Document Coversheet

Study Title:

Phase II Study of Targeting CD28 in Multiple Myeloma with Abatacept (CTLA4-Ig) to Overcome Resistance to Chemotherapy

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1. OBJECTIVES

1.1. Primary Objective

- To determine the therapeutic efficacy (as measured by response rate) of abatacept + ixazomib + dexamethasone in multiple myeloma patients who have relapsed (or who are primary refractory) following treatment with their first proteasome inhibitor-containing regimen (excluding ixazomib), compared to historical controls of ixazomib + dexamethasone.

1.2. Secondary Objectives

- To assess the toxicity profile of abatacept + ixazomib + dexamethasone in multiple myeloma patients who have relapsed (or who are primary refractory) following treatment with their first proteasome inhibitor-containing regimen (excluding ixazomib), compared to historical controls of ixazomib + dexamethasone.
- To assess progression-free and overall survival profile of abatacept + ixazomib + dexamethasone in multiple myeloma patients who have relapsed (or who are primary refractory) following treatment with their first proteasome inhibitor-containing regimen (excluding ixazomib), compared to historical controls of ixazomib + dexamethasone.

Exploratory Objective

- Assess whether myeloma expression of CD28, CD86, serum kynurenine, and/or IL-6 are correlated with specific clinical outcomes.

2. BACKGROUND

2.1. Multiple myeloma and the pro-survival/chemotherapy-resistance effect of CD28 activation

Multiple myeloma (MM) is a malignancy of post-germinal center, Ig class-switched BM-resident plasma cells (PC) that comprises 20% of all hematologic malignancies (second only to non-Hodgkin's lymphoma) and is incurable for most patients. Myeloma cells are highly dependent on interactions with BM stromal niches for their survival (1), and MM is rarely found outside of the BM until very late in the disease course. Furthermore, the anti-myeloma efficacy of the newer chemotherapy agents is thought to be due in part to their disruption of MM-bone marrow stromal cell (BMSC) interactions via unclear mechanisms (2), although immune modulation has been clearly implicated. In defining which specific receptors interact with the stromal niche, we found that CD28 expressed on myeloma cells (which correlates significantly with poor prognosis and disease progression(3-6) transduces a survival signal that confers significant protection against chemotherapy, growth factor deprivation and other stresses (7-9). We have subsequently found that PC-intrinsic CD28 function is also essential for the survival of normal BM-resident long lived plasma cells (LLPC) and maintenance of durable antibody responses (10). Thus it appears CD28 regulates fundamental aspects of normal PC biology that are conserved in MM biology due to their essential role in survival(1).

The discovery that CD28 plays a key pro-survival role in MM/PC points to BMSC expressing the CD28 ligands CD80 and/or CD86 as the cellular partners in the myeloma niche. CD80/CD86^{+} cells are predominantly immune cells, including B cells and myeloid cells (eosinophils (11),

basophils (12), monocyte/macrophages, and most highly expressed on myeloid DC). DC have been best characterized as professional antigen presenting cells involved in T cell activation (13), but also support normal B→PC differentiation via cell-cell contact and production of the Pro-survival cytokines (14-16),(17). Consistent with this role in normal PC biology, we and others have found that myeloid DC (both mature and immature), plasmacytoid DC and monocyte/macrophages are preferentially recruited into murine myeloma tumors as well as the myelomatous regions in patient BM, and *in vitro* can by themselves (i.e. without other BMSC) directly support the survival of MM cells in a cell-contact dependent manner (18-24). Thus the myeloma ME represents a clear case where normal immune cells are functioning as bona fide pro-survival stroma(25). Interestingly, some of the most effective therapies for MM have myelotoxicity as the major side effect.

We have also found that CD28 on MM cells directly modulates the stromal myeloid DC via ligation of CD80/CD86, inducing DC production of IL-6 and the immunosuppressive enzyme indoleamine 2, 3 dioxygenase (IDO) (10, 26). IL-6 is a well-established B-lineage survival cytokine. IDO catabolizes the essential amino acid tryptophan (Trp) into the toxic metabolite kynurenine, depleting Trp from the microenvironment and resulting in effector T cell suppression (27) and regulatory T cell (Treg) generation (28). We have recently defined the CD80/CD86 signal transduction pathways in human DC, finding that both IL-6 and IDO production require activation of a downstream PI3K→Akt→NF-κB pathway that modulates FoxO3a transcriptional activity - and this pathway involves previously unrecognized crosstalk with Notch1 signaling(29). Thus in addition to directly transducing a pro-survival signal to the MM cell, CD28 back-signaling through DC CD80/CD86 creates a stromally-produced soluble microenvironment that supports MM survival and suppresses anti-tumor immunity (26). This is, however, not unique to transformed MM cells, as we have found that normal PC also interact with DC within the BM niche, and this PC-DC interaction also results in both a CD28/CD80-CD86 dependent survival signal to the PC and induction of IL-6/IDO production from the DC ((30) and unpublished data).

In addition to CD28, we (7, 31) and L. Boise, (manuscript under review) and others (32) have found that MM cells also express CD86, this expression is associated with poor prognosis. This is likely due to our finding that CD86 also directly delivers a pro-survival signal to myeloma cells in addition to its cis/trans activation of CD28 expressed on the same and neighboring myeloma cells. We have found that abatacept is also capable of inhibiting the pro-survival effects of CD86 activation.

Treatment of multiple myeloma has been aimed almost entirely at directly killing the multiple myeloma (MM) cells. Although there is a clear understanding in the field about the dependence of MM on the bone marrow microenvironment (ME) for survival, and evidence that certain therapies may also be modulating the ME as part of their efficacy, specifically targeting the ME itself has been largely unexplored. Such an approach has been hampered by the complexity and incomplete molecular/cellular characterization of the MM ME. Our published (1, 7-9) and preliminary data identifies the myeloid dendritic cell (DC) component of the ME, and the molecular interactions between MM and myeloid stroma, as potential therapeutic targets (**Figure 1**).

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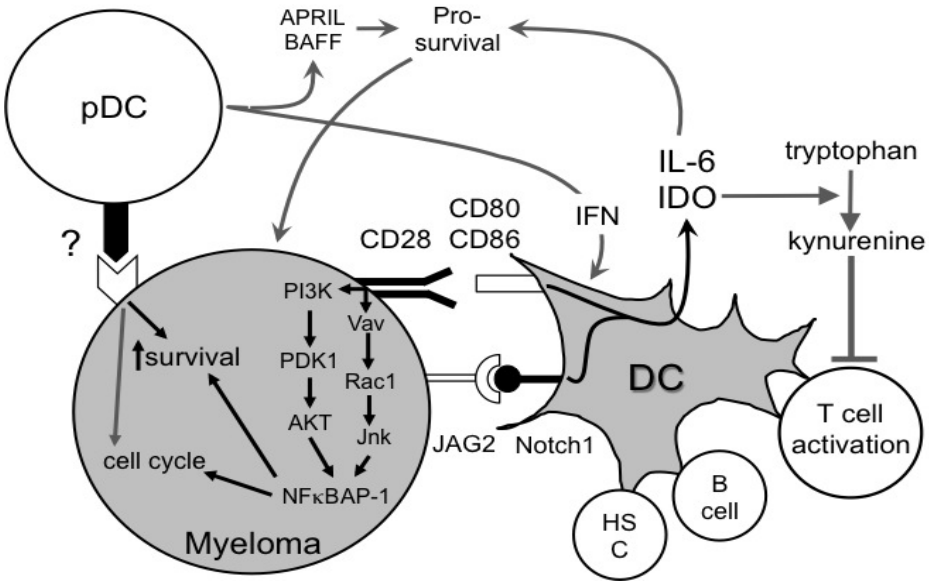

Figure 1: CD28-CD80/CD86-dependent interactions between MM cells and stromal DC induce both MM pro-survival/chemotherapy resistance and DC IDO-mediated immunosuppressive.

We have recently shown that blocking the MM CD28 - CD80/CD86 interaction by treatment with CTLA4-Ig (a soluble chimeric receptor that binds to CD80/CD86) in Vk*MYC mice sensitizes MM cells to chemotherapy *in vivo*(9). CTLA4-Ig has been well characterized as an inhibitor of T cell activation through blocking T cell costimulation through CD28(33), and its efficacy in MM underscores the largely unexplored concept that immunotherapy for immune cell cancers also encompasses immune suppression. Because CTLA4-Ig (abatacept) is a clinically available FDA-approved treatment for rheumatoid arthritis, we very recently were able to treat a patient with highly refractory $CD28^+$ MM with CTLA4-Ig + chemotherapy in an IRB-approved compassionate use setting. The patient had relapsed through 10 different chemotherapy regimens, including: bortezomib (BZ)+dexamethasone (D), BZ+D+lenalidomide (L), BZ+cyclophosphamide (C)+D+thalidomide (T), BZ+liposomal doxorubicin (dox)+T, carfilzomib (CFZ)+L+D, BZ+L+D+cisplatin+dox+C+etoposide, high dose melphalan+autologous stem cell transplantation and BZ+L+D+biaxin (bia) maintenance (within 5 months), CFZ+pomalidomide (pom)+D+bia and Pom+bendamustine (**Figure 2**). He had also developed significant pulmonary and retroperitoneal extramedullary disease with renal compromise (Cr 1.92). Because the patient had exhausted all FDA-approved MM therapies, he was treated with CTLA4-Ig + melphalan + prednisone + bortezomib, with the hope that blocking the MM CD28-CD80/CD86 interaction would re-sensitize the myeloma to chemotherapy.

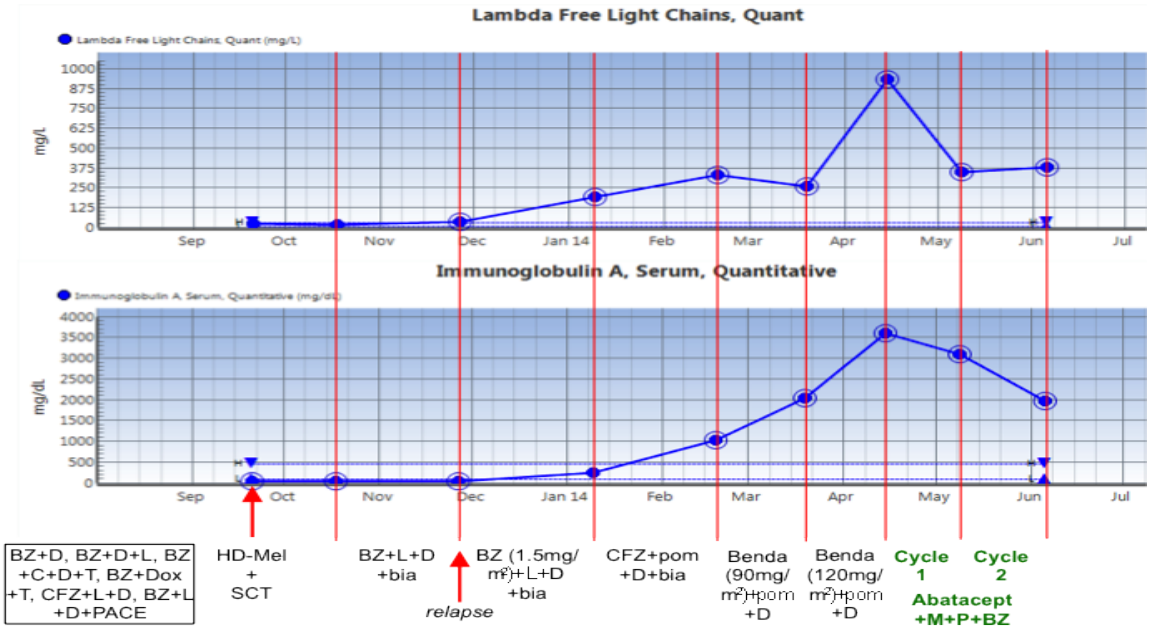

Figure 2: Clinical response to abatacept + chemotherapy in a case of highly refractory MM. The patient's MM disease burden was followed clinically by the serum levels of lambda free light chain and IgA. The different chemotherapy regimens are annotated along the bottom.

As seen in **Figure 2**, after two cycles the patient had a significant reduction in his MM disease markers, normalization of his renal function and significant reduction of his extramedullary disease symptomatically and by CT scan – with no side effects attributable to CTLA4-Ig. Unfortunately, after the 2nd cycle the patient suffered an unrelated surgical complication that prevented continuation of this regimen. With the very large caveat that this is only one patient, these results suggest that specifically targeting MM interaction with the myeloid ME may have clinical efficacy.

Although MM is initially responsive to chemotherapy, it almost invariably relapses with progressively more chemo-resistant disease, and it is this resistant disease that is the primary cause of patient deaths. Our data suggests that CD28 expressed on myeloma cells interacts with CD80/CD86 on stromal DC in the ME or CD86 on the MM cells themselves, and this transduces a major pro-survival signal to the MM cells that is significant component of the chemotherapy resistance in relapsed disease. Our preclinical murine model and single patient results suggest that blocking the MM CD28 – DC CD80/CD86 interaction with abatacept can re-sensitize MM cells to chemotherapy, which would have major clinical impact.

The first-generation proteasome inhibitor (PI) bortezomib is the backbone of chemotherapy treatment of newly diagnosed MM patients, and resistance to BZ is a primary cause of disease relapse. We propose to examine the ability of abatacept to reverse this resistance in a Phase II clinical trial in relapsed MM patients that have progressed after being treated with a proteasome inhibitor -containing regimen (bortezomib, carfilzomib, but not ixazomib), as these patients are likely to have disease that is relatively resistant to the FDA-approved 2nd generation proteasome inhibitor ixazomib. While one standard of care regimen for bortezomib-resistant patients is ixazomib (ixa) + dexamethasone (dex, 40 mg weekly), because of the pre-existing resistance to

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proteasome inhibition this regimen has only modest clinical efficacy (31% overall response rate (34)). We believe that concurrent treatment with abatacept + ixa + dex will overcome this proteasome inhibitor-resistance, resulting in a significantly higher overall response rate.

2.2. Study Drugs

All the study drugs used in the protocol are FDA-approved for the treatment of either multiple myeloma (i.e., ixazomib and dexamethasone) or, rheumatoid arthritis (i.e., abatacept). A detailed discussion of the preclinical pharmacology, pharmacokinetics, and toxicology of each study drug can be found in the Package Inserts (see **Appendix F**).

2.2.1. Abatacept

Abatacept (ORENCIA®) is a soluble fusion protein that consists of the extracellular domain of human cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) linked to the modified Fc (hinge, CH2, and CH3 domains) portion of human immunoglobulin G1 (IgG1). Abatacept is produced by recombinant DNA technology in a mammalian cell expression system.

Abatacept, a selective costimulation modulator, inhibits T cell (T lymphocyte) activation by binding to CD80 and CD86, thereby blocking interaction with CD28. This interaction provides a costimulatory signal necessary for full activation of T lymphocytes implicated in the pathogenesis of RA.

2.2.2. Ixazomib

Ixazomib (NINLARO®) is a reversible proteasome inhibitor and antineoplastic agent. Ixazomib preferentially binds and inhibits the chymotrypsin-like activity of the beta 5 subunit of the 20S proteasome.

Ixazomib citrate, a prodrug, rapidly hydrolyzes under physiological conditions to its biologically active form, ixazomib. *In vitro*, ixazomib induced apoptosis against myeloma cells from patients who had relapsed after multiple prior therapies, including bortezomib, lenalidomide, and dexamethasone.

The NCCN Guidelines Version 3.2017 for Multiple Myeloma (https://www.nccn.org/professionals/physician_gls/PDF/myeloma.pdf) has included the combination of ixazomib plus dexamethasone as a treatment option for patients with relapsed/refractory multiple myeloma who have received at least one prior therapy.

2.2.3. Dexamethasone

Dexamethasone is a synthetic adrenal corticosteroid with potent anti-inflammatory properties. In addition to binding to specific nuclear steroid receptors, dexamethasone also interferes with NF-κB activation and apoptotic pathways. Dexamethasone's anti-myeloma effect is thought to occur via binding to the corticosteroid receptor, which induces apoptosis in B lineage lymphocytes that include plasma cells.

2.3. Rationale

The rationale for the combination of abatacept + ixazomib + dexamethasone is detailed Section 2.1 above. The overall hypothesis of this proposal is that blocking the pro-survival CD28 activation on myeloma cells with abatacept will reverse chemotherapy resistance and re-sensitize multiple

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myeloma cells to agents they were previously resistant to. We will specifically test this hypothesis in multiple myeloma patients who have relapsed following treatment with a bortezomib-containing regimen, with the trial hypothesis being that abatacept co-treatment will reverse pre-existing resistance to proteasome inhibitors and significantly improve response rates to the second-generation proteasome inhibitor, ixazomib.

3. INCLUSION AND EXCLUSION CRITERIA

3.1. Inclusion Criteria

To be included in this study, participants must meet the following criteria:

1. Patients with multiple myeloma who have relapsed (or who are primary refractory) following treatment with a proteasome inhibitor-containing regimen (excluding ixazomib), and who have not been treated with a second proteasome inhibitor (ixazomib, bortezomib, carfilzomib, or other proteasome inhibitor).
2. Age ≥ 18 years of age at time of consent.
3. Have an ECOG Performance Status of ≤ 2 at study entry. Refer to **Appendix A**.
4. Must be free of systemic infection:
    - Subjects with active infections (whether or not they require antibiotic therapy) may be eligible after complete resolution of the infection.
    - Subjects on antibiotic therapy must be off antibiotics for at least 7 days before beginning treatment.
5. Have the following clinical laboratory values:
    - Absolute neutrophil count ≥ 750/mm^3
    - Platelet count ≥ 25,000/mm^3
    - Creatinine clearance ≥ 30 mL/min
    - Total bilirubin: AST (SGOT) and ALT (SGPT) ≤ 3x ULN
6. Patient's multiple myeloma cells are positive for CD28 or CD86 expression by flow cytometry or immunohistochemistry (in any proportion). CD28 or CD86 positivity can have been determined on previous bone marrow aspirates or biopsies.
7. Disease free of prior malignancies for >2 years with exception of currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma "in situ" of the cervix or breast.
8. Participants of child-bearing potential must agree to use adequate contraceptive methods (e.g., hormonal or barrier method of birth control; abstinence) prior to study entry. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.
9. Participant must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.

Refer to **Appendix B** for the ELIGIBILITY VERIFICATION FORM: INCLUSION CRITERIA CHECKLIST.

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3.2. Exclusion Criteria

Participants will be excluded from this study for the following:

1. Prior treatment with ixazomib.
2. Inability to take ixazomib or abatacept.
3. Life expectancy less than 4 months.
4. Patients with a known diagnosis of plasma cell leukemia.
5. Known active tuberculosis or fungal infection.
6. Known seropositive for or active viral infection with, human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV). Patients who are seropositive because of immunization with the hepatitis B virus vaccine are eligible.
7. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
8. Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or, which confounds the ability to interpret data from the study.
9. Pregnant or nursing female participants.
10. Unwilling or unable to follow protocol requirements.
11. Any condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive study drug.
12. Received an investigational agent within 30 days prior to enrollment.

Refer to **Appendix C** for the ELIGIBILITY VERIFICATION FORM: EXCLUSION CRITERIA CHECKLIST.

3.3. Special Populations

The following Special Populations will be excluded:

1. Cognitively impaired adults/adults with impaired decision-making capacity, as there are other standard of care therapies available for these myeloma patients that are known to be effective,
2. Individuals who are not yet adults, as multiple myeloma is extremely uncommon in this population and,
3. Pregnant women, as the effects of the combination of abatacept and ixazomib on the fetus are not known.

Prisoners are not excluded from this trial if they otherwise qualify and wish to voluntarily participate. If a prisoner is enrolled or a patient becomes incarcerated while participating in the study, the Roswell Park IRB will be contacted to allow for review of the study using the prisoner criteria [(refer to: CHECKLIST: Prisoners (HRP-415)].

3.4. Inclusion of Women and Minorities

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

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4. LOCAL AND STUDY-WIDE NUMBER OF SUBJECTS

A maximum of 19 patients at multiple sites, including Roswell Park will be enrolled. Accrual is expected to take up to 4 years.

Patients will participate in this study for approximately 48 months from the time of enrollment.

5. LOCAL AND STUDY-WIDE RECRUITMENT METHODS

Participants will be identified/recruited/screened from patients at the Lymphoma/Myeloma Clinic at Roswell Park and from other participating sites.

6. MULTI-SITE RESEARCH

It is the responsibility of the Principal Investigator to ensure that:

- All sites have the most current version of the protocol, consent document, and HIPAA authorization.
- All required approvals (initial, continuing review and modifications) have been obtained at each site (including approval by the site's IRB of record).
- All modifications have been communicated to sites, and approved (including approval by the site's IRB of record) before the modification is implemented.
- All engaged participating sites will safeguard data, including secure transmission of data, as required by local information security policies.
- All local site investigators will conduct the study in accordance with applicable federal regulations and local laws.

All non-compliance with the study protocol or applicable requirements will be reported in accordance with local policy.

Refer to **Appendix G**: Instructions for Network Sites.

7. STUDY TIMELINES

A maximum of 19 participants at multiple sites, including Roswell Park will be enrolled. Accrual is expected to take 4 years, with safety follow-up at 30 days from the end of investigational treatment. Additional follow-up safety evaluations will occur monthly through 48 months.

8. STUDY ENDPOINTS

8.1. Primary Endpoints

- Response rate will be used to determine the therapeutic efficacy of abatacept + ixazomib + dexamethasone in MM patients who have relapsed (or who are primary refractory) following treatment with their first proteasome inhibitor-containing regimen (excluding prior treatment with ixazomib), compared to historical controls of ixazomib + dexamethasone.

8.2. Secondary Endpoints

- The NCI Common Terminology Criteria for adverse events (CTCAEv5.0) will be used to evaluate toxicity.

- Progression-free survival is defined as the time from the date of the first study treatment to the date of first observed disease progression or death due to any cause. Study participants will be followed every 3 months following end of treatment (until initiation of a new therapy or until death, whichever occurs first) to determine overall survival.

8.3. Exploratory Endpoints

- CD28 and CD86 expression on myeloma cells will be assessed by flow cytometry at the time of trial enrollment and then at disease progression (or off study).
- Blood will be assayed for serum kynurenine and IL-6 levels.

9. DESIGN

This is a Phase II study designed to test the efficacy and safety of combining abatacept with the oral PI ixazomib + dexamethasone in multiple myeloma patients ≥18 years of age who have relapsed (or are primary refractory) following treatment with their first proteasome-inhibitor containing regimen (excluding prior treatment with ixazomib).

10. TREATMENT

10.1. Dosing and Administration

For the purpose of this study, 1 cycle = 28 days.

Treatment will be administered on an outpatient basis. All drugs will be stored, prepared and administered as detailed in their Package Inserts (see **Appendix F**). Study patients will be treated with:

Abatacept: A loading dose of abatacept (30 minute IV infusion) will be administered on Day 1 Cycle 1 (refer to **Table 1**), followed by 125 mg SQ on Day 2 and then 125 mg once weekly during Cycle 1 (i.e., Days 8, 15, 22) thereafter. After Cycle 1, abatacept 125 mg SQ is given on Days 1, 8, 15, 22 for all subsequent cycles.

Table 1 Dose of Abatacept for IV Infusion in Adult Patients

Body Weight of Patient	Dose	Number of Vials[a]
Less than 60 kg	500 mg	2
60 to 100 kg	750 mg	3
More than 100 kg	1000 mg	4

[a] Each vial provides 250 mg of abatacept for administration [taken from Orencia™ (abatacept) package insert: March 2017 revision].

Patients should be monitored for 30 minutes after the completion of the abatacept dose on Days 1 and 2 of Cycle 1 for clinical signs of toxicity. If the patient remains symptom free, no additional post-abatacept infusion monitoring is required. If the patient does develop symptoms, that patient should be monitored for 30 minutes (or longer if called for) after each abatacept administration.

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Instructions for subcutaneous abatacept injection

- Allow prefilled syringe and auto injector to warm to room temperature (for 30 to 60 minutes and 30 minutes, respectively) prior to administration.
- Inject into the front of the thigh (preferred), abdomen (except for 2-inch area around the navel), or the outer area of the upper arms.
- Rotate injection sites (1 inch or more apart): do not administer into tender, bruised, red, or hard skin.

Ixazomib: 4 mg po on Days 1, 8, and 15 of a 28-day cycle.

Dexamethasone: 40 mg po of Days 1, 8, 15, and 22 of a 28-day cycle. At the discretion of the treating physician, the weekly dose of dexamethasone may be split between two days.

Ixazomib and dexamethasone can be taken by the patient at home prior to the abatacept infusion, if the patient desires. Alternatively, the patient can bring their ixazomib and dexamethasone to the clinic and take it there.

Acyclovir: 400 mg po BID will be prescribed by the study physician for varicella prophylaxis, as per NCCN recommendation for all patients receiving proteosome inhibitor-based therapies (35).

Patients will be treated until Stringent CR (see **Section 16.1**), disease progression, death, intolerable side effects or, Investigator judgment.

Reported adverse events (AEs) and potential risks are described in **Section 13**. Appropriate dose modifications are described in **Section 10.3.**

Treatment is intended for an outpatient setting. However, at the investigator's/physician's discretion, the participant may receive treatment as an inpatient, if deemed necessary.

10.2. Safety Lead-in

The first 6 patients who have completed the first cycle of the treatment regimen without experiencing dose limiting toxicity (see Section 10.3) will comprise the safety lead-in group.

Patient data for the safety lead-in portion of the study will be discussed and monitored by The Early Phase Clinical Trials committee, which meets on a regular basis per the Roswell Park Data Safety Monitoring Plan.

After a minimum of 6 patients have completed at least one cycle of the treatment regimen, the study team will meet to examine the safety/tolerability of the combination. If 0 or 1 patient out of the 6 has experienced a drug related toxicity requiring treatment delay or suspension, an additional n_2=13 patients will be enrolled to complete the study. Otherwise, the study will be suspended and the research team will meet to discuss possible safety concerns and will decide what actions to take with respect to study continuation (e.g., changes in treatment regimen/ dose modifications or discontinue the study).

10.3. Definition of Dose Limiting Toxicity and Discontinuation of Therapy

DLTs are AEs that occur within Cycle 1 and meet any of the following criteria:

1. Treatment-emergent Grade 4 or 5 AE related to ixazomib + abatacept + dex treatment (see exceptions listed in #4 below).

2. Treatment-emergent Grade 3 AE related to ixazomib + abatacept + dex (see exceptions listed in # 4 below).
3. Treatment-emergent Grade 3 seizures.

The above AEs are considered to be DLTs if they are judged probably or definitely associated with treatment. Should they occur, individual participants will be taken off study and no further injections will be given. Toxicity will be determined using the revised NCI Common Toxicity Criteria (CTC) version 5.0 for Toxicity and Adverse Event Reporting (http://ctep.info.nih.gov).

4. The following ***will not*** be considered DLTs:

- Non-hematologic AEs
    - Grade 3 fatigue lasting ≤ 7 days
    - Grade 3 or 4 fever or febrile neutropenia for ≤ 2 weeks
    - Grade 3 increase in transaminases for ≤ 2 weeks or Grade 4 increase in transaminases for ≤ 7 days
    - Grade 3 Tumor Lysis Syndrome (TLS) for ≤2weeks
    - Grade 3 or 4 asymptomatic, non-hematological clinical laboratory abnormalities that return to ≤ Grade 2 within 7 days or electrolyte abnormalities that resolve with replacement
    - Grade 3 diarrhea lasting ≤ 72 hours that does not require total parenteral nutrition (TPN), tube feeding, or hospitalization, and the toxicity resolves to less than grade 3 within 72 hours
    - Grade 3 nausea/vomiting lasting ≤ 72 hours that does not require total parenteral nutrition (TPN), tube feeding, or hospitalization, and the toxicity resolves to less than grade 3 within 72 hours
    - Grade 3 peripheral neuropathy
    - Grade 3 hyperglycemia, or Grade 4 that responds to insulin therapy
- Hematologic AEs
    - Grade 3 neutropenia of any duration or Grade 4 neutropenia lasting < 14 days
    - Grade 3 or 4 lymphopenia
    - Grade 3 or 4 leukopenia
    - Grade 3 or 4 thrombocytopenia without bleeding or requiring platelet transfusion
    - Grade 3 or 4 anemia
    - Grade 3 or 4 B-cell aplasia and hypogammaglobulinemia

10.4. Dose Modifications and Treatment Delays

Dose modifications are allowed as recommended by the Package Inserts (see **Appendix F**) of the individual study drugs.

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10.4.1. Abatacept

There is no planned dose modification for abatacept.

10.4.2. Ixazomib

The starting dose of ixazomib is 4 mg administered orally once a week on Days 1, 8, and 15 of a 28-day treatment cycle.

Dose reductions due to adverse reactions are as follows:

Table 2 Ixazomib Dose Reductions

Dose Level	Dose of Ixazomib
Starting dose*	4 mg
First reduction	3 mg
Second reduction	2.3 mg
Discontinue	-

* Reduce the starting dose of ixazomib to 3 mg in patients with moderate (total bilirubin greater than 1.5-3 x ULN) or severe (total bilirubin greater than 3 x ULN) hepatic impairment.

The following dose modification rules will be used with respect to potential toxicity. Dose reescalation with Ixazomib will be allowed at the treating Investigators discretion.

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Table 3 Dose Modification Guidelines for Ixazomib

Hematological Toxicities	Recommended Actions
Thrombocytopenia (Platelet Count)	
Platelet count less than 30,000/mm^3	• Withhold ixazomib until platelet count is at least 30,000/mm^3. • Following recovery, resume ixazomib at the next lower dose.
Neutropenia (Absolute Neutrophil Count)	
Absolute neutrophil count less than 500/mm^3	• Withhold ixazomib until absolute neutrophil count is at least 500/mm^3. Consider adding G-CSF as per clinical guidelines. • Following recovery, resume ixazomib at the next lower dose.
Non-Hematological Toxicities	**Recommended Actions**
Rash	
Grade† 2 or 3	• Withhold ixazomib until rash recovers to Grade 1 or lower. • Following recovery, resume ixazomib at the next lower dose.
Grade 4	• Discontinue treatment regimen.
Peripheral Neuropathy	
Worsening Peripheral Neuropathy over Baseline (Grade 2 with pain or Grade 3)	• Reduce ixazomib to the next lower dose. Reevaluate after 1 cycle, if improved or stable, continue at the reduced dose.
Grade 4 Peripheral Neuropathy	• Discontinue treatment regimen.
Other Non-Hematological Toxicities	
Other Grade 3 or 4 Non-Hematological Toxicities	• Withhold ixazomib. If attributable to ixazomib, resume at the next lower dose following recovery.

†Grading based on National Cancer Institute Common Terminology Criteria (CTCAE) Version 5.0.

10.4.3. Dexamethasone

For dexamethasone-attributable adverse events, the first dose reduction should be to 20 mg/weekly, the second reduction to 12 mg/weekly and the third dose reduction to 8 mg/weekly.

10.5. General Concomitant Medication and Supportive Care

Medications taken in the month prior to registration will be recorded on the baseline case report form; this includes prescription medications, over-the-counter medications, injected medications, biological products, blood products, imported drugs or, illicit drugs.

Participants should be maintained on drugs that they were taking prior to entry unless a change in regimen is medically indicated.

Supportive medications per standard accepted clinical guidelines are allowed.

Participants may be pretreated for nausea and vomiting with appropriate anti-emetics.

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10.6. Duration of Treatment

Participants may remain on study and continue to receive treatment until achievement of a Stringent CR, unacceptable toxicity; intercurrent illness that prevents further administration of treatment or, participant withdraws from study. For patients that achieve Stringent CR, treatment may be continued at the discretion of the treating Investigator.

10.6.1. Stopping Rules for Chronic Toxicity

Upon completion of the DLT assessment period, the same DLT/ AE criteria used during the DLT assessment period (see **Section 10.3**) for determining treatment discontinuation will be followed if a participant develops a treatment-related chronic toxicity.

11. PROCEDURES INVOLVED

All on-study visit procedures are allowed **a window of ± 2 days** unless otherwise noted.

Unless otherwise defined in the written protocol text, all procedures/assessments will be conducted in accordance with Roswell Park Clinical Research Services Standard Operating Procedures.

11.1. Patient Registration

Informed consent ***MUST*** be completed prior to receiving any study related procedures.

Eligibility of each participant will be established prior to enrollment:

- Patient eligibility, insurance verification and the existence of a signed consent form will be checked by the CRS before a patient will be registered for this study.
- Treatment cannot begin prior to registration.
- Pre-treatment tests must be performed within the guidelines specified on the test schedule.
- All baseline symptoms must be documented and graded in the study record

11.2. Baseline Evaluations

The following evaluations will be performed within 28 days prior to first dose of the study regimen unless otherwise specified:

- Complete history with pre-existing conditions (demographic information will also be recorded)
- Documentation of pathological diagnosis (see International Myeloma Working Group (IMWG) Diagnostic Criteria: Appendix D)
- Physical examination with vital signs (i.e., temperature, heart rate, respiratory rate, blood pressure) and weight. Height collected at baseline only.
- Skeletal survey, bone marrow MRI or PET/CT: Baseline evaluation should be completed within 8 weeks prior to first dose, and annually or as per local institutional guidelines
- Bone marrow biopsy/aspirate with flow cytometry for CD28 and CD86, molecular and cytogenetics, per investigator discretion. A fresh sample is not required if CD28 or CD86 positivity has been determined on a previous bone marrow aspirate or biopsy.

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  - An additional 20 mL of aspirate will be collected for isolation of multiple myeloma cells.

- Hematology: CBC with automated differentials
- Chemistry: CMP to include chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap). In addition: phosphorus, magnesium, lactate dehydrogenase (LDH)
- Pregnancy test (serum) in females of childbearing potential: to be performed ≤ 7 days prior to start of study treatment.
- ECOG Performance Status (**Appendix A**)
- Disease Status Evaluation:
  - Blood:
    - Qualitative immunoglobulins:
    - SPEP
    - serum IFE
    - serum free light chain
  - Urine:
    - 24-hour UPEP and UIFE
- Blood draw for serum kynurenine and IL-6 levels
- Concomitant Medications: List any medications taken in the month prior to registration and any that will be discontinued within 1 week prior to first dose of the study regimen.

11.3. Evaluations Performed on Day 1 of each Treatment Cycle

Unless otherwise indicated, the following evaluations will be performed on Day 1 of each treatment cycle (1 cycle=28 days).

- Complete history and physical examination (with vital signs and weight)
- Hematology: CBC with differential.
- Chemistry: CMP to include chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap). In addition: phosphorus, magnesium, lactate dehydrogenase (LDH)
- ECOG Performance Status (**Appendix A**).
- Disease Status Evaluation (***NOTE****: No need for disease status evaluation on Cycle 1-Day 1*)
  - Blood:
    - Qualitative immunoglobulins:
    - SPEP
    - serum IFE
    - serum free light chain

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  - Urine:
    - 24-hour UPEP and UIFE

- Blood draw for serum kynurenine and IL-6 levels *(NOTE: Not needed on Cycle 1-Day 1)*
- Concomitant medications
- Adverse events

11.4. Evaluations performed on Cycle 1 Day 2

- Vital signs
- Adverse events

11.5. Evaluations performed on Cycle 1: Day 8, Day 15, and Day 22

- History and Physical Examination: (including vital signs and weight)
- Hematology: CBC with differential.
- Chemistry: CMP to include chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap). In addition: phosphorus, magnesium, lactate dehydrogenase (LDH)
- ECOG Performance Status
- Adverse events

11.6. Evaluations Performed at End of Treatment

The following evaluations will be performed at the end of treatment or at time of treatment discontinuation:

- Complete history and physical examination (with vital signs and weight)
- Bone marrow biopsy/aspirate with flow cytometry for CD28 and CD86, molecular and cytogenetics will be done at the time of progression or to confirm Stringent CR or CR (Section 16.1).
  - For patients who are progressing, an additional 20 mL of aspirate (heparinized or in green tops) will be collected for isolation of MM cells.
- Hematology: CBC with differential.
- Chemistry: CMP to include chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap). In addition: phosphorus, magnesium, lactate dehydrogenase (LDH).
- ECOG Performance Status (**Appendix A**).
- Blood draw for serum kynurenine and IL-6 levels.
- Concomitant medication: List any ongoing medications with dose changes, as applicable.

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- Adverse events.

11.7. Post-Treatment Follow-Up Evaluations

Follow-up safety evaluations will occur 30 days (± 3 days) after last dose of study drug or until resolution of any drug-related toxicity (telephone contact is acceptable).

- Complete history and physical examination (with vital signs and weight)
- Hematology: CBC with differential.
- Chemistry: CMP to include chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap). In addition: phosphorus, magnesium, lactate dehydrogenase (LDH).
- ECOG Performance Status (**Appendix A**).
- Blood draw for serum kynurenine and IL-6 levels.
- Concomitant medication: List any ongoing medications with dose changes, as applicable.
- Adverse events.

The following assessments are only ***required for patients that achieve a Stringent CR***:

- Disease Status Evaluation:
    - Blood:
        - Qualitative immunoglobulins:
        - SPEP
        - Serum IFE
        - Serum free light chain
    - Urine:
        - 24-hour UPEP and UIFE

Additional follow-up safety evaluations will occur monthly through 48 months. All patients with abatacept-related toxicity will be followed until it resolves to ≤ Grade 1. After 48 months, patients will move to long-term follow-up and will be monitored for survival status (telephone contact or medical record check is acceptable). Patients will be monitored until death or study closure, whichever occurs first.

11.7.1. Survival Status

Patients that discontinue treatment due to progressive disease, toxicity (treatment-related or unrelated) or withdrawal for any other reason will be monitored every 3 months after end of treatment for one year, then annually until death or study closure, whichever occurs first (telephone contact or medical record check is acceptable) to document survival status.

11.8. Long Term Follow-Up Evaluations

Disease-free survival status assessments for patients that achieve a Stringent CR will be performed every 3 months (± 7 days) after the completion of treatment until disease progression or death due to any cause; whichever comes first.

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- Disease Status Evaluation:
    - Blood:
        - Qualitative immunoglobulins:
        - SPEP
        - Serum IFE
        - Serum free light chain
    - Urine:
        - 24-hour UPEP and UIFE

Participants who are unavailable for follow-up evaluations should be classified as lost to follow-up for 1 of the following reasons:

- Lost to follow-up: For a participant to be considered lost to follow-up, the investigator must make two separate attempts to re-establish contact with the participant. The attempts to re-establish participant contact must be documented (e.g., certified letter).
- Death: Date and cause of death will be recorded for those participants who die within 30 days after last dose of study drug (telephone verification is acceptable).

11.9. Schedule of Procedures and Observations

The schedule of procedures and observations for this study is summarized in **Appendix E.**

11.9.1. Blood Sample Collection

Blood samples will be collected via venipuncture for serum kynurenine and IL-6 assays. Samples will be collected using five (5), 3.5 mL gold top SST collection tubes.

Samples for analysis will be obtained on:

- Baseline
- Cycle 2 Day 1 and on Day 1 of every subsequent 28-day cycle
- End of Treatment
- Post-Treatment Follow-Up

Correlative samples will be drawn at the same time as the other scheduled standard of care lab tests. Collection tubes are to be labeled with the participant's MR number, participant's initials, participant's study number, clinical study number, time of collection, and protocol day. Samples will be sent at room temperature to the attention of Laboratory Medicine – Protocol Clinical Research Support (pneumatic Station 19) where they will get accessioned for tracking in the source document. Once sample receipt has been documented, the samples will be sent at ambient temperature to pneumatic Station 86 (located in GBSB S524) to the DBBR lab. The DBBR laboratory will be notified via telephone *and* email (see contact information below) prior to sample shipment and, the samples will be held in CSPO until a response is received acknowledging that personnel are available to procure the samples from the pneumatic tube station. Samples will be processed in DBBR and will be immediately frozen at -80°C or below until analyzed. Additional sample that may remain once the analysis is complete will be stored for future use in DBBR (see Section 15).

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Roswell Park Comprehensive Cancer Center
DBBR Laboratory
GBSB Bldg. 7th Floor, Rm. 726 via Tube station # 86
Attn: Study Number – I 47217
Elm & Carlton Streets
Buffalo, NY 14263
Tel: 716-845-1036
Fax: 716-845-1350
Warren.Davis@roswellpark.org

*Please notify Warren Davis and Nicholas Kisiel (via phone or email calendar invitation). Please include all the relevant information in the calendar invite and the email e.g. Study Name, Protocol #, MRN, Initials, timepoint / collection information. This should be done for all blood sample collections.

EXTERNAL (NETWORK) SITES: Follow directions above for sample collection. Process and aliquot samples to cryovials prior to freezing. Store frozen samples at or below -80°C until the samples are shipped. The cryovials will be labeled with the Subject ID # (unique to Network patients), initials, the participant's study number, clinical study number, protocol time point, dose, and protocol day. Frozen samples will be shipped via Fed Express Overnight on dry ice with delivery on Mon-Fri. NO SATURDAY DELIVERY. All samples should be shipped batched quarterly to the address above with shipping log. Be sure to email CRSNetworkCoordinators@RoswellPark.org and Jens.Hillengass@RoswellPark.org when samples are shipped.

Note: All investigator or analyzing research laboratories housing research samples need to maintain current **Temperature Logs** and study-specific **Sample Tracking and Shipping Logs**. The Principal Investigator/Laboratory Manager **must** ensure that the stated lab(s) have a process in place to document the receipt/processing/storage/shipping of study-related samples/specimens. This is required for both observational and interventional clinical studies collecting clinical samples.

11.9.2. Bone Marrow Biopsy and Aspirate

A bone marrow biopsy and bone marrow aspiration will be taken at Baseline (per Investigator discretion) and at the end of treatment (defined as: time of achievement of CR, disease progression or, off study). Samples will be sent to Flow Cytometry for assessment of CD28 and CD86 expression on the multiple myeloma cells, as well as the standard multiple myeloma Flow Cytometry panel. The biopsy and aspirate will also be sent to Pathology for standard evaluation.

An additional 20 mL of aspirate (2, 10 mL, heparinized, green top tubes) will also be collected at Baseline and at End of Treatment (from patients who progress on therapy).

Collection tubes are to be labeled with the participant's MR number, participant's initials, participant's study number, clinical study number, time of collection, and protocol day. Samples will be sent at room temperature to the attention of Laboratory Medicine – Protocol Clinical Research Support (pneumatic Station 19) where they will get accessioned for tracking in the source document. Once sample receipt has been documented, the samples will be sent at ambient temperature to pneumatic Station 86 (located in GBSB S524), to the DBBR lab. The DBBR laboratory will be notified via telephone *and* email (see contact information above: Section 11.9.1)

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prior to sample shipment and, the samples will be held in CSPO until a response is received acknowledging that personnel are available to procure the samples from the pneumatic tube station

Remaining samples will be frozen at -80°C or below until analyzed. Additional sample that may remain once the analysis is complete will be stored for future use in the DBBR (see Section 15).

Please notify Warren Davis and Nicholas Kisiel (via phone or email calendar invitation) with the contact information given in Section 11.9.1. Please include all the relevant information in the calendar invite and the email e.g. Study Name, Protocol #, MRN, Initials, timepoint / collection information. This should be done for all bone aspirate sample collections.

EXTERNAL (NETWORK) SITES: Network Sites will follow the above outlined process with sample collection and assessment will be conducted either locally or if needed at The Flow Cytometry Department at Roswell Park. For bone marrow samples sent to Roswell Park Flow Cytometry, 5 mL is requested and assuming an adequate white cell count 4 mL is required. Samples must be labeled with the specimen type (e.g. BM = bone marrow), date of collection, Protocol Name, and the Subject number. Samples should be shipped at **ambient temperature** and placed first in a leak-proof container which is subsequently placed into a suitable transport box. Please do not ship samples with cooled ice packs. Also, please include a completed Test Request Form to avoid confusion upon receipt at the laboratory.

Samples and the completed Test Request Form should be shipped to the Laboratory by FedEx using standard next day delivery service. Samples shipped on Friday must be marked on the FedEx manifest "For Saturday Delivery" or the sample will be received on Monday which is too late to process. We suggest that each site contact FedEx directly for any other questions about shipping potentially hazardous materials. Please ship samples to the attention of:

Paul K. Wallace, Ph.D.
Roswell Park Cancer Institute
Department of Flow & Image Cytometry
Elm & Carlton Streets
Buffalo, NY 14263
Tel: (716) 845-3528
Fax: (716) 845-8066

Site should **notify Flow Cytometry** via email (flowlab@roswellpark.org) and rachel.evans@roswellpark.org ahead of time whenever a flow cytometric sample is being sent. Providing the Laboratory with the shipment's tracking number will allow us to work with FedEx to locate the sample if it is not received within 24 hours. We cannot process or reliably analyze samples that are older than 48 hours or have a viability of less than 85%.

Unless prior arrangements are made, samples are routinely accepted **Monday through Saturday (shipped Sunday through Friday)**. Without prior arrangement, samples cannot be processed on a Sunday.

Note: All investigator or analyzing research laboratories housing research samples need to maintain current **Temperature Logs** and study-specific **Sample Tracking and Shipping Logs**. The Principal Investigator/Laboratory Manager **must** ensure that the stated lab(s) have a process in place to document the receipt/processing/storage/shipping of study-related samples/specimens. This is required for both observational and interventional clinical studies collecting clinical samples.

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12. WITHDRAWAL OF SUBJECTS

12.1. Treatment Discontinuation

Upon treatment discontinuation all end of treatment evaluations and tests will be conducted. All participants who discontinue due to an AE must be followed until the event resolves or stabilizes. Appropriate medical care should be provided until signs and symptoms have abated, stabilized, or until abnormal laboratory findings have returned to acceptable or pre-study limits. The final status of the AE will be reported in the participant's medical records and the appropriate eCRF.

Reasons for treatment discontinuation should be classified as follows:

- Death
- Progressive disease
- Toxicity; treatment related or unrelated
- Investigator judgment
    - The Investigator may withdraw a participant if, in his/her judgment, it is in the best interest of the participant to do so.
- Noncompliance
- Participant voluntary withdrawal
    - A participant may withdraw from the study at any time, for any reason. If a participant discontinues treatment, an attempt should be made to obtain information regarding the reason for withdrawal.
- Sponsor decision.

13. RISKS TO SUBJECTS

Although abatacept has been approved by the FDA for the treatment of rheumatoid arthritis, it has not been given to patients with multiple myeloma (other than the single patient described in Section 2.1 and Figure 2). Because abatacept has never been combined with standard chemotherapy before, there is a risk that there may be additional side effects that arise from the combination. What these side effects will be is unknown but may reflect increased side effects from the ixazomib + dexamethasone chemotherapy combination: these include tumor lysis syndrome (TLS), decreased blood counts, increased blood sugar, hypertension, diarrhea, and nerve damage. In addition, since abatacept, ixa, and dex are immunosuppressive, patients may be at additional risk for infection; however, we do not anticipate that the combination of abatacept + ixazomib + dexamethasone to generate unique side effects that are not already reported for the single agents.

13.1. Abatacept

The most commonly reported adverse events (occurring in ≥ 10% of RA patients treated with abatacept) are: headache, upper respiratory tract infection, nasopharyngitis and, nausea.

The most serious adverse reactions of abatacept alone in RA patients include: hypersensitivity reactions (<1% of patients), serious infections and an increased risk for the development of secondary malignancies.

Since abatacept can suppress the immune system, patients may be at additional risk of serious infection from diseases that do not ordinarily cause significant problems in people with normal immune systems. Serious infections were reported in 3.0% of patients treated with abatacept and 1.9% of patients treated with placebo. The most common (0.2%-0.5%) serious infections reported with abatacept were pneumonia, cellulitis, urinary tract infection, bronchitis, diverticulitis, and acute pyelonephritis. Additional side effects presented in the package insert are listed as follows [from Table 3, ORENCIA (abatacept) Package Insert (see **Appendix F**): Revised March 2017]:

Adverse Events Occurring in 3% or More of Patients and at Least 1% More Frequently in Abatacept-Treated Patients During Placebo-Controlled RA Studies		
Adverse Event	**Abatacept (n=1955)[a] Percentage**	**Placebo (n=989)[b] Percentage**
Headache	18	13
Nasopharyngitis	12	9
Dizziness	9	7
Cough	8	7
Back pain	7	6
Hypertension	7	4
Dyspepsia	6	4
Urinary tract infection	6	5
Rash	4	3
Pain in extremity	3	2

[a] Includes 204 patients on concomitant biologic DMARDs (adalimumab, anakinra, etanercept, or infliximab).

[b] Includes 134 patients on concomitant biologic DMARDs (adalimumab, anakinra, etanercept, or infliximab).

13.2. Ixazomib

The most frequently reported adverse events (≥ 20%) are: diarrhea, constipation, thrombocytopenia and neutropenia, peripheral neuropathy, nausea and vomiting, peripheral edema, back pain, rash and, upper respiratory tract infection.

Serious adverse reactions reported in ≥ 2% of patients include thrombocytopenia (2%) and diarrhea (2%).

Commonly reported adverse reactions (1% to 10%) are: blurred vision (6%), conjunctivitis (6%), xerophthalmia (5%), hepatic insufficiency (6%), and infection (herpes zoster, 4%).

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Drug-induced livery injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic and hepatotoxicity were reported rarely in clinical trials. Frequent monitoring of hepatic enzymes during treatment is recommended.

13.3. Dexamethasone

Common toxicities described for dexamethasone include:

Cardiovascular: Hypertension, edema, pulmonary edema, syncope, tachycardia, thromboembolism.

Dermatologic: Ecchymosis and petechiae impaired wound healing, thin fragile skin, thinning scalp hair.

Endocrine: Decreased carbohydrate and glucose tolerance, development of cushingoid state, hyperglycemia, glycosuria, hirsutism, hypertrichosis, increased requirements for insulin or oral hypoglycemic agents in diabetes, manifestations of latent diabetes mellitus, menstrual irregularities, secondary adrenocortical and pituitary unresponsiveness (particularly in times of stress, as in trauma, surgery, or illness.

Fluid and Electrolyte Disturbances: Fluid retention, hypokalemic alkalosis, potassium loss, sodium retention.

Gastrointestinal: Elevation in serum liver enzyme levels (usually reversible upon discontinuation), hepatomegaly, increased appetite, nausea, pancreatitis, peptic ulcer with possible perforation and hemorrhage, perforation of the small and large intestine (particularly in patients with inflammatory bowel disease), ulcerative esophagitis.

Metabolic: Negative nitrogen balance due to protein catabolism.

Musculoskeletal: Aseptic necrosis of femoral and humeral heads, loss of muscle mass, muscle weakness, osteoporosis, and pathologic fracture of long bones, steroid myopathy, tendon rupture, and vertebral compression fractures.

Neurological/Psychiatric: Depression, emotional instability, euphoria, headache, increased intracranial pressure with papilledema (pseudotumor cerebri) usually following discontinuation of treatment, insomnia, mood swings, neuritis, neuropathy, paresthesia, personality changes, psychic disorders, vertigo.

Ophthalmic: Exophthalmos, glaucoma, increased intraocular pressure, posterior subcapsular cataracts.

Other: Abnormal fat deposits, decreased resistance to infection, hiccups, malaise, moon face, weight gain.

14. POTENTIAL BENEFITS TO SUBJECTS

Laboratory studies, animal models of multiple myeloma and, the single patient detailed in Section 2.1 suggest that abatacept may be effective in reversing the resistance to chemotherapy, which is the major cause of treatment failure in patients. This could significantly enhance the therapeutic efficacy of the whole portfolio of agents currently used in the treatment of multiple myeloma. However, since abatacept is not an FDA approved drug for multiple myeloma, its effectiveness in humans is unknown.

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Patients will be advised verbally and in a written consent form that this is a study of abatacept + ixazomib + dexamethasone, of which the type and likelihood of side effects are not known. Patients will be advised that the drugs used in this study may cause all, some, or none of the side effects listed in the consent and in the Package Inserts for the individual drugs. There may be other side effects of the drugs that we do not know about yet. They will be told that the side effects could be mild, moderate, or severe and that these side-effects could go away shortly after the treatment stops or, that they could be serious, long lasting, or may be permanent. They will be advised to notify their doctor right away about any side effects or problems that they experience while on this study and that this may decrease the chance that the side effects continue or become worse. If severe side effects develop, it may lead to their being taken off-study.

15. DATA AND SPECIMEN BANKING

All samples for correlative analysis (blood and bone marrow aspirate) will be sent to DBBR for processing. All samples will be processed and stored in the DBBR laboratory (GBSB Bldg. 7th Floor, Rm. 726). Samples will be used for planned study assays as well as for future analysis for other, yet to be identified biomarkers that may be related to clinical outcome. Any clinical data that is associated with the samples will be stored on a secured server in the Immunology Department, will be accessible only by the PI, Co-investigators, and PI-designated data manager and, will be password protected. All computer entry and networking programs will be done using PIDs only.

Any excess samples that remain following completion of the planned study correlates will continue to be stored in DBBR. A separate IRB approval will be obtained prior to any future research-related use of these banked samples.

Note: All investigator or analyzing research laboratories housing research samples need to maintain current Temperature Logs and study-specific Sample Tracking and Shipping Logs. The Principal Investigator/Laboratory Manager must ensure that the stated lab(s) have a process in place to document the receipt/processing/storage/shipping of study-related samples/specimens. This is required for both observational and interventional clinical studies collecting clinical samples.

16. MEASUREMENT OF EFFECT

Disease response will be assessed for each group using criteria based on the **International Working Group Uniform Response Criteria** detailed in **Section 16.1**. If the only measurable parameter is serum immunoglobulins free light chain (FLC), the participant will be followed by **FreeLite™ Disease Response Criteria** provided in **Section 16.2**. **Measurable Disease Parameter** is provided in **Section 16.3**.

All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive disease or new bone lesions if radiographic studies were performed. Radioactive studies are not required to satisfy these response requirements.

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16.1. International Working Group Uniform Response Criteria

- **Stringent Complete Response (Stringent CR):** CR as defined below plus normal free light chain ratio and absence of clonal cells in bone marrow* by immunohistochemistry or immunofluorescence**

  *Confirmation with repeat bone marrow biopsy is not needed

  **Presence/absence of clonal cells is based upon the κ/λ. ratio. An abnormal κ/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is κ/λ of > 4:1 or < 1:2.

- **Complete Response (CR):** Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and ≤5% plasma cells in bone marrow*

  *Confirmation with repeat bone marrow biopsy is not needed.

- **Very Good Partial Response (VGPR):** Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level <100 mg per 24 hours.

- **Partial Response (PR):** ≥ 50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥ 90% or to < 200 mg per 24 hours.
  - If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved free light chain levels is required in place of the M-protein criteria.
  - If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30%.
  - In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required.

- **Stable Disease (SD):** Not meeting criteria for CR, VGPR, PR or progressive disease. This is not recommended as an indicator of response; stability of disease is best described by providing the time to progression estimates.

- **Progressive Disease (PD):** Increase of ≥ 25% of serum M-protein (which must also be an absolute increase of ≥ 0.5 g/dL) and/or urine M-protein (which must also be an absolute increase of ≥ 200 mg/24hr).
  - If serum and urine M-protein are unmeasurable, there must be an absolute increase of ≥ 100 mg/L between involved and uninvolved FLC levels. PD is also measured by an absolute increase in bone marrow plasma cells ≥ 10%.
  - In addition to the above listed criteria, progression may also be measured by a definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas or, development of hypercalcemia (corrected serum calcium ≥ 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder.

16.2. FreeLite™ Disease Response Criteria

- **Complete Response:** For those patients being followed by serum free light chain (and NO measurable serum or urine M-spike), which were immunofixation negative, normalization of serum free light chain ratio.
    - 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.
- **Partial Response:** 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 (or normalization) in the ratio of involved/uninvolved FLC.
- **Progressive Disease:** 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.

16.3. Measurable Disease Parameter

Measurable disease is disease that can be measured either by serum or urinary evaluation of the monoclonal component or by serum assay of FLC and is defined by at least one of the following three measurements:

- Serum M-protein ≥ 0.5 g/dl
- Urine M-protein ≥ 200 mg/24 h
- Serum FLC assay: Involved FLC level ≥ 10 mg/dl (≥ 100 mg/1) provided serum FLC ratio is abnormal

17. SAFETY EVALUATION

17.1. Adverse Events

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

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The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

- **Related**: There is a reasonable causal relationship between study drug administration and the AE.
- **Not related**: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject: in order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.

17.1.1. Diagnosis Versus Signs and Symptoms

If known, a diagnosis should be recorded on the CRF rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated transaminases). However, if a constellation of signs and/or symptoms cannot be clinically characterized as a single diagnosis or syndrome at the time of reporting, each individual event should be recorded as an AE or SAE on the CRF. If a diagnosis is subsequently established, it should be reported as follow-up information.

17.1.2. Adverse Events Occurring Secondary to Other Events

In general, AEs occurring secondary to other events (e.g., cascade events or clinical sequelae) should be identified by their primary cause. For example, if severe diarrhea is known to have resulted in dehydration, it is sufficient to record only diarrhea as an AE or SAE on the CRF.

However, clinically significant AEs occurring secondary to an initiating event that are separated in time should be recorded as independent events on the CRF. For example, if a severe gastrointestinal hemorrhage leads to renal failure, both events should be recorded separately on the CRF.

17.1.3. Abnormal Laboratory Values

Only clinically significant laboratory abnormalities that require active management will be recorded as AEs or SAEs on the CRF (e.g., abnormalities that require study drug dose modification, discontinuation of study treatment, more frequent follow-up assessments, further diagnostic investigation, etc.).

If the clinically significant laboratory abnormality is a sign of a disease or syndrome (e.g., alkaline phosphatase and bilirubin 5 x the upper limit of normal associated with cholecystitis), only the diagnosis (e.g., cholecystitis) needs to be recorded on the Adverse Event CRF.

If the clinically significant laboratory abnormality is not a sign of a disease or syndrome, the abnormality itself should be recorded as an AE or SAE on the CRF. If the laboratory abnormality can be characterized by a precise clinical term, the clinical term should be recorded as the AE or SAE. For example, an elevated blood potassium level of 7 mEq/L should be recorded as “hyperkalemia”.

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Observations of the same clinically significant laboratory abnormality from visit to visit should not be repeatedly recorded as AEs or SAEs on the CRF, unless their severity, seriousness, or etiology changes.

17.1.4. Preexisting Medical Conditions (Baseline Conditions)

A preexisting medical condition should be recorded as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When recording such events on an Adverse Event CRF, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

17.2. Non-serious Adverse Event Reporting

- Non-serious Adverse Events (AE) are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [e.g., IND US trial] as part of an annual reporting requirement.
- Non-serious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

A ***non-serious adverse event*** is an AE not classified as serious.

17.3. Grading and Reporting Adverse Events

17.3.1. Grading and Relationship to Drug

The descriptions and grading scales found in the CTEP Version 4 of the NCI Common Terminology Criteria for Adverse Events (CTCAE) will be utilized for AE reporting. CTEP Version 5.0 of the CTCAE is identified and located at:

http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

AEs not covered by specific terminology listed should be reported with common medical terminology, and documented according to the grading scales provided in the CTCAE Version 5.0. The relationship of event to study drug will be documented by the Investigator as follows:

- **Unrelated:** The event is clearly related to other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs administered to the participant.
- **Unlikely:** The event is doubtfully related to investigational agent(s). The event was most likely related to other factors such as the participant's clinical state, other therapeutic interventions, or concomitant drugs.
- **Possible:** The event follows a reasonable temporal sequence from the time of drug administration, but could have been produced by other factors such as the participant's clinical state, other therapeutic interventions or concomitant drugs.
- **Probable:** The event follows a reasonable temporal sequence from the time of drug administration, and follows a known response pattern to the study drug. The event cannot be reasonably explained by other factors such as the participant's clinical state, therapeutic interventions or concomitant drugs.

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- **Definite:** The event follows a reasonable temporal sequence from the time of drug administration, follows a known response pattern to the study drug, cannot be reasonably explained by other factors such as the participant's condition, therapeutic interventions or concomitant drugs; AND occurs immediately following study drug administration, improves upon stopping the drug, or reappears on re-exposure.

17.3.2. Reporting Adverse Events:

Guidelines for Routine Adverse Event Reporting for Phase 2 Studies (Regardless of Expectedness)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4
Unrelated			X	X
Unlikely			X	X
Possible	X	X	X	X
Probable	X	X	X	X
Definite	X	X	X	X

Routine AEs occurring between the start date of intervention until 30 days after the last intervention, or until the event has resolved, the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible, will be reported. New information will be reported after it is received.

17.3.3. Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin at initiation of study drug. All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 30 days following the last dose of study treatment.

Non-serious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for non-serious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

17.4. Serious Adverse Events

A serious adverse event (SAE) is any adverse event (experience) that in the opinion of either the investigator or sponsor results in **ANY** of the following:

- Death.
- A life-threatening adverse event (experience). Any AE that places a participant or participants, in the view of the Investigator or sponsor, at immediate risk of death from the reaction as it occurred. It does NOT include an AE that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization (for > 24 hours). See **NOTE** below.

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- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly or birth defect.
- Important Medical Event (IME) that, based upon medical judgment, may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.
- Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, potential drug-induced liver injury (DILI), and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (e.g., death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

NOTE: (PI determines if this information regarding hospitalizations is considered SAEs and should be included in the protocol. This is supplemental information that is included in BMS-sponsored trials)

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases.
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

17.4.1. Protocol-Specific Serious Adverse Events

17.4.2. Potential Drug Induced Liver Injury (DILI)

For protocols without known abnormalities in liver function at baseline, use the mandatory standard DILI definition listed below:Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

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Potential drug induced liver injury is defined as:

1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)

AND

2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)

AND

3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

17.4.3. Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for participant).

The investigator must immediately notify Worldwide.Safety@bms.com of this event via the Pregnancy Surveillance Form in accordance with SAE reporting procedures.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form (provided upon request from BMS).

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

17.4.4. Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

17.4.5. Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, X-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a non-serious or serious AE, as appropriate, and reported accordingly.

17.4.6. Reporting Serious Adverse Events

All new SAEs occurring from the date the participant signs the study consent until 30 days after the last intervention or a new treatment is started, whichever comes first, will be reported. The Roswell Park SAE Source Form is to be completed with all available information, including a brief narrative describing the SAE and any other relevant information.

SAEs occurring after the 30 day follow-up period that the investigator determines to be possibly, probably or definitely related to the study intervention should be reported.

SAEs that are unexpected and possibly, probably or definitely related must be reported as an Unanticipated Problem. Please refer to Section 17.6 for details on reporting Unanticipated Problems.

17.5. Investigator Reporting: Notifying Bristol-Myers Squibb

All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 30 days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g., a follow-up skin biopsy).

Follow-up safety evaluations will occur 30 days (± 3 days) after last dose of study drug or until resolution of any drug-related toxicity. Assessment may be collected via telephone if the patient elects to come off study and is no longer coming to clinic.

- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these aforementioned time periods, which is believed to be related to study drug or protocol-specified procedure.
- An SAE report should be completed for any event where doubt exists regarding its seriousness.
- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

Investigators MUST report within 1 business day upon becoming aware, to the sponsor ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention.

The investigator must inform Bristol-Myer Squibb (using MedWatch Form 3500A) of any SAE within 24 hours of being aware of the event. The MedWatch Form 3500A can be accessed at: http://www.accessdata.fda.gov/scripts/medwatch/ (the website will instruct you where to send the SAE forms).The BMS protocol ID number must be included on whatever form is submitted by the Sponsor/Investigator.

The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values

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received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required.

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

The BMS tracking number (IM101-692) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to BMS. A copy of the fax transmission confirmation of the SAE report to BMS should be attached to the SAE and retained with the patient records.

For studies with long-term follow-up periods in which safety data are being reported, include the timing of SAE collection.

The Sponsor will reconcile the clinical database SAE cases (case level only) transmitted to BMS Global Pharmacovigilance Worldwide.Safety@bms. Frequency of reconciliation should be every 3 months and prior to the database lock or final data summary. BMS GPV&E will email, upon request from the Investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS.

Completed SAE reports are to be submitted to:

Bristol-Myers Squibb
SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: +1 609-818-3804

17.5.1. Suspected/ Unexpected Serious Adverse Reaction

In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). An event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of a SUSAR Report.

- Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (e.g., animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.
- Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

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- In addition to the Sponsor Investigator's responsibility to report events to their local HA, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

17.6. Follow-Up for Serious Adverse Events

All related SAEs should be followed to their resolution, until the study participant is lost to follow-up, the start of a new treatment, or until the study investigator assesses the event(s) as stable or irreversible. New information will be reported when it is received.

17.7. Unanticipated Problems

An Unanticipated Problem (UP) is any incident, experience, or outcome that meets all of the following criteria:

- Unexpected (in terms of nature, severity, or frequency) given:
  - The research procedures that are described in the study-related documents, including study deviations, as well as issues related to compromise of participant privacy or confidentiality of data.
  - The characteristics of the participant population being studied.
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research).
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized and if in relation to an AE is also deemed Serious per Section 17.3.

17.7.1. Reporting Unanticipated Problems:

The Reportable New Information (RNI) Form will be submitted to the CRS Quality Assurance (QA) Office within 1 business day of becoming aware of the Unanticipated Problem. After review, CRS QA Office will submit the RNI to the IRB.

When becoming aware of new information about an Unanticipated Problem, submit the updated information to CRS QA Office with an updated Reportable New Information Form. The site Investigator or designated research personnel will report all unanticipated problems, whether related or unrelated to the investigational agent(s) to the IRB in accordance with their local institutional guidelines.

17.8. FDA Reporting

When Roswell Park is the IND holder the following describes the FDA reporting requirements by timeline for AEs and new safety findings that meet the criteria outlined below:

Within 7 Calendar Days

Any adverse event that meets **ALL** the following criteria:

- Related or possibly related to the use of the study drug;

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- Unexpected; and
- Fatal or life-threatening

Within 15 Calendar Days

Any adverse event that meets **ALL** the following criteria:

- Related or possibly related to the use of the study drug;
- Unexpected; and
- Serious but not fatal or life-threatening,

Or, meets **ANY** of the following criteria:

- A previous adverse event that is not initially deemed reportable but is later found to fit the criteria for reporting (report within 15 days from when event was deemed reportable).
- Any findings from other studies, including epidemiological studies, pooled analysis of multiple studies, or other clinical studies conducted with the study drug that suggest a significant risk in humans exposed to the drug.
- Any findings from animal or in vitro testing that suggest a significant risk for human participants including reports of mutagenicity, teratogenicity, or carcinogenicity or reports of significant organ toxicity at or near the expected human exposure.
- Any clinically important increase in the rate of occurrence of a serious, related or possibly related adverse event over that listed in the protocol or investigator brochure.

Sponsors are also required to identify in IND safety reports, all previous reports concerning similar adverse events and to analyze the significance of the current event in the light of the previous reports.

Reporting Process

The principal investigator or designee will complete and submit a FDA Form 3500A MedWatch for any event that meets the above criteria. Forms will be submitted to the CRS QA Office via email to CRSQA@RoswellPark.org.

18. DATA MANAGEMENT AND CONFIDENTIALITY

18.1. Data Collection

Full build studies are managed by Roswell Park CRS Data Management for analysis by Roswell Park Biostatisticians. All electronic case report form (eCRF) data are captured for these studies.

Data management activities are performed using a CTMS system that enables the collection, cleaning and viewing of clinical trial data. CRS data management designs the study-specific database and facilitates development by the Information Technology team. Once the database design is approved by the Investigator, Statistician, and Clinical Research Coordinator, the database is put into production and data entry can begin. Data can be entered and changed only by those with the rights to do so into the eCRFs.

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18.2. Maintenance of Study Documents

Essential documents will be retained per Roswell Park's policy for 6 years from the study termination date. These documents could be retained for a longer period, however, if required by the applicable local regulatory requirements or by an agreement with Roswell Park.

18.3. Revisions to the Protocol

Roswell Park may make such changes to the protocol as it deems necessary for safety reasons or as may be required by the U.S. FDA or other regulatory agencies. Revisions will be submitted to the IRB/ERC for written approval before implementation.

18.4. Termination of the Study

It is agreed that, for reasonable cause, either the Roswell Park Investigators or the Sponsor, may terminate this study, provided a written notice is submitted within the time period provided for in the Clinical Trial Agreement. In addition, Roswell Park may terminate the study at any time upon immediate notice if it believes termination is necessary for the safety of participants enrolled in the study.

18.5. Confidentiality

All information provided to the Investigator by Roswell Park including preclinical data, protocols, CRFs, and verbal and written information, will be kept strictly confidential and confined to the clinical personnel involved in conducting this study, and no disclosure shall be made except in accordance with any right of publication granted to the Investigator. This information may be related in confidence to the IRB/ERC or other committee functioning in a similar capacity. No report or information about the study will be provided to anyone not involved in the study without consent of Roswell Park except if required by law.

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only. Information will not be released without written authorization of the participant.

19. STATISTICAL PLAN

This is a single-arm, open-label, Phase II study of abatacept + ixazomib + dexamethasone in relapsed, multiple myeloma patients.

Summary statistics for continuous variables will include the mean, standard deviation, percentiles and range (minimum/maximum). Categorical variables will be presented as frequencies and relative frequencies; and time-to-event variables will be summarized using Kaplan-Meier methods.

The analyses will be conducted using the intent-to-treat principle, where all patients who receive or attempt to receive treatment are included. All analyses will be conducted in SAS v9.4 (Cary, NC) at a significance level of 0.1.

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19.1. Sample Size Determination

The sample size determination is based on the primary analysis of response rate. Prior studies have demonstrated a second-line treatment response rate of approximately 30% in this patient population (34), and we would consider a response rate for the proposed treatment combination (abatacept + ixazomib + dexamethasone) of 50-60% to be a clinically relevant improvement. Therefore, we will test the following hypotheses:

$H_0: \pi = 0.3$
$H_A: \pi > 0.3$,

where π is the true response rate, using a one-sided Binomial exact test. If the true response rate for the proposed treatment combination is 60%, then our study design (n=19) as a 90% chance of achieving statistical significance at$\alpha = 0.1$.

19.2. Demographics and Baseline Characteristics

Descriptive statistics (as appropriate: n, percent, mean, median, min and max) will be used to summarize demographic and baseline characteristics.

19.3. Safety Cohort

A safety lead-in cohort of n_1=6 patients will be enrolled and, after each patient completes at least 1 cycle of the treatment regimen, the study will be suspended and evaluated for the safety/tolerability of the regimen. If 0 or 1 patient out of 6 has experienced a drug related toxicity requiring treatment delay or suspension, then an additional n_2=13 patients are enrolled to complete the study. Otherwise, the study will be suspended and the research team will meet to discuss possible safety concerns and will decide what actions to take with respect to study continuation.

DLTs are AEs that occur within Cycle 1 and meet any of the following criteria:

1. Treatment-emergent Grade 4 or 5 AE related to ixazomib + abatacept + dex treatment (see exceptions listed in #4 below).

2. Treatment-emergent Grade 3 AE related to ixazomib + abatacept + dex (see exceptions listed in # 4 below).

3. Treatment-emergent Grade 3 seizures.

4. The following will not be considered DLTs:

    - Non-hematologic AEs
        - Grade 3 fatigue lasting ≤ 7 days.
        - Grade 3 or 4 fever or febrile neutropenia for ≤ 2 weeks.
        - Grade 3 increase in transaminases for ≤ 2 weeks or Grade 4 increase in transaminases for ≤ 7 days.
        - Grade 3 Tumor Lysis Syndrome (TLS) for ≤2weeks.
        - Grade 3 or 4 asymptomatic, non-hematological clinical laboratory abnormalities that return to ≤ Grade 2 within 7 days or electrolyte abnormalities that resolve with replacement.
        - Grade 3 diarrhea lasting ≤ 72 hours that does not require total parenteral nutrition (TPN), tube feeding, or hospitalization, and the toxicity resolves to

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less than grade 3 within 72 hours.
- Grade 3 nausea/vomiting lasting ≤ 72 hours that does not require total parenteral nutrition (TPN), tube feeding, or hospitalization, and the toxicity resolves to less than grade 3 within 72 hours.
- Grade 3 peripheral neuropathy.
- Grade 3 hyperglycemia or Grade 4 that responds to insulin therapy.

- Hematologic AEs
  - Grade 3 neutropenia of any duration or Grade 4 neutropenia lasting < 14 days.
  - Grade 3 or 4 lymphopenia.
  - Grade 3 or 4 leukopenia.
  - Grade 3 or 4 thrombocytopenia without bleeding or requiring platelet transfusion.
  - Grade 3 or 4 anemia.
  - Grade 3 or 4 B-cell aplasia and hypogammaglobulinemia.

19.4. Primary Analyses

The primary objective is to determine the therapeutic efficacy (as measured by response rate) of abatacept + ixazomib + dexamethasone in multiple myeloma patients who have relapsed after treatment with their first proteasome inhibitor-containing regimen (excluding ixazomib) and have not been treated with a second proteasome inhibitor.

Previous studies have demonstrated a response rate of approximately 30% for ixazomib + dexamethasone as second line therapy in this patient population (34). We hypothesize that the proposed treatment combination (abatacept + ixazomib + dexamethasone) will improve the second-line response rate in this patient population. Therefore, we will test the following hypotheses:

$$H_0: \pi = 0.3$$
$$H_A: \pi > 0.3 \text{ ,}$$

where π is the true response rate, using a one-sided Binomial exact test. A total of n=19 patients will be enrolled and if T=9 or more patients have a response, then the treatment combination will be considered promising; otherwise the treatment combination is not promising. Additionally, the response rate will be summarized using a 90% confidence interval obtained using Jeffrey's prior method.

***Replacement*:** Patients that withdraw from the study prior to completing the first cycle of treatment due to toxicity, disease progression, or other treatment related reasons will be considered as 'non-responders' and included in the primary analysis.

Patients that withdraw from the study prior to completing the first cycle of treatment due to non-treatment related reasons will be considered 'unevaluable' for the primary outcome and will be replaced.

***Efficacy Analysis*:** Responses to treatment will be measured by serum immunoglobulins, serum free kappa and lambda light chains, serum protein electrophoresis/immunofixation electrophoresis, and 24-hour urine protein electrophoresis/immunofixation. International uniform response criteria will be used. The anti-myeloma activity will be evaluated on an exploratory basis

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and will be summarized using descriptive statistics or graphical methods. No formal comparison will be carried forth

19.5. Secondary Analyses

The secondary objectives include: 1) assessment of the abatacept + ixazomib + dexamethasone toxicity profile; 2) assessment of progression-free and overall survival.

The adverse events and drug related toxicities will be summarized by grade using frequencies and relative frequencies. The rate of grade 3 or higher toxicities that are probably or definitely related to abatacept will be reported with 90% confidence intervals obtained using Jeffrey's prior method.

Progression-free and overall survival will be summarized using standard Kaplan-Meier methods; where estimates of median survival and survival rates will be obtained with 90% confidence intervals

***Safety Analysis*:** The NCI Common Terminology Criteria for adverse events (CTCAEv5.0) will be used to evaluate toxicity. We will consider a toxicity to be an adverse event that is possibly, probably or definitely related to treatment. The maximum grade of toxicity for each category of interest will be recorded for each patient and the summary results will be tabulated by category and grade. Regimen limiting toxicities (RLT) include any Grade 3 or greater toxicity probably or definitely related to abatacept. The rate of grade 3 or higher toxicities that are probably or definitely related to abatacept will be reported with 90% confidence intervals obtained using Jeffrey's prior method.

19.6. Exploratory Analyses

Exploratory analyses will determine whether myeloma expression of CD28, CD86 serum kynurenine, IL-6 levels influences the clinical outcomes.

The CD28, CD86 expression, serum kynurenine and IL-6 levels will be summarized in the overall sample and by response status using the mean, standard deviation, and percentiles. The association between CD28, CD86, serum kynurenine and IL-6 expression/levels and response will be evaluated using logistic regression models; while the association with the survival outcomes will be evaluated using Cox regression models. Odds and hazard ratios, with corresponding 90% confidence intervals, will be obtained from model estimates.

19.7. Interim Analysis and Criteria for Early Termination of the Study

No explicit interim analyses are planned for this study.

19.8. Monitoring of Chronic Toxicities

Upon completion of the DLT assessment period, patients will be monitored for chronic toxicities utilizing the same DLT/ AE criteria used during the DLT assessment period (see **Section 10.3**).

This monitoring will be done continuously using Bayesian methods. If the posterior probability is 0.80 or greater that 25% or more of treated subjects experience a chronic toxicity, the study will be suspended pending review. This posterior probability will be calculated from the study's accumulating data and a weakly informative prior distribution. If π denotes a random variable representing the proportion of subjects who will experience a chronic toxicity, we assume π has a beta distribution with parameters a = 1 and b = 2.

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Selected values of the posterior distribution PP($\pi \geq .25$ | chronic toxicities and prior) are shown in the table below. Also shown are the binomial probabilities of suspending the study for observed count of chronic toxicities. Note that the study-suspension rules using the Bayesian analysis do not correspond to traditional values of statistical significance, such as 0.05 or 0.10, because our purpose is not to demonstrate unexpected harm, but rather to ensure subject safety.

Number of Subjects Observed to Have Treatment-Related Chronic Toxicities and Corresponding Posterior and Binomial Probabilities Needed to Suspend the Study

Subjects	Treatment-Related Chronic Toxicities	PP($\pi > 25\%$)*	Pr($X \geq r \mid p = .25$)
2	2	.949	.063
3	2	.896	.156
4	2	.831	.262
5	3	.929	.104
6	3	.886	.169
7	3	.834	.244
8	4	.921	.114
9	4	.885	.166
10	4	.842	.224
11	5	.920	.115
12	5	.888	.158
13	5	.852	.206
14	5	.810	.258
15	6	.893	.148
16	6	.861	.190
17	6	.825	.235
18	7	.898	.139
19	7	.870	.175

*π is the chronic toxicity rate. The minimum acceptable upper bound of treatment-related chronic toxicities is 25%. PP($\pi > 25\%$) is the posterior probability that the chronic toxicity rate exceeds this 25% upper bound. This posterior probability of a chronic toxicity is calculated from the prior distribution, the number of subjects treated and the observed number of treatment-related chronic toxicities.

The table above presents the minimum number of subjects experiencing treatment-related chronic toxicities that would dictate suspension of the trial in accordance with the stopping rule.
If a study is suspended for safety concerns, the research team will meet to discuss study termination or possible adjustments to the treatment combination.

20. PROVISIONS TO MONITOR THE DATA TO ENSURE THE SAFETY OF SUBJECTS

The Roswell Park Data Safety Monitoring Committee will assess the progress of the study, the safety data, and critical efficacy endpoints (Phase I studies will be reviewed quarterly; Phase II, III and pilot investigator-initiated studies will be reviewed semi-annually). The DSMC will review the study and will make recommendations that include but not limited to; (a) continuation of the study, (b) modifications to the design, (c) suspension of or (d) termination of the study.

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21. VULNERABLE POPULATIONS

- Not Applicable

22. COMMUNITY-BASED PARTICIPATORY RESEARCH

Delete the following if not applicable

- Describe involvement of the community in the design and conduct of the research.
- Note: "Community-based Participatory Research" is a collaborative approach to research that equitably involves all partners in the research process and recognizes the unique strengths that each brings. Community-based Participatory Research begins with a research topic of importance to the community, has the aim of combining knowledge with action and achieving social change to improve health outcomes and eliminate health disparities.

OR

- Not Applicable

23. SHARING OF RESULTS WITH SUBJECTS

Individual response data is shared with the participant as a part of their clinical care.

24. SETTING

All treatment will be conducted on an outpatient basis at Roswell Park's Lymphoma/Myeloma Clinic within the Roswell Park Comprehensive Cancer Center. Potential study participants will be identified and recruited from current clinic patients and from community referral.

25. PROVISIONS TO PROTECT THE PRIVACY INTERESTS OF SUBJECTS

Any data, specimens, forms, reports, video recordings, and other records that leave the site will be identified only by a participant identification number (Participant ID, PID) to maintain confidentiality. All records will be kept in a limited access environment. All computer entry and networking programs will be done using PIDs only. Information will not be released without written authorization of the participant.

26. RESOURCES AVAILABLE

- Not Applicable

27. PRIOR APPROVALS

- Not Applicable

28. COMPENSATION FOR RESEARCH-RELATED INJURY

If the subject believes they have been injured as a direct result of their participation in this research study, they will be advised to notify the Roswell Park Patient Advocate at (716) 845-1365 or the Study Doctor at (716) 845-8515.

Medical diagnosis and treatment for the injury will be offered, and a determination will be made regarding appropriate billing for the diagnosis and treatment of the injury. A financial counselor

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(716-845-3161) will be able to provide an explanation of coverage and to answer questions the subject may have regarding study related billing.

The subject is not prevented from seeking to collect compensation for injury related to malpractice, fault, or blame on the part of those involved in the research.

29. ECONOMIC BURDEN TO SUBJECTS

The participants will not be subject to any economic burden.

30. CONSENT PROCESS

The Roswell Park SOP: Informed Consent Process for Research (HRP-090) will be followed.

This study will not be initiated until the protocol and informed consent document(s) have been reviewed and approved by a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC). Each participant (or legal guardian) shall read, understand, and sign an instrument of informed consent prior to performance of any study-specific procedure. It is the responsibility of the investigator to ensure that the participant is made aware of the investigational nature of the treatment and that informed consent is given.

The Investigator is responsible for the retention of the participant log and participant records; although personal information may be reviewed by authorized persons, that information will be treated as strictly confidential and will not be made publicly available. The investigator is also responsible for obtaining participant authorization to access medical records and other applicable study specific information according to Health Insurance Portability and Accountability Act regulations (where applicable).

This study will be conducted in compliance with all applicable laws and regulations of the state and/or country and institution where the participant is treated. The clinical trial should be conducted in accordance with the ethical principles embodied in the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, consistent with good clinical practice and the applicable regulatory requirements and according to the guidelines in this protocol, including attached appendices.

31. PROCESS TO DOCUMENT CONSENT IN WRITING

The Roswell Park "SOP: Written Documentation of Consent (HRP-091)" will be followed.

The Investigator (or IRB specified designee) is responsible for obtaining written consent from each participant in accordance with GCP guidelines using the approved informed consent form, before any study specific procedures (including screening procedures) are performed. The informed consent form acknowledges all information that must be given to the participant according to applicable GCP guidelines, including the purpose and nature of the study, the expected efficacy and possible side effects of the treatment(s), and specifying that refusal to participate will not influence further options for therapy. Any additional information that is applicable to the study must also be included. Additional national or institutionally mandated requirements for informed consent must also be adhered to. The participant should also be made aware that by signing the consent form, processing of sensitive clinical trial data and transfer to other countries for further processing is allowed.

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The Investigator shall provide a copy of the signed consent form to the participant and the signed original shall be maintained in the Investigator File. A copy of the signed consent form must be filed in the participant file. At any stage, the participant may withdraw from the study and such a decision will not affect any further treatment options.

32. DRUGS OR DEVICES

All the drugs being used in this study have been approved by the FDA for the treatment of multiple myeloma (ixazomib, dexamethasone) or rheumatoid arthritis (abatacept). The storage, reconstitution, dosing, route of administration and management of side effects/dose reduction will be done as detailed in each of the agents respective Package Insert (see **Appendix F**).

Abatacept (ORENCIA®) is being used off-label. Roswell Park will request a Letter of Authorization from Bristol-Myers Squibb to cross reference their IND.

32.1. Abatacept

32.1.1. Active Substance and Source

Abatacept lyophilized powder for intravenous infusion is supplied as a sterile, white, preservative-free, lyophilized powder for intravenous administration. Following reconstitution of the lyophilized powder with 10 mL of sterile water for injection, USP, the solution of abatacept is clear, colorless to pale yellow, with a pH range of 7.2 to 7.8. Each single-use vial of abatacept provides 250 mg abatacept, maltose (500 mg), monobasic sodium phosphate (17.2 mg), and sodium chloride (14.6 mg) for administration.

Abatacept solution for subcutaneous administration is supplied as a sterile, preservative-free, clear, colorless-to-pale-yellow solution with a pH of 6.8 to 7.4. Each single dose of subcutaneous injection provides 125 mg abatacept, dibasic sodium phosphate anhydrous (0.838 mg), monobasic sodium phosphate monohydrate (0.286 mg), poloxamer 188 (mg), sucrose (170 mg), and quantity sufficient to 1 mL with water for injection.

32.1.2. Drug Shipment

Commercial abatacept (ORENCIA®) will be provided by Bristol-Myers Squibb and shipped to Roswell Park Investigational Drug Service and to other participating sites.

The date of receipt and the amount of drug received will be documented. Drug shipment records will be retained by the investigational pharmacist or designee.

32.1.3. Storage and Stability

The Investigator or designate will be responsible for ensuring that the investigational product is securely maintained in a locked, limited-access facility, as specified by Bristol-Myers Squibb and in accordance with the applicable regulatory requirements.

Vials should be refrigerated at 2°C to 8°C (36°F to 46°F) – do not allow to freeze. Do not use solution beyond the expiration date. Protect from light by storing in the original package until time of use. Please refer to package insert (**Appendix F**) for additional details.

Drug storage temperature will be maintained and recorded, as applicable.

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32.2. Ixazomib

Ixazomib is commercially available and will be dispensed per standard of care. Ixazomib will not be provided by this study and will be paid for by the patient's insurance carrier as part of the standard of care treatment.

32.3. Dexamethasone

Dexamethasone is commercially available and will be dispensed per standard of care. Dexamethasone will not be provided by this study and will be paid for by the patient's insurance carrier as part of the standard of care treatment.

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33. REFERENCES

1. Boise LH, Kaufman JL, Bahlis NJ, Lonial S, Lee KP. The Tao of myeloma. Blood. 2014. Epub 2014/08/07. doi: 10.1182/blood-2014-05-578732. PubMed PMID: 25097176.

2. Anderson KC. Lenalidomide and thalidomide: mechanisms of action--similarities and differences. Semin Hematol. 2005;42(4 Suppl 4):S3-8. Epub 2005/12/14. doi: S0037-1963(05)00203-9 [pii]
10.1053/j.seminhematol.2005.10.001. PubMed PMID: 16344099.

3. Robillard N, Jego G, Pellat-Deceunynck C, Pineau D, Puthier D, Mellerin MP, Barille S, Rapp MJ, Harousseau JL, Amiot M, Bataille R. CD28, a marker associated with tumoral expansion in multiple myeloma. Clin Cancer Res. 1998;4(6):1521-6. PubMed PMID: 9626472.

4. Almeida J, Orfao A, Ocqueteau M, Mateo G, Corral M, Caballero MD, Blade J, Moro MJ, Hernandez J, San Miguel JF. High-sensitive immunophenotyping and DNA ploidy studies for the investigation of minimal residual disease in multiple myeloma. British journal of haematology. 1999;107(1):121-31. PubMed PMID: 10520032.

5. Mateo G, Castellanos M, Rasillo A, Gutierrez NC, Montalban MA, Martin ML, Hernandez JM, Lopez-Berges MC, Montejano L, Blade J, Mateos MV, Sureda A, de la Rubia J, Diaz-Mediavilla J, Pandiella A, Lahuerta JJ, Orfao A, San Miguel JF. Genetic abnormalities and patterns of antigenic expression in multiple myeloma. Clin Cancer Res. 2005;11(10):3661-7. PubMed PMID: 15897562.

6. Johnsen HE, Bogsted M, Klausen TW, Gimsing P, Schmitz A, Kjaersgaard E, Damgaard T, Voss P, Knudsen LM, Mylin AK, Nielsen JL, Bjorkstrand B, Gruber A, Lenhoff S, Remes K, Dahl IM, Fogd K, Dybkaer K. Multiparametric flow cytometry profiling of neoplastic plasma cells in multiple myeloma. Cytometry B Clin Cytom. 2010;78(5):338-47. Epub 2010/06/10. doi: 10.1002/cyto.b.20523. PubMed PMID: 20533391.

7. Bahlis NJ, King AM, Kolonias D, Carlson LM, Liu HY, Hussein MA, Terebelo HR, Byrne GE, Jr., Levine BL, Boise LH, Lee KP. CD28-mediated regulation of multiple myeloma cell proliferation and survival. Blood. 2007;109(11):5002-10.

8. Nair JR, Carlson LM, Koorella C, Rozanski CH, Byrne GE, Bergsagel PL, Shaughnessy JP, Jr., Boise LH, Chanan-Khan A, Lee KP. CD28 expressed on malignant plasma cells induces a prosurvival and immunosuppressive microenvironment. JImmunol. 2011;187(3):1243-53. doi: jimmunol.1100016 [pii];10.4049/jimmunol.1100016 [doi].

9. Murray ME, Gavile CM, Nair JR, Koorella C, Carlson LM, Buac D, Utley A, Chesi M, Bergsagel PL, Boise LH, Lee KP. CD28-mediated pro-survival signaling induces chemotherapeutic resistance in multiple myeloma2014;123(24):3770-9. PubMed PMID: 24782505.

10. Rozanski CH, Arens R, Carlson LM, Nair J, Boise LH, Chanan-Khan AA, Schoenberger SP, Lee KP. Sustained antibody responses depend on CD28 function in bone marrow-resident

plasma cells. J Exp Med. 2011;208(7):1435-46. Epub 2011/06/22. doi: 10.1084/jem.20110040. PubMed PMID: 21690252; PMCID: 3135367.

11. Celestin J, Rotschke O, Falk K, Ramesh N, Jabara H, Strominger J, Geha RS. IL-3 induces B7.2 (CD86) expression and costimulatory activity in human eosinophils. J Immunol. 2001;167(11):6097-104. Epub 2001/11/21. PubMed PMID: 11714768.

12. Yoshimoto T, Yasuda K, Tanaka H, Nakahira M, Imai Y, Fujimori Y, Nakanishi K. Basophils contribute to T(H)2-IgE responses in vivo via IL-4 production and presentation of peptide-MHC class II complexes to CD4+ T cells. Nat Immunol. 2009;10(7):706-12. Epub 2009/05/26. doi: 10.1038/ni.1737. PubMed PMID: 19465908.

13. Steinman RM. Dendritic cells: understanding immunogenicity. European journal of immunology. 2007;37 Suppl 1:S53-60. Epub 2007/11/01. doi: 10.1002/eji.200737400. PubMed PMID: 17972346.

14. Fayette J, Durand I, Bridon JM, Arpin C, Dubois B, Caux C, Liu YJ, Banchereau J, Briere F. Dendritic cells enhance the differentiation of naive B cells into plasma cells in vitro. Scandinavian journal of immunology. 1998;48(6):563-70. Epub 1999/01/05. PubMed PMID: 9874489.

15. Dubois B, Barthelemy C, Durand I, Liu YJ, Caux C, Briere F. Toward a role of dendritic cells in the germinal center reaction: triggering of B cell proliferation and isotype switching. J Immunol. 1999;162(6):3428-36. PubMed PMID: 10092798.

16. Litinskiy MB, Nardelli B, Hilbert DM, He B, Schaffer A, Casali P, Cerutti A. DCs induce CD40-independent immunoglobulin class switching through BLyS and APRIL. Nat Immunol. 2002;3(9):822-9. Epub 2002/08/03. doi: 10.1038/ni829
ni829 [pii]. PubMed PMID: 12154359.

17. Mohr E, Serre K, Manz RA, Cunningham AF, Khan M, Hardie DL, Bird R, MacLennan IC. Dendritic cells and monocyte/macrophages that create the IL-6/APRIL-rich lymph node microenvironments where plasmablasts mature. J Immunol. 2009;182(4):2113-23. Epub 2009/02/10. doi: 182/4/2113 [pii]
10.4049/jimmunol.0802771. PubMed PMID: 19201864.

18. Corthay A, Skovseth DK, Lundin KU, Rosjo E, Omholt H, Hofgaard PO, Haraldsen G, Bogen B. Primary antitumor immune response mediated by CD4+ T cells. Immunity. 2005;22(3):371-83. PubMed PMID: 15780993.

19. Bahlis NJ, King AM, Kolonias D, Carlson LM, Liu HY, Hussein MA, Terebelo HR, Byrne GE, Jr., Levine BL, Boise LH, Lee KP. CD28-mediated regulation of multiple myeloma cell proliferation and survival. Blood. 2007;109(11):5002-10. Epub 2007/02/22. doi: blood-2006-03-012542 [pii]
10.1182/blood-2006-03-012542. PubMed PMID: 17311991; PMCID: 1885531.

20. Rettig MB, Ma HJ, Vescio RA, Pold M, Schiller G, Belson D, Savage A, Nishikubo C, Wu C, Fraser J, Said JW, Berenson JR. Kaposi's sarcoma-associated herpesvirus infection of

bone marrow dendritic cells from multiple myeloma patients. Science. 1997;276(5320):1851-4. Epub 1997/06/20. PubMed PMID: 9188529.

21. Said JW, Rettig MR, Heppner K, Vescio RA, Schiller G, Ma HJ, Belson D, Savage A, Shintaku IP, Koeffler HP, Asou H, Pinkus G, Pinkus J, Schrage M, Green E, Berenson JR. Localization of Kaposi's sarcoma-associated herpesvirus in bone marrow biopsy samples from patients with multiple myeloma. Blood. 1997;90(11):4278-82. Epub 1997/12/31. PubMed PMID: 9373238.

22. Dembic Z, Schenck K, Bogen B. Dendritic cells purified from myeloma are primed with tumor-specific antigen (idiotype) and activate CD4+ T cells. Proc Natl Acad Sci U S A. 2000;97(6):2697-702. Epub 2000/03/08. doi: 10.1073/pnas.050579897 050579897 [pii]. PubMed PMID: 10706628; PMCID: 15992.

23. Zheng Y, Cai Z, Wang S, Zhang X, Qian J, Hong S, Li H, Wang M, Yang J, Yi Q. Macrophages are an abundant component of myeloma microenvironment and protect myeloma cells from chemotherapy drug-induced apoptosis. Blood. 2009;114(17):3625-8. Epub 2009/08/28. doi: blood-2009-05-220285 [pii] 10.1182/blood-2009-05-220285. PubMed PMID: 19710503; PMCID: 2766678.

24. Chauhan D, Singh AV, Brahmandam M, Carrasco R, Bandi M, Hideshima T, Bianchi G, Podar K, Tai YT, Mitsiades C, Raje N, Jaye DL, Kumar SK, Richardson P, Munshi N, Anderson KC. Functional interaction of plasmacytoid dendritic cells with multiple myeloma cells: a therapeutic target. Cancer cell. 2009;16(4):309-23. Epub 2009/10/06. doi: S1535-6108(09)00292-X [pii] 10.1016/j.ccr.2009.08.019. PubMed PMID: 19800576.

25. Noonan K, Borrello I. The immune microenvironment of myeloma. Cancer microenvironment : official journal of the International Cancer Microenvironment Society. 2011;4(3):313-23. Epub 2011/08/26. doi: 10.1007/s12307-011-0086-3. PubMed PMID: 21866321; PMCID: Pmc3234331.

26. Nair JR, Carlson LM, Koorella C, Rozanski CH, Byrne GE, Bergsagel PL, Shaughnessy JP, Jr., Boise LH, Chanan-Khan A, Lee KP. CD28 expressed on malignant plasma cells induces a prosurvival and immunosuppressive microenvironment. J Immunol. 2011;187(3):1243-53. Epub 2011/07/01. doi: 10.4049/jimmunol.1100016. PubMed PMID: 21715687; PMCID: 3152989.

27. Grohmann U, Orabona C, Fallarino F, Vacca C, Calcinaro F, Falorni A, Candeloro P, Belladonna ML, Bianchi R, Fioretti MC, Puccetti P. CTLA-4-Ig regulates tryptophan catabolism in vivo. Nat Immunol. 2002;3(11):1097-101. Epub 2002/10/09. doi: 10.1038/ni846 ni846 [pii]. PubMed PMID: 12368911.

28. Chung DJ, Rossi M, Romano E, Ghith J, Yuan J, Munn DH, Young JW. Indoleamine 2,3-dioxygenase-expressing mature human monocyte-derived dendritic cells expand potent autologous regulatory T cells. Blood. 2009;114(3):555-63. Epub 2009/05/26. doi: blood-2008-11-191197 [pii] 10.1182/blood-2008-11-191197. PubMed PMID: 19465693; PMCID: 2713474.

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29. Koorella C, Nair JR, Murray ME, Carlson LM, Watkins SK, Lee KP. Novel regulation of CD80/CD86-induced phosphatidylinositol 3-kinase signaling by NOTCH1 protein in interleukin-6 and indoleamine 2,3-dioxygenase production by dendritic cells. The Journal of biological chemistry. 2014;289(11):7747-62. Epub 2014/01/15. doi: 10.1074/jbc.M113.519686. PubMed PMID: 24415757; PMCID: Pmc3953285.

30. Rozanski CH, Arens R, Carlson LM, Nair J, Boise LH, Chanan-Khan AA, Schoenberger SP, Lee KP. Sustained antibody responses depend on CD28 function in bone marrow-resident plasma cells. JExpMed. 2011;208(7):1435-46. doi: jem.20110040 [pii];10.1084/jem.20110040 [doi].

31. Murray ME, Gavile CM, Nair JR, Koorella C, Carlson LM, Buac D, Utley A, Chesi M, Bergsagel PL, Boise LH, Lee KP. CD28-mediated pro-survival signaling induces chemotherapeutic resistance in multiple myeloma. Blood. 2014;123(24):3770-9. doi: 10.1182/blood-2013-10-530964. PubMed PMID: 24782505; PMCID: PMC4055924.

32. Pope B, Brown RD, Gibson J, Yuen E, Joshua D. B7-2-positive myeloma: incidence, clinical characteristics, prognostic significance, and implications for tumor immunotherapy. Blood. 2000;96(4):1274-9. PubMed PMID: 10942368.

33. Linsley PS, Brady W, Urnes M, Grosmaire LS, Damle NK, Ledbetter JA. CTLA-4 is a second receptor for the B cell activation antigen B7. J Exp Med. 1991;174(3):561-9. PubMed PMID: 1714933.

34. Kumar SK, LaPlant BR, Reeder CB, Roy V, Halvorson AE, Buadi F, Gertz MA, Bergsagel PL, Dispenzieri A, Thompson MA, Crawley J, Kapoor P, Mikhael J, Stewart K, Hayman SR, Hwa YL, Gonsalves W, Witzig TE, Ailawadhi S, Dingli D, Go RS, Lin Y, Rivera CE, Rajkumar SV, Lacy MQ. Randomized phase 2 trial of ixazomib and dexamethasone in relapsed multiple myeloma not refractory to bortezomib. Blood. 2016;128(20):2415-22. Epub 2016/10/21. doi: 10.1182/blood-2016-05-717769. PubMed PMID: 27702799; PMCID: Pmc5114487.

35. Network NCC. NCCN Guidelines Version 3.2017: Multiple Myeloma [September 6, 2017]. Available from: https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf.

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34. APPENDICES/SUPPLEMENTS

Appendix A ECOG Performance Status Scores

Description	Status
Fully active, able to carry on all pre-disease performance without restriction.	0
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.	1
Ambulatory and capable of all self-care but unable to carry out any work activities.	2
Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	3
Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	4
Dead	5

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Appendix B ELIGIBILITY VERIFICATION FORM INCLUSION CRITERIA

Participant Name: (Multi-site: use participant initials): _____

Medical Record No.: (Multi-site: use participant ID): _____

Title: Phase II Study of Targeting CD28 in Multiple Myeloma with Abatacept (CTLA4-Ig) to Overcome Resistance to Chemotherapy

INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Patients with multiple myeloma who have relapsed (or who are primary refractory) following treatment with a proteasome inhibitor-containing regimen (excluding ixazomib), and who have not been treated with a second proteasome inhibitor (ixazomib, bortezomib, carfilzomib, or other proteasome inhibitor).	
☐	☐	☐	2. Age ≥ 18 years of age at time of consent.	
☐	☐	☐	3. Have an ECOG Performance Status of ≤ 2 at study entry. Refer to Appendix A.	
☐	☐	☐	4. Must be free of systemic infection: • Subjects with active infections (whether or not they require antibiotic therapy) may be eligible after complete resolution of the infection. • Subjects on antibiotic therapy must be off antibiotics for at least 7 days before beginning treatment.	
☐	☐	☐	5. Have the following clinical laboratory values: • Absolute neutrophil count ≥ 750/mm^3 • Platelet count ≥ 25,000/mm^3 • Creatinine clearance ≥ 30 mL/min • Total bilirubin: AST (SGOT) and ALT (SGPT) ≤ 3x ULN	
☐	☐	☐	6. Patient's multiple myeloma cells are positive for CD28 or CD86 expression by flow cytometry or immunohistochemistry (in any proportion). CD28 or CD86 positivity can have been determined on previous bone marrow aspirates or biopsies.	
☐	☐	☐	7. Disease free of prior malignancies for >2 years with exception of currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma "in situ" of the cervix or breast.	
☐	☐	☐	8. Participants of child-bearing potential must agree to use adequate contraceptive methods (e.g., hormonal or barrier method of birth control; abstinence) prior to study entry. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.	

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INCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "Yes" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	9. Participant must understand the investigational nature of this study and sign an Independent Ethics Committee/Institutional Review Board approved written informed consent form prior to receiving any study related procedure.	

Investigator Signature: _____ **Date:** _____

Printed Name of Investigator: _____

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Appendix C ELIGIBILITY VERIFICATION FORM EXCLUSION CRITERIA

Participant Name: (Multi-site: use participant initials): _____

Medical Record No.: (Multi-site: use participant ID): _____

Title: Phase II Study of Targeting CD28 in Multiple Myeloma with Abatacept (CTLA4-Ig) to Overcome Resistance to Chemotherapy

EXCLUSION CRITERIA				
Yes	**No**	**N/A**	**All answers must be "No" or "N/A" for participant enrollment.**	**Date**
☐	☐	☐	1. Prior treatment with ixazomib.	
☐	☐	☐	2. Inability to take ixazomib or abatacept.	
☐	☐	☐	3. Life expectancy less than 4 months.	
☐	☐	☐	4. Patients with a known diagnosis of plasma cell leukemia.	
☐	☐	☐	5. Known active tuberculosis or fungal infection.	
☐	☐	☐	6. Known seropositive for or active viral infection with, human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV). Patients who are seropositive because of immunization with the hepatitis B virus vaccine are eligible.	
☐	☐	☐	7. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.	
☐	☐	☐	8. Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or, which confounds the ability to interpret data from the study.	
☐	☐	☐	9. Pregnant or nursing female participants	
☐	☐	☐	10. Unwilling or unable to follow protocol requirements.	
☐	☐	☐	11. Any condition which in the Investigator's opinion deems the participant an unsuitable candidate to receive study drug.	
☐	☐	☐	12. Received an investigational agent within 30 days prior to enrollment.	

Participant meets all entry criteria: ☐ Yes ☐ No
If "NO", do not enroll participant in study.

Investigator Signature: _____ **Date:** _____

Printed Name of Investigator: _____

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Appendix D IMWG Diagnostic Criteria

Presence of an M-component[a] in serum and/or urine plus clonal plasma cells in the bone marrow and/or a documented clonal plasmacytoma

PLUS one or more of the following:[b]
- Calcium elevation (> 11.5 mg/dl) [> 2.65 mmol/l]
- Renal insufficiency (creatinine > 2 mg/dl) [177 μmol/l or more]
- Anemia (hemoglobin < 10 g/dl or 2 g/dl < normal) (hemoglobin < 12.5 mmol/l[c] or 1.25 mmol/l < normal)
- Bone disease (lytic lesions or osteopenia)

[a]In patients with no detectable M-component, an abnormal serum FLC ratio on the serum FLC assay can substitute and satisfy this criterion. For patients, with no serum or urine M-component and normal serum FLC ratio, the baseline bone marrow must have ⩾10% clonal plasma cells; these patients are referred to as having 'non-secretory myeloma'. Patients with biopsy-proven amyloidosis and/or systemic light chain deposition disease (LCDD) should be classified as 'myeloma with documented amyloidosis' or 'myeloma with documented LCDD,' respectively if they have ⩾30% plasma cells and/or myeloma-related bone disease.
[b]Must be attributable to the underlying plasma cell disorder.
[c]*Note*: Hemoglobin of 10 g/dl is 12.5 mmol/l [or 100 g/l].

Appendix E Schedule of Procedures and Observations

Evaluation	Baseline[1]	Cycle 1				Cycle 2 and every cycle thereafter (± 7 days)				End of Treatment (CR, progression or, off study)	Post-Treatment Follow-Up[2]	Long Term Follow-Up[3]
		Day 1	Day 2	Day 8 & Day 15 (± 2 days)	Day 22 (± 2 days)	Day 1	Day 8 (± 2 days)	Day 15 (± 2 days)	Day 22 (± 2 days)			
Documentation of Pathological Diagnosis (IMWG Diagnostic Criteria: Appendix D)	X											
Pre-Existing Conditions	X											
History and Physical Examination (including vital signs[4])	X	X	X[4]	X	X	X				X	X	
Skeletal survey, bone marrow MRI or PET/CT[5]	X											
Bone Marrow Biopsy/Aspirate with Flow Cytometry for CD28 and CD86 expression, molecular and cytogenetics	X[6]									X[19]		
Hematology[7]	X	X		X	X	X				X	X	

Evaluation	Baseline[1]	Cycle 1				Cycle 2 and every cycle thereafter (± 7 days)				End of Treatment (CR, progression or, off study)	Post-Treatment Follow-Up[2]	Long Term Follow-Up[3]
		Day 1	Day 2	Day 8 & Day 15 (± 2 days)	Day 22 (± 2 days)	Day 1	Day 8 (± 2 days)	Day 15 (± 2 days)	Day 22 (± 2 days)			
Chemistry[8]	X	X		X	X	X				X	X	
Pregnancy Test (Serum)[9]	X											
ECOG Performance Status	X	X		X	X	X				X	X	
Quantitative Immunoglobulins (QIgs)	X					X					X[20]	X[20]
Immunofixation (IFE) Serum Test	X					X					X[20]	X[20]
Serum Protein Electrophoresis (SPEP)	X					X					X[20]	X[20]
Serum Free Light Chain Assay	X					X					X[20]	X[20]
24 hr. Urine Protein Electrophoresis (UPEP) and UIFE	X					X					X[20]	X[20]
Serum kynurenine and IL-6 levels[10]	X					X				X	X	
Abatacept-Once weekly until discontinuation of Ixazomib		X[11]	X[12]	X	X	X	X	X	X			
Ixazomib[13]		X		X		X	X	X				
Dexamethasone[14]		X		X	X	X	X	X	X			

Evaluation	Baseline[1]	Cycle 1				Cycle 2 and every cycle thereafter (± 7 days)				End of Treatment (CR, progression or, off study)	Post-Treatment Follow-Up[2]	Long Term Follow-Up[3]
		Day 1	Day 2	Day 8 & Day 15 (± 2 days)	Day 22 (± 2 days)	Day 1	Day 8 (± 2 days)	Day 15 (± 2 days)	Day 22 (± 2 days)			
Acyclovir[15]		X	Daily with start of ixazomib and continue for 1 month following discontinuation of ixazomib									
Concomitant Medications[16]	X	X[17]				X				X	X	
Adverse Events		X	X	X	X	X	X	X	X	X	X	
Survival Status [18]											X	X

1 Performed within 28 days prior to first dose of study drug (unless otherwise noted).

2 Follow-up safety evaluations will occur 30 days (± 3 days) after last dose of study drug or until resolution of any drug-related toxicity. Additional follow-up safety evaluations will occur monthly through 48 months. All patients with abatacept-related toxicity will be followed until it resolves to ≤ Grade 1. After 48 months, patients will move to long-term follow-up and will be monitored for survival status for up to an additional 3 years (telephone contact or medical record check is acceptable) to document survival status. Patients will be monitored until initiation of a new therapy or until death, whichever occurs first.

3 Disease free survival for patients that achieve a Stringent CR: disease status evaluation with blood (QIgs, SPEP, serum IFE, serum free light chains), urine (24 hour UPEP) will be performed every 3 months (± 7 days) after the completion of treatment until disease progression or death due to any cause; whichever comes first.

4 Vital signs (temperature, heart rate, respiratory rate, blood pressure), body weight and, height. Height collected at baseline only.

5 Skeletal survey, bone marrow MRI or PET/CT for quantification of bone lesions, done at baseline (within 8 weeks of first dose) and then annually or as per local institutional guidelines.

6 Bone marrow biopsy and aspiration will be used for assessment of CD28 and CD86 expression on MM cells. A fresh sample is not required if CD28 or CD86 positivity has been determined on a previous bone marrow aspirate or biopsy. For patients that do undergo biopsy, an additional 10-20 mL of aspirate (heparinized or in green tops) will be collected for isolation of MM cells.

7 Hematology (i.e., CBC with differential). Note: Patients experiencing Grade 4 neutropenia should be monitored according to institutional guidelines. As needed at each study visit as determined by the Investigator or study physician.

8 Chemistry: CMP to include chloride, CO_2, potassium, sodium, BUN, glucose, calcium, creatinine, total protein, albumin, total bilirubin, alkaline phosphatase, AST, ALT, A/G ratio, BUN/creatinine ratio, osmol (Calc), anion gap). In addition: phosphorus, magnesium, lactate dehydrogenase (LDH).

9 At baseline, perform ≤ 7 days prior to start of study treatment.

10 Blood for serum kynurenine and IL-6 (Refer to Section 11.9.1).

Evaluation	Baseline[1]	Cycle 1				Cycle 2 and every cycle thereafter (± 7 days)				End of Treatment (CR, progression or, off study)	Post-Treatment Follow-Up[2]	Long Term Follow-Up[3]
		Day 1	Day 2	Day 8 & Day 15 (± 2 days)	Day 22 (± 2 days)	Day 1	Day 8 (± 2 days)	Day 15 (± 2 days)	Day 22 (± 2 days)			

11 Abatacept IV loading Day 1 Cycle 1: followed by 125 mg SQ on Day 2.
12 SQ, 125 mg; continue 125 mg SQ, once weekly thereafter.
13 Ixazomib 4 mg po on Days 1, 8, and 15 of a 28-day cycle.
14 Dexamethasone 40 mg po of Days 1, 8, 15, and 22 of a 28-day cycle. Weekly dose of dexamethasone may be split into two doses at the discretion of the treating physician.
15 Acyclovir 400 mg po BID with the start of ixazomib treatment for varicella prophylaxis and continue one month past the discontinuation of ixazomib treatment.
16 Medications taken in the month prior to registration (ongoing or discontinued).
17 Medications taken within 1 week prior to first dose of study drug.
18 Patients that discontinue treatment due to progressive disease, toxicity (treatment-related or unrelated) or withdrawal for any other reason will be monitored every 3 months after end of treatment (telephone contact acceptable) to document survival status. Patients will be monitored until initiation of a new therapy or until death, whichever occurs first.
19 Bone marrow biopsy/aspirate with flow cytometry for CD28 and CD86 upon progression, or to confirm Stringent CR or CR. For patients who are progressing, an additional 20 mL of aspirate (heparinized or in green tops) will be collected for isolation of MM cells (see Section 11.9.2regarding sample handling).
20 Only required for patients that achieve a Stringent CR: disease status evaluation with blood (QIgs, SPEP, serum IFE, serum free light chains), urine (24 hour UPEP) will be performed every 3 months after the completion of treatment until disease progression or death due to any cause; whichever comes first.

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Appendix F Study Drugs: Package Inserts

Abatacept:
http://packageinserts.bms.com/pi/pi_orencia.pdf

Ixazomib:
https://www.ninlarohcp.com/pdf/prescribing-information.pdf

Dexamethasone:
http://docs.boehringer-ingelheim.com/Prescribing%20Information/PIs/Roxane/Dexamethasone/Dexamethasone%20Tablets%20Solution%20and%20Intensol.pdf.

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Appendix G Instructions for Multi-Site Studies

1. CONTACT INFORMATION

All questions related to the protocol or study implementation should be directed to:

Roswell Park Cancer Institute
CRS Quality Assurance (QA) Network Office
CRSNetworkCoordinators@RoswellPark.org
GBSB 1930
Buffalo, New York 14263
Telephone:
Monday - Friday; 8: 00 AM to 4: 00 PM EST
716-845-8084
After hours, weekends, and holidays request the Roswell Park Investigator
716-845-2300
Fax: 716-845-8743

2. INFORMED CONSENT

- Informed consent must be obtained by the **site Investigator/designee** from any participants wishing to participate, **prior to any study specific procedures.**
- An informed consent template is provided by Roswell Park and can be amended to reflect institutional requirements.
- All consent changes **must** be reviewed by Roswell Park QA Network Office prior to submission to the site IRB.
- The informed consent must be IRB approved.
- Always check that the most up to date version of the IRB approved consent is being used.
- Within 5 business days, notify the Roswell Park CRS QA Network Office of all participant withdrawals or consent to limited study participation and appropriately document the discontinuation and the reason(s) why.

3. PARTICIPANT REGISTRATION

The participant completes the Gender, Race, and Ethnicity Form and this is placed in the study binder.

RPCI does not grant exceptions to eligibility criteria.

Phase 2 Protocol Registration Instructions

The Subject Screening and Enrollment Log must be faxed or emailed (CRSNetworkCoordinators@RoswellPark.org) to the Roswell Park CRS QA Network Office within 1 business day of the date the participant is consented. Once the Investigator has determined that eligibility has been met, complete the eligibility check list and fax or email it to the Roswell Park Network Quality Assurance Coordinator at 716-845-8743.

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4. STUDY DEVIATIONS

- If a deviation has occurred to eliminate hazard, this must be reported to the Roswell Park Network Quality Assurance Office, site IRB and any other regulatory authority involved in the study.
- ALL study deviations will be recorded on the **Study Deviation Log**.
- Participants inadvertently enrolled with significant deviation(s) from the study-specified criteria will be removed from the study, at the discretion of the Principle Investigator.

5. STUDY DOCUMENTATION

- Study documents must be filled out completely and correctly. Ditto marks are not allowed.
- If an entry has been documented in error put a single line through the entry and initial and date the change. The Roswell Park Network QA Coordinator must be able to read what has been deleted.
- Do **NOT** use white-out, magic marker, scratch-outs.
- Do **NOT** erase entries.
- Use only black ink for documentation on the accountability form and any other study forms.
- It is the responsibility of Roswell Park to inform the Investigator/ institution as to when these documents no longer need to be retained. If, for any reason, the Investigator desires to no longer maintain the study records, they may be transferred to another institution, another investigator, or to Roswell Park upon written agreement between the Investigator and Roswell Park.

6. DRUG ACCOUNTABILITY

Drug accountability must be strictly maintained.

- Responsibility rests solely with the Investigator but can be delegated as appropriate (e.g., to pharmacy personnel).
- A drug accountability record form (DARF) will record quantities of study drug received, dispensed to participants and wasted, lot number, date dispensed, participant ID number and initials, quantity returned, balance remaining, manufacturer, expiration date, and the initials of the person dispensing the medication.
- Study drug supply will only be used in accordance with the IRB approved study.
- Drug accountability forms are protocol and agent specific, they are study source documents and will be used to verify compliance with the study.
- An inventory count must be performed with each transaction. Any discrepancies shall be documented and explained.
- Drug accountability forms must be stored with study related documents.

- Each medication provided for this study and each dosage form and strength must have its own DARF.
- Dispensing the wrong study supply is considered a **medication error**.
- **NEVER** replace investigational agents with commercial product.
- Do **NOT** "transfer", "borrow" or "replace" supplies between studies.

7. SERIOUS ADVERSE EVENT REPORTING

The site Investigator or designated research personnel will report all SAEs, whether related or unrelated to the investigational agent(s) to the **IRB in accordance with their local institutional guidelines**. The site will notify the Roswell Park Network Quality Assurance Coordinator within 1 business day of being made aware of the SAE. A preliminary written report must follow within 1 business day of the first notification using the following forms:

- RPCI SAE Source form
- MedWatch 3500A

See section 17.4 for additional reporting information

A complete follow-up report must be sent to the Roswell Park Network Quality Assurance Coordinator when new information becomes available.

8. UNANTICIPATED PROBLEM REPORTING

An unanticipated problem (UP) is any incident, experience, or outcome that meets all of the criteria in **Section 17.7**.

For all adverse events occurring that are unanticipated and related or possibly related to the research drug, biologic or intervention, the participating physician or delegated research staff from each site will notify their local **IRB in accordance with their local institutional guidelines**. The site must also notify the Roswell Park Network Quality Assurance Coordinator within 1 business day of being made aware of the Unanticipated Problem by completing the **Roswell Park Unanticipated Problem Report Form** and faxing or emailing it to the Roswell Park Network Quality Assurance Coordinator.