UNIVERSITY OF UTAH
HUNTSMAN CANCER INSTITUTE

SPOTLIGHT: **S**moldering myeloma High-risk **P**atient **O**bserva**t**ion and **L**ongitudinal **I**nsi**ght** Trial

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DOCUMENT HISTORY

Document	Date	Overall Rationale
Original Protocol	30NOV2023	Not applicable
Amendment 1	19MAR2024	Protocol clarifications
Amendment 2	30OCT2024	Schedule of Events Clarifications

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STATEMENT OF COMPLIANCE

The trial will be conducted in accordance with International Conference on Harmonization Good Clinical Practice (ICH GCP), applicable United States (US) Code of Federal Regulations (CFR). The Principal Investigator will assure that no deviation from, or changes to the protocol will take place without prior agreement from the Investigational New Drug (IND) or Investigational Device Exemption (IDE) sponsor, funding agency and documented approval from the Institutional Review Board (IRB), except where necessary to eliminate an immediate hazard(s) to the trial participants. All personnel involved in the conduct of this study have completed Human Subjects Protection and ICH GCP Training.

The protocol, Informed consent form(s), recruitment materials, and all participant materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. All changes to the consent form will be IRB approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

PROTOCOL SIGNATURE

I confirm that I have read this protocol, and I will conduct the study as outlined herein and according to the ethical principles stated in the latest version of the Declaration of Helsinki, the applicable ICH guidelines for good clinical practice, and the applicable laws and regulations of the federal government. I will promptly submit the protocol to the IRB for review and approval. Once the protocol has been approved by the IRB, I understand that any modifications made during the study must first be approved by the IRB prior to implementation except when such modification is made to remove an immediate hazard to the subject.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study treatment, the conduct of the study, and the obligations of confidentiality.

This document is signed electronically through submission and approval by the Principal Investigator at Huntsman Cancer Institute in the University of Utah IRB Electronic Research Integrity and Compliance Administration (ERICA) system. For this reason, the Principal Investigator at Huntsman Cancer Institute will not have a hand-written signature on this signature page.

_____ _____

Signature of Principal Investigator **Date**

_____

Principal Investigator Name (Print)

ABBREVIATIONS

Abbreviation	Definition/Explanation
AE	Adverse event
ALT	Alanine aminotransferase
ASCO	American Society of Clinical Oncology
AST	Aspartate aminotransferase
AV	Atrioventricular
BCVA	Best-corrected distance visual acuity
BICR	Blinded Independent Central Review
β-HCG	Beta-human chorionic gonadotropin
BID	Twice daily
BMI	Body mass index
BP	Blood pressure
BUN	Blood urea nitrogen
CBC	Complete blood count
CFR	Code of Federal Regulations
CHF	Congestive heart failure
CI	Confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CL_{cr}	Creatinine clearance
C_{max}	Maximum observed concentration
C_{min}	Trough observed concentration
CMP	Comprehensive metabolic panel
CNS	Central nervous system
CR	Complete response
CRF	Case report form
CT	Computed tomography
CTCAE	Common Toxicity Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CYP	Cytochrome P450
CQ	Chloroquine
DILI	Drug-Induced Liver Injury

Abbreviation	Definition/Explanation
DoR	Duration of Response
DSMB	Data Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
ECG	Electrocardiogram
Eg	Exempli Gratia (for example)
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GFR	Glomerular filtration rate
GGT	Gamma-glutamyltransferase
GI	Gastrointestinal
GMP	Good Manufacturing Practice
hBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
HR	Heart rate
i.e.	Id est (that is)
IEC	Independent ethics committee
IND	Investigational New Drug
INR	International normalized ratio
IRB	Institutional review board
LDH	Lactate dehydrogenase
MRI	Magnetic resonance imaging
NIH	National Institute of Health
PD	Pharmacodynamic(s)
PDAC	Pancreatic Ductal Adenocarcinoma
PFS	Progression-Free Survival
PK	Pharmacokinetic(s)
PO	Per os (administered by mouth)
PR	Partial response

Abbreviation	Definition/Explanation
PT	Prothrombin time
PTT	Partial thromboplastin time
QTc	QT interval corrected
QTcF	QT interval corrected using Fredericia equation
RBC	Red blood cell
RP2D	Recommended Phase 2 Dose
SAE	Serious adverse event
SD	Stable disease
SD-OCT	Spectral-domain ocular coherence tomography
$T_{1/2}$	Terminal elimination half-life
TdP	Torsades de Pointes
T_{max}	Time of maximum observed concentration
ULN	The upper limit of normal
VF	Visual field
WBC	White blood cell

1 PROTOCOL SUMMARY

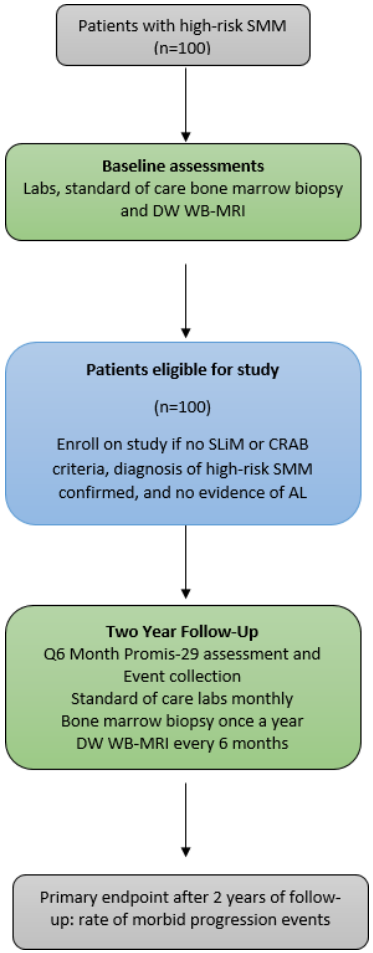
1.1 Synopsis

Title:	SPOTLIGHT: **S**moldering myeloma High-risk **P**atient **O**bservat**i**on and **L**ongitudinal **I**nsi**ght** Trial
Protocol Short Title	SPOTLIGHT
Study Description:	Single arm, prospective cohort, non-interventional study
Objectives:	**Primary Objective:** Ascertain the frequency and nature of progression events in a prospective cohort of patients with smoldering myeloma undergoing active surveillance with diffusion weighted whole body MRI. **Secondary Objectives:** To determine longitudinal Quality of Life as assessed by the PROMIS-29 instrument- physical function, pain interference, and anxiety at enrollment and every 6 months during this study
Endpoints:	**Primary Endpoint:** The primary endpoint is the cumulative incidence of morbid progression events at two years of follow-up (defined as death attributed to plasma cell dyscrasia, fracture attributed to plasma cell dyscrasia, lack of achievement of renal complete response defined as achievement of GFR≥ 60ml/min within 4 weeks in the event of new onset renal insufficiency attributable to plasma cell dyscrasia, lytic bone lesions, development of AL Amyloidosis or development of plasma cell leukemia). **Secondary Endpoints:** Change in the quality of life as measured by physical function, pain interference, and anxiety domains on the PROMIS-29, from baseline to the end of study at 24 months of follow-up.
Study Population:	**Key Inclusion Criteria** (see section 5. Study Population for additional criteria)**:** • Diagnosis of High-Risk Smoldering Myeloma made within 365 days of enrollment in the study. See section 5. Study Population for additional criteria.

	Key Exclusion Criteria (see section 5. Study Population for additional criteria)**:** • Presence of any features that would meet diagnostic criteria for myeloma as per the IMWG Criteria • Presence of extramedullary plasmacytomas

	• Presence of any focal bone marrow lesions or lytic bone lesions on imaging done prior to screening or on screening
Number of subjects:	100 evaluable subjects
Study Duration:	5 years
Participant Duration:	2 years
Enrollment Duration:	3 years

Schema


Patients with high-risk SMM (n=100)
Baseline assessments
Labs, standard of care bone marrow biopsy and DW WB-MRI
Patients eligible for study
(n=100)
Enroll on study if no SLiM or CRAB criteria, diagnosis of high-risk SMM confirmed, and no evidence of AL
Two Year Follow-Up
Q6 Month Promis-29 assessment and Event collection
Standard of care labs monthly
Bone marrow biopsy once a year
DW WB-MRI every 6 months
Primary endpoint after 2 years of follow-up: rate of morbid progression events

Schedule of Events

Protocol Procedures[1]	SCREENING	Follow-Up Period (+/- 2 month)				
	- 2 Months	Month 6	Month 12	Month 18	Month 24	Progression
Consent[2]	X					
Demographics	X					
Eligibility	X					
PROMIS-29 v.2.1[3]	X	X	X	X	X	X
Chart Review and Morbid Event Assessment		X	X	X	X	X
Complete Blood Count (CBC) with Platelet Count, Differential	Per SOC	Per SOC				
Comprehensive Metabolic Panel (CMP)	Per SOC	Per SOC				
Urine 24 Hour Immunofixation/electrophoresis (recommended within 1 year prior to enrollment)	Per SOC	Per SOC				
Tumor Markers (serum monoclonal protein, serum kappa/lambda light chains, serum immunoglobulin levels. Recommended within 2 months prior to enrollment)	Per SOC	Per SOC				
Bone Marrow Biopsy (recommended within 6 months prior to enrollment)	Per SOC	Per SOC				
Diffusion weighted whole body MRI (recommended within 3 months prior to enrollment)	Per SOC	Per SOC				

[1] Standard of care assessments completed prior to enrollment, unless otherwise specified, should be used for screening.
[2] See Section 7.1.1.
[3] Completion window is +/- 2 months for optional PROMIS-29 V.2.1. See section 4.1 for further details.

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objective

Ascertain the frequency and nature of progression events in a prospective cohort of patients with smoldering myeloma undergoing active surveillance with diffusion weighted whole body MRI.

Primary Endpoint: The primary endpoint is the cumulative incidence of morbid progression events at two years of follow-up (defined as death attributed to plasma cell dyscrasia, fracture attributed to plasma cell dyscrasia, lack of achievement of renal complete response defined as achievement of GFR≥ 60ml/min within 4 weeks in the event of new onset renal insufficiency attributable to plasma cell dyscrasia, lytic bone lesions, development of AL Amyloidosis or development of plasma cell leukemia).

2.2 Secondary Objective

To determine longitudinal Quality of Life as assessed by the PROMIS-29 instrument- physical function, pain interference, and anxiety at enrollment and every 6 months during this study.

Secondary Endpoint: Change in the quality of life as measured by physical function, pain interference and anxiety domains on the PROMIS-29, from baseline to the end of study at 24 months of follow-up.

3 BACKGROUND AND RATIONALE

3.1 Patient Population Background

Smoldering myeloma (SMM) is a precursor stage of multiple myeloma (MM), which is a cancer of the plasma cells that is characterized by the accumulation of malignant plasma cells in the bone marrow, and characteristic features of end-organ damage referred to as the CRAB criteria (hypercalcemia, renal dysfunction, anemia and bone lytic lesions)[4]. SMM is associated with a higher risk of progression to multiple myeloma than monoclonal gammopathy of undetermined significance (MGUS)[3] and is present in one in 200 individuals over the age of 40[5]. Historically, the diagnosis of MM has required the presence of end-organ damage, however changes to diagnostic criteria in 2014 led to reclassification of some patients previously classified as ultra- high risk SMM as MM[4]. These included patients with more than one focal lesion on magnetic resonance imaging (MRI), bone marrow plasma cells more than 60%, and serum free light chain ratio more than 100[4]. These patients were estimated to have an 80% risk of progression to MM at 2 years from diagnosis and thus reclassified as MM based on this risk[4]. As such, external validity of trials that enrolled patients with SMM prior to 2014 remains uncertain.

Historically, lytic lesions seen on a skeletal survey was part of the standard diagnostic workup for MM. However, a skeletal survey can miss up to 40% of lytic lesions that can be picked up by more advanced detection modalities such as whole-body diffusion weighted MRI (WB DW-MRI) or PET/CT[6,7]. Widespread usage of these modalities can thus lead to reclassification of patients to MM, who would have previously been diagnosed as SMM based on a negative skeletal survey.

Numerous criteria exist today to stratify patients with SMM into different risk status. These models include the Spanish PETHEMA model that incorporates the ratio of plasma cells ≥95% with an atypical immunophenotype on flow cytometry of the bone marrow aspirate and the presence of

serum immunoparesis[8], the 2008 Mayo Clinic model that involves serum monoclonal protein ≥30 g/l, BMPCs ≥10%, and an abnormal serum free light chain ratio [κ/λ] of either ≤0.125 or ≥8.0[9], the 2018 Mayo Clinic (a M-spike greater than 2 g/dL, an involved/uninvolved free light chain ratio greater than 20, and bone marrow plasmacytosis greater than 20%) model[3] and the most recent International Myeloma Working Group scoring model[2]. Unfortunately, these models have significant discordance with each other[10]. Furthermore, they also lack prospective validation in clinical trials.

Although two trials have shown that early intervention with lenalidomide (with or without dexamethasone) can decrease the likelihood of progression for patients with high-risk SMM to MM[11,12], these trials have important limitations that limit broad applicability to today's landscape. The first trial by the Spanish Group began enrolling in 2007, well before the use of advanced imaging and diagnostic reclassification of ultra-high risk SMM and MM[12]. As such, a substantial proportion of participants in that trial would have MM today. Although an overall survival advantage was seen in this trial upon extended follow-up, most patients in the control arm did not receive lenalidomide (or other contemporary therapies) when they experienced disease progression, and this trial was not statistically powered for overall survival either[13].

The E3A06 trial comparing lenalidomide to observation also began enrolling prior to the reclassification of SMM to MM, although the diagnostic reclassification occurred during the trial period[11]. This trial demonstrated that there was a decreased risk of progression with early therapy with lenalidomide compared to observation, the exact nature of progression events was not clearly defined in these studies. It is thus unclear whether early treatment led to prevention of asymptomatic bone lesions picked up on imaging or whether actual fractures or irreversible end organ damage was prevented. Furthermore, this trial is not powered for, or has shown an overall survival difference either at latest follow-up, with approximately 70% of patients in the observation arm without evidence of disease progression at three years of follow-up. Thus, although it is known that treatment for high risk SMM comes with increased financial toxicity, side effects, and secondary malignancies- whether patients live longer or better with early intervention in the modern era is unknown**.**

The most recent data on progression events for smoldering myeloma comes from the German group in their observational study of 96 patients[14]. Utilizing WB DW-MRI, they demonstrated that most progression events did not involve catastrophic end-organ damage. Out of a total of 22 patients who progressed, three developed osteoporotic compression fractures, and in all three, moderate or severe diffuse infiltration was present on MRI before onset of fracture. Only one patient presented with worsening renal function as the progression feature[14]. However, this study was not designed a priori to ascertain how progression events happened, and this study did not limit enrollment to high-risk SMM. Also, the reversibility of events like anemia or renal damage was not described, and quality of life was not evaluated. Furthermore, while myeloma and precursor diseases disproportionately affect Blacks/African Americans, they remain under-represented in clinical trials, and further data is needed for this patient population in a prospective fashion. As risk stratification models have been devised from predominantly White populations, there is a need to prospectively ascertain the risk of progression in a contemporary diverse patient population.

In summary, there is an unmet need for a rigorous prospective cohort study with an a priori defined threshold of detection of end-organ damage and longitudinal quality of life assessment to truly

establish the natural history of smoldering myeloma in the modern era of advanced imaging, as well as demonstrate prospectively that patients with high-risk SMM can be safely observed.

4 STUDY DESIGN

4.1 Description

This is a prospective, non-interventional study of a cohort of patients with high-risk smoldering myeloma (HR-SMM).

We will conduct a prospective single-arm study of 100 evaluable patients with high-risk SMM. We hypothesize that the event probability of morbid progressions is less than 0.08 (in 8 or less enrolled patients) at two years of follow-up.

Subjects enrolled in this prospective cohort study are expected to receive standard of care procedures as outlined below in section 4.1. As these procedures are considered non-research related, departure from the expected frequency will not be considered a protocol deviation.

Standard of care assessments should be used for screening.

In cases where follow-up assessments are completed outside of the expected timeframe, the study PI should be notified and an individual decision will be made on a case-by-case basis to keep patients on that study or consider them unevaluable.

It is recommended, but not mandated that the following procedures be done prior to enrollment to the study.

- A bone marrow biopsy within 6 months of enrollment
- A diffusion weighted MRI within 3 months prior to enrollment
- A 24-hour urine protein electrophoresis/immunofixation 1 year prior to enrollment
- Serum myeloma assessment (electrophoresis/immunofixation and light chains within 2 months of enrollment)
- Routine blood work (complete blood count (CBC) and complete metabolic panel (CMP) within 2 prior of enrollment)

If a patient has had the following procedures done outside the recommended window, they may still be enrolled on the trial, as long as they meet inclusion criteria, namely a diagnosis of high-risk smoldering myeloma within the past year. It is especially important to have a recent diffusion weighted MRI prior to enrollment (or PET for those who are claustrophobic and/or have a contraindication to MRI), as the presence of focal lesions on MRI precludes enrollment. For patients who have smoldering myeloma but have not yet undergone MRI, it is recommended that enrollment be delayed until after a baseline MRI is obtained and confirmed to show no focal lesions.

All patients on the study are recommended to undergo the following standard of care surveillance protocol:

- Complete Blood Count (CBC), Complete Metabolic Panel (CMP), myeloma blood tests (serum kappa/lambda light chains, monoclonal protein evaluation, immunoglobulin

levels), to be done monthly for first year, and then every two months for the second year.

- WB DW-MRIs every 6 months during the study period.
- 24-hour urine Immunofixation/electrophoresis is expected to be completed approximately every 6 months.
- Bone marrow biopsy will be performed annually during the study time-period.

The primary objective is the occurrence of morbid progression events defined in section 7.2.2. Chart review and assessment of morbid events will occur every 6 months during the follow-up period. Staff will document every 6 months and retroactively complete when progression occurred and how it occurred. A patient will be considered as having progressed to MM, if they meet criteria for progression to MM, as per the IMWG 2014 diagnostic criteria for myeloma.[4]

Secondary endpoints will include longitudinal measurement of quality of life. This will be done at baseline and at 6, 12, 18, and 24 months using the optional PROMIS-29 questionnaire[15]. The domains of interest on the PROMIS-29 instrument would be physical function, pain interference, and anxiety. The PROMIS-29 instrument may be completed +/- 2 months for each time point. If a patient progresses to MM, the details of how their progression occurred will be recorded, they will be taken off the clinical study, the PROMIS-29 may be completed, and standard of care treatment at the local institution would be offered to them.

4.2 Study Duration

5 years (3 years to enroll patients, two years of follow-up)

4.3 End of Study

A subject is considered to have completed the study if he or she has completed all phases of the study including the last visit (two years of follow-up) or they experience disease progression to MM.

5 STUDY POPULATION

5.1 Inclusion Criteria

1. _____ Adult subject aged ≥ 18 years.
2. _____Diagnosis of smoldering myeloma as per the IMWG criteria, specifically:
   - Serum monoclonal protein (IgG or IgA) of 30g/L or greater per 24 hours or urinary monoclonal protein of 500mg or greater per 24 hours

   and/or
   - Clonal bone marrow plasma cells 10-59% with the absence of myeloma-defining events or amyloidosis

Percentage of clonal bone marrow plasma cells (if applicable) _____%	Date bone marrow results (DD/MMM/YYYY): _____

3. _____ High-risk smoldering myeloma defined as two or more out of four of the following criteria:
   - M-spike greater than 2 g/dL
   - An involved/uninvolved free light chain ratio greater than 20
   - Bone marrow plasmacytosis greater than 20%
   - Presence of any of translocation (4;14), deletion 17p, deletion 13q or 1q gain by conventional cytogenetics/fluorescence in situ hybridization (FISH) studies)[10]

   and/or

   - An IMWG SMM score of 9 or greater[14] according to the IMWG risk model for smoldering multiple myeloma (SMM)

4. ____ Diagnosis of high-risk SMM made within 365 days of enrollment in the study. Note: If a patient previously had MGUS or low/intermediate SMM- the date at which high-risk SMM was diagnosed would have to be within 365 days of enrollment in the study.

_____ Date of Diagnosis (DDMMMYYYY)

5.2 Exclusion Criteria

1. _____ Presence of any features that would meet diagnostic criteria for myeloma as per the IMWG Criteria
2. _____ Presence of extramedullary plasmacytomas
3. _____ Presence of any focal bone marrow lesions, or lytic bone lesions on imaging done prior to screening or on screening. However, presence of diffuse or patchy infiltration of the marrow (without any clear lesions) on MRI, will not be an exclusion criteria. Patients with 1 focal marrow lesion on MRI that is attributable to plasma cell dyscrasia, will be excluded from study, even if they do not meet criteria for myeloma.
4. _____ Creatinine clearance of less than 40ml/min.
5. _____ Presence of AL Amyloidosis (the amount of workup necessary to exclude AL Amyloidosis is per the discretion of the treating investigator, however the investigator must attest that they do not believe AL Amyloidosis to be present at time of enrollment. Serum nt-PROBNP is recommended as part of evaluation in order to ascertain for cardiac amyloidosis).
6. _____ Hemoglobin of less than 11g/dl, unless a clearly reversible reason for anemia is identified, at which point they can be rescreened in two months if Hgb is greater than 11g/dl.

   Note: The Hgb cut-offs can vary between institutions (lower cut-off for Hgb University of Utah for men is a Hgb of 14.8, rendering a patient with Hgb of 12.7 as having a CRAB feature). If the Hgb is above 10g/dl but the patient meets the definition of anemia according to the IMWG criteria, by virtue of this being more than 2 g/dl below the limit of normal, the investigator can decide whether to call a patient being considered for screening as having multiple myeloma OR smoldering myeloma and allow enrollment on this study.

I certify that this patient meets all inclusion and exclusion criteria for enrollment onto this study.

Investigator Signature	**Date**	**Time**

5.3 Screen Failures

Screen failures are defined as participants who consent to participate in the clinical trial but do not meet subject eligibility criteria. These subjects will not be entered into the study or begin study intervention. However, minimal information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements. Minimal information includes, but may not be limited to, demography (including zip codes), screen failure details, eligibility criteria. Individuals who do not meet the criteria for participation in this trial (screen failure) may be rescreened at the Investigator's discretion.

5.4 Strategies for Recruitment

This trial allows for enrollment procedures to be done virtually. Participants are identified by their providers during clinic visits at HCI and/or through referral by their local physician. Participants may also self-refer themselves to the study team. A brochure may also be utilized for promoting the study, as well as social media. Participants receiving care at HCI may also be identified through their participation in Total Cancer Care (IRB 89989). Demographic, name, date of birth, and medical record numbers, when possible, will be documented in the research database for potentially eligible patients to ensure the study approaches all eligible patients. This information will remain confidential and within the research database for patients who refuse participation in order for study staff to 1) ensure patients are not re-approached after refusal and 2) identify potential solutions to address refusals. Patients enrolled virtually will receive the consent or consent cover letter electronically via REDCap or mail. An email or paper template will be included (see documents for reference).

Additionally, a recruitment letter may be sent to other oncologists with high-risk smoldering myeloma patients. Those providers could then refer potentially eligible patients to the study team at HCI. This study will be posted on clinicaltrials.gov. In situations where a patient contacts HCI to participate in the study, the patient will be encouraged to inform their provider of their interest. Staff may use the personalized dear doctor letter to facilitate communication with their provider after receiving approval from the participant to do so. After consent, the study staff will send the local physician a questionnaire regarding their typical routine monitoring schedule to confirm if his/her standard of care monitoring schedule is compatible with the MRI frequency outlined in the study protocol. The patient will no longer be considered if the MRI frequency is not compatible.

5.4.1 Number of Subjects

We plan to enroll 100 evaluable patients over approximately three years.

6 STUDY PLAN

6.1 Duration of Study

Subjects will be consented, screened, and then followed for two years.

6.1.1 Criteria for the Discontinuation of Study

Subjects may withdraw from the study overall at any time at their request, or they may be withdrawn at the discretion of the Investigator or an oncologist/hematologist clinician.

Subjects will be taken off study for the following:

- Completed study follow-up period.
- Participant or legally authorized representative requests to be fully withdrawn from the study.
- If, in the investigators or oncologist/hematologist clinician opinion, the continuation of the study would be harmful to the subject's well-being.
- The subject is lost to follow-up.
- Screen failure.
- Death.
- Documented and confirmed progression to MM
    - Should worsening of kidney function be the sole reason for progression to MM, progression will not be confirmed until standard of care follow up has been performed for at least four additional weeks beyond initiation of MM treatment to ascertain reversibility of kidney dysfunction.

6.1.2 Withdrawal of consent

Subjects are free to withdraw from the study at any time without any prejudice. If a subject withdraws consent, they will be specifically asked if they are withdrawing consent to all further participation in the study including any further follow-up (e.g., survival contact telephone calls). Survival status may be obtained from public records for subjects who have withdrawn from any further follow-up contact.

6.1.2.1 Lost to Follow-Up

Subjects will be considered lost to follow-up only if no contact has been established by the time the study is completed, such that there is insufficient information to determine the subject's status at that time. Subjects who refuse to continue participation in the study, including telephone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing subjects throughout the study period. If contact with a missing subject is re-established, the subject should not be considered lost to follow-up and evaluations should resume according to the protocol.

When a subject is lost to follow-up, site personnel should check hospital records, the subjects' current physician, and a publicly available death registry to obtain a current survival status.

In the event that the subject has actively withdrawn consent, the survival status of the subject can be obtained by site personnel from publicly available death records.

7 STUDY ASSESSMENTS

Every effort should be made to ensure that the protocol-required procedures are completed as described. However, it is anticipated that there may be circumstances, outside of the control of the Investigator that may make it unfeasible to perform the test. In these cases, the Investigator will take all steps necessary to ensure the safety and well-being of the subject. When a protocol-required test cannot be performed, the Investigator will document the reason for this and any corrective and preventive actions that he or she has taken to ensure that normal processes are adhered to as soon as possible.

7.1 General Assessments

7.1.1 Participant Consent

As this is a non-interventional study there are minimal risks to being enrolled. However, all potential subjects or their legal representative must be fully informed of the risks and potential benefits of trial participation and demonstrate understanding. For patients not enrolled in Total Cancer Care (IRB 89989), an informed consent document must be signed and dated by the participant or their legal representative indicating that they understand the risks and consent to participation and treatment on the study. A copy of the signed document should be provided to the subject.

Procedures, laboratory tests, or imaging performed as part of the standard of care prior to subject consent may contribute to the assessment of eligibility and/or screening procedures if performed during the screening period. Participants will also be asked to complete the NIH Demographic Form.

7.1.1.1 *HCI Patients Enrolled in Total Cancer Care*

HCI patients who have previously consented to the Total Cancer Care protocol (IRB 89989) will be provided with a cover letter for this study if eligible. A Waiver of Informed Consent Request will be submitted for Total Cancer Care consented patients whose samples and data are utilized. This will reduce patient burden in filling out two separate consent forms. Individuals under this criteria will be considered consented once PROMIS questionnaire is completed per the cover letter. The PROMIS questionnaire is highly recommended, but not mandatory for enrollment. For potential patients that are unable/unwilling to complete the questionnaire, they will receive the cover letter consent, review the cover letter with study staff, and will be enrolled after their verbal agreement to participate in the study. Potential subjects who are not enrolled in Total Cancer Care will be provided with a study specific consent, if they wish to participate.

7.2 PROMIS-29 v. 2.1

The optional PROMIS-29 questionnaire may be administered according to the time points indicated in the Study Calendar and if a participant progresses to MM. Administration may be completed either with pen and paper or electronically and is available in a variety of languages. Study staff may document participant responses on the participant's behalf if the participant needs assistance to complete the form. Participants may be reminded by phone or email to complete the questionnaire. This questionnaire is strongly encouraged, but it will not be considered a deviation if the patient is unable or unwilling to complete the assessment.

7.3 Chart Review and Morbid Event Assessment

Chart review and Morbid Event Assessment should occur at the time points indicated in the Study Calendar. The following items will be documented in REDCap and UBox and evaluated as possible morbid events:

- Death attributed to plasma cell dyscrasia,
- Fracture attributed to plasma cell dyscrasia,
- Lack of achievement of renal complete response defined as achievement of GFR≥ 60ml/min within 4 weeks in the event of new onset renal insufficiency attributable to plasma cell dyscrasia,
- Lytic bone lesions,
- Development of AL Amyloidosis
- Development of plasma cell leukemia

Additionally, information pertaining to demographics, bone marrow biopsies, 24-hour urine, tumor markers, CMP, CBC, and MRI/PET results may be abstracted from the participants record. Electronic health record information will be stored in REDCap.

7.3.1 Criteria for Progression to MM and Nuances of Assessment

Specifically, for our study: Any of the following criteria will qualify as progression to MM.

Note: Progression does not automatically qualify as an event towards primary endpoint of study**.**

1) Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    a) Hypercalcemia: serum calcium >0.25 mmol/L (>1mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11mg/dL)
    b) Renal insufficiency: creatinine clearance <40 mL per minute or serum creatinine >177mol/L (>2mg/dL)
    c) Anemia: hemoglobin value of >20g/L below the lowest limit of normal, or a hemoglobin value <100g/L. The Hb cut-offs can vary between institutions (lower cut-off for Hb University of Utah for men is a Hb of 14.8, rendering a patient with Hb of 12.7 as having a CRAB feature). If the Hb is above 10g/dl but the patient meets the definition of anemia according to the IMWG criteria, by virtue of this being more than 2 g/dl below the limit of normal, the investigator can decide whether to call a patient as having progressed to MM or still refer as SMM.
    d) Bone lesions: one or more osteolytic lesion on skeletal radiography, MRI, CT, or PET/CT. If bone marrow has <10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement

NOTE: These lab findings have to be attributable to a plasma cell dyscrasia by the investigator in order to be considered as progression to MM, as there may be other reasons that can cause hypercalcemia, anemia and renal insufficiency etc.

2) Any one or more of the following biomarkers of malignancy, or myeloma-defining events (MDEs):
    a) 60% or greater clonal plasma cells on bone marrow examination
    b) Serum involved / uninvolved free light chain ratio of 100 or greater, provided the absolute level of the involved light chain is at least 100mg/L (a patient's involved free light chain is the one that is produced by the aberrant plasma cells, and is the one that is typically higher than upper limit of normal, whereas the uninvolved light chain is made by normal plasma cells and typically falls in or below the normal range)
    c) More than one focal bone marrow lesion on MRI that is at least 5mm or greater in size.

As documentation of the nature of progression is critical to primary endpoint ascertainment of our study, the characteristics of tumor progression will be clearly documented and recorded. With respect to MRI imaging, the following caveats must be noted.

1) Development of “new” focal bone marrow lesions on an MRI will not be counted as a morbid progression event, but if there is more than one focal bone marrow lesion on an MRI that is at least 5mm or greater in size, this will be considered as progression to MM, and patients will be taken off the study. If only one focal bone marrow lesion on MRI develops, patients will not be considered as having progressed to MM, but a follow-up MRI in three months may be considered as per standard of care per the investigator’s discretion. Patients progressing with new focal lesions on MRI should have a CT or

PET/CT as per investigators discretion to evaluate for lytic lesions definitively.

2) Development of “diffuse or focal bone marrow infiltration” on MRI will not be counted as a progression event to MM, or as a morbid progression event.

Development of new ‘lytic” bone lesions on MRI or any other form of imaging will be counted as a morbid progression event, and patient will be taken off the study. Patients progressing with new focal lesions on MRI should have a CT or PET/CT as per investigators discretion to evaluate for lytic lesions definitively.

Anemia considerations may require assessment by the investigator, as the Hgb cut-offs can vary between institutions (lower cut-off for Hgb University of Utah for men is a Hgb of 14.8, rendering a patient with Hgb of 12.7 as having a CRAB feature). If the Hgb is above 10g/dl but the patient meets the definition of anemia according to the IMWG criteria, by virtue of this being more than 2 g/dl below the limit of normal, the investigator can decide whether to call a patient as having progressed to MM, or still be considered as SMM.

If an indication develops for plasma cell directed therapy (such as development of myeloma), the decision to pursue such therapy will be done as per the treating physicians discretion.

Nevertheless, should an investigator decide to pursue plasma cell directed therapy for rising/abnormal lab values (such as a rising light chain level), in the absence of any clear MM defining feature, this will not count towards the primary endpoint of the study. This will be documented as initiation of MM therapy, and similar to the process for when patients are diagnosed with MM- these patients will then be taken off study and removed from further-follow-up. We will not enroll additional patients (beyond target of 100) to adjust for this situation, as these patients would be considered eligible for primary endpoint ascertainment and would be considered to have not met the primary endpoint.

7.3.2 Criteria for Morbid Progression Events

The primary endpoint is the cumulative incidence of morbid progression events at two years of follow-up defined as any of the following:

- Death attributed to plasma cell dyscrasia
- Fracture attributed to plasma cell dyscrasia,
- Lack of achievement of renal complete response defined as achievement of GFR≥ 60ml/min within 4 weeks in the event of new onset renal insufficiency attributable to plasma cell dyscrasia,
- Lytic bone lesions
- Development of AL Amyloidosis
- Development of plasma cell leukemia

7.3.3 Use of PET/CT as alternative to MRI

Use of MRI for imaging surveillance is strongly preferred. In cases where an MRI result is unavailable or MRI could not be performed as per standard of care for reasons such as claustrophobia or metallic device, PET/CT results may be utilized at the discretion of the PI.

7.4 Remote Visits/Telehealth

Patients may choose to complete their study related and routine visits remotely or via telehealth as per their discretion. The method of telehealth should be documented in the participants' charts.

8 STATISTICAL CONSIDERATIONS

8.1 Sample size determination

Our primary research hypothesis is that event probability morbid progressions is less than 0.08 at two years of follow-up. If the true probability of progression is 0.08 or less, then a 1-sided hypothesis test with $\alpha\alpha$ =0.10 will achieve at least 82% power. This 1-sided hypothesis test is based on the rule that if we observe 10 or fewer morbid progressions, then we reject the null hypothesis that the progression probability is ≥ 0.15 in favor of the alternative hypothesis that the progression probability is < 0.15. In addition, with 100 evaluable patients, the margin of error corresponding to the upper 95% confidence bound (one-sided) for the true progression probability is approximately 0.05.

Descriptive analysis will be conducted to explore the characteristics of the patient population using means (standard deviations) and numbers (percentages) for quantitative and qualitative variables. Patients who die before the 24-month endpoint ascertainment due to disease progression will be regarded as “failures” and will count towards the event. Patients lost to follow-up will be censored. Subjects who withdraw prior to 1-year post-enrollment will be censored and replaced. Using the Wilson’s score-based proportion confidence interval technique, a one-sided 95% confidence bound for the rate of morbid progression events will be constructed.

Pitfalls: Shortcomings of this approach include a lack of a control arm to ascertain whether treatment could lower the risk of progression further, although this approach is being investigated in other randomized trials. The follow-up is limited to two years of follow-up, and overall survival will not be ascertained as that would require a longer follow-up. Further funding in the future could be used to extend follow-up on this study.

8.2 Primary Endpoint

The primary endpoint of this study is rate of morbid progression events. We hypothesize that most progression to MM that occurs during our study follow-up, will be asymptomatic biochemical changes in labs, or development of bone marrow lesions on imaging, rather than lytic lesions, fracture, or irreversible renal failure. We hypothesize that the primary endpoint is the cumulative incidence of morbid progression events at two years of follow-up (defined as death attributed to plasma cell dyscrasia, fracture attributed to plasma cell dyscrasia, lack of achievement of renal complete response defined as achievement of GFR≥ 60ml/min within 4 weeks in the event of new onset renal insufficiency attributable to plasma cell dyscrasia, lytic bone lesions, development of AL Amyloidosis or development of plasma cell leukemia). With 100 patients, we will ensure that a 95% confidence bound (one-sided) can be estimated with a margin of error ≤0.05.

If a patient progresses to MM, the details of how their progression occurred will be recorded, they will be taken off the study, and standard of care treatment would be offered to them.

8.3 Secondary Endpoints

Secondary endpoints will include longitudinal measurement of quality of life. This will be done at baseline and at 6, 12, 18 and 24 months using the PROMIS-29 questionnaire[15]. The domains of interest on the PROMIS-29 instrument would be physical function, pain interference, and anxiety. We hypothesize that there will not be a significant change from baseline in any of the patient reported outcome domains at follow-up.

9 ETHICAL AND REGULATORY CONSIDERATIONS

9.1 Informed Consent

Informed consent will be obtained from all research participants prior to performing any study procedures using the most recent IRB approved version.

9.2 Human Subjects Protection

The study will be conducted in accordance with the protocol, 21 CFR, HIPAA regulations, the Belmont Principles, ICH Guidelines for Good Clinical Practice (GCP), and the Declaration of Helsinki. Informed consent will be obtained from all research participants or their legally

authorized representative before performing any study procedures using the most recent IRB approved version.

9.2.1 Personal Data Protection

All parties will take all necessary actions required for the protection of subject personal data. Subjects enrolled in the study will be assigned a subject number and will be referenced by this number. Directly identifiable data will be omitted from reports, publications, and other disclosures. All personal data will be stored at the study site in encrypted electronic and/or paper form stored in a locked and secured facility. The site will be responsible for maintaining a list of subjects linking each subject with their subject number. Data will only be accessed by appropriate personnel and will be password protected or securely stored in a locked room. In the case of a potential breach of personally identifiable data, the site will take responsibility to ensure appropriate action is taken according to institutional practice and applicable laws and regulations.

9.3 Institutional Review

Before the initiation of the study, the Investigator will have prospective approval of the study protocol, protocol amendments, informed consent documents, and other relevant documents, (e.g., recruitment advertisements, questionnaires, if applicable), from the IRB. All correspondence with the IRB should be retained in the Investigator's regulatory file. Changes to the protocol or approved documents may not be made until IRB approval has been received. However, if a change is necessary to eliminate immediate hazards to the subjects, prospective approval is not necessary.

The investigator or designee should provide the IRB with reports, updates and other information (e.g., expedited safety reports, amendments, and administrative letters) according to regulatory requirements or institution procedures.

9.4 Investigator Responsibilities

The Investigator is responsible for ensuring the trial is conducted in compliance with the current IRB approved version of the protocol, GCP, the Declaration of Helsinki, and any applicable national and local laws and regulations.

9.5 Protocol Amendments

Any amendments or administrative changes to an IRB approved protocol will not be initiated without submission of an amendment for IRB review and approval. However, prospective IRB approval will not be sought when an amendment is required to eliminate immediate risk to subjects on study. In these cases, amendments will be retrospectively submitted to the IRB for review and approval.

Any amendments to the protocol that significantly affect the safety of subjects, the scope of the investigation, or the scientific quality of the study will be submitted to the FDA for review.

9.6 Protocol Deviations

A deviation will be defined as any noncompliance with ICH GCP or the clinical protocol requirements. The noncompliance may be either on the part of the participant, the Investigator, or the study staff. As a result of the deviation, a corrective action must be implemented to

ensure future deviation does not occur. It is the Investigator's responsibility to identify and report deviations from ICH GCP or protocol requirements. These deviations and corrective action should be documented in the subject's research chart, the associated eCRF, and reported to the IRB per their policy.

10 DATA HANDLING

10.1 Recording and Collection of Data

Primary source documentation will come directly from the subject's medical record. All source documentation should be attributable, legible, contemporaneous, original, accurate, complete, and available. All documentation should be signed and dated by applicable personnel. Relevant source data will be transcribed into the electronic case report forms (eCRFs) and should be completed as soon as possible after data availability. The eCRFs will be part of a computerized database grounded in the protocol requirements and study objectives. The database will be designed to comply with 21 CFR Part 11.

The Investigator has ultimate responsibility for ensuring that all data collected and recorded is accurate and consistent.

10.2 Data Management

To accommodate evaluations, inspections, and/or audits from regulatory authorities, the Investigator must maintain all study records including subject identity, source documentation, original signed consent form, safety reporting forms, monitoring logs, relevant correspondence (e.g., letters, emails, meeting minutes, etc.), and any other documents pertaining to the conduct of the study. For the duration of record maintenance, records must be stored in a secure location and protected from the elements.

10.3 Clinical Trials Data Bank

The study will be registered on http://clinicaltrials.gov and the NCI CTRP (Clinical Trials Reporting Program).

11 PUBLICATION PLAN

In accordance with U.S. regulations and the best interest of research ethics and transparency, this study will be registered on ClinicalTrials.gov before subject enrollment. US Basic Results will also be reported and available on ClinicalTrials.gov within one year of the primary completion date, regardless of formal journal publication. All results will be reported objectively, accurately, balanced, and completely, regardless of the study outcome. We will plan on submitting the results within three months of study completion to a major journal (Lancet Hematology). Our study outline/plan may also be published in a journal for wider dissemination.

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Appendix 2: PROMIS–29 Profile v2.1

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

	Physical Function	**Without any difficulty**	**With a little difficulty**	**With some difficulty**	**With much difficulty**	**Unable to do**
PFA11	Are you able to do chores such as vacuuming or yard work?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA21	Are you able to go up and down stairs at a normal pace?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA23	Are you able to go for a walk of at least 15 minutes?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
PFA53	Are you able to run errands and shop?	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	Anxiety **In the past 7 days…**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDANX01	I felt fearful.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX40	I found it hard to focus on anything other than my anxiety.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX41	My worries overwhelmed me. ...	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDANX53	I felt uneasy.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Appendix 2: PROMIS–29 Profile v2.1

	Depression **In the past 7 days...**	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
EDDEP04	I felt worthless.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP06	I felt helpless.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP29	I felt depressed.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
EDDEP41	I felt hopeless.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Fatigue **During the past 7 days…**	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
HI7	I feel fatigued.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
AN3	I have trouble starting things because I am tired.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP41	How run-down did you feel on average?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
FATEXP40	How fatigued were you on average?.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Appendix 2: PROMIS–29 Profile v2.1

	Sleep Disturbance In the past 7 days…	**Very poor**	**Poor**	**Fair**	**Good**	**Very good**
Sleep109	My sleep quality was.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
	In the past 7 days.....	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
Sleep116	My sleep was refreshing.	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
Sleep20	I had a problem with my sleep.....	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Sleep44	I had difficulty falling asleep.	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
	Ability to Participate in Social Roles and Activities	**Never**	**Rarely**	**Sometimes**	**Usually**	**Always**
SRPPER 11_CaPS	I have trouble doing all of my regular leisure activities with others	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER 18_CaPS	I have trouble doing all of the family activities that I want to do....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER 23_CaPS	I have trouble doing all of my usual work (include work at home).....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1
SRPPER 46_CaPS	I have trouble doing all of the activities with friends that I want to do.....	☐ 5	☐ 4	☐ 3	☐ 2	☐ 1

Appendix 2: PROMIS–29 Profile v2.1

	Pain Interference In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
PAININ9	How much did pain interfere with your day to day activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ22	How much did pain interfere with work around the home?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
PAININ31	How much did pain interfere with your ability to participate in social activities?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	Pain Interference In the past 7 days…	**Not at all**	**A little bit**	**Somewhat**	**Quite a bit**	**Very much**
PAININ34	How much did pain interfere with your household chores?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

	Pain Intensity In the past 7 days…											
Global07	How would you rate your pain on average?	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6	☐ 7	☐ 8	☐ 9	☐ 10
		No pain										**Worst pain imaginable**