you up?	○	○	○	○	○	○
10. have you been a very nervous person?	○	○	○	○	○	○
11. have you felt tense or high-strung?	○	○	○	○	○	○
12. have you felt calm or peaceful?	○	○	○	○	○	○
13. have you been anxious or worried?	○	○	○	○	○	○
14. have you felt restless, fidgety, or impatient?	○	○	○	○	○	○
15. were you a happy person?	○	○	○	○	○	○
16. have you felt loved and wanted?	○	○	○	○	○	○
17. have you felt emotionally stable?	○	○	○	○	○	○

MHI-17: Stewart and Ware, 1992 [questions 1-9 are depression and 10-14 for anxiety and 15-17 other]

V. Your Social Support:

1. Instrumental Support

Please respond to each item by marking one box per row.

	Never	Rarely	Sometimes	Usually	Always
Do you have someone to help you if you are confined to bed?	○ 1	○ 2	○ 3	○ 4	○ 5
Do you have someone to take you to the doctor if you need it?	○ 1	○ 2	○ 3	○ 4	○ 5
Do you have someone to help with your daily chores if you are sick?	○ 1	○ 2	○ 3	○ 4	○ 5
Do you have someone to help run errands if you need it?	○ 1	○ 2	○ 3	○ 4	○ 5

PROMIS Instrumental Support

2. Social Isolation

Please respond to each item by marking one box per row.

	Never	Rarely	Sometimes	Usually	Always
I feel left out.	○ 1	○ 2	○ 3	○ 4	○ 5
I feel that people barely know me.	○ 1	○ 2	○ 3	○ 4	○ 5
I feel isolated from others.	○ 1	○ 2	○ 3	○ 4	○ 5
I feel that people are around me but not with me.	○ 1	○ 2	○ 3	○ 4	○ 5

PROMIS Social Isolation

VI. PROMIS Global Health Measures:

	Excellent	Very good	Good	Fair	Poor
1. In general, would you say your health is:	○	○	○	○	○
2. In general, would you say your quality of life is:	○	○	○	○	○
3. In general, how would you rate your physical health?	○	○	○	○	○
4. In general, how would you rate your mental health, including your mood and your ability to think?	○	○	○	○	○
5. In general, how would you rate your satisfaction with your social activities and relationships?	○	○	○	○	○
6. In general, please rate how well you carry out your usual social activities and roles. (This includes activities at home, at work and in your community, and responsibilities as a parent, child, spouse, employee, friend, etc).	○	○	○	○	○

	Never	**Rarely**	**Sometimes**	**Often**	**Always**
8. How often have you been bothered by emotional problems such as feeling anxious, depressed, or irritable?	○	○	○	○	○

	None	**Mild**	**Moderate**	**Severe**	**Very Severe**
9.How would you rate your fatigue on average?	○	○	○	○	○

	No Pain 1	2	3	4	5	6	7	8	9	Worst Pain Imaginable 10
10. How would you rate your pain on average?	○	○	○	○	○	○	○	○	○	○

VII. Health Behaviors Questionnaire

1. Which of the following describes your smoking habits?

○ I have never smoked (skip to #4)
○ I used to smoke
○ I smoke

2. How many years have you/did you smoke?

☐☐☐ years

3. How many packs a day did you/do you smoke?

☐☐.☐ packs

4. How often do you do vigorous physical activities for at least 10 minutes that cause heavy sweating or large increases in heart rate or breathing?

○ Never (skip to #6)
○ A few times a month
○ 1-2 times per week
○ 3-4 times per week
○ 5 or more times per week

5. How long do you do these vigorous physical activities each time?

☐☐☐ minutes

6. Do you drink alcohol?

○ Yes
○ Almost never
○ No (skip to #9)

7. If you drink alcohol, about how many drinks do you have each week?

☐☐☐ drinks

8. What do you drink most often?

○ Beer
○ Red Wine
○ White and red wine
○ Hard liquor (such as bourbon, gin, vodka)
○ All of the above

VIII. Final Questions:

Did you require assistance with the questionnaire?

○ No
○ Yes

Date you completed questionnaire:

THANK YOU VERY MUCH!

13.12 Appendix L. Gait Speed

Instructions for and form for administering gait speed testing will be provided separately to sites.

Gait Speed Instructions

Preparation: Measure and mark a standard distance, e.g. 5 meters (16.4 feet).

Then measure and mark 5 feet before the start, and 5 feet after the end.

Put **cones or other similarly visible marker** at the starting line and the finish line. Instruct the participant to walk at a comfortable pace. Have the participant start at the starting line. Instruct the participant when to start, once the participant walks to the 5 feet mark, start timing. Stop timing once the participant walks 16.4 feet (5 meters) and record their time. You should do two practice trials and then a real trial in which you will record the participant's time in seconds.

Use the GAIT SPEED FOR VISIT form to document the participant's study ID, the date, the seconds recorded, and the calculated gait speed in meters per second.

5 feet	**5 meters (16.4 feet)**	5 feet
← Starting line	← begin timing stop timing →	Finish line →

Gait Speed = distance / time e.g. 5 meters / __ sec.

Instructions: "Walk at a comfortable pace".

Participant's performance: _____ seconds

Calculated gait speed: _____ m/sec

e.g. the person takes 8.5 seconds to walk 5 meters → 5/8.5 = 0.6 m/sec

Name of person completing this document:_____

Signature: _____ Date: ☐☐/☐☐/☐☐☐☐

13.13 Appendix M. Cockcroft-Gault and Calculated eGFR

Cockcroft-Gault Formula

Males:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}.$$

Females:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

Estimated Glomerular Filtration Rate (eGFR) by Modification of Diet in Renal Disease (MDRD)

eGFR = 186 X (serum creatinine in mg/dL)$^{-1.154}$ X age$^{-0.203}$ X [1.210 if black] X [0.742 if female].

13.14 Appendix N. New York Heart Association Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease.

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

13.15 Appendix O. Response Criteria for Multiple Myeloma

This study will use the Revised Uniform Response Criteria by the International Myeloma Working Group (IMWG) provided below [51].

Response Category*	Standard IMWG response criteria‖
sCR, stringent complete response	Complete response as defined below plus normal FLC ratio and absence of clonal cells in bone marrow biopsy by immunohistochemistry (κ/λ ratio ≤ 4:1 or ≥ 1:2 for κ and λ patients, respectively, after counting ≥ 100 plasma cells)
CR, complete response**	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow aspirates
VGPR, very good partial response**	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein, plus urine M-protein level < 100 mg per 24 h
PR, partial response	≥ 50% reduction of serum M-protein plus reduction in 24 h urinary M-protein by ≥ 90% or to < 200 mg per 24 h; If the serum and urine M-protein are unmeasurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria; If serum and urine M-protein are unmeasurable, and serum-free light assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma-cell percentage was ≥ 30%. In addition to these criteria, if present at baseline, a ≥ 50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required
MR, minimal response	≥ 25% but ≤ 49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%. In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size (SPD)§§ of soft tissue plasmacytomas is also required
SD, stable disease	Not recommended for use as an indicator of response; stability of disease is best described by providing the time-to-progression estimates. Not meeting criteria for complete response, very good partial response, partial response, minimal response, or progressive disease

Response Category*	Standard IMWG response criteria‖
Progressive disease ¶¶,‖‖	Any one or more of the following criteria: Increase of 25% from lowest confirmed response value in one or more of the following criteria: Serum M-protein (absolute increase must be ≥ 0.5 g/dL); Serum M-protein increase ≥ 1 g/dL, if the lowest M component was ≥ 5 g/dL; Urine M-protein (absolute increase must be ≥ 200 mg/24 h); In patients without measurable serum and urine M-protein levels, the difference between involved and uninvolved FLC levels (absolute increase must be > 10 mg/dL [100 mg/L]); In patients without measurable serum and urine M-protein levels and without measurable involved FLC levels, bone marrow plasma cell percentage irrespective of baseline status (absolute increase must be ≥ 10%); Appearance of a new lesion(s), ≥ 50% increase from nadir in SPD§§ of > 1 lesion, or ≥ 50% increase in the longest diameter of a previous lesion >1 cm in short axis; ≥ 50% increase in circulating plasma cells (minimum of 200 cells per μL) if this is the only measure of disease
Clinical relapse	Clinical relapse requires one or more of the following criteria: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features) related to the underlying clonal plasma-cell proliferative disorder. It is not used in calculation of time to progression or progression-free survival but is listed as something that can be reported optionally or for use in clinical practice; Development of new soft tissue plasmacytomas or bone lesions (osteoporotic fractures do not constitute progression); Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and ≥ 1 cm) increase as measured serially by the SPD§§ of the measurable lesion; Hypercalcemia (> 11 mg/dL); Decrease in hemoglobin of ≥ 2 g/dL not related to therapy or other non-myeloma-related conditions; Rise in serum creatinine by 2 mg/dL or more from the start of the therapy and attributable to myeloma; Hyperviscosity related to serum paraprotein

Reference for table and footnotes: Kumar, et al. Lancet 2016;17:e328-46.

*All response categories require two consecutive assessments (confirmation by repeat) made any time before starting any new therapy. All response categories (excepting PD) also require no known evidence of progressive or new bone lesions or extramedullary plasmacytomas if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments do not need to be confirmed by repeat assessment. Each category, except for stable disease, will be considered unconfirmed until the confirmatory repeat test is performed. The date of the initial test is considered as the date of response for evaluation of time dependent outcomes such as duration of response.

** Clarification to IMWG criteria: When the only method to measure disease is by serum FLC levels: complete response can be defined as a normal FLC ratio of 0.26 to 1.65 in addition to the

complete response criteria listed previously. Very good partial response in such patients requires a ≥90% decrease in the difference between involved and uninvolved FLC levels.

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

¶ ¶ Positive immunofixation alone in a patient previously classified as achieving a complete response will not be considered progression.

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