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TITLE: A Randomized, Double-Blind, Placebo-Controlled Phase 2 Study of Metformin for the Prevention of Progression of Monoclonal Gammopathy of Undetermined Significance and Smoldering Multiple Myeloma

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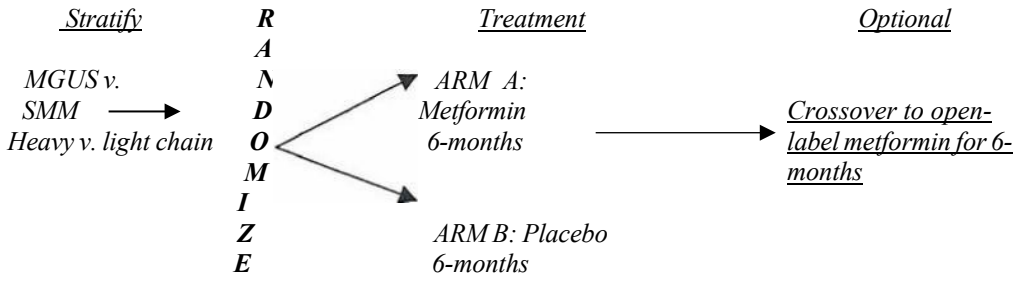
SCHEMA

N=60

Diseases:
***MGUS**–Monoclonal Gammopathy of Undetermined Significance*
***SMM**- Smoldering multiple myeloma*



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1. OBJECTIVES

1.1 Study Design

We will conduct a randomized placebo-controlled trial in patients with higher-risk monoclonal gammopathy of undetermined significance (MGUS) and low-risk smoldering multiple myeloma (SMM) to test the efficacy of metformin in reducing clinical indicators of disease progression in MGUS and SMM patients. The target enrollment of the trial is 60 patients. After informed consent is signed, participants will be randomized in equal numbers to metformin or its corresponding placebo. The treatment period for the trial is 6-months, with study assessments for the trial's primary outcome occurring at baseline and at the end of the 6-month treatment period. Participants will have the option to learn their treatment assignment after primary (6-month) outcome assessments are complete, and individuals randomized to metformin will have the opportunity to continue to take metformin for an additional 6-months to allow for the observation of potentially longer-term treatment response. Participants who choose to be unblinded and are taking placebo will discontinue study medication. Passive follow-up via medical record review will occur for up to 5 years post-randomization.

1.2 Primary Objectives

To determine whether metformin can reduce or stabilize serum monoclonal (M-)protein concentrations from baseline to 6-months in patients with MGUS and SMM.

1.3 Secondary Objectives

- Identify changes in m-protein/light chains using mass spectrometry.
- Identify changes in hemoglobin concentrations among patients treated with metformin vs. placebo.
- To examine molecular evolution of the tumor cells in response to metformin.
- To determine the impact of metformin on the immune landscape of individuals with MGUS/SMM.
- To explore the degree to which metformin changes plasma metabolites and metabolomic signatures.
- To examine the impact of the metformin on changes in quality-of-life indicators form baseline to 6-months.
- To understand patients' willingness to continue to take metformin beyond the 6-month primary assessment period.
- To examine the response trajectory in individuals who choose to take metformin for up to 1-year.

2. BACKGROUND

2.1 Myeloma (MM) and its Precursor Conditions.

Multiple Myeloma (MM) is an incurable and fatal malignancy, with a 5-year survival rate of just over 50%.[1] The incidence rate of MM in the US has been steadily rising; few cancers have

demonstrated a greater increase in incidence since 2004.[1] MM is a plasma cell dyscrasia characterized by the proliferation of clonal plasma cells in the bone marrow and the production of monoclonal immunoglobulin and/or light chain, with subsequent end organ damage.[2]

MM always evolves from precursor states of monoclonal gammopathy of undetermined significance (MGUS) and smoldering MM (SMM), which are relatively common blood conditions affecting ~3% of the general population over 50 years.[2] Both conditions are often clinically detected through the presence of abnormal proteins called "monoclonal (M-)proteins" in the blood and/or urine. In 2010 the International Myeloma Working Group (IMWG) defined monoclonal gammopathy of undetermined significance (MGUS) by the presence of serum M-protein < 3g/dL, clonal plasma cell population in the bone marrow < 10%, and the absence of end-organ damage such as hypercalcemia (serum calcium ≥ 11.5 mg/dL), renal insufficiency (serum creatinine ≥ 2 mg/dL), anemia (hemoglobin value below the lower limit of normal by more than 2 g/dL or hemoglobin value < 10 g/dL) and lytic bone lesions (CRAB features) that can be attributed to the plasma cell proliferative disorder.[3] Smoldering multiple myeloma was defined by the presence of serum M-protein ≥ 3 g/dL or IgA> 2g/ dL or urinary monoclonal protein > 500 mg/ dL and/or clonal bone marrow plasma cells ≥ 10% and the absence of CRAB features clinically.

In general, MGUS progresses to overt MM at a slow rate of 1% per year, but in some patients, the risk may be as high as 58% in 20 years.[4,5] SMM has an annual risk of progression of 10%, but in some patients, risk is considerably higher.[4] These conditions also confer a decreased life expectancy compared to the general population[6,7], raising the possibility that there are other disorders associated with MGUS and SMM that have yet to be determined.

2.2 Clinical Management of MGUS and SMM and Status of Treatment.

The cornerstone of management for both entities is to delay therapy until progression to MM, at which time patients have overt end-organ damage.[8,9] It is therefore unsurprising that patients with MGUS and SMM report high levels of anxiety and distress about their conditions,[10] and cure is seldom achieved.[11] However, this paradigm may change as there are already clinical trials that show that early use of MM therapies in the precursor setting may alter the natural history of the disease[12], and importantly, may improve survival.[13] For example, in a randomized open-label phase 3 trial [13], 119 patients with high-risk smoldering myeloma were randomized to treatment or observation. Patients in the treatment group received an induction regimen (lenalidomide at a dose of 25 mg per day on days 1 to 21, plus dexamethasone at a dose of 20 mg per day on days 1 to 4 and days 12 to 15, at 4-week intervals for nine cycles), followed by a maintenance regimen (lenalidomide at a dose of 10 mg per day on days 1 to 21 of each 28-day cycle for 2 years). The primary endpoint was time to progression to symptomatic disease. Secondary endpoints were response rate, overall survival, and safety. After a median follow-up of 40 months, the median time to progression was significantly longer in the treatment group than in the observation group (median not reached vs. 21 months; hazard ratio for progression, 0.18; 95% confidence interval [CI], 0.09 to 0.32; P<0.001). The 3-year survival rate was also higher in the treatment group (94% vs. 80%; hazard ratio for death, 0.31; 95% CI, 0.10 to 0.91; P=0.03). A partial response or better was achieved in 79% of patients in the treatment group after the induction phase and in 90% during the maintenance phase. Toxic effects were mainly grade 2 or lower. Early treatment for patients with high-risk smoldering myeloma delays progression to active disease and increases overall survival. (NCT00480363).

Despite the promise of early treatment in the precursor MM disease setting, it has remained highly controversial given the high cost and risk of toxicity and harm to patients who may never progress to overt MM.[14-16] For example, the treatments currently being investigated in the precursor disease setting carry considerable short- and long-term risks, including but not limited to arterial thromboembolic events, neutropenia and thrombocytopenia, and increased risk for secondary malignancies.[17] These toxicities, in effect, mostly limit the use of existing therapies to the highest risk patient subsets. Therefore, the identification lower-risk, cost-effective strategies to prevent disease progression in patients with less aggressive forms of MGUS and SMM is of considerable importance.

2.3 Metformin

Metformin is a biguanide derivative that is FDA approved for the treatment of type 2 diabetes but is also considered safe for use in non-diabetic populations;[18] serious adverse events are rare and are mostly limited to lactic acidosis. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin, at therapeutic doses, does not cause hypoglycemia when used alone in man or in the non-diabetic animal, except when using a near lethal dose. Metformin has no effects on the pancreatic beta cells.

Metformin absorption is relatively slow, is delayed to some extent by food consumption, and may extend over a period of hours. The drug is excreted in urine at high renal clearance rate of about 642 mL/min, which varies based on dosage. The initial elimination of metformin is rapid with a plasma elimination half-life of approximately 6.2 hours. Metformin is not metabolized and is therefore excreted unchanged in the urine.

2.4 Trial Rationale

2.4.1.1 Clinical experience in cancer prevention

There is a growing body of literature indicating a benefit to the repurposing metformin in the cancer prevention setting, by demonstrating its efficacy in improving biological systems putatively associated with cancer prognosis among non-diabetics. For examples, in an observational cohort study using UK-based record-linkage databases, there was a significantly reduced risk of cancer associated with metformin use, with a hazard ratio for metformin reported to be 0.63 (95% CI, 0.53– 0.75). In this same study, total and cancer-specific mortality were also significantly lower among metformin users.[19] In addition, a 2008 study among 32 non-diabetic breast cancer patients, which demonstrated that a 6-month intervention consisting of 1500mg of metformin significantly reduced fasting insulin and improve insulin sensitivity.[20] More recently, a univariate interim analysis among 492 non-diabetic breast cancer survivors enrolled in the NCIC Clinical Trials Group (NCIC CTG) MA.32 trial of metformin vs. placebo found metformin use for 6-months to be associated with improved glucoregulation (insulin, glucose, HOMA-IR), in addition to leptin and C-reactive protein.[21]

2.4.2 Rationale for investigation in precursor MM

Metformin is of particular interest as a disease interception tool in the precursor MM setting given that it is relatively inexpensive and is sustainable for long-term risk reduction,[22]—all of which are characteristics that the current investigational therapies do not possess. The converging lines of evidence supporting the benefit of metformin in preventing MGUS/SMM progression are briefly outlined below:

In vivo and *in vitro* xenograft models have demonstrated metformin's ability to inhibit MM cell proliferation by inducing apoptosis and cell cycle arrest through mechanisms of action that include the IGF-1R/PI3K/AKT/mTOR signaling pathway;[23] it also appears to work synergistically with other MM therapies, including dexamethasone,[23] bortezomib[24] and ritonavir[25] to limit MM cell proliferation. Metformin has also been shown to regulate other aspects of the bone marrow microenvironment in ways that may inhibit myelomagenesis, including but not limited to reducing bone marrow adipose tissue, which is a highly active endocrine organ that resides directly in the bone marrow niche and supports MM cell proliferation, as well as immune cells.[26,27]

Data from observational studies further support the use of metformin in preventing disease progression in individuals with MGUS/SMM. For example, metformin use was associated with a statistically significant 53% reduced risk of MM in a cohort of 2,003 diabetics diagnosed with MGUS (95% CI: 0.25, 0.87),[28] and similar observations were reported in an independent cohort of MGUS patients from The Health Improvement Network.[29] Given the consistent laboratory science and epidemiologic evidence suggesting a beneficial role of metformin in regulating the activity of MM and other bone marrow niche cells, a number of ongoing clinical trials are testing its efficacy (in combination with other drugs) for the treatment of MM patients with relapsed and refractory disease (see ClinicalTrials.gov). However, we are not aware of any ongoing or planned clinical trials investigating the use of metformin in patients with MGUS or SMM.

2.4.3 M-Protein and Light-chain Concentrations as Clinically Relevant Disease Endpoints.

Monoclonal (M-)proteins and light chains produced in excess by an abnormal clonal proliferation of plasma (MM) cells that can be measured in the serum using Serum Protein Electrophoresis (SPEP) and the Serum Free Light Chain Assay. These quantitative tests usually correlate with overall tumor burden, and thus the SPEP is one of the most common clinical tests used to monitor patients with all stages of the disease continuum (MGUS, SMM and MM). Importantly, concentrations of these biomarkers have been repeatedly shown to reduce after treatment with a range of mild and aggressive MM therapies,[30-32] underscoring their utility as a sensitive and measurable marker of tumor response to treatment.[33]

2.4.4 Mass Spectrometry

Quantitative immunopurification mass spectrometry (QIP-MS) combines Ig immunopurification with mass spectrometry resulting in a methodology that is more sensitive and specific than serum protein electrophoresis (SPEP) and immunofixation (IFX). The technique works by first isolating Ig's using isotype specific beads. Purified Ig's are then separated into light chains and heavy chains by the addition of a reducing agent. A mass spectrometer is then used to detect a monoclonal light chain from an M-protein observed as a peak above the normal polyclonal

background. Mills et al. demonstrated that QIP-MS could detect an M-protein in patient serum when SPEP and IFX were negative.[34] They also showed in serial dilution studies that a monoclonal light chain peak could be detected by QIP-MS at a level < 0.05 g/L; a level that was negative when analyzed by SPEP and IFX. The specificity of QIP-MS is provided by the superior resolving capability and mass measurement accuracy of the mass spectrometer. Barnidge and colleagues demonstrated that molecular mass could be used to monitor a specific monoclonal kappa light chain in a patient GK MM over a 7-year period.[35] The monoclonal light chain could easily be detected in samples that were negative by SPEP and IFX. Multiple clones can be easily identified in serum using QIP-MS technology since the mass spectrometer provides superior resolution compared to gel electrophoresis. M-protein quantification is performed by comparing monoclonal light chain peak intensities with an internal reference.

2.5 Correlative Studies Background

2.5.1 Immune cell characterization in the peripheral blood and bone marrow

Tumors are complex ecosystems characterized by interactions between heterogeneous cell types, including malignant cells and immune cells[36]. An important step in the progression of tumors is their ability to evade and suppress the host immune system in a way that fosters immune escape and tumor growth.[37,38] Therefore, therapies that modify immune microenvironment may be effective anti-myeloma therapies.[39] For example, metformin can interfere with immunopathological mechanisms implicated in MGUS/SMM disease progression,[40] including but not limited to the T helper 17/regulatory T cell balance, cytokine synthesis, and natural killer cell response,[39,41,42] suggesting that the putative benefits of metformin on the prevention of disease progression in MGUS/SMM may be mediated, in part, through the effects on the immune microenvironment.

2.5.2 Value of Metabolomics

Metabolomics, e.g., the high-throughput identification and quantification of small molecule metabolites produced by metabolism, can yield novel insights into pathogenesis and risk of cancer and chronic disease.[43,44] Metabolomics is the study of metabolic changes in biological systems and provides the small molecule fingerprints that reflect the complex relationships between diet, lifestyle (obesity), genes, and disease processes.[44] We believe that metabolomics offers a unique lens to study progression in the precursor MM, given that of all molecular entities (e.g., genes, transcripts, proteins, metabolites), metabolites have the closest relationship to expressed phenotype, as they are the final endpoints of biochemical processing.[45] Despite the growing interest and application of metabolomics to cancer and chronic disease research, metabolomics-based studies of MM, MGUS, or SMM are sparse.[46-51] One small study by Ludwig et al identified 25 bone marrow metabolites that differed between 10 MGUS and 10 MM patients,[46] but this work has not yet been expanded in larger samples with clinical and lifestyle data. A larger metabolomics investigation of precursor MM patients could contribute important knowledge regarding the landscape of the metabolic changes underlying the disease, and ultimately lend important insights into interception strategies and druggable targets. Particularly important categories of metabolites

in cancer and metabolic disease are metabolites of glycolysis and the TCA cycle. These are of interest to the current study because of their critical role in tumor growth[52,53] and because they have been shown to be obesity related.[54] Importantly, these metabolite categories have consistently shown to be sensitive to metformin[55-57]—likely because of their relationship to the mammalian target of rapamycin (mTOR),[58,59] which is the cellular signaling cascade that serves as a master regulator of metabolism, cell growth, and proliferation.[60]

2.5.3 Quality of life in the Precursor Disease Setting

As an exploratory objective, given the high rates of anxiety and distress document in individuals with MGUS and SMM[61,62] and lack of evidence-based risk reduction strategies available for preventing disease progression to MM, we will explore the psychosocial benefits of offering a low-risk pharmacologic intervention to this patient population.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 Diagnosed with high-risk MGUS or low-risk SMM[63] defined below:

Higher-Risk MGUS: bone marrow plasma cell concentration <10%[#] AND either serum M-protein level ≥1.5 g/dL to <3 g/dL, abnormal free light-chain (FLC) ratio (<0.26 or >1.65), or IgA MGUS.
Note: individuals with an abnormal FLC ratio that are classified as light-chain only are eligible. Light-chain only patients are defined as complete loss of immunoglobulin heavy-chain, accompanied by abnormal FLC ratio with an increased level of the appropriate involved light-chain (increased kappa FLC in patient with ratio >1.65, and increased lambda FLC in patients with ratio <0.26).

Low-Risk Smoldering Myeloma: bone marrow plasma cells ≥10%[#] with the absence of additional high-risk features, which are further defined in the exclusion criteria (3.2.1)[64]

[#]A new bone marrow biopsy is preferred for plasma cell determination at screening; however, determination of eligibility can be made from most recent bone marrow biopsy performed as long as it was within 2 years of enrollment.

3.1.2 Absence of evidence of CRAB criteria* or new criteria of active MM or active WM which including the following (note if one or more criteria has not been evaluated (e.g., no MRI), the criteria for active MM or WM for that feature is considered unmet):

- Increased calcium levels (corrected serum calcium >0.25 mmol/dL above the upper limit of normal or >.275 mmol/dL) related to MM
- Renal insufficiency (attributable to MM)

- Anemia (Hb 2g/dL below the lower limit of normal or <10g/dL) related to MM
- Bone lesions (lytic lesions or generalized osteoporosis with compression fractures)
- Bone marrow plasma cells ≥60%
- Serum involved/uninvolved FLC ratio ≥100, provided the absolute level of the involved free light chain is at least 100 mg/L and repeated twice (light chain smoldering myeloma as described in section 2.4 is not an exclusion criteria).
- MRI with two or more focal lesion that is at least 5 mm or greater in size
- Hyperviscosity symptoms per WM guidelines for symptomatic WM

**Participants with CRAB criteria that are attributable to conditions other than the disease under study may be eligible*

3.1.3 At least 18 years of age.

3.1.4 Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.

3.1.5 The following laboratory values obtained prior to the first dose of study drug/placebo:

- AST and ALT < 1.5 x institutional ULN
- Serum bilirubin < institutional ULN (in patients with Gilbert's Disease, direct bilirubin < institutional ULN)
- Calculated creatinine clearance ≥ 45 mL/min
    - Estimation of renal function will be assessed using the CrCl calculated based on the Cockcroft-Gault formula:
        - CrCl (mL/min) = (140-age) (weight [kg]/72 (serum creatinine [mg/dL]; for females the formula is multiplied by 0.85
- Random glucose < 160 mg/dL or fasting glucose < 126 mg/dL (other values require workup to rule out undiagnosed diabetes that may require treatment)

3.1.6 Ability to understand and the willingness to sign a written informed consent document

3.1.7. For participants who wish to enroll in the open label extended treatment (crossover arm), participants can be unblinded and learn of their drug group AFTER completing primary endpoint collection. Patient must be randomized to metformin in order to continue taking metformin for 6 additional months.

3.2 Exclusion Criteria

3.2.1 Presence of high-risk smoldering myeloma, as defined by IMWG/Mayo 2018 "20-2-20" Criteria (at least 2 of the following)
- Bone marrow plasmacytosis ≥20%
- ≥2g/dl M protein
- ≥20 involved: uninvolved serum free light chain ratio

3.2.2 Diagnosed or treated for another malignancy within the study period.

3.2.3 Currently on medications for diabetes treatment
- Patients with hyperglycemia (random glucose < 160 mg/dL or fasting glucose < 126 mg/dl) but who are not on any drug treatment are eligible

3.2.4 Participants who are receiving any other investigational agents.

3.2.5 Women who are pregnant or who are unable or unwilling to use contraception during the study period are excluded from this study because it is a class B agent which is known to cross the placenta rapidly and is unbound in serum.

3.2.6 Any condition associated with increased risk of metformin-associated lactic acidosis (prior renal failure or liver failure, history of acidosis of any type) or habitual intake of 3 or more alcoholic beverages per day.

3.2.7 Known intolerance to metformin

3.2.8 Known malabsorption syndrome or diagnosis with a medical condition that may alter gastrointestinal absorption of medications including but not limited to inflammatory bowel disease impacting the small intestine or recent history of bariatric surgery.

3.2.9 Any other condition that, in the investigator's judgment, would contraindicate the use of metformin or otherwise interfere with participation in the trial

3.3 Inclusion of Women and Minorities

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

4. REGISTRATION AND RANDOMIZATION PROCEDURES

4.1 Recruitment

Participants will be primarily recruited from the Center for the Prevention of Progression (CPOP) Clinic at Dana-Farber, but we may expand recruitment to other Mass General Brigham sites. We will utilize multiple active recruitment techniques to maximize participation and generalizability. We will use the following strategies to identify potential participants:

- We will review clinic schedules and patient lists at DFCI and other Partners Healthcare institutions. HIPAA waivers will be obtained prior to review of these patient lists.

Once a potential participant is identified, they will be contacted by phone/email by a study coordinator to solicit interest, or during a clinic visit or through other approved methods of communication.

Interested subjects identified through these recruitment strategies will be pre-screened by study staff either in person or by phone initially and if potentially eligible, he or she will meet with a member of the study staff to review the protocol and sign informed consent.

Consenting will occur in person or remotely via 45 CFR part 46, local CON-100 and 21 CFR part 11 compliant Adobe eSign. Adobe eSign consent may be utilized for patients who have recently been seen by study clinicians, but who live far away/ out of state and are unwilling to return to the main campus to consent to study. Participants that are consented electronically will utilize the same version as the paper version of the consent form. Patients will be provided with a copy of the consent form. They will have the opportunity to discuss and ask questions about the study with their clinician prior to signing consent form and discuss any potential questions with study staff. Once review of the consent has concluded, the study staff will email another consent form via Adobe eSign Consent through an official Dana-Farber email to the participant's authenticated and confirmed email address that is on file in their medial record.

4.2 Registration process

All eligible participates who consent and wish to enroll in the intervention will be registered in the Clinical Trials Management System (CTMS) OnCore. Registrations must occur prior to the initiation of any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied. Any participant who wishes to become unblinded after primary endpoint completion and is interested and eligible to enroll in the open-label crossover arm of the study must be registered to the crossover arm in OnCore.

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

The eligibility checklist(s) and all pages of the consent form(s) will be faxed or emailed to ODQ at 617-632-2295. The ODQ will (a) review the eligibility checklist, (b) register the participant on the protocol, and (c) randomize the participant.

Randomization can only occur during ODQ business hours (8:30am - 5pm Eastern Time, Monday through Friday excluding holidays).

The ODQ Protocol Systems Coordinator is responsible for randomizing subjects to treatment arms for investigator-sponsored research

The statistician in the Department of Biostatistics and Computational Biology provides ODQ with any necessary randomization sheets and instructions specific to the protocol.

For blinded protocols: The ODQ Protocol Systems Coordinator conveys the randomization assignment to the appropriate departments as directed by the randomization instructions.

An email confirmation of the registration and/or randomization will be sent to the study coordinator(s) from the registering site, treating investigator and registering person immediately following the registration and/or randomization.

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

4.2.1 Registration Process for DF/HCC Sites

DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (SOP #: REGIST-101) must be followed.

Following registration, patients will be randomized to the metformin/placebo. Initiation of metformin/placebo should begin within 4 weeks of screening/baseline blood collection.

5. TREATMENT PLAN

We will conduct a randomized placebo-controlled trial in patients with higher-risk monoclonal gammopathy of undetermined significance (MGUS) and low-risk smoldering multiple myeloma (SMM). After informed consent is signed, total of 60 eligible and evaluable participants will be randomized 1:1 either to metformin or placebo. Stratification factors will be disease stage (MGUS vs. SMM) and heavy vs. light-chain status. The treatment period will be 6 months and primary outcome assessments as outlined below will occur at baseline and after 6 months of treatment or for those that discontinue medication, as close to the 6-month timepoint as possible. To explore participants' willingness to continue to take metformin after the 6-month treatment period and observe longer-term response, participants will be given the option to learn their treatment assignment after completing the primary study endpoints. Any participant randomized to the metformin group will be invited to continue to take metformin for an additional 6 months.

Treatment will be administered on an outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6.

Participants will dose escalate in a stepwise fashion beginning with 500mg and increasing by 500mg until they reach 1500mg. The duration of this study and corresponding treatment period is 6 months.

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the participant's premalignancy.

5.1 Unblinding

In the event of a medical emergency where breaking the blind is required to provide medical care to the subject, the primary investigator or treating investigator with approval by the primary-investigator may obtain the treatment assignment directly from the research pharmacy. Blinding of study treatment is critical to the integrity of this clinical trial and therefore, if a subject's treatment assignment is disclosed to the investigator, the subject will have study treatment discontinued. Documentation of the decision to unblind will be recorded in the subject's medical record.

After primary outcome measures are collected (blood collection at 6 month end of treatment visit), participants will have the option to learn their treatment assignment (be unblinded) and any patients randomized to the metformin arm will be invited to continue to take metformin for an additional 6 months on a crossover arm. Participants randomized to the placebo will discontinue study medication at the 6-month time point.

In addition, at the end of the study the PI will obtain a list from the research pharmacy of each patient's randomization for data analysis.

5.2 Treatment Regimen

Metformin and its corresponding placebo are the proposed pharmacological treatments. Metformin can be safely used in nondiabetics without significantly impacting quality of life. Minor adverse events associated with this agent are nausea/vomiting, diarrhea, or constipation. All patients will be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin, since alcohol intake potentiates the effect of metformin on lactate metabolism.

A cycle is defined as 28 days. In the absence of toxicity, withdrawal or other event, treatment may continue for up to 6 cycles. The metformin dose will be 1500 mg/day, provided in 500 mg pills. To minimize gastrointestinal symptoms, metformin will be started at a low dose of 500 mg (1 pill) and the patient will be advised to take it with food at water. A drug dairy/schedule will be provided for each patient for the duration of the treatment period, and telephone contact will be made periodically to assess compliance and toxicity.

As noted in the study calendar, adherence to the medication will be assessed throughout the study period by means of telephone calls at day 7, day 28, day 48 (optional at the discretion of clinical team), at the end of cycle 3, and at the end of study visit within the window specified (Section 10 Study Calendar footnote 10). All remaining pills will also be returned to study staff and counting will occur in the DFCI research pharmacy.

Please refer to section 6.1 for criteria and guidance for dose escalation.

As this is a blinded study, all participants will be asked to adhere to this dosing schedule and the pill-taking guidelines specified below. Therefore, the dosing regimen for the placebo is the same as described above for metformin.

Week 1 (Days 1-7)

Agent	Dose	Route	Schedule

Metformin/Placebo	500mg	Oral	Once daily with meals and at least 8 ounces of water

Week 2-4 (Days 8-28)

Agent	Dose	Route	Schedule
Metformin/Placebo	1000mg	Oral	Once daily with meals and at least 8 ounces of water

Week 5 through week 24 (Day 29 through end of study)

Agent	Dose	Route	Schedule
Metformin/Placebo	1500mg	Oral	Once daily with meals and at least 8 ounces of water

NOTE: The participant will be required to maintain a medication diary of each dose of medication. The medication diary will be returned to clinic staff at their 6-month/end of study visit or mailed back along with any extra medication to the study team to perform accountability per local policies.

Patients will be invited to continue to take metformin for an additional 6 months on a crossover arm after completing the study's primary endpoints. This option will only be available to individuals who are taking metformin during the blinded study phase. Patients taking placebo will discontinue all study medication at the 6-month timepoint.

Optional Extended Treatment Period (crossover arm): Week 24-48.

Agent	Dose	Route	Schedule
Metformin	1500mg or highest tolerated dose	Oral	Once daily with meals and at least 8 ounces of water

NOTE: A new open-label metformin diary will be provided to participants who wish to participate in the optional extended treatment period. As done previously, the medication diary will be returned to clinic staff at the end of the additional 6-month treatment period or mailed back along with extra medication to the study team to perform accountability per local policies.

5.3 General Concomitant Medication and Supportive Care Guidelines

Participants may receive any supportive care necessary to address side effects of metformin so long as it is not considered investigational.

5.4 Prohibited Medications and Procedures

There are several medications and procedures which may increase the risk of lactic acidosis associated with metformin. Medical records will be reviewed for potential metformin contraindications including but not limited to the following: acetazolamide (Diamox), dichlorphenamide (Keveyis), methazolamide, topiramate (Topamax, in Qsymia), or zonisamide (Zonegran). In addition, participants will be advised to tell the study team if they plan to have surgery or any medical procedures requiring iodinated contrast agents, which can also increase the risk of lactic acidosis. In the event of a surgery or procedure that requires a contrast agent, participants will be advised to stop taking study medication 48 hours prior to the procedure and to refrain from re-starting study medication until they have undergone a blood test showing normal kidney function.

Participants are also prohibited from taking any investigational medications, or any cancer directed therapy during the study. In the event that a cancer-directed therapy is clinically warranted (e.g., progression to MM), participants will come off study so that appropriate care can be received.

5.5 Agent Administration

Participants will be provided 3 months of study medication at study entry after randomization; the remaining pills will be mailed to the patient at a later date to minimize drug waste per local policies. A drug diary will also be provided for participants to record study drug compliance/adherence. Participants in the extended treatment (crossover arm) will receive a 3-month supply of medication in person or by mail at the 6-month visit if eligible. To minimize drug waste and ensure patient safety, the final 3-month supply will be sent to participants at a later date once safety labs are reviewed by the research team.

The Office of Data Quality (ODQ) will have a randomization schedule which has been prepared and provided by the Study Statistician. Study agent randomization to placebo or active SDG will be provided for each sequential post-randomization study ID number and sent by ODQ to the research pharmacy.

Both Metformin and matched placebo are to be provided by the DFCI Research Pharmacy. Metformin (containing 500 mg of the active ingredient) placebo (containing the same filler material but without the active ingredient) will be given to all trial participants for the 6 months of participation (two shipments each containing a 3-month supply). All subjects should have off-study procedures ideally no later than 7 days of the last dose of Metformin or placebo. However, if a participant stops study agent prematurely in an unscheduled situation, s/he should come in for re-assessment as early as possible. Participants in the crossover arm will be provided 1500 mg Metformin by the DFCI Research Pharmacy. As indicated previously, the pills will be given in two batches, each containing a 3-month supply. All participants in the crossover arm should also have off-study procedures ideally no later than 7 days of the last dose of Metformin.

Metformin/Placebo tablets (Study Drug) are to be taken orally and tablets are to be taken whole, not broken or crushed. Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified sub investigator(s). As described above, it is recommended that all tablets are taken with food to minimize gastrointestinal side effects.

Please refer to section 8 for further information about the study agent.

5.6 Participant Diary

Participants should be instructed to document all oral study drug administration on a patient diary and return unused tablet and packaging for review of compliance at the end of the study. Sites are responsible to maintain the diary as source documentation.

5.7 Removing a Participant from Treatment (Off Treatment)

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. In the absence of toxicity or withdrawal from therapy, treatment may continue for up to 6 cycles when each cycle is defined as 28 days (or 12 cycles for those in the crossover arm), or until one of the following criteria applies:

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

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

When a participant is removed from protocol therapy and/or is off of the study, the participant's status must be updated in OnCore in accordance with REGIST-OP-1.

5.8 Duration of Follow Up

The total study intervention period is 6 months, with the final assessment occurring at the end of the scheduled 6-month treatment period. However, some participants may choose to be unblinded after primary outcome assessments are complete and will agree to continue to take metformin for an additional 6-month observational period (crossover arm). In addition, participants will be followed for survival and disease events via medical record review for up to 5-years after randomization.

5.9 Removing a Participant from Study (Off Study/Off Follow Up)

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

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

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). In addition, the study team will ensure the participant's status is updated in OnCore in accordance with REGIST-OP-1.

6. DOSING DELAYS/DOSE MODIFICATIONS

The major toxic effects of which limit metformin dose are gastrointestinal (nausea, abdominal bloating, diarrhea). Dose adjustments, for reasons of toxicity will be as in the tables below. Please note that none of the recommended dose adjustments require splitting of the study drug.

If multiple adverse events are seen, dose modifications should be based on the worst preceding toxicity. The AE should be attributed to a specific drug, if possible, so that the dose modifications can be made accordingly. Reduction of the study drug is appropriate if toxicity is thought to be primarily related to the agent under study.

The dose modification guidelines should be regarded as guidelines and should be followed unless otherwise discussed with the principal investigator.

Reductions are based on toxicity noted within a cycle and may contribute to the dose level for the subsequent cycle. Dose re-escalation can be considered after discussion with the treating investigator. Each cycle is defined as 28 days.

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

6.1 Criteria to Escalate- Gastrointestinal Toxicity

6.1.1 Criteria to Escalate from 500mg to 1000mg

1. Participants must not have any gastrointestinal toxicity > Grade 1 on day of anticipated escalation
    - If toxicity is Grade 2, hold for one week, and re-evaluate
        - If in one week, the toxicity has not resolved to Grade 1 or better, hold treatment for a second week and re-evaluate
        - If the participant is unable to dose escalate after 3 weeks beyond the expected escalation date, consider treatment at 500mg for the duration of the study or discontinuation at PI discretion
    - If toxicity is Grade 3, hold medication for 1 week, and re-evaluate
        - If in one week, toxicity has not resolved to Grade 1 or better, consider holding for one additional week, and re-evaluate
        - If the participant is unable to dose escalate after 3 weeks beyond the original expected escalation date, or without resolution of symptoms to Grade 1, maintain 500mg as final dose for the duration of the study, or discontinue altogether at the investigator's discretion

6.1.2 Criteria to Escalate from 1000mg to 1500mg

1. Participants must not have any gastrointestinal toxicity > Grade 1 on day of anticipated escalation
    - If toxicity is Grade 2, hold for one week, and re-evaluate
        - If in one week, the toxicity has not resolved to Grade 1 or better, hold treatment for a second week and re-evaluate
        - If after the second week the toxicity has not resolved to Grade 1 or better, consider holding for one additional week
        - If the participant is unable to dose escalate after 3 weeks beyond the expected escalation date maintain at 1000mg or reduce to 500mg for the duration of the study or discontinue treatment at PI discretion
    - If toxicity is Grade 3, hold for 1 week, and re-evaluate
        - If in one week toxicity has not resolved to Grade 1 or better, consider holding for one additional week, and re-evaluate
        - If the participant is unable to dose escalate after 3 weeks beyond the expected escalation date, or without resolution of symptoms to Grade 1 or better, discontinue treatment at PI discretion.

6.2 Criteria to Dose Escalate - Other Toxicities

For all other toxicities thought to be possibly, probably or definitely related to the study medication, the following guidance for dose escalation is advised:

6.2.1 Criteria to Escalate from 500mg to 1000mg

1. Participants must not have any toxicity > Grade 1 on day of anticipated escalation
    - If toxicity is Grade 2, hold for one week, and re-evaluate
        - If in one week, the toxicity has not resolved to Grade 1 or better, hold treatment for a second week and re-evaluate
        - If the participant is unable to dose escalate after 3 weeks beyond the expected escalation date, consider treatment at 500mg for the duration of the study or discontinuation at PI discretion
    - If toxicity is Grade 3, hold medication for 1 week, and re-evaluate
        - If in one week, toxicity has not resolved to Grade 1 or better, consider holding for one additional week, and re-evaluate
        - If the participant is unable to dose escalate after 3 weeks beyond the original expected escalation date, or without resolution of symptoms to Grade 1, maintain 500mg as final dose for the duration of the study, or discontinue altogether at the investigator's discretion

6.2.2 Criteria to Escalate from 1000mg to 1500mg

1. Participants must not have any toxicity > Grade 1 on day of anticipated escalation
    - If toxicity is Grade 2, hold for one week, and re-evaluate
        - If in one week, the toxicity has not resolved to Grade 1 or better, hold treatment for a second week and re-evaluate
        - If after the second week the toxicity has not resolved to Grade 1 or better, consider holding for one additional week
        - If the participant is unable to dose escalate after 3 weeks beyond the expected escalation date maintain at 1000mg or reduce to 500mg for the duration of the study or discontinue treatment at PI discretion
    - If toxicity is Grade 3, hold for 1 week, and re-evaluate
        - If in one week toxicity has not resolved to Grade 1 or better, consider holding for one additional week, and re-evaluate
        - If the participant is unable to dose escalate after 3 weeks beyond the expected escalation date, or without resolution of symptoms to Grade 1 or better, discontinue treatment at PI discretion.

6.3 Dose Modification Schedule

Dose Level	Dose
0 (Starting Dose)	1500mg Daily
-1	1000mg Daily
-2	500mg Daily
-3	Discontinue

Dose Level	Dose

0 (Starting Dose)	1000mg Daily
-1	500mg Daily
-2	Discontinue

Dose Level	Dose
0 (Starting Dose)	500mg Daily
-1	Discontinue

- With the investigator's discretion, dose re-escalation can be considered, or an alternative dose ramp up plan or dose management plan proposed
- If a participant needs to be dose reduced during the dose ramp up period, the principal investigator may decide to not escalate further, or escalate after improvement of symptoms

6.4 Toxicity Management Guidelines For Toxicity After Escalation Period

The following guidelines should be followed if thought to be related to the study medication:

Nausea, Vomiting, Diarrhea	**Management/Next Dose for Study Drug**
≤ Grade 1	No change in dose. Patient should be encouraged to remain on full dose; if unwilling to remain on therapy, stop study treatment for one week. Resume at same dose. If symptoms recur, then reduce to one tablet daily (if applicable) permanently for remainder of study.
Grade 2	Hold until ≤ Grade 1. Resume at one dose level lower, if indicated at PI discretion.
Grade 3	Hold* until ≤ Grade 1. Resume at 1-2 dose levels lower, if indicated at PI discretion.
Grade 4	Off protocol therapy
Recommended management: antiemetics or Loperamide antidiarrheal therapy as needed	

Other Toxicity*	**Management/Next Dose for Study Drug**
≤ Grade 1	No change in dose. Patient should be encouraged to remain on full dose; if unwilling to remain on therapy, stop study treatment for one week. Resume at same dose. If symptoms recur, then reduce to one dose level

	lower permanently for remainder of study.
Grade 2	Hold until ≤ Grade 1. Resume at one dose level lower, if indicated at PI discretion.
Grade 3	Hold until ≤ Grade 1. Resume at 1-2 dose levels lower, if indicated at PI discretion.
Grade 4	Off protocol therapy

* all other toxicities include any other hematologic or non-hematologic toxicity that is not listed specifically above.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.1 Expected Toxicities

7.1.1 Adverse Events List for Metformin

Lactic acidosis is an uncommon but serious adverse event associated with metformin administration. The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases / 1000 patient/years with approximately 0.015 fatal cases / 1000 patient/years).

Other side effects include: Diarrhea, Nausea, Vomiting, Flatulence, Lack of energy/weakness (asthenia), Abdominal pain, Constipation, Distention of the stomach/abdomen, Dyspepsia (heartburn), Dizziness, Headache, Upper respiratory infection, Change or disturbance of taste Abnormal stools, Low blood sugar (hypoglycemia), Muscle aches (myalgias), Lightheadedness, Dyspnea (shortness of breath), Nail changes, Rash. Increased sweating, Chest discomfort, Chills, Flu-like syndrome, Flushing, and Heart palpitations

7.2 Adverse Event Characteristics

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

- **For expedited reporting purposes only:**

- AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
- Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Adverse Event Reporting

7.3.1 In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the PI.

7.3.2 Investigators **must** report to the PI any adverse event (AE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form.

7.3.3 Adverse Event Reporting Guidelines

All participating sites will report AEs to the Sponsor-Investigator per DF/HCC requirements, and the IRB of record for each site as applicable per IRB policies. The table below indicates which events must be reported to the DF/HCC Sponsor-Investigator.

- **CTCAE Grade 2 and Grade 3 Events** – that are Unexpected and there is a Reasonable Possibility that the Adverse Event is related to the study intervention.
- **CTCAE Grade 4 Events** – Report all events that are Unexpected. Events that are Expected and listed within the protocol and/or current consent form do not need to be reported to the DFCI IRB. Please note, an event that presents at a higher severity than what is currently listed within the protocol and/or current consent as expected would be considered unexpected and reportable. See protocol for additional reporting requirements (to sponsor, FDA, etc.).
- **ALL CTCAE Grade 5 Events**

7.3.4 Protocol-Specific Adverse Event Reporting Exclusions

Only events that are considered possibly, probably or definitely related to the study drug will be captured on the database for the purpose of this study.

7.4 Reporting to the Food and Drug Administration

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

7.5 Reporting to Hospital Risk Management

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

7.6 Routine Adverse Event Reporting

Any Adverse Events related to metformin administration that led to dose-reductions or discontinuation of study medication **must** be reported in routine study data submissions to the PI on the toxicity case report forms. **AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must <u>also</u> be reported in routine study data submissions.**

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the investigational agent administered in this study can be found in Section 7.1.

8.1 Metformin Hydrochloride

8.1.1 Description

Metformin HCl is a white crystalline powder soluble in water and 95% ethyl alcohol. It is practically insoluble in ether and in chloroform. Melting Point: 218-220

Metformin HCl is a biguanide derivative producing an antihyperglycemic effect which can only be observed in man or in the diabetic animal and only when there is insulin secretion. Metformin, at therapeutic doses, does not cause hypoglycemia when used alone in man or in the non-diabetic animal, except when using a near lethal dose. Metformin has no effects on the pancreatic beta cells. Metformin absorption is relatively slow and may extend over about 6 hours. The drug is excreted in urine at high renal clearance rate of about 450 mL/min. The initial elimination of metformin is rapid with a half-life varying between 1.7 and 3 hours. The terminal elimination phase accounting for about 4 to 5 % of the absorbed dose is slow with a halflife between 9 and 17 hours. Metformin is not metabolized. Its main sites of concentration are the intestinal mucosa and the salivary glands. The plasma concentration at steady-state ranges about 1 to 2 mcg/mL. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when

taking metformin HCl, since alcohol intake potentiates the effect of metformin on lactate metabolism.

8.1.2 Form of Medication

Metformin tablets will be purchased from commercially available source.

8.1.3 Storage and Stability

Metformin HCL should be stored at room temperature (15 to 30C) in well closed containers.

8.1.4 Handling

There are no special requirements for the handling of metformin HCl.

8.1.5 Availability

Metformin or it's corresponding placebo will be provided at no cost to research participants. The drug/placebo combination will be purchased by research pharmacy.

8.1.6 Preparation

Metformin capsules and matched placebo will be prepared at DFCI Research Pharmacy.

Metformin Active Drug capsules: Metformin tablets (500 mg ER) will be encapsulated in empty capsules (opaque, "000" size). The remaining capsule space will be filled by cellulose microcrystalline (NF).

Matched Placebo capsules: The identical empty capsules will be filled with cellulose microcrystalline (NF) to prepare matched placebo capsules.

6-Month Crossover Metformin Active Drug capsules: Patients will receive the metformin tablets (500 mg ER) directly from stock bottles within the DFCI Research Pharmacy.

Active Drug and Matched Placebo capsules look identical in appearance.

8.1.7 Administration

The institutional research pharmacy will dispense ample medication for the duration of the 6-month treatment phase based on the randomization schedule provided by institutional statisticians and the Office of Data Quality.

All subjects will be dispensed and mailed a 3-month supply of the study agent after the baseline visit, once eligibility is confirmed and randomization occurs. The remainder of the medication will be shipped at the end of cycle 3, after a safety assessment is completed. If additional study agent is required because of extended delays in scheduling, it may be shipped to the subject per

local policies. At the end of the 6-month treatment phase at the end of study visit, the unused study agent will be counted for compliance and returned to the study team.

For participants in the optional extended treatment (crossover arm), a 3-month supply of metformin will be dispensed at the 6-month visit or by mail shortly after the visit. The remainder of the medication will be shipped after the next safety assessment is completed (end of extended treatment cycle 9). If additional study agent is required because of extended delays in scheduling, it may be shipped to the subject per local policies.

The study team may give instructions to take pills at approximately the same time of day in conjunction with intake of food and at least eight ounces of water and to keep track of missed doses or lost pills on their study diary.

Participants are to be given the following drug administration instructions:

- Keep capsules in the bottle(s) provided and do not transfer them to any other container. Store at room temperature. Capsules are to be taken whole, and not broken or emptied.
- Please take your medication by mouth at the same time every day per the instructions on the study diary or as directed by instructions on the label of your study drug bottle.
- Your medication should be taken with food and water, preferably in the evening to avoid gastrointestinal side effects. If your dose is more than one capsule, please take all capsules at the same time.
- If you vomit after taking a capsule, do NOT take another dose. Please note any vomiting in the Comments section of the diary on the next page.
- If you miss a dose of study drug, take it as soon as you remember on the same day. If you miss taking study drug for the entire day, take your regular dose the next scheduled day (do NOT take double your regular dose to make up for the missed dose).
- If you miss a full dose (all of your assigned medication capsules), please record "0" for Number Taken on your diary
- If you are taking 500 mg (1 capsule) and accidentally take an extra capsule, skip the following day's dose and resume your assigned schedule on the third day, and record the extra capsule on your diary.
- If you are taking 1000mg (2 capsules) and accidently take an extra capsule, resume your assigned schedule the following day and record the extra capsule on your dairy
- If you are taking 1500mg (3 capsules) and accidently take an extra capsule, resume your assigned schedule the following day and record the extra capsule on your dairy
- Please bring any unused metformin and all empty containers and diary to your next visit.

8.1.8 Blinding and Unblinding Methods

In the event of a serious adverse event or other circumstance requiring unblinding, the investigator will contact the research pharmacy, who will then unblind the subject to the investigator if necessary. If the treatment blind is broken, the reason and the date should be

recorded and signed by the investigator. Participants will have the option to be unblinded after the primary outcome measures have been collected.

8.1.9 Ordering and dispensing

The active drug or placebo will be dispensed in blinded fashion by research pharmacy based on randomization result. Each bottle will be labeled with a label identifying study specific information, such as protocol number, dosing instructions, and a caution statement indicating that the agent is limited by United States law to investigational use only and the agent should be kept out of reach of children.

For those participants who are unblinded, found to be on Metformin, and wishing to continue taking Metformin after the 6-month primary treatment/outcome period is complete, an unblinded supply of metformin will be provided. Again, each bottle will be labeled with a label identifying study specific information, such as protocol number, dosing instructions, and a caution statement indicating that the agent is limited by United States law to investigational use only and the agent should be kept out of reach of children.

8.1.10 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

It is necessary to maintain a careful record of the inventory and disposition of all study agent using a drug accountability record form. The Investigational Pharmacy at each participating site is required to maintain adequate records of receipt, dispensing and final disposition of study agent. Include on receipt record from whom the agent was received and to whom study agent was shipped, date, quantity and batch or lot number. On dispensing record, note quantities and dates study agent was dispensed to and returned by each participant.

8.1.11 Destruction and Return

At the end of the treatment phase, unused or expired supplies of the study drug should be returned to the research pharmacy and destroyed according to institutional policies after accountability is performed. Destruction will be documented in the Drug Accountability Record Form.

9. STUDY MEASURES

9.1 Screening/Baseline Assessments

After the prospective participant signs the informed consent form, eligibility will be assessed including review of medical history and clinical blood tests. To minimize additional visits to DFCI during the COVID-19 pandemic, all in-person screening assessments as well as any baseline measures that require in-person collection will occur at the time of a scheduled clinical appointment at DFCI.

All clinical blood tests to confirm eligibility will be reviewed by a clinician; any values outside the normal range will be discussed with the patient's primary oncologist. Participants meeting eligibility criteria will be randomized to metformin or it's corresponding placebo and ideally will be mailed the medication/placebo no later than 5 business days after randomization occurs unless a later date is requested by the participant. The participant will be instructed to begin taking the study medication upon receipt.

9.1.1 Pregnancy Screening

For women of child-bearing potential, a urine pregnancy test will be collected. A serum pregnancy test can be waived in certain conditions, such as post-hysterectomy. A urine or serum pregnancy test will only be performed as a Screening/Baseline assessment. As noted in Exclusion Criteria 3.2.5, "Women who are pregnant or who are unable or unwilling to use contraception during the study period are excluded from this study because it is a class B agent which is known to cross the placenta rapidly and is unbound in serum." Although maternal use of metformin is generally considered safe during pregnancy and is not associated with any teratogenic effects to a fetus, any woman who becomes pregnant during the study period will be removed from treatment to avoid any unknown harm.

9.2 Final assessments

End of Study primary outcome assessments should ideally be done within 7 days of completing 6 months of treatment, or for those that were not able to complete 6 months of treatment, as close to the 6 month timepoint as possible. At this visit, a study staff member will collect pill bottles in person or by mail (empty and unused), participants will have 6-month research blood draw and clinical labs performed, bone marrow samples collected if being done as part of standard of care procedures, have weight measured and recorded, and be asked to complete the Final Questionnaire. For individuals who agree to continue to take metformin for an additional 6-months after primary outcomes are assessed, these secondary outcomes will ideally be done within 7 days of completing 12-months of treatment, or as close to that timepoint as possible. Similar to the 6-month assessment, a study staff member will collect pill bottles in person or by mail, participants will have a research blood draw and clinical labs performed, and bone marrow core biopsy/aspirate samples collected if being done as part of standard of care procedures. At this time, weight will be measured and recorded.

9.3 Endpoint assessment

Primary endpoints of the trial are serum monoclonal (M-)protein concentrations/light chains from baseline to 6-months. Mass spectrometry will also be performed on all samples in the Ghobrial lab at Dana-Farber Cancer Institute on a machine from The Binding Site. Mass spectrometry is of particular utility given its increased sensitivity for the detection of plasma cell dyscrasias.

Rationale for primary endpoint: Most cancer prevention trials relay on inferences from surrogate endpoints to measure the intervention impact on cancer risk. MGUS and SMM are unique diseases given that (1) malignant plasma cells are already present in the bone marrow, and (2) their presence can be easily measured in the peripheral blood through the use of M-protein measurements. These measures usually bear a direct relationship with overall tumor burden, and thus the serum protein electrophoresis test used to quantify M-protein concentrations is one of the most common clinical tests used to monitor patients with all stages of the disease continuum (MGUS, SMM and MM). Importantly, M-protein concentrations have been repeatedly shown to reduce after treatment with a range of mild and aggressive MM therapies,[30-32] indicating that serum M-protein levels can serve as a sensitive and measurable marker of tumor response to an intervention.[33]

9.4 Correlative Studies

9.4.1 Bone Marrow Aspirate Collection

Collection of bone marrow aspirate specimens for analysis will be obtained at the times of standard of care bone marrow collections. These collections are highly encouraged but are considered optional. As noted per Eligibility Criteria 3.1.1, a new bone marrow biopsy is preferred for plasma cell determination at screening; however, determination of eligibility can be made from the most recent bone marrow biopsy performed if it was within 2 years of enrollment. As such, bone marrow aspirate specimens may not be available from these procedures for correlative studies. Please note that some participants enrolling in this study will already have research orders in place for biobanking protocols (e.g., protocol #14-174). In this case, every effort will be made to coordinate and synergize with existing effort so that the minimum amount of marrow is collected for research participants. Any sample collected on this trial that has not been exhausted for the purposes of the aims detailed in this study will be stored for future use. Specimens will be collected and subsequently processed, analyzed, and stored at Dana-Farber Cancer Institute at the following address for the Ghobrial Lab:

Ghobrial Lab
Dana-Farber Cancer Institute
[redacted]

Bone Marrow Specimens Requested (if available):

- 2x10mL Purple Top Tubes (K2EDTA)
  - Tubes types may be substituted if requested by the study team

Timepoints Requested:

- At any time a standard of care marrow biopsy/aspirate is being performed

Specimens should be labeled with the following:

- Subject Initials
- Subject study number (will include protocol number)
- Visit at which sample was drawn
- Date sample drawn (mm/dd/yyyy)
- Time sample drawn (24-hour clock)

9.4.2 Blood Collection

Collection of blood specimens for analysis will be obtained at the times of standard of care blood draws, whenever feasible. Collection will occur at pre-specified study intervals and may be collected more often if additional standard of care draws are scheduled. Any sample collected on this trial that has not been exhausted for the purposes of the aims detailed in this study will be stored for future use. Please note that some participants enrolling in this study will already have research orders in place for biobanking protocols (e.g., protocol #14-174). In this case, every effort will be made to coordinate and synergize with existing effort so that the minimum amount of blood is collected for research participants. Specimens will be collected and subsequently processed, analyzed, and stored at Dana-Farber Cancer Institute at the following address for the Ghobrial Lab:

Ghobrial Lab
Dana-Farber Cancer Institute
[redacted]

Blood Specimens Requested:

- 3 x 10ml Purple Top Tubes (K2EDTA)
- 1x 6ml Red Top Tube (no additive)
    - Tubes types may be substituted if requested by the study team

Timepoints Requested:

- Pre-Treatment/Baseline
- Post Treatment/6-month timepoint (ideally within 7 days)

Label all specimens with the following:

- Subject Initials
- Subject study number (will include protocol number)
- Visit at which sample was drawn
- Date sample drawn (mm/dd/yyyy)
- Time sample drawn (24-hour clock)

9.4.3 Sample Collection Table

Sample Time Point	Recipient	Sample Type	Shipping Method	Container[1,2]
Baseline/Pre-Treatment	DFCI	Peripheral Blood	Same day delivery to Ghobrial Lab	3x 10mL Purple Top 1x6ml Red Top
		Bone Marrow Aspirate[4]		2x10mL Purple Top[1]
End of Study (6 month visit)	DFCI	Peripheral Blood	Same day delivery to Ghobrial Lab	3x 10mL Purple Top 1x6ml Red Top
		Bone Marrow Aspirate[4]		2x10mL Purple Top

[1] Purple Top= K2EDTA Tube; Red Top= No Additive
[2] Samples at these time points are **voluntary**, and do not exclude patients from treatment
[3] Cell Secure tubes or other tube may be used in place of listed tube types where necessary at the request of the Ghobrial Lab
[4] Bone marrow aspirate/biopsy only collected if being done as part of routine clinical care. These sample collections are highly encouraged, but are **optional**

9.4.4 DNA and RNA sequencing of tumor cells from the bone marrow

The "clonal evolution" model of cancer emerged amid ongoing advances in technology, especially in recent years during which next generation sequencing has provided ever higher resolution pictures of the genetic changes in cancer cells and heterogeneity in tumors where tumor progression proceeds in a branching rather than in a linear manner, leading to substantial clonal diversity and coexistence of wide genetic heterogeneity[49,50]. The genomic complexity in MM was recently corroborated by massive parallel-sequencing studies displaying the lack of a universal driving mutation[35]. Recent studies have shown intraclonal heterogeneity that occurs at different stages of MM[36,37]. Most recently, exome sequencing confirmed that the heterogeneity observed in MM and how it is likely to be an essential feature of clonal evolution and disease progression[51,52]. Although treatment is very effective in MM patients nowadays; however, new resistant clones may arise in certain patients causing disease relapse and resistance to maintenance treatment. Moreover, the recent advances in RNA sequencing technologies, like single cell RNA(ScRNA) sequencing is now enabling us to better understand the composition and state of the tumor microenvironment including immune cells and stromal cells. ScRNA sequencing coupled with bulk RNA sequencing will allow us to accurately identify expression levels of CD38 and other proteins on both tumor and immune cells at different time points, and how this would affect treatment response and disease course.

Circulating cell-free DNA (cfDNA) and tumor cells (CTCs) are considered emerging and promising approaches to capture the genomic landscape and heterogeneity of the tumor cells in bone marrow, but from blood samples. We published a proof of concept study in Nature Communication on how blood biopsies were good surrogates for the mutational profile in bone marrow. We plan to expand on this by studying serial samples from patients throughout treatment as a tool for detecting minimal residual disease and new mutations that can rise during treatment.

We plan to perform exome sequencing and RNA sequencing studies on tumor cells obtained at the time of screening as well as from subsequent bone marrow biopsy samples to examine clonal heterogeneity, resistant clones at best response and at time of end of study or at disease progression.

The tumor research samples will be collected at the time of scheduled bone marrow biopsies. From these samples, high quality DNA and RNA for both exome sequencing and RNA sequencing of tumor cells will be obtained. In brief, BM aspirates will be obtained after informed consent. The tumor cells will be collected using CD138+ bead selection (over 90% purity based on prior publications)[35,36]. For samples that have a small fraction of plasma cells, we will use flow sorting for CD138/CD38/CD56 and CD19-ve to obtain a pure malignant plasma cell population based on prior published markers of malignant plasma cells[55].

WES of tumor and germline DNA

WES will be performed on all samples pre and post-treatment on the clinical trial to study clonal evolution of malignant cells. DNA will be isolated and libraries will be hybridized to Illumina human whole exome capture kit as previously described. All sequencing studies will be performed at the Genomic Platform of the Broad Institute. Samples will be multiplexed and sequenced on Illumina Novaseq to obtain an average depth of coverage of 175x for tumors and 70x for germlines to have enough sensitivity for mutation detection [41].

9.4.3 WGS of tumor and germline DNA

Considering the emerging importance of structural variants like, jumping translocations involving important oncogenes, Chromothripsis, and Chromoplexy in MM, we will use an innovative approach to study translocations in MM by low pass WGS (12x mean coverage). Libraries will be prepared using new HiseqX technology (Illumina®) which offers long range phased (i.e. barcoded) reads which enable much more accurate structural characterization. Libraries will be sequenced on a HiSeq X Ten sequencer available at the Broad Institute. This will be performed on the same samples of WES.

9.4.4 Targeted deep sequencing:

To be able to analyze small sub-clones, we will design a specific hybrid capture targeted panel of baits to detect the main MM drivers by deep sequencing. This panel includes exons of significantly mutated genes in MM as well as those identified in WES of our samples, baits on the main CNA regions (17p, 1q, 13q) and baits on the IGH, IGL, IGK and MYC loci, enabling us to detect somatic mutations, CNAs and translocations. The total size of the bait set is 2Mb. This will be used for samples at the time of best response and in those samples that do not have enough DNA for WES or WGS. Libraries will be prepared using Agilent's SureSelect XT library prep kit and hybridized to a customized targeted bait set. Samples will be multiplexed and sequenced on Illumina Novaseq with the goal of an average depth of coverage of 1500x to have enough sensitivity for mutation detection at low allelic fraction (1%)41.

9.4.5 Computational analysis and expected outcome.

All bioinformatics and statistical analyses will be performed with guidance of the biostatistics and bioinformatics Core B. Briefly, BAM files aligned to the hg19 human genome will be produced using Illumina sequencing reads and the Picard pipeline42. SNVs will be determined using the MuTect2 algorithm43, in single mode for targeted sequencing with additional filters for mutation call such as 1000 genome and COSMIC mutations. Indels and translocations will be determined by the algorithms IndelLocator37 and dRanger, respectively. Focal as well as arm-level copy number variations will be determined based on WES and subsequent application of the GISTIC44 algorithm. We will use MutSigCV45 to detect candidate cancer genes using three signals of positive selection: (i) increased mutation burden as compared to a background model; (ii) clustering of mutations along the gene; and (iii) enrichment of mutations at likely functional sites. The output of MutSigCV consists of a list of the most significantly genomic events across samples. False-discovery rates (q values) ≤ 0.1 will be considered as significantly mutated. All candidate SNVs/indels/CNVs will be reviewed in the IGV46.

9.4.6 RNA sequencing of tumor cells.

For RNA Sequencing, poly-A selection and cDNA synthesis will be performed, followed by library preparation, sequencing (76bp or 101bp paired reads), and sample identification with quality control. Details of experimental design are described in[62,63-65]. We will perform library construction using a non-strand specific Illumina TruSeq Protocol and sequence coverage to 100M total reads. Analysis will be performed as described in the preliminary data and in previous studies[63-65].

The DNA and or RNA library will be prepared at the Ghobrial Lab, and then sequencing will be done at the following external lab:
Broad Institute Genomics Services
320 Charles Street
Cambridge, MA 02141

Sequencing data will then be provided back to Ghobrial lab in the form of BAM file. The samples that are sent for analysis are exhausted during the process, and thus not able to be returned.

9.4.7 Single-cell sequencing of the tumor microenvironment.

Single-cell RNA sequencing (RNA-seq) of the tumor microenvironment can define genotypic and phenotypic states of tumor cells and surrounding microenvironment, and that the microenvironment affected the gene expression program of tumor cells and their resistance to therapy. We will apply 10X genomics in this study to evaluate the tumor microenvironment and assess specific changes in cell type and transcriptional signature of BM niche cells that correlate with tumor progression or resistance to therapy.

9.4.8 cfDNA and circulating tumor cells (CTCs) from the peripheral blood.

cfDNA sequencing can be challenging because of the small fragment size of DNA in the peripheral blood (average of 166bp), the low yield of DNA and the usual low allelic fraction of tumor-derived DNA among the cfDNA. Therefore, we developed two different approaches to sequence cfDNA. The first approach applies WES and is performed by the Blood Biopsy Group at the Broad Institute. After high-speed centrifugation of frozen samples to eliminate residual cells from plasma, cfDNA was extracted using the Qiagen circulating nucleic acid kit. As little as 5ng of cfDNA was then subjected to library preparation using the Kapa HyperPlus kit, which enables us to prepare libraries from small DNA fragments and minimal DNA yield. CfDNA libraries were initially qualified for further sequencing using ultra-low-pass whole genome sequencing (ULP- WGS). The ULP-WGS is a low-cost approach developed by the Blood Biopsy Group to nominate samples containing sufficient tumor fraction in cfDNA samples for WES. Large numbers of cfDNA libraries were multiplexed and sequenced to an average of 0.1X genome-wide sequencing coverage.

9.4.9 Whole-exome sequencing of cfDNA and CTCs:

These studies will be performed at the Blood Biopsy Group at the Broad Institute in collaboration. As described in the preliminary data, cfDNA and CTCs will be subjected to library preparation using the Kapa HyperPlus kit and initially qualified for WES by ULP-WGS. The ULP-WGS will be used to nominate samples containing sufficient fraction of tumor-derived DNA for WES. Qualified matched samples will be hybridized to the Agilent XT v5 enrichment kit, with additional baits on MYC, IGH, IGL and IGK loci. For both cfDNA and CTCs, the coverage goal will be increased to 200x, which enables us to accurately call mutations even with low allelic fraction samples.

All analyses concerning the ULP-WGS will be performed by the bioinformatics team of the Getz Lab and Blood Biopsy Group at the Broad Institute. WES analyses will be performed through the FireCloud, including MuTect[43], IndelLocator[37], dRanger, GISTIC2.0[44] and ABSOLUTE[18] algorithms to evaluate SNVs, Indels, translocations, CNVs and mutated cancer fractions. We will further study the correlation of mutated cancer fractions between matched cfDNA, CTCs and BM tumor cells for each patient to characterize the mutational spectrum in the 3 compartments; thus identify their overlapping landscape as well as their potential specificities. Based on our preliminary data, we expect to identify in cfDNA and CTCs more than 80% of the somatic mutations present in BM.

9.4.10 Metabolomics

Blood and bone marrow supernatant samples will be sent to Metabolon for quantification using the Global Metabolomic Platform, which consists of four independent methods: ultrahigh performance liquid chromatography/tandem mass spectrometry (UHLC-MS/MS) with positive ion mode electrospray ionization, UPLC-MS/MS with negative ion mode electrospray ionization, and UPLC-MS/MS polar platform (negative ionization).[65] LC-MS will be performed on a Waters ACQUITY ultra-performance liquid chromatography (UPLC) and a Thermo Scientific Q-Exactive high resolution/accurate mass spectrometer interfaced with a heated electrospray ionization (HESI-II) source and Orbitrap mass analyzer operated at 35,000 mass resolution. All analytes will undergo quality control and curation processes, which are designed to ensure accurate, consistent

identification, and to minimize system artifacts, mis-assignments, and background noise.[65] Library matches for each compound will be verified for each sample. It is notable that the median intraclass correlations between duplicate samples on Metabolon's platform has been shown to be 0.96 (25th – 75th percentile: 0.82–0.99), and the average coefficient of variation across all named metabolites has been shown to be 0.16 (25th – 75th percentile: 0.06–0.20).[66]

Metabolite features will be analyzed as measures of peak areas, which are proportional to feature concentration and can be compared for any given metabolite. The metabolite variables will be standardized to a mean of 0 and standard deviation of 1.

9.4.11 Longer-Term Benefit

It is notable that the vast majority of interventions investigated in clinical trials have involved aggressive pharmacologic agents. The proposed trial is the first to examine preliminary evidence of efficacy that metformin is a low-risk strategy to prevent progression in this population of higher-risk MGUS and low-risk SMM patients. Although we are powered to detect small but clinically relevant between group differences in M-protein concentrations from baseline to six months, we acknowledge the possibility that a six-month treatment period is too short in some patients to demonstrate a clinical benefit. To maximize the learning opportunity but maintain the rigor of the trial's short-term primary endpoints, we will allow participants to become unblinded after the primary outcome assessments are complete and participants randomized to the metformin arm of the study will be invited to continue to take metformin for an additional six months.

We will descriptively report the number of participants randomized to the metformin arm who wish to continue taking metformin, which will provide an assessment of participant's willingness to take metformin for longer-term risk-reduction. In addition, we will utilize well-established measures of response to therapy using a modified version of the International Myeloma Working Group Response Criteria defined below, as well as mass spectrometry-based estimates of minimal residual disease.

Response	Criteria for Response
Complete Response (CR)	Negative immunofixation on the serum and ≤5% plasma cells in bone marrow (if performed clinically), or normalization of serum free light chain ratio if followed by serum free light chain. Normalization is defined as the serum free light chain ratio being within the normal range. If the serum free light chain ratio is not within the normal range, but the individual kappa and lambda light chain values are within normal range, this may be considered CR.
Very Good Partial Response	Serum M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein.

(VGPR)	
Partial Response (PR)	≥ 50% reduction of serum M-protein. If only measurable parameter is serum immunoglobulins free light chain (FLC), EITHER of the following changes qualify as partial response: - A 50% decrease in the difference between involved and uninvolved FLC levels; OR - A 50% decrease in the level of involved FLC AND a 50% decrease (normalization) in the ratio of involved/uninvolved FLC
Stable Disease (SD)	Not meeting criteria for CR, VGPR, PR or progressive disease.

Progressive Disease (PD)	> 25% increase of serum M-protein (which must also be an absolute increase of ≥ 0.5 g/dL). PD is also measured by an absolute increase in bone marrow plasma cells > 10%. If only measurable parameter is serum immunoglobulins free light (FLC), either of the following qualify as progression: - 50% increase in the difference between involved and uninvolved FLC levels from the lowest response level, which must also be an absolute increase of at least 10 mg/dL; OR - 50% increase in the level of involved FLC AND a 50% increase in the ratio of involved/uninvolved FLC from the lowest response level.

10. STUDY CALENDAR

Registration and randomization should be conducted within 28 days (4 weeks) of baseline assessments. The 3-month safety labs should ideally be performed within 7 days of scheduled day 84 (preferably before). End of study/6- (or 12-) month assessment should ideally be completed within 7 days of last dose of study drug for those who completed 6 (or 12) months of treatment, or for those who were not able to complete 6 months of treatment, within 7 days of the 6 month timepoint or as close as feasible. Assessments must be performed prior to administration of any study agent and only after signing consent unless done as part of standard of care procedure. Each cycle is defined as 28 days.

	Screening/ Baseline	Day 1	Day 7	End of Cycle 1 (Day 28)	Day 48 (Optional)	End of Cycle 3 (Day 84)	End of Cycle 6 (Day 168)	End of Study Visit [10]	Survival Follow Up[11]	EDC Timepoints
Metformin/Placebo[1]		----------Day 1-168----------								Day 1-168
Informed consent	X									N/A
Telephone Drug Adherence /AE Collection[2]			X	X	(X)	X		X		N/A
Questionnaire/Survey[3]	X							X		Baseline and EOT
Demographics	X									Baseline
Serum or Urine Pregnancy Test (if applicable)	X									Baseline
Medical history	X									Baseline
Physical exam[4]	X					(X)		X		Baseline and EOT
Vital signs (BP, respiratory rate, temperature)	X							X		Baseline and EOT
Height	X									Baseline
Weight	X							X		Baseline and EOT
Performance status	X							X		Baseline and EOT
CBC w/diff, plts[5]	X					X		X		Baseline and EOT
Serum chemistry[6]	X					X		X		Baseline and EOT
Serum Free Light Chains (SFLC) Serum Protein Electrophoresis (SPEP), Immunofixation (SIFX), and Quantitative Immunoglobulins	X							X		Baseline and EOT
Research Bone Marrow Aspirate and Core[7]	X							X		If a bone marrow biopsy or aspirate is performed at any time during the study as part of SOC, it should be captured in Inform
Research Blood Collection[8]	X							X		N/A
Adverse Event Collection[9]		From Time of Informed Consent to 30 days from Last Dose of Metformin								Record related AEs in database only

Survival and Event Collection[11]					X	N/A

1 Enough drug will be supplied for 3 cycles at a time. Labs will be reviewed prior to shipment of any medication. Participants may be shipped drug directly to their home following local policy, and will be instructed to return any unused drug, empty bottles, and completed diaries in pre-labeled return packaging to the lead site if they do not present in person to clinic.
2 Study staff will contact the participant on day 7, day 28, and Day 168 (+/-3 days) to document AEs and assess study adherence. Day 48 is optional at the discretion of the clinical team. AEs and adherence will also be assessed at the End of Study Visit. Generally, End of Study assessments will be done in person, and interim assessments will be made by telephone, however exceptions can be made given COVID-19 precautions.
3 Questionnaires may be completed in person, through RedCap, by mail, or other acceptable method.
4 Physical exams may be waived or modified due to COVID precautions or travel restrictions with approval from a study MDbut if done, should include review of critical body systems.
5 Labs will be drawn as part of routine care and may include WBC with differential, Hgb, platelet count and ANC, as determined by the patient's clinical team.
6 Labs will be drawn as part of routine care, and may include sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, glucose, albumin, ALT (SGPT), total protein, AST (SGOT), total bilirubin, magnesium, phosphorus, B2M, and LDH, as determined by the patient's clinical team. The only labs that are required at the 3-month timepoint are AST, ALT, bilirubin, creatinine, and glucose, to ensure patient safety. These select safety labs are also required to determine eligibility.
7 Research bone marrow samples are not required but highly encouraged. If a bone marrow aspirate is performed at any time following consent, please refer to sample collection section 9.4 for biobanking protocols.
8 Research blood sample collection at the time of routine clinical blood draw any time prior to treatment – Please refer to Sample Collection Table in section 9.4
9 Adverse events should be collected up to 30 days after the last dose of study drug. Any event that is thought related to metformin should be followed until resolution or stabilization.
10 End of Study assessments should ideally be done within 7 days of completing 6 months of treatment, or for those that were not able to complete 6 months of treatment, as close to the 6 month timepoint as possible, ideally within 7 days.

11 Survival status and data relating to disease response, treatment and status may be collected for up to 5 years from end of treatment.

CALENDAR FOR EXTENDED TREATMENT (CROSSOVER ARM)

DFCI Protocol #: 21-008

Version Date: 02AUG2022

	Optional Extended Treatment Period (Crossover Arm)	End of Extended Treatment Cycle 3 Safety Assessment 3 (Day 84)	End of Extended Treatment Cycle 6 follow up (Day 168)	EDC Timepoints
Metformin[1]	Day 1		336	Day 168
Telephone Drug Adherence /AE Collection[2]		x		N/A
Physical exam[3]		(X)	x	EOT
Vital signs (BP, respiratory rate, temperature)			x	EOT
Weight			x	EOT
Performance status			x	EOT
CBC w/diff, plts[4]		x	x	EOT
Serum chemistry[5]		x	x	EOT
Serum Free Light Chains (SFLC) Serum Protein Electrophoresis (SPEP), Immunofixation (SIFX), and Quantitative Immunoglobulins			x	EOT
Research Bone Marrow Aspirate and Core[6]			x	If a bone marrow biopsy or aspirate is performed at any time during the study as part of SOC, it should be captured in Inform
Research Blood Collection[7]			x	N/A
Adverse Event Collection[8]				Record related AEs in database only
Survival and Event Collection[9]				N/A

1 Enough drug will be supplied for 3 cycles at a time. Labs will be reviewed prior to shipment of any medication. Participants may be shipped drug directly to their home following local policy, and will be instructed to return any unused drug, empty bottles, and completed diaries in pre-labeled return packaging to the lead site if they do not present in person to clinic.

2 Study staff will contact the participant to document AEs and assess study adherence. AEs and adherence will also be assessed at the End of Study Visit (and 1-year follow up for extended treatment group). Generally, End of Study assessments will be done in person, and interim assessments will be made by telephone, however exceptions can be made given COVID-19 precautions.

3 Physical exams may be waived or modified due to COVID precautions or travel restrictions with approval from a physician investigator but if done, should include review of critical body systems.

4 Labs will be drawn as part of routine care and may include WBC with differential, Hgb, platelet count and ANC, as determined by the patient's clinical team.

5 Labs will be drawn as part of routine care, and may include sodium, potassium, chloride, bicarbonate, BUN, creatinine, calcium, glucose, albumin, ALT (SGPT), total protein, AST (SGOT), total bilirubin, magnesium, phosphorus, B2M, and LDH, as determined by the patient's clinical team. The only labs that are required at the 3-month timepoint are AST, ALT, bilirubin, creatinine, and glucose, to ensure patient safety.

6 Research bone marrow samples are not required but highly encouraged. If a bone marrow aspirate is performed at any time following consent, please refer to sample collection section 9.4 for biobanking protocols.

7 Research blood sample collection at the time of routine clinical blood draw any time prior to treatment – Please refer to Sample Collection Table in section 9.4

8 Adverse events should be collected up to 30 days after the last dose of study drug. Any event that is thought related to metformin should be followed until resolution or stabilization.

9 End of Study assessments should ideally be done within 7 days of completing 6 months of treatment, or for those that were not able to complete 6 months of treatment, as close to the 6 month timepoint as possible, ideally within 7 days.

11. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

11.1 Data Reporting

11.1.1 Method

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

11.1.2 Responsibility for Data Submission

Investigative sites are responsible for submitting data and/or data forms to the Office of Data Quality (ODQ) in accordance with DF/HCC policies.

11.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Board (DSMB) will review and monitor study progress, toxicity, safety and other data from this study. The Board is chaired by a medical oncologist from outside of DF/HCC and its membership composed of internal and external institutional representation. Information that raises any questions about participant safety or protocol performance will be addressed by the Sponsor-Investigator, statistician and study team. Should any major concerns arise, the DSMB will offer recommendations regarding whether or not to suspend the study.

The DSMB will meet twice a year to review accrual, toxicity, response and reporting information. Information to be provided to the DSMB may include: participant accrual; treatment regimen information; all adverse events and serious adverse events reported across all sites by category; summary of any deaths on study; audit results; and a summary provided by the study team. Other information (e.g. scans, laboratory values) will be provided upon request.

12. STATISTICAL METHODS

12.1 Study Design/Endpoints Sample Size and Power

We powered the study to detect clinically meaningful changes in the primary endpoint of M-protein and levels.[67-69] To facilitate precise baseline calculations, we ascertained M-protein level data from a representative clinical sample of MGUS and SMM patients at Dana-Farber. Accordingly, assuming a standard deviation of 0.99 g/dL, a type I error rate of 0.05, 60 participants will provide 80% statistical power to detect a between group difference of 0.73 g/dL, and 90% power to detect a between group difference of 0.84 g/dL which are considered clinically meaningful changes.[69-71] Specifically, a change of 0.73 g/dL indicates that we are

powered to detect > a 10% change in M-protein within the 6-month intervention period. Notably, a 10% change is consistent with the definition of "evolving M-protein" concentrations by Ravi et al and others[68] and evolving M-protein concentrations of this magnitude are associated with a shorter time to progressing than patients with non-evolving disease. It is also notable that although this trial should have a minimal drop-out rate or MM-defining events (and need to initiate standard MM treatment) during the 6-month intervention period.

12.2 Statistical Analysis

The primary hypothesis being tested in this trial is that patients randomized to metformin will experience a significant reduction in M-protein levels compared to patients randomized to the placebo. This parameter has been selected as the primary endpoint because of its known clinical utility in predicting progression to overt MM in MGUS and SMM patients;[67-69] Changes in this endpoint will be evaluated from baseline to follow-up in the two groups using a repeated measures mixed-effects model that accounts for the correlation between baseline and follow-up measures and is generally robust to missing data. The baseline value of the dependent variable (M-protein level) and disease subtype will be included as covariates in the regression models. Group-by-time interaction terms will be included as fixed-effects in the regression model. Model fit will be assessed using standard methods. Primary analysis of this endpoint will utilize stratified testing and intention-to-treat methods, using data from all participants randomized to an intervention group.[72] Secondary/exploratory analyses will evaluate the influence of metformin on M-protein level in a per-protocol analysis.

A study project manager who is not involved in the statistical analysis will request information on treatment allocation from the DFCI Research Pharmacy. The Research Pharmacy is permitted to give the project manager information after the trial is closed to accrual and data collection on primary endpoints have been completed. However, all individuals performing the statistical analysis will remain blind to treatment group (metformin vs. placebo) for the primary outcome analysis.

12.3 Sample Size, Accrual Rate and Study Duration

Our estimated target accrual is 60 participants over 24 months, which requires a monthly accrual of 3-4 participants per month. Our goal for accrual into the study is 4 or more participants per month. Up to an additional 6 months of follow-up will be required on the last participant accrued to observe the participant's response after the 6 months of taking metformin/placebo, for a total study duration of 2.5 years. Estimated accrual targets are provided below:

Accrual Targets

Ethnic Category	Sex/Gender				
	Females		**Males**		**Total**
Hispanic or Latino	1	+	2	=	
Not Hispanic or Latino	30	+	27	=	
Ethnic Category: Total of all subjects	(A1)	+	(B1)	=	(C1)
Racial Category					
American Indian or Alaskan Native	1	+	1	=	
Asian	2	+	1	=	
Black or African American	4	+	4	=	
Native Hawaiian or other Pacific Islander	0	+	1	=	
White	24	+	22	=	
Racial Category: Total of all subjects	(A2)	+	(B2)	=	(C2)

(A1 = A2) (B1 = B2) (C1 = C2)

12.4 Stratification Factors

Randomization will be stratified by disease stage (MGUS vs. SMM) and heavy- vs light-chain status.

12.5 Interim Monitoring Plan

Refer to section 11.2

12.6 Analysis of Primary Endpoints

Refer to section 12.2

12.7 Analysis of Secondary Endpoints

The secondary endpoint of this trial will be changes in a variety of biomarkers detailed in section 1.2. Changes in continuous variable outcomes will be evaluated from baseline to follow-up in the two groups using a repeated measures mixed-effects model that accounts for the correlation between baseline and follow-up measures and is generally robust to missing data. The baseline value of the dependent variable and disease subtype will be included as covariates in the regression models. Group-by-time interaction terms will be included as fixed-effects in the regression model. Model fit will be assessed using standard methods. All primary analyses will utilize stratified testing and intention-to-treat methods.[72]

For changes in gene expression patterns, the precise methods are subject to change pending advancements in technology, but a general overview is provided below:

Paired-ended reads will be aligned against UCSC hg19 human annotation using Tophat 2.0.10; read counts for each gene will be determined using HTSeq 0.5.4. A subset of cells with more than 100,000 total reads across all genes will be selected for further analysis (70-80% of cells). To determine population average gene expression, the read counts observed in each cell will be normalized by the effective library size, determined by edgeR 'calcNormFactors' method. NMF-based consensus clustering will be used to cluster all single-cell RNA profiles. We will use coexpression networks-based gene prioritization tool GRAIL (https://www.broadinstitute.org/mpg/grail/) to select the most promising genes using gene expression signature as seeds. Cufflinks and Cuffdiff will be used to identify differentially expressed genes between the treatment arms.[73]

Metabolite features will be analyzed as measures of peak areas, which are proportional to feature concentration and can be compared for any given metabolite. The metabolite variables will be standardized to a mean of 0 and standard deviation of 1.

For optional treatment extenders, this analysis is exploratory. We will assess the proportion of participants who are willing to take metformin for an additional 6 months. We will also evaluate response, duration of response, and depth of response according to modified IMWG criteria, or by mass spectrometry assessment.

12.8 Reporting and Exclusions

As mentioned in 12.2, all primary analyses will utilize intention-to-treat methods.

12.9 Stopping Rules for Safety

All participants will be evaluable for treatment-related toxicity from the time of therapy initiation to 30 days after the last dose of study treatment. The severe adverse event is defined as grade 4/5 hematologic or non-hematologic AEs that are considered related to study treatment.

We anticipate that the rate of SAE is low in this study population. However, if 2 or more SAEs (as defined above) are observed at any time in the first 20 enrolled, further patient enrollment will be paused.

In addition to the above, the study team will also halt accrual for analysis and safety review at any time if the following Grade 4 or 5 toxicities are observed:

- Grade 4 hematologic adverse event (AEs) thought to be related to the study combination
- Grade 4 non-hematologic AEs thought to be related to the study combination with the exception of Grade 4 diarrhea that rapidly responds to best supportive care.

In addition to the events listed above, the study team will halt accrual for analysis and safety review at any time the following treatment-related deaths are observed:

- Grade 5 hematologic adverse events (AEs) thought to be related to the study drug
- Grade 5 non-hematologic AEs thought to be related to the study drug

13. PUBLICATION PLAN

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

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APPENDIX A PERFORMANCE STATUS CRITERIA

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