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DF/HCC Protocol #: 19-283

TITLE: A Phase II Study of Nivolumab in Combination with Ixazomib, Cyclophosphamide, and Dexamethasone in Relapsed and Refractory Multiple Myeloma

Coordinating Center: Massachusetts General Hospital
Cancer Center Protocol Office
Program for Coordination and Oversight of Research Protocols

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IND # 145043

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Agents: Nivolumab, Bristol-Myers Squibb
Ixazomib, Takeda
Cyclophosphamide, commercially available
Dexamethasone, commercially available

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Reference numbers: Bristol-Myers Squibb # CA209-8NJ
Takeda # X16109

SCHEMA

Nivolumab on day 1

Cyclophosphamide on days 1, 8, 15

Ixazomib on days 1, 8, 15

Dexamethasone on days 1, 8, 15, 22

28 day cycle

PROTOCOL SUMMARY

Study Title: A phase II study of nivolumab in combination with ixazomib, cyclophosphamide, and dexamethasone in relapsed and refractory multiple myeloma

Phase: II

Accrual Goal: 43 evaluable

Study Objectives

Primary

- To evaluate the objective response rate of nivolumab in combination with ixazomib, cyclophosphamide, and dexamethasone in patients with relapsed and refractory multiple myeloma.
- To evaluate the safety profile of nivolumab in combination with ixazomib, cyclophosphamide, and dexamethasone.

Secondary

- To evaluate the progression free survival (PFS) of nivolumab in combination with ixazomib, cyclophosphamide, and dexamethasone.
- To evaluate biomarkers that may correlate with response to nivolumab in combination with ixazomib, cyclophosphamide, and dexamethasone.

Overview of Study Design:

This phase II, multi-center, open-label study will evaluate 43 patients with relapsed and refractory MM.

Participants will receive nivolumab, ixazomib, cyclophosphamide, and dexamethasone on a 28-day cycle. Nivolumab 480 mg will be administered intravenously on day 1. Ixazomib 4 mg will be given orally on days 1, 8, and 15. Cyclophosphamide 300 mg/m^2 will be given intravenously on days 1, 8, 15. Dexamethasone will be given 40 mg orally on days 1, 8, 15, 22. Treatment will be until progressive disease or toxicity.

The first six participants will comprise the safety run-in cohort.

Study Population:

Relapsed and refractory multiple myeloma who have completed at least two cycles of lenalidomide and two cycles of proteasome inhibitor, either in separate regimens or in the same regimen as well as an anti-CD38 monoclonal antibody. Patients who have received at least three prior lines of therapy are eligible to participate. Prior therapy with ixazomib and prior therapy with any anti-PD1 antibody or anti-PDL1 antibody are exclusions.

Duration of Study:

Participants will remain on study until disease progression or unacceptable toxicity, if earlier. The study will be completed 60 days after the last participant remaining on study medication discontinues study medication.

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1. OBJECTIVES

1.1 Study Design

This is a phase II study that will evaluate up to 43 patients with relapsed and refractory multiple myeloma.

1.2 Primary Objectives

1. To evaluate the objective response rate of nivolumab in combination with ixazomib, cyclophosphamide, and dexamethasone in patients with relapsed and refractory multiple myeloma.
2. To evaluate the safety profile of nivolumab in combination with ixazomib, cyclophosphamide, and dexamethasone.

1.3 Secondary Objectives

1. To evaluate the progression free survival (PFS) of nivolumab in combination with ixazomib, cyclophosphamide, and dexamethasone.
2. To evaluate biomarkers that may correlate with response to nivolumab in combination with ixazomib, cyclophosphamide, and dexamethasone (exploratory).

2. BACKGROUND

2.1 Study diseases

2.1.1 Multiple myeloma

Multiple myeloma (MM) is an incurable plasma cell malignancy and the second most common hematologic malignancy in the United States. There has been a dramatic increase in response rates in MM achieved over the past several years with newer agents such as lenalidomide and bortezomib and in combination as RVD as front-line therapy in newly diagnosed disease (Richardson et al., 2010). However, the majority of patients with myeloma will relapse or become refractory, regardless of the line of therapy.

The rate of complete response in refractory disease remains relatively low with substantial opportunity for improvement. Patients who are refractory to standard treatment with both an immunomodulatory drug (e.g. lenalidomide) and a proteasome inhibitor (e.g. bortezomib) have a poor prognosis, with a median progression-free survival of five months and median overall survival of 15.2 months in the next line of treatment (Kumar et al., 2017). Moreover, the anti-CD38 monoclonal antibody daratumumab is increasingly being used in multiple myeloma, and its use is being moved to newly-diagnosed patients after being reserved for relapsed disease. Patients with disease refractory to anti-CD38 monoclonal antibody have a poor prognosis with a median overall survival of 8.6 months (Gandhi et al., 2019). There

is a significant unmet need for novel strategies to treat these patients with refractory disease.

2.2 IND Agents

2.2.1 Nivolumab

Nivolumab (Opdivo) is a programmed death receptor-1(PD-1) blocking antibody. Nivolumab (as monotherapy) has been approved by FDA in multiple indications, including, but not limited to:

- Unresectable or metastatic melanoma, as a single agent or in combination with ipilimumab.
- Non-small cell lung cancer with progression on or after platinum-based chemotherapy.
- Advanced renal cell carcinoma who have received prior anti-angiogenic therapy.
- Hodgkin's lymphoma that has relapsed after autologous stem cell transplant and brentuximab vedotin or three or more lines of treatment that includes autologous stem cell transplant.
- Recurrent or metastatic squamous cell carcinoma of the head and neck with disease progression on or after a platinum-based therapy.
- Locally advanced or metastatic urothelial carcinoma who have disease progression during or following platinum-containing chemotherapy or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

2.2.1.1 *Mechanism of action*

Cancer immunotherapy rests on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. An effective immune response in this setting is thought to rely on immune surveillance of tumor antigens expressed on cancer cells that ultimately results in an adaptive immune response and cancer cell death. Meanwhile, tumor progression may depend upon acquisition of traits that allow cancer cells to evade immunosurveillance and escape effective innate and adaptive immune responses (Dunn et al., 2002; Horne et al., 2011; Zitvogel et al., 2006).

Current immunotherapy efforts attempt to break the apparent tolerance of the immune system to tumor cells and antigens by either introducing cancer antigens by therapeutic vaccination or by modulating regulatory checkpoints of the immune system. T-cell stimulation is a complex process involving the integration of numerous positive as well as negative co-stimulatory signals in addition to antigen recognition by the T-cell receptor (TCR) (Zhang et al., 2010). Collectively, these signals govern the balance between T-cell activation and tolerance to antigens. PD-1 is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA-4, ICOS, and BTLA.31 PD-1 signaling has been shown to inhibit CD-28-mediated upregulation of IL-2, IL-10, IL-13, interferon-γ (IFN-γ) and Bcl-xL. PD-1 expression also been noted to inhibit T cell activation, and expansion of previously activated cells. Evidence for a negative regulatory role of PD-1 comes from studies of PD-1 deficient mice, which develop a variety of autoimmune phenotypes (Topalian et al., 2012). These results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a

universal loss of tolerance to self-antigens.

Nivolumab is a fully human, IgG4 (κ) isotype monoclonal antibody that binds PD-1 on activated immune cells and disrupts engagement of the receptor with its ligands PD-L1(B7-H1/CD274) and PD-L2 (B7-DC/CD273), thereby abrogating inhibitory signals and augmenting the host antitumor response. In vitro, nivolumab binds to PD-1 with high affinity (EC50 0.39-2.62 nM) and inhibits the binding of PD-1 to its ligands PD-L1 and PD-L2 (IC50 ± 1 nM). Nivolumab binds specifically to PD-1 and not to related members of the CD28 family such as CD28, ICOS, CTLA-4 and BTLA. Blockade of the PD-1 pathway by nivolumab results in a reproducible enhancement of both proliferation and IFN-γ release in the mixed lymphocyte reaction (MLR). Using a CMV re-stimulation assay with human PBMC, the effect of nivolumab on antigen specific recall response indicates that nivolumab augmented IFN-γ secretion from CMV specific memory T cells in a dose-dependent manner versus isotype-matched control. In vivo blockade of PD-1 by a murine analog of nivolumab enhances the anti-tumor immune response and result in tumor rejection in several immunocompetent mouse tumor models (MC38, SA1/N, and PAN02) (Alegre et al., 1996).

Please also refer to investigator brochure for additional information.

2.2.2 Ixazomib

Ixazomib citrate, or MLN9708, is a citrate ester that in aqueous solution and plasma is hydrolyzed to the biologically active dipeptide boronic acid proteasome inhibitor, ixazomib (MLN2238). Importantly, ixazomib has been formulated for oral administration, making it one of the first orally bioavailable proteasome inhibitors in clinical development. Like bortezomib, ixazomib is a reversible inhibitor of the β5 subunit of the proteasome. However, ixazomib has a proteasome dissociation half-life that is approximately 6-fold faster than bortezomib. This faster dissociation half-life is hypothesized to play a critical role in the ability of ixazomib to distribute to tumors more efficiently than bortezomib, owing to the fact that high levels of whole blood proteasome activity sequester bortezomib from sites of disease. Indeed, studies have shown an increased blood volume of distribution at steady state, increased tumoral proteasome inhibition, and increased efficacy of ixazomib compared to bortezomib in pre-clinical models of multiple myeloma (Chauhan et al., 2011; Kupperman et al., 2010; Lee et al., 2011). Importantly, synergistic activity with lenalidomide was also seen.

Ixazomib was recently approved based on the findings of the TOURMALINE-MM1 trial, which showed that the combination of ixazomib with lenalidomide and dexamethasone was superior to lenalidomide and dexamethasone in patients with relapsed/refractory multiple myeloma (Moreau et al., 2016). Please refer to investigator brochure for additional information.

2.3 Other agents

2.3.1 Cyclophosphamide

Cyclophosphamide is an alkylating drug widely used in solid tumors and in hematologic malignancies as well as in rheumatologic conditions. It has an established role in treating multiple myeloma in various

combinations with bortezomib (Kumar et al., 2012), ixazomib (Kumar et al., 2019), and pomalidomide (Baz et al., 2016) at time of diagnosis and at relapse.

2.3.2 Dexamethasone

Glucocorticoids such as dexamethasone have significant activity in myeloma. They are a core component of treatment regimens in newly-diagnosed patients and in relapsed and refractory disease. For example, in a study of 112 patients with untreated myeloma, the response rate with dexamethasone alone was 43% (Alexanian et al., 1992). Combination of dexamethasone with novel agents like bortezomib or lenalidomide from several phase II trials suggests that the addition of dexamethasone consistently increases response rates from 25-30% to 50-60% (Jagannath et al., 2004; Richardson et al., 2006; Weber et al., 2003).

2.4 Study Rationale

The use of anti-PD1 antibodies is starting to be explored in hematological malignancies (Ansell et al., 2015), and nivolumab was recently approved in Hodgkin's disease. MM cells have increased levels of PD-L1 (Gorgun et al., 2015), providing the rationale for anti-PD1 therapy in MM.

Proteasome inhibitors such as bortezomib, carfilzomib and ixazomib are a class of drugs widely used across all lines of therapy in multiple myeloma. This drug class could be rationally combined with anti-PD-1 therapy. Several clinical studies consistently indicate proteasome inhibitor activity is enhanced when combined with immune-modulatory drugs (Cavo et al., 2010; Garderet et al., 2012; Moreau et al., 2011; Richardson et al., 2010; Richardson et al., 2014). Moreover, in immunotherapy animal models involving low-avidity antigens (Shanker et al., 2015; Thounaojam et al., 2015), the proteasome inhibitor bortezomib activated NF-κB p65 in CD8+ T cells, stabilizing expression of T-cell receptor CD3ζ and IL2 receptor-α, while maintaining IFNγ secretion to improve FasL-mediated tumor lysis. Notably, bortezomib increased tumor cell surface expression of Fas in mice as well as human melanoma tissue from a responsive patient. In renal tumor-bearing immunodeficient Rag2−/− mice, bortezomib treatment after adoptive T-cell immunotherapy reduced lung metastases and enhanced host survival (Shanker et al., 2015). These findings highlight the potential of proteasome inhibitors such as ixazomib to enhance antitumor T-cell function in the context of cancer immunotherapy with nivolumab.

Additionally, combining anti-PD1 therapy with traditional cytotoxic chemotherapy may enhance the activity of checkpoint inhibition. The combination may be synergistic by improving the ratio of T cells to tumor, reducing immunosuppressive factors released by tumor, or by exposing new antigens and thereby broadening the antitumor T cell response. For example, in non-squamous non-small cell lung cancer, combining the anti PD-1 antibody pembrolizumab with carboplatin and pemetrexed led to enhanced responses over chemotherapy alone (Langer et al., 2016). This strategy is under investigation in hematologic malignancies, e.g. nivolumab in combination with traditional chemotherapy in peripheral T cell lymphoma (NCT03586999); or nivolumab in combination with gemcitabine, oxaliplatin, and rituximab in patients with relapsed/refractory lymphoma (NCT03366272). In multiple myeloma, given these findings, the effect of combining anti-PD1 antibody with both proteasome inhibitors and traditional

chemotherapy merits further investigation. They set the stage for evaluating the combination of nivolumab with ixazomib, cyclophosphamide, and low dose dexamethasone in patients with relapsed disease (ICd). ICd is an effective regimen, motivated by prior experience with the combination of cyclophosphamide, bortezomib, and dexamethasone (Kumar et al., 2016a; Kumar et al., 2019). The proposed nivolumab combination with ICd may offer a compelling and unique therapeutic advance for this patient population with challenging treatment needs.

2.5 Correlative Studies Background

We will evaluate biomarkers that may correlate with response to nivolumab in combination with ixazomib, cyclophosphamide and dexamethasone. These biomarkers may include assessing by flow cytometry, PD-L1 expression on myeloma cells and tumor stroma and PD1 expression on CD4 T cells, T- and B- cell subsets; expression profiling of peripheral blood mononuclear cells and myeloma cells; and T-cell phenotyping including expression of other co-stimulatory molecules e.g. OX40 and 4-1BB (Gorgun et al., 2015). These biomarkers will be assessed before and over the course of treatment.

In collaboration with Dr. Jens Lohr, we may also evaluate both circulating tumor cells (CTCs) and circulating tumor free DNA from the peripheral blood. Their group has developed a method for noninvasive and highly sensitive isolation and characterization of CTCs from peripheral blood at single-cell resolution that recapitulates the findings in the bone marrow. They demonstrated that CTCs provide the same genetic information as bone marrow MM cells and even reveal mutations with greater sensitivity than bone marrow biopsies in some cases (Guo et al., 2018; Lohr et al., 2016). This study will allow such an analysis to take place on a well-characterized, uniformly treated patient population to see how heterogeneity and resistance may evolve to treatment with an intensive and active regimen. Similarly, we may evaluate whole genome sequencing of circulating tumor free DNA from peripheral blood to assess it change in response to treatment and relapse.

The above analyses will be exploratory.

3. PARTICIPANT SELECTION

3.1 Eligibility criteria

3.1.1 Previously treated relapsed **and** refractory multiple myeloma per International Myeloma Working Group consensus criteria (Munshi et al., 2011).

3.1.2 Patients must have received at least three prior lines of therapy, including an immunomodulatory drug (e.g. lenalidomide, pomalidomide), a proteasome inhibitor (e.g. bortezomib, carfilzomib), and anti-CD38 monoclonal antibody (e.g. daratumumab)

3.1.3 Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 (see Appendix A).

3.1.4 Age ≥ 18 years

3.1.5 All laboratory assessments for eligibility should be performed within 21 days of initiation of protocol therapy unless otherwise specified.

3.1.6 Measurable disease of multiple myeloma as defined by at least one of the following (IgD and IgA with monoclonal protein < 0.5 g/dL may be permitted after discussion with PI):

- Serum monoclonal protein ≥ 0.5 g/dL (or quantitative IgA ≥ 1000 mg/dL), or
- ≥ 200 mg of monoclonal protein in the urine on 24-hour urine protein electrophoresis, and/or
- Serum free light chain ≥ 100 mg/L (10 mg/dL) and abnormal serum free kappa to serum free kappa light chain ratio

3.1.7 ANC ≥ 1000/μL. G-CSF is not permitted within 14 days of screening.

3.1.8 Platelet count ≥ 75,000/μL. Platelet transfusions are not permitted within 7 days of screening.

3.1.9 Hemoglobin ≥ 8 g/dL. Red blood cell transfusions *are* permitted to meet eligibility criteria.

3.1.10 Calculated creatinine clearance of ≥ 30 mL/min according to Cockroft-Gault equation.

3.1.11 Adequate hepatic function, as evidenced by each of the following:

- Alanine Aminotransferase (ALT) and/or Aspartate Aminotransferase(AST) values < 3 × the institutional upper limit of normal (ULN).
- Serum bilirubin values < 1.5 mg/dL. Patients with elevated bilirubin due to Gilbert's syndrome may be permitted with PI approval.

3.1.12 Able to swallow capsules whole (ixazomib capsules should not be crushed, dissolved or broken).

3.1.13 Women of childbearing potential (WOCBP)* must agree to follow instructions for methods of contraception for the duration of study treatment with nivolumab and for five months after the last dose of study treatment. If they are of childbearing potential, agree to practice 2 effective methods of contraception, at the same time, from the time of signing the informed consent form through five months after the last dose of study drug OR agree to practice true abstinence when it in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

*Women of child bearing potential are women who are not postmenopausal for at least one year and who are not surgically sterile.

3.1.14 Males who are sexually active (even if surgically sterilized, i.e. vasectomy) with WOBCP must agree to follow instructions for methods of contraception for the duration of study treatment with nivolumab and 7 months after the last dose of study treatment. Agree to practice effective barrier contraception during the entire study treatment period and through 7 months after the last dose of study drug, OR agree to practice true abstinence when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

3.1.15 Patient has given voluntary, signed written informed consent before performance of any study-related procedure that is not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to their future medical care.

3.2 Exclusion criteria

3.2.1 Prior therapy with ixazomib

3.2.2 Prior therapy with any anti-PD1 antibody (e.g. nivolumab, pembrolizumab) or anti-PDL1 antibody (e.g. atezolizumab, avelumab, durvalumab)

3.2.3 Participants who have had chemotherapy within 2 weeks (6 weeks for nitrosoureas or mitomycin C) or with monoclonal antibodies 3 weeks of C1D1 or those who have not recovered from adverse events due to agents administered more than 2 weeks earlier. Patients may have received

dexamethasone within 2 weeks prior to C1D1.

3.2.4 Participation in other clinical trials, including those with other investigational agents, within five half-lives prior to C1D1and throughout the duration of this trial. Prior treatment with an investigational agent within five half lives prior to C1D1 may be permitted after discussion with the PI.

3.2.5 Concomitant high-dose corticosteroid use except chronic steroids (maximum dose 10 mg/day prednisone equivalent) if they are being given for disorders other than myeloma, e.g. adrenal insufficiency, rheumatoid arthritis, etc.

3.2.6 Female patients who are lactating or have a positive serum pregnancy test during the screening period (within 21 days of C1D1).

3.2.7 Prior history of malignancies, other than MM, unless the patient has been free of the disease for ≥ 3 years. Exceptions include the following if the patient has undergone complete resection:

a. Basal or squamous cell carcinoma of the skin
b. Carcinoma in situ of the cervix
c. Ductal carcinoma in situ of the breast
d. Incidental histologic finding of prostate cancer (T1a or T1b)

3.2.8 Patients with another malignancy undergoing active treatment with the exception of non-melanoma skin cancer or in situ cervical cancer.

3.2.9 Patients with plasma cell leukemia, POEMS syndrome, or amyloidosis are excluded from this trial.

3.2.10 HIV infection.

3.2.11 Active hepatitis B infection or active hepatitis C infection. Participants who have prior hepatitis C infection and who have received an antiviral treatment and show no detectable viral RNA for 6 months prior to screening are eligible.

3.2.12 Peripheral neuropathy ≥ grade 2 despite supportive therapy.

3.2.13 Prior allogeneic stem cell transplant within five years prior to study registration. Patients who have had an allogeneic stem cell transplant within five years prior to study registration may participate as long as there are no symptoms of graft versus host disease.

3.2.14 Patient has a history of significant cardiovascular, neurological, endocrine, gastrointestinal, respiratory, or inflammatory illness that could preclude study participation, pose an undue medical hazard, or interfere with the interpretation of the study results, including, but not limited to, patients with congestive heart failure (New York Heart Association [NYHA] Class 3 or 4); unstable angina; cardiac arrhythmia; recent (within the preceding 6 months) myocardial infarction or stroke; hypertension requiring > 2 medications for adequate control; diabetes mellitus with > 2 episodes of ketoacidosis in the preceding 12 months; or chronic obstructive pulmonary disease (COPD) requiring > 2 hospitalizations in the preceding 12 months.

3.2.15 Autoimmune disease: patients with a history of inflammatory bowel disease, including ulcerative colitis and Crohn's disease, are excluded from this study, as are patients with a history of symptomatic disease (e.g., rheumatoid arthritis, systemic progressive sclerosis [scleroderma],

systemic lupus erythematosus, autoimmune pneumonitis, autoimmune vasculitis (e.g., Wegener's granulomatosis) and motor neuropathy considered of autoimmune origin (e.g. Guillain-Barré syndrome and myasthenia gravis). Patients with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

3.2.16 Patients with history of interstitial lung disease and/or pneumonitis, or pulmonary hypertension.

3.2.17 Major surgery within 14 days prior to study registration.

3.2.18 Central nervous system involvement.

3.2.19 Infection requiring systemic antibiotic therapy or other serious infection within 14 days prior to study registration

3.2.20 Systemic treatment with strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of St. John's wort within 14 days prior to C1D1.

3.2.21 Receipt of a live or attenuated vaccine within 30 days of C1D1.

3.2.22 Any serious medical of psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

3.2.23 Known allergy to any study medications, their analogs, or excipients in the various formulations of any agent.

3.3 Inclusion of women and minorities

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

4. REGISTRATION PROCEDURES

4.1 General Guidelines for DF/HCC Institutions

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

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

Following registration, participants may begin protocol therapy. Issues that would cause treatment delays should be discussed with the overall principal investigator (PI). If the participant does not receive protocol therapy following registration, the participant must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

4.2 Registration Process for DF/HCC Institutions

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

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at Massachusetts General Hospital by the Coordinating Center. All sites should contact the Coordinating Center to verify treatment slot availability prior to registration.

Following registration, participants may begin protocol treatment. Issues that would cause treatment delays should be discussed with the PI. If a participant does not receive protocol therapy following registration, the participant must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered. The Coordinating Center should be notified of participant status changes as soon as possible.

4.4 Registration Process for Other Investigative Sites

To register a subject, the following documents should be completed by the participating institution and forwarded to the Coordinating Center:

- Copy of source documentation for inclusion/exclusion criteria and screening procedures including, but not limited to:
    - Pathology report
    - Medical history, including prior therapies, and physical exam
    - Laboratory reports
    - Concomitant medication list
- Demographics information
- Signed study consent form
- Study entry note with documentation of consent process
- HIPAA authorization form, if applicable.
- Eligibility checklist
- External Site Subject Registration Form.

The Coordinating Center will review the above documentation to confirm eligibility and consent. To complete the registration process, the Coordinating Center will follow DF/HCC Standard Operating Procedure for Human Subject Research Titled *Subject Protocol Registration* (Policy#: REGIST-101) and register the participant on the protocol. Once registered a confirmation email with the participant study number, and if applicable the dose treatment level, will be sent to the participating site.

NOTE: Registrations can only be conducted by the Coordinating Center during the business hours of 8:30 AM and 5:00 PM Eastern Standard Time (or Eastern Daylight Time when applicable), Monday through Friday. A complete registration packet, including all documents listed above, must be received at

least 24 hours *prior to* the anticipated registration to ensure adequate review. Same day treatment registrations will only be accepted with prior notice and discussion with the Coordinating Center.

Treatment may not begin without confirmation from the Coordinating Center that the participant has been registered.

5. TREATMENT PLAN

5.1 Treatment Regimen

Treatment will be administered on an outpatient basis.

A treatment cycle is 28 days long.

Participants will remain on study until disease progression, unacceptable toxicity, or withdrawal of participant consent. With the exception of participants who had disease progression at study discontinuation, all participants will continue to be evaluated until disease progression, initiation of new therapy, death, or study completion. The study will be completed 60 days after the last participant remaining on study discontinues treatment.

No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the disease under investigation.

Agent	**Dose**	**Route**	**Schedule**
Nivolumab	480 mg	IV	Day 1
Ixazomib	4 mg	PO	Days 1, 8, 15
Cyclophosphamide	300 mg/m^2	IV	Days 1, 8, 15
Dexamethasone	40 mg 20 mg if participant >75 y.o.	PO	Days 1, 8, 15, 22

A treatment window of ± 3 days is allowed. Doses that fall outside this window are skipped.

The dose of dexamethasone may be split over two days. For participants over the age of 75, the dexamethasone dose is 20 mg weekly, and this dose may be split over two days.

5.1.1 Safety Run-in

The first six participants who complete cycle 1 will be assessed for safety and adverse events prior to enrolling the rest of the participants. If two or more participants experience a dose limiting toxicity (DLT), the study will be stopped. See below for definition of DLT. Following successful completion of the safety run-in phase, participants will continue to enroll in the study.

5.1.2 Pre-treatment criteria

5.1.2.1 *Day 1 of All Cycles*

- ANC ≥ 1,000/μL. G-CSF is permitted except for screening and for C1D1.
- Platelet count ≥ 75,000/μL. Platelet transfusions are permitted except for screening and for C1D1.
- Any nivolumab-, cyclophosphamide-, or ixazomib-related adverse event that may have occurred has resolved to Grade ≤ 2.
    - Grade 3 lymphopenia or leukopenia does not require dose delay.
- Herpes zoster lesions, if present, are dry, and participants have had at least 10 days of anti-VZV systemic treatment.
- The maximum amount of time for which a drug may be held due to toxicity is 4 weeks. If drug is held for more than 4 weeks due to toxicity, the participant will be removed from study treatment (though participants may continue after discussion with the PI). However, treatment delay for reasons other than toxicity for more than 4 weeks (for any study treatment) will require authorization from the PI. Dose modification guidelines are described in Dosing Delays/Dose Modifications.
- If there were ixazomib dose modifications or delays in the previous cycle, use the following guidelines:
    - If ixazomib was held during the previous cycle and restarted at a reduced dose level, without interruption for the remainder of the cycle, then the reduced dose level will be initiated on Day 1 of the new cycle.
    - If ixazomib dosing was omitted for the remainder of the previous cycle or if a new cycle is delayed due to ixazomib-related toxicity encountered on the scheduled Day 1, then the new cycle will be started with one-level dose reduction.

5.1.3 Intra-Cycle Dosing

For intra-cycle dosing with cyclophosphamide or ixazomib, the following criteria must be met if laboratory studies are performed:

- ANC ≥ 500/μL (G-CSF is permitted)
- Platelet count ≥ 30,000/μL (platelet transfusion support is permitted)

Intra-cycle dose modifications for all drugs will be allowed based on toxicity and according to dose modifications outlined.

5.2 Agent Administration

5.2.1 Nivolumab

Participants will receive nivolumab as an IV infusion over 30 minutes ± 10 minutes according to the schedule above. Administer through an intravenous line containing a sterile, non-pyrogenic, low protein

binding in-line filter (pore size of 0.2 to 1.2 μm). Do not coadminster other drugs through the same intravenous line.

5.2.2 Cyclophosphamide

Cyclophosphamide will be given according to institutional practice. Cyclophosphamide will be given after nivolumab.

5.2.3 Ixazomib

Ixazomib should be taken on an empty stomach (no food or drink) at least one hour before or at least two hours after food. Each capsule should be swallowed separately with water. The capsule should not be crushed, chewed, or opened. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules.

If a dose of ixazomib is delayed or missed, the dose should be taken only if the next scheduled dose is 72 hours or more later. A missed dose should not be taken within 72 hours of the next scheduled dose.

If a participant vomits after taking a dose, the participant should not repeat the dose but should resume dosing at the time of the next scheduled dose. Participants who take more than the prescribed dose of ixazomib should be instructed to seek emergency medical care if needed and contact study staff immediately.

A drug diary will be provided to participants to record oral administration of doses.

5.2.4 Dexamethasone

Dexamethasone will be given according to institutional practice.

Each oral dexamethasone dose should be taken with food and at the same time each day (± 6 hours). If a dose is missed or vomited, the dose should not be made up and the participant should continue with regular scheduling of the drug.

5.3 Definition of Dose-Limiting Toxicity

Dose-limiting toxicities are defined as:

- Grade 4 neutropenia
- Grade ≥ 3 thrombocytopenia with clinically significant bleeding
- Grade 4 thrombocytopenia lasting >7 days despite transfusion support
- Grade 3 or higher non hematological toxicity except:
    - Grade 3 nausea, vomiting, or diarrhea that can be controlled within 48 hours with maximal supportive care.
    - Grade 3 hyperglycemia that can be controlled within 48 hours with appropriate supportive care.

- Asymptomatic grade 3 or higher electrolyte disturbances that can be controlled with repletion within 24 hours.

Alopecia, lymphopenia, and anemia will not be part of DLT determination.

Asymptomatic lipase or amylase or laboratory abnormalities that correct to Grade 1 within 72 hours after treatment will not be part of DLT determination.

5.4 General Concomitant Medication and Supportive Care Guidelines

5.4.1 Prophylaxis Against Herpes Zoster Reactivation

Participants on proteasome inhibitor-containing regimens are at increased risk of herpes zoster reactivation. Therefore, all participants should receive appropriate prophylaxis (e.g. acyclovir 400 mg twice daily or investigator preference).

5.4.2 Prohibited Medications and Procedures

The following medications and procedures are prohibited during the study:

- Any antineoplastic treatment with activity against MM, other than study drugs.
- Systemic treatment with any of the following metabolizing enzyme inducers should be avoided unless there is no appropriate alternative medication for the participant's use. If there were to be a drug-drug interaction with an inducer, ixazomib exposure would be decreased. Strong CYP3A inducers include:
  - rifampin,
  - rifapentin,
  - rifabutin,
  - carbamazepine,
  - phenytoin,
  - phenobarbital, and
  - St. John's wort.
- Radiation therapy. However, radiation therapy may be permitted after discussion with the PI.
- Any live or attenuated vaccine (e.g. varicella, yellow fever, rotavirus, oral polio, Zostavax, or measles, mumps, rubella) during treatment and until 100 days post last dose of nivolumab.

5.5 Criteria for Taking a Participant Off Protocol Therapy

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

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)

- Participant demonstrates an inability or unwillingness to comply with the oral medication regimen and/or documentation requirements
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator
- Study termination

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

When a participant is removed from protocol therapy, the relevant Off-Treatment information will be updated in OnCore. The DF/HCC research team will update the relevant information in OnCore and the Coordinating Center will update this information for external site participants.

In the event of unusual or life-threatening complications, treating investigators must immediately notify the Coordinating Center and the overall PI, Andrew Yee, MD at 617-726-2000.

5.6 Duration of Follow Up

Participants will be followed every three months after removal from protocol therapy or until confirmation of progressive disease, initiation of subsequent myeloma therapy, death, withdrawal of consent, or loss of follow up, whichever occurs first. Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event. The first follow up visit should occur three months after the end of treatment visit.

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

5.7 Criteria for Taking a Participant Off Study

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

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

The reason for taking a participant off study, and the date the participant was removed, must be documented in the case report form (CRF). The DF/HCC research team will update the relevant Off Treatment/Off Study information in OnCore in accordance with DF/HCC policy REGIST-101. The Coordinating Center will update this information for external site participants

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose delays and modifications will be made as indicated in the following table(s). The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website

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

6.1 Nivolumab

Nivolumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related AE, with the following exceptions:
  - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related AE
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for lymphopenia, leukopenia, AST, ALT, total bilirubin, or asymptomatic amylase or lipase:
  - Grade 3 lymphopenia or leukopenia does not require dose delay.
  - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity.
  - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity.
- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the treating investigator, warrants delaying the dose of study medication.

Immuno-oncology (I-O) agents are associated with AEs that can differ in severity and duration than AEs caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent in this protocol. Early recognition and management of AEs associated with immuno-oncology agents may mitigate severe toxicity. Management algorithms have been developed to assist investigators in assessing and managing the following groups of AEs:

- Gastrointestinal
- Renal
- Pulmonary
- Hepatic
- Endocrinopathies
- Skin
- Neurological.

For subjects expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage an AE, consider recommendations provided in the algorithms. These algorithms are found in the nivolumab IB and in the Appendix of this protocol. The guidance provided in these algorithms should not replace the Investigator's medical judgment but should complement it.

If nivolumab is held on day 1 of a new cycle, treatment with cyclophosphamide, ixazomib and dexamethasone will also be delayed.

Nivolumab may be delayed for up to 28 days. A delay of up to 14 days will be allowed for participants for non-AE-related events (e.g. vacation, family situations, etc.) after discussion with the overall PI.

If the participant discontinues nivolumab, the participant may continue ixazomib/dexamethasone after discussion with the overall PI.

6.2 Ixazomib

See Pre-Treatment Criteria above.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of treatment of nivolumab, ixazomib, cyclophosphamide, and dexamethasone will not be initiated until the toxicity has resolved as described above. The maximum delay before treatment should discontinued will be 4 weeks or at the discretion of the PI.

For dosing recommendations upon recovery, refer to tables below.

Table 6-1 Ixazomib Dose Adjustments

Dose Level	Dose
Starting Dose	4.0 mg
–1	3.0 mg
–2	2.3 mg
–3	Discontinue

For participants with total bilirubin > 1.5 × ULN, suggest starting ixazomib at 3 mg.

Treatment modifications due to ixazomib-related AEs are outlined in the accompanying tables.

Dosage adjustments for hematologic toxicity are outlined in Table 6-2.

Table 6-2. Ixazomib Dose Adjustments for Hematologic Toxicities

Criteria	Action
Within-Cycle Dose Modifications	
• If platelet count ≤ 30 × 10^9/L or ANC ≤ 0.50 × 10^9/L on an ixazomib dosing day (other than Day 1)	• Ixazomib dose should be withheld. • Complete blood count (CBC) with differential should be repeated at least every other day until the ANC and/or platelet counts have exceeded the prespecified values) on at least 2 occasions (or frequency at investigator discretion). • Upon recovery, ixazomib may be reinitiated with 1 dose level reduction.

Dosage adjustments for hematologic toxicity are outlined in Table 6-2.

Table 6-2. Ixazomib Dose Adjustments for Hematologic Toxicities

Criteria	Action
Dose Modifications for Subsequent Treatment Cycles	
• Delay of > 2 weeks in the start of a subsequent cycle due to lack of toxicity • ANC < 1.0×10^9/L, platelet count < 75×10^9/L, or other nonhematologic toxicities > Grade 1 or not to the participant's baseline condition	• Hold ixazomib until resolution as per above criteria. • Upon recovery, reduce ixazomib 1 dose level. • The maximum delay before treatment should be discontinued will be 4 weeks or at the discretion of the PI.
Dose Modifications for Subsequent Treatment Cycles	
• All hematologic toxicities	• For hematologic toxicity that occurs during a cycle but recovers in time for the start of the next cycle: o If dose was reduced within the cycle, start the next cycle at that same dose. o If due to toxicity timing, i.e., after Day 15 dosing thus a dose reduction was not required at that point in the cycle, reduce ixazomib by 1 dose level at the start of that cycle. o Do not reduce the dose both within a cycle and at the start of the cycle for the same most severe toxicity.

Table 6-3. Ixazomib Treatment Modification (Delays, Reductions, and Discontinuations) Due to Adverse Events (Non-Hematologic Toxicities)

Adverse Event (Severity)	Action on Study Drug	Further Considerations
Peripheral Neuropathy:		
Grade 1 peripheral neuropathy	• No action	Grade 1 signs and symptoms: asymptomatic; without pain or loss of function; clinical or diagnostic observations only
New or worsening Grade 1 peripheral neuropathy with pain or Grade 2	• Hold study drug until resolution to Grade ≤ 1 or baseline	Grade 2 signs and symptoms: Moderate symptoms; limiting instrumental activities of daily living (ADL)

Table 6-3. Ixazomib Treatment Modification (Delays, Reductions, and Discontinuations) Due to Adverse Events (Non-Hematologic Toxicities)

Adverse Event (Severity)	Action on Study Drug	Further Considerations
New or worsening Grade 2 peripheral neuropathy with pain or Grade 3	• Hold study drug until resolution to Grade ≤ 1 or baseline • Reduce study drug to next lower dose upon recovery	Grade 3 signs and symptoms: severe symptoms; limiting self-care ADL; assistive device indicated
New or worsening Grade 4 peripheral neuropathy	• Discontinue study drug	
Grade 2 Rash	• Manage supportively (see below)	The investigator and project clinician may discuss considerations for dose modifications and symptom management.
Grade 3 non-hematologic toxicity judged to be related to study drug	• Hold study drug until resolution to Grade < 1 or baseline	
If not recovered to < Grade 1 or baseline within 4 weeks	• Reduce study drug 1 to next lower dose upon return to < Grade 1 or baseline	
Subsequent recurrence Grade 3 that does not recover to < Grade 1 or baseline within 4 weeks	• Hold study drug until resolution to Grade < 1 or baseline • Reduce study drug to next lower dose	Monitor closely, take appropriate medical precautions, and provide appropriate symptomatic care
Grade 4 non-hematologic toxicities judged to be related to study drug	• Consider permanently discontinuing study drug	Exceptions are cases in which the investigator determines the participant is obtaining a clinical benefit

Once ixazomib is reduced for any toxicity, the dose may be re-escalated after discussion with the PI.

6.3 Cyclophosphamide

See Pre-Treatment criteria above.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of treatment of nivolumab, ixazomib, cyclophosphamide, and dexamethasone will not be initiated until the toxicity has resolved as described above. The maximum delay before treatment should discontinued will be 4 weeks or at the discretion of the PI

Cyclophosphamide Treatment Modification (Delays, Reductions, and Discontinuations) Due to Adverse Events (Hematologic Toxicities)	
Criteria	Action
Within-Cycle Dose Modifications	
• If platelet count ≤ 30×10^9/L or ANC ≤ 0.50×10^9/L on a cyclophosphamide dosing day (other than Day 1)	• Cyclophosphamide dose should be withheld. • Complete blood count (CBC) with differential should be repeated at least every other day until the ANC and/or platelet counts have exceeded the prespecified values) on at least 2 occasions (or frequency at investigator discretion). • Upon recovery, cyclophosphamide may be reinitiated with 1 dose level reduction or at same dose level, at investigator discretion.
Dose Modifications for Subsequent Treatment Cycles	
• Delay of > 2 weeks in the start of a subsequent cycle due to lack of toxicity • ANC < 1.0×10^9/L, platelet count < 75×10^9/L, or other nonhematologic toxicities > Grade 1 or not to the participant's baseline condition	• Hold cyclophosphamide until resolution as per above criteria. • Upon recovery, reduce cyclophosphamide 1 dose level or at same level, at investigator discretion. • The maximum delay before treatment should be discontinued will be 4 weeks or at the discretion of the PI.
Dose Modifications for Subsequent Treatment Cycles	
• All hematologic toxicities	• For hematologic toxicity that occurs during a cycle but recovers in time for the start of the next cycle: o If dose was reduced within the cycle, start the next cycle at that same dose. o If due to toxicity timing, i.e., after Day 15 dosing thus a dose reduction was not required at that point in the cycle, reduce ixazomib by 1 dose level at the start of that cycle. o Do not reduce the dose both within a cycle and at the start of the cycle for the same most severe toxicity.

Cyclophosphamide Treatment Modification (Delays, Reductions, and Discontinuations) Due to Adverse Events (Non-Hematologic Toxicities)

Adverse Event (Severity)	Action on Study Drug	Further Considerations
Grade 2 Rash	• Manage supportively (see below)	The investigator and project clinician may discuss considerations for dose modifications and symptom management.
Grade 3 nonhematologic toxicity judged to be related to cyclophosphamide	• old cyclophosphamide until resolution to Grade < 1 or baseline	
If not recovered to < Grade 1 or baseline within 4 weeks	• Reduce cyclophosphamide to next lower dose upon return to < Grade 1 or baseline	
Subsequent recurrence Grade 3 that does not recover to < Grade 1 or baseline within 4 weeks	• Hold cyclophosphamide until resolution to Grade < 1 or baseline • Reduce cyclophosphamide to next lower dose	Monitor closely, take appropriate medical precautions, and provide appropriate symptomatic care
Grade 4 nonhematologic toxicities judged to be related to study drug	• Consider permanently discontinuing cyclophosphamide	Exceptions are cases in which the investigator determines the participant is obtaining a clinical benefit

Cyclophosphamide dose adjustments

Dose level	Dose
Starting	300 mg/m^2
−1	225 mg/m^2
−2	170 mg/m^2
−3	125 mg/m^2

6.4 Dexamethasone

Instructions for Dexamethasone Dose Modifications or Interruption During a Cycle

Toxicity	**Low Dose Dexamethasone Dose Modification**
Dyspepsia = Grade 1-2	Maintain dose and treat with histamine (H2) blockers or equivalent. Decrease by one dose level if symptoms persist.
Dyspepsia ≥ Grade 3	Withhold dose until symptoms are controlled. Add H2 blocker or equivalent and decrease one dose level when dosing is resumed.
Edema ≥ Grade 3	Use diuretics as needed and decrease dose by one dose level.

Toxicity	Low Dose Dexamethasone Dose Modification
Confusion or mood alteration ≥ Grade 2	Withhold dose until symptoms resolve. When dosing is resumed decrease dose by one dose level.
Muscle weakness (steroid myopathy) ≥ Grade 2	Withhold dose until muscle weakness ≤ grade 1. When dosing is resumed, decrease dose by one dose level.
Hyperglycemia ≥ Grade 3	Decrease dose by one dose level. Treat with insulin or oral hypoglycemic agents as needed.
Acute pancreatitis	Discontinue dexamethasone from treatment regimen.
Other ≥ Grade 3 dexamethasone-related adverse events	Withhold dexamethasone dosing until the adverse event resolves ≤ grade 2. Decrease by one dose level when dosing is resumed.

Dexamethasone Dose Reduction Levels

Dose level	Dose
Starting	40 mg
Level −1	20 mg
Level −2	10 mg

Dose reduction for age, grade 2 or grade 3 AEs believed to be related to dexamethasone and not listed above are permitted. The AE must be documented in medical record and the CRF.

Additional dose reductions for lower grade toxicity than those listed above or beyond level −2 should be discussed with the PI.

Dose escalation of dexamethasone is permitted after toxicities resolve, at the treating physician's discretion.

7. Adverse Events List and Reporting Requirements

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

7.1 Expected Toxicities

7.1.1 Adverse Event List

7.1.1.1 *Nivolumab*

Adverse events experienced in ≥10% of patients include the following:

- Diarrhea, nausea, fatigue, rash, and pruritus

Adverse events experienced in ≥1% to <10% of patients include:

- Hypothyroidism, hyperthyroidism, hyperglycemia
- Colitis, stomatitis, mouth ulceration, vomiting, abdominal pain, constipation, dry mouth
- Pyrexia, edema (general and peripheral), hepatitis, infusion-related reactions
- Upper respiratory infections
- Increased lipase, increased amylase, increased aspartate aminotransferase, increase alanine aminotransferase, increased blood bilirubin, hyponatremia
- Decreased appetite, musculoskeletal pain, arthralgias, peripheral neuropathy, headache, dizziness, nephritis, pneumonitis, dyspnea, cough,
- Vitiligo, dry skin, erythema, alopecia
- Hypertension

Events that are listed as uncommon and experienced in ≥ 0.001% to < 1% of patients include:

- Urticaria
- Vasculitis, rosacea, psoriasis, erythema multiforme
- Tubulointerstitial nephritis, renal failure, acute kidney injury
- Encephalitis, autoimmune neuropathy, facial nerve paresis, myasthenic syndrome, demyelization, Guillain-Barré syndrome
- Polymyalgia rheumatica, histiocytic necrotizing lymphadenitis
- Bronchitis, lung infiltration
- Hypersensitivity, anaphylactic reaction, duodenal ulcer, pancreatitis, uveitis, diabetes mellitus, diabetic ketoacidosis, thyroiditis, autoimmune hypophysitis, hypopituitarism, adrenal insufficiency, tachycardia, arrhythmias,

A rare risk experienced by ≥0.00001% to <0.001% of patients includes:

- Toxic epidermal necrolysis (including Stevens-Johnson syndrome)

7.1.1.2 *Ixazomib*

Adverse events experienced in ≥ 10% of patients include the following:

- Blood and lymphatic system disorders: anemia , thrombocytopenia , neutropenia , leukopenia
- Gastrointestinal disorders: diarrhea , nausea , vomiting , abdominal pain , constipation
- General disorders and administration site conditions: fatigue , fever , peripheral edema
- Skin and subcutaneous tissue disorders: rash, maculopapular
- Respiratory, thoracic and mediastinal disorders: cough , dyspnea
- Nervous system disorders: headache , dizziness
- Metabolism and nutrition disorders: anorexia , dehydration
- Musculoskeletal and connective tissue disorders: arthralgia , back pain
- Infections and infestations: upper respiratory infection

Events that are listed as uncommon and experienced in ≥ 0.001% to < 1% of patients include :

- Drug-induced liver injury, hepatocellular injury, hepatic steatosis, hepatitis cholestatic and hepatotoxicity

7.1.1.3 *Cyclophosphamide*

Adverse events with cyclophosphamide include the following (note that the frequency for many of these adverse events below is anticipated to be less due to the lower dose of cyclophosphamide that is used) in this trial.

Adverse events that may occur ≥ 10% of participants:

- Neutropenia
- Nausea and vomiting
- Anorexia
- Abdominal discomfort
- Diarrhea
- Fatigue
- Oral ulcers
- Amenorrhea

Adverse events that may occur in <10% of participants

- Elevation in AST, ALT, or other liver function tests
- Jaundice
- Alopecia
- Rash
- Change in pigmentation of skin
- Nail changes

Adverse events that may occur in <1% of participants:

- Myocarditis
- Myopericarditis
- Pericardial effusion, including cardiac tamponade
- Pneumonitis, pulmonary fibrosis, pulmonary veno-occlusive disease
- Secondary malignancies
- Veno-occlusive disease
- Infertility
- Impairment of wound healing
- Hyponatremia
- Hemorrhagic cystitis
- Hemorrhagic colitis

7.1.1.4 *Dexamethasone*

Adverse events experienced in > 10% of patients treated with dexamethasone:

- Increased appetite
- Weight gain
- Sleep disturbance
- Hypertension
- Fluid retention
- Ankle swelling
- Bruising
- Infection
- Mood changes
- Slow wound healing
- Depression
- Hyperglycemia, which may lead to fatigue, weight loss, excessive thirst, and frequent urination

Adverse events experienced in < 10% of patients treated with dexamethasone:

- Loss of appetite
- Muscle twitching
- Increased thirst
- Frequent urination
- Increased perspiration
- Diarrhea
- Nausea
- Headache
- Spinal fracture or fracture of bones
- Tachycardia
- Fungal infections

Adverse events experienced in < 1% of patients treated with dexamethasone:

- Blurred vision
- Personality changes
- Stomach ulcers with bleeding that may cause hematemesis
- Blood in the stool
- Abdominal pain

Other, less frequent, events that may occur in patients treated with dexamethasone:

- Bowel perforation
- Irritation and bleeding of the esophagus
- Heart failure

- Allergic reaction that may lead to facial redness
- Shortness of breath
- Abdominal cramps
- Hypotension
- Convulsions
- Brain swelling
- Dizziness
- Cataracts
- Glaucoma and increased blood pressure in the eye
- Development of diabetes
- Pancreatic inflammation
- Abdominal swelling
- Hypokalemia
- Deep vein thrombosis or pulmonary embolism
- Malaise
- Swelling and/or redness of skin
- Allergic skin reactions
- Itching
- Hirsutism
- Muscle weakness or loss of muscle mass
- Rupture of tendons
- Menstrual cycle disturbances
- Hiccups

7.2 Definitions

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

7.2.1 Adverse Events (AE)

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

Abnormal laboratory values or diagnostic test results constitute adverse events only if they induce clinical signs or symptoms or require treatment or further diagnostic tests. Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

7.2.2 Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence at any dose that:

- Results in death
- Is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- Requires inpatient hospitalization or causes prolongation of existing hospitalization (see below for exceptions)
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event, defined as a medical event that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the subject or may require intervention (e.g., medical, surgical) to prevent one of the other serious outcomes listed above. Examples of such events include but are not limited to intensive treatment in an emergency department or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.
- Potential drug-induced liver injury (DILI) is also considered an important medical event.
- Suspected transmission of an infectious agent (e.g., pathogenic or non-pathogenic) via the study drug is an SAE.
- Although pregnancy, overdose, cancer and potential drug induced liver injury (DILI) are not always serious by regulatory definition, these events must be handled as SAEs.

The following hospitalizations are not considered SAEs:

- A visit to the emergency room or other hospital department lasting less than 24 hours that does not result in admission (unless considered an "important medical event" or a life-threatening event)
- Elective surgery planned before 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 remedying ill health state that was planned before study entry. 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)

7.2.3 Expectedness

Adverse events can be expected or unexpected.

7.2.3.1 *Expected Adverse Event*

Expected adverse events are those that have been previously identified as resulting from administration of the agent. For the purposes of this study, an adverse event is considered expected when it appears in the current adverse event list, the Investigator's Brochure, the package insert or is included in the informed consent document as an associated risk. Refer to Section 6.1 for a listing of expected adverse events

associated with the study agent(s).

7.2.3.2 *Unexpected Adverse Event*

For the purposes of this study, an adverse event is considered unexpected when it varies in nature, intensity or frequency from information provided in the current adverse event list, the Investigator's Brochure, the package insert or when it is not included in the informed consent document as an associated risk.

7.2.4 Attribution

Attribution is the relationship between an adverse event or serious adverse event and the study treatment. Attribution will be assigned as follows:

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

7.3 Expedited Adverse Event Reporting

All serious adverse events (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment must be reported to the Coordinating Center and the PI on the local institutional SAE form.

For expedited reporting purposes, AEs for the **agents** that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided

Expedited reporting includes SAEs and AEs as defined above as well as the following:

- Grade 2 (moderate) and Grade 3 (severe) events that are unexpected and at least possibly related/associated with the intervention.
- All Grade 4 (life-threatening or disabling) events that are unexpected or not specifically listed in the protocol as not requiring reporting.
- All Grade 5 (fatal) events while the participant is enrolled and actively participating in the trial OR when the event occurs within 30 days of the last study intervention. Note: If the participant is in long term follow up, death must be reported at the time of continuing review.

For multi-institution studies where a DF/HCC investigator is serving as the PI, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any medical event equivalent to an unexpected grade 2 or 3 with a possible, probable or definite attribution, unexpected grade 4 toxicities, and grade 5 (death) regardless of study phase or attribution.

For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to IP (attribution), expectedness, action taken regarding IP, and outcome. All SAEs should be followed to resolution or stabilization. A final report to document resolution of the SAE is required.

In the event of an unanticipated problem or life-threatening complications treating investigators must immediately notify the Coordinating Center and overall PI.

7.3.1 DF/HCC Expedited Reporting Guidelines

Investigative sites within DF/HCC will report AEs directly to the DFCI Office for Human Research Studies (OHRS) per the DFCI IRB reporting policy.

Other investigative sites will report AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. A copy of the submitted institutional AE form should be forwarded to the Coordinating Center within the timeframes detailed in the table below. The Coordinating Center will submit AE reports from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events.

Attribution	DF/HCC Reportable AEs				
	Gr. 2 & 3 AE Expected	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*
# If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.					
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within *1 business day* of learning of the event.					

Participating investigators must report each adverse event to the Coordinating Center in accordance with these timeframes. In the event that the participating investigator does not become aware of the adverse event immediately (e.g., participant sought treatment elsewhere) or within the reporting timeframes listed in the table above, the participating investigator is to report the event within 1 business day after learning of it and document the time of first awareness of the adverse event..

7.4 Expedited Reporting to the Food and Drug Administration (FDA)

The overall PI, as study sponsor, will be responsible for all communications with the FDA. The Coordinating Center, on behalf of the overall PI, will report to the FDA, Takeda, and Bristol-Myers

Squibb, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.5 Expedited Reporting to Hospital Risk Management

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

7.6 Reporting to Takeda

SAEs must be reported to Takeda Oncology Pharmacovigilance (or designee) from the first dose of study drug through 30 days after administration of the last dose of ixazomib. Any SAE that occurs at any time after completion of ixazomib treatment or after the designated follow-up period that the sponsor-investigator and/or sub-investigator considers to be related to any study drug must be reported to Takeda Pharmacovigilance (or designee). In addition, new primary malignancies that occur during the follow-up periods must be reported, regardless of causality to study regimen, for a minimum of three years after the last dose of the investigational product, starting from the first dose of study drug. All new cases of primary malignancy must be reported to Takeda Oncology Pharmacovigilance (or designee).

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered SAEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned).

All SAEs should be monitored until they are resolved or are clearly determined to be due to a participant's stable or chronic condition or intercurrent illness(es).

Regardless of expectedness or causality, all SAEs (including serious pretreatment events) must be reported to Takeda Oncology Pharmacovigilance (or designee):

- **Fatal and life threatening SAEs** within 24 hours of the study team and/or investigator's observation or awareness of the event.
- **All other serious (non-fatal/non-life threatening) events** within 4 calendar days of the investigator's observation or awareness of the event

See below for contact information for the reporting of SAEs to Takeda Oncology Pharmacovigilance.

The Coordinating Center must fax or email the SAE Form per the timelines above.

The SAE report must include at minimum:

- Event term(s)
- Serious criteria
- Intensity of the event(s): Sponsor-investigator's or sub-investigator's determination. Intensity for each SAE, including any lab abnormalities, will be determined by using the NCI CTCAE version 4.0.
- Causality of the event(s): Sponsor-investigator's or sub-investigator's determination of the

relationship of the event(s) to study drug administration.

Relationship to all study drugs for each SAE will be determined by the investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

As a multi-center study, the sponsor-investigator (PI) is responsible to ensure that the SAE reports are sent to Takeda Pharmacovigilance (or designee) from all sites participating in the study. Sub-investigators must report all SAEs to the Coordinating Center so that the sponsor-investigator can meet his/her foregoing reporting obligations to the required regulatory agencies and to Takeda Pharmacovigilance.

Sponsor-investigator must also provide Takeda Pharmacovigilance with a copy of all communications with applicable regulatory authorities related to the study product(s), as soon as possible but no later than 4 calendar days of such communication.

Follow-up information on the SAE may be requested by Takeda.

Takeda SAE and Pregnancy Reporting Contact Information

US
Fax Number: 1-800-963-6290
Email: *TakedaOncoCases@cognizant.com*

Suggested reporting form:

- SAE Report Form (provided by Takeda)
- US FDA MedWatch 3500A: http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

7.6.1 Product Complaints or Medication Errors

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact Takeda (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Takeda Quality representative.

A medication error is a preventable event that involves an identifiable participant and that leads to inappropriate medication use, which may result in participant harm. While overdoses and underdoses constitute medication errors, doses missed inadvertently by a participant do not. Investigators must record all medication errors (including overdose) on the appropriate form. Individuals who identify a

potential medication error situation should immediately contact Takeda (see below) and report the event.

For Product Complaints or Medication Errors (Including Overdose), contact Takeda Pharmacovigilance

For NINLARO:
Phone: 1-844-N1-POINT (1-844-617-6468)
E-mail: *GlobalOncologyMedinfo@takeda.com*
Fax: 1-800-881-6092
Hours: Mon-Fri, 9 a.m. – 7 p.m. ET

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Takeda Pharmacovigilance.

7.7 SAE Reporting to BMS

SAEs following the participant's written consent to participate in the study through day 100 of discontinuation of nivolumab dosing, whether or not related to the study drug, and pregnancies must be reported to BMS within 1 business day of notification of the event. SAEs must be recorded in writing on the SAE Report Form; pregnancies on a Pregnancy Surveillance Form. All reports should be submitted to the Coordinating Center. The Coordinating Site will facilitate PI review and submission of initial reports and any follow-up reports to BMS.

BMS SAE REPORTING

BMS SAE Email Address: *Worldwide.Safety@BMS.com*

BMS SAE Fax Number: 609-818-3804

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, and expectedness of the event. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. 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 to the Coordinating Center (or monitor) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization. A final report to document resolution of the SAE is required. Follow-up SAE reports should include the same investigator term(s) initially reported.

The Sponsor will reconcile the clinical database SAE cases (case level only) transmitted to BMS Global Pharmacovigilance (*Worldwide.Safety@bms.com*). Frequency of reconciliation should be every 3 months and prior to the database lock or final data summary. BMS Global Pharmacovigilance & Epidemiology (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.

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.

7.8 Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

If a female participant becomes pregnant or suspects that she is pregnant while participating in this study or within five months after the last dose of nivolumab, she must inform the investigator immediately and permanently discontinue study drugs. The Coordinating Center must immediately fax a completed Pregnancy Form to the Takeda Department of Pharmacovigilance and to BMS. The pregnancy must be followed for the final pregnancy outcome.

If a female partner of a male participant becomes pregnant during participation in this study, the Coordinating Center must also immediately fax a completed Pregnancy Form to the Takeda Department of Pharmacovigilance and BMS. Every effort should be made to follow the pregnancy for the final pregnancy outcome.

7.9 Routine Adverse Event Reporting

All adverse events (serious and non-serious) must be reported in routine study data submissions to the overall PI on the toxicity case report forms. AEs reported through expedited processes (e.g., reported to the IRB, FDA, Takeda and BMS) must *also* be reported in routine study data submissions.

7.9.1 Non-Serious Adverse Event Reporting to BMS

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, as part of an annual reporting requirement.

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 100 days following the last dose of nivolumab or start of a new line therapy (whichever is sooner).

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.

8. PHARMACEUTICAL INFORMATION

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

8.1 Nivolumab

8.1.1 Description

Nivolumab is a fully human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the PD-1 cell surface membrane receptor. Nivolumab inhibits the interaction of PD-1 with its ligands, PD-L1 and PD-L2, resulting in enhanced T-cell proliferation and interferon gamma (IFN-γ) release in vitro.

8.1.2 Form

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) or 40 mg/4 mL (10 mg/mL), is a clear to opalescent, colorless to pale yellow liquid, which may contain light (few) particulates. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), and polysorbate 80, pH 6.0 and includes a 0.7 mL overfill to account for vial, needle, and syringe (VNS) holdup. It is supplied in 10-cc Type I flint glass vials, stoppered with butyl rubber stoppers and sealed with aluminum seals. The only difference between the two drug product presentations is the vial fill volume.

8.1.3 Storage and Stability

The product does not contain a preservative. Vials of nivolumab injection must be stored at 2°-8°C (36°-46°F) and protected from light, freezing, and shaking. After preparation, store the nivolumab infusion either:

- At room temperature for no more than 4 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion or
- Under refrigeration at 2°C to 8°C (36°F-46°F) for no more than 24 hours from the time of infusion preparation.
- Do not freeze.

If a temperature excursion is noted at your site, the site must complete a temperature excursion form provided by the lead site. The Coordinating Center will then submit to Bristol-Myers Squibb to assess if the drug is appropriate for use or should be destroyed.

8.1.4 Compatibility

Do not co-administer other drugs through the same intravenous line.

Flush the intravenous line at end of infusion.

No incompatibilities between nivolumab and polyvinyl chloride (PVC), non PVC/non DEHP (di(2-ethylhexyl)phthalate) IV components, or glass bottles have been observed.

8.1.5 Handling

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

8.1.6 Availability

Nivolumab for injection will be supplied free of charge by BMS. The Coordinating Center will provide all external sites with a study specific order form

8.1.7 Preparation

Visually inspect drug product solution for particulate matter and discoloration prior to administration. Nivolumab is a clear to opalescent, colorless to pale-yellow solution. Discard the vial if the solution is cloudy, is discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.

- Withdraw the required volume of nivolumab and transfer into an intravenous container.
- Dilute nivolumab with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP, to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL.
- Mix diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials of nivolumab.

8.1.8 Administration

See above in Section 5.

The administration of nivolumab infusion must be completed within 24 hours of preparation.

8.1.9 Ordering

Each participating institution will order nivolumab directly from the supplier BMS. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded by the Coordinating Center. A study specific order form will be supplied.

8.1.10 Accountability

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

8.1.11 Destruction and Return

For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes may be destroyed on site. Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible Study Monitor or designee unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (e.g., cytotoxics or biologics). On-site destruction is allowed provided the following minimal standards are met:

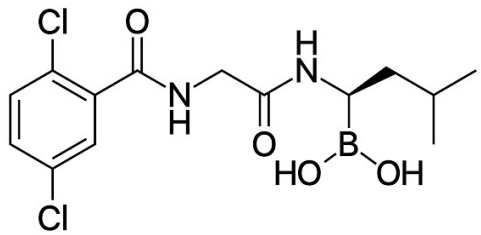
- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's SOPs and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, (e.g., incinerator, licensed sanitary landfill, or licensed waste disposal vendor) must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study drug. It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept. If study drug will not be destroyed upon completion or termination of the study, all unused and/or partially used study drug that was supplied by BMS must be returned to BMS. The return of study drug will be arranged by the responsible study monitor.

8.2 Ixazomib

8.2.1 Description

The chemical name is: B-[(IR)-1-[[2-[(2,5-dichlorobenzoyl)amino]acetyl]amino]-3-methylbutyl]boronic acid. Ixazomib, also known as MLN9708 and Ninlaro, is an oral proteasome inhibitor. The molecular formula of ixazomib citrate is $C_{20}H_{23}BCl_2N_2O_9$, and its molecular weight is 517.12.



Ixazomib

8.2.2 Form

The ixazomib drug product is provided in strengths of 4.0-, 3.0-, and 2.3-mg capsules as the active boronic acid. The different dose strengths are differentiated by both capsule size and color as described below:

Dose Strength	Capsule Size	Capsule Color
4.0 mg	Size 4	Ivory
3.0 mg	Size 3	Light gray
2.3 mg	Size 2	Light pink

For additional details, please see the ixazomib IB.

8.2.3 Storage and Stability

On receipt at the investigative site, ixazomib should remain in the blister and carton provided until use or dispensation. Store at room temperature, do not store above 86°F (30°C). Do not freeze ixazomib. Store capsules in original packaging until immediately prior to use. Ensure that the drug is used before the retest expiry date provided by Millennium. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life.

In countries where local regulations permit, ixazomib capsules dispensed to the participant for take-home dosing should remain in the blister packaging as noted above until the point of use. The investigative site is responsible for providing the medication to the participant in the correct daily dose configurations. Comprehensive instructions should be provided to the participant in order to ensure compliance with dosing procedures. Participants who are receiving take-home medication should be given only 1 cycle of medication at a time. Participants should be instructed to store the medication at room temperature, below 86°F (30°C), for the duration of each cycle. Participants should be instructed to return their empty blister packs to the investigative site, rather than discarding them. Reconciliation will occur accordingly when the participant returns for their next cycle of take-home medication. Any extreme in temperature should be reported as an excursion and should be dealt with on a case-by-case basis.

8.2.4 Compatibility

Not applicable, as ixazomib is an oral drug

8.2.5 Handling

Because ixazomib is an investigational agent, it should be handled with due care. Participants should be instructed not to chew, break, or open capsules. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful by inhalation, ingestion, or skin absorption. Gloves and protective clothing should be worn during cleanup and return of broken capsules and powder to minimize skin contact.

The area should be ventilated, and the site washed with soap and water after material pick-up is complete. The material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations.

In case of contact with the powder (e.g., from a broken capsule), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified. Participants are to be instructed on proper storage, accountability, and administration of ixazomib, including that ixazomib is to be taken as intact capsules

8.2.6 Availability

Ixazomib will be supplied by Takeda as capsules of 2.3 mg, 3.0 mg, and 4.0 mg ixazomib and will be sent to the participating site research pharmacy. The study drug will be labeled and handled as open-label material, and packaging labels will fulfill all requirements specified by governing regulations.

The study drug ixazomib capsules will be provided by Takeda free of charge.

8.2.7 Preparation

Ixazomib is an anticancer drug and as with other potentially toxic compounds caution should be exercised when handling ixazomib capsules.

One cycle worth of ixazomib will be provided at each cycle day 1, and participants will not be required to take doses in clinic.

Participants are to be instructed on proper storage, accountability, and administration of ixazomib, including that ixazomib is to be taken as intact capsules

8.2.8 Administration

Ixazomib will be taken on days 1, 8, and 15 of each 28-day cycle on an out-patient basis. At all times when dispensing ixazomib protocol therapy, study site personnel will review the instructions, printed on the packaging, with participants. Participants should be instructed to swallow ixazomib capsules whole, with water, and not to break, chew, or open the capsules. Study drug should be taken on an empty stomach (no food or drink) at least 1 hour before or 2 hours after food. Each capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules.

For additional information on administration, see also Section 5.

8.2.9 Ordering

The investigator or designee will order ixazomib from Takeda, according to the ordering instructions

provided by company.

8.2.10 Accountability

Study drug will be administered or dispensed only to eligible participants under the supervision of the investigator or identified sub-investigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing and participants will maintain a drug diary.

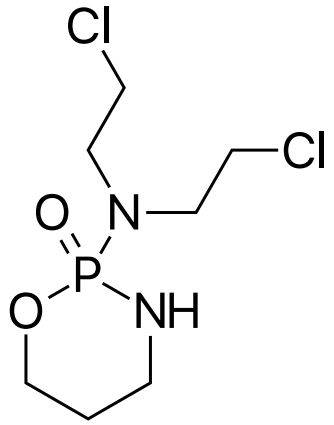
8.2.11 Destruction and Return

Investigational ixazomib (unused, expired or end of study) should be destroyed on site according to the institution's standard operating procedure. Removal and destruction should be documented on drug accountability logs.

8.3 Cyclophosphamide

8.3.1 Description

Cyclophosphamide is a prodrug biotransformed to active alkylating metabolites by a mixed function microsomal oxidase system. It is a synthetic drug chemically related to the nitrogen mustards. The chemical name for cyclophosphamide is 2-[bis(2-chloroethyl)amino]tetrahydro-2H-1,3,2-oxazaphosphorine 2-oxide monohydrate, and has the following structural formula.



Cyclophosphamide has a molecular formula of $C_7H_{15}Cl_2N_2O_2P{\bullet}H_2O$ and a molecular weight of 279.1. Cyclophosphamide is soluble in water, saline, or ethanol.

8.3.2 Form

Cyclophosphamide for injection is a sterile white cake available in different strength vials.

8.3.3 Storage and Stability

Cyclophosphamide will be stored according to institutional practice.

8.3.4 Compatibility

Do not co-administer other drugs through the same intravenous line.

8.3.5 Handling

Cyclophosphamide will be handled according to institutional practice

8.3.6 Availability

Commercial supplies of cyclophosphamide will be used for this study.

8.3.7 Preparation

Cyclophosphamide will be prepared according to institutional practice.

8.3.8 Administration

Cyclophosphamide will be administered according to institutional practice and according to Section 5.

8.3.9 Ordering

Cyclophosphamide will be ordered according to institutional practice.

8.3.10 Accountability

Per institutional practice.

8.3.11 Destruction and Return

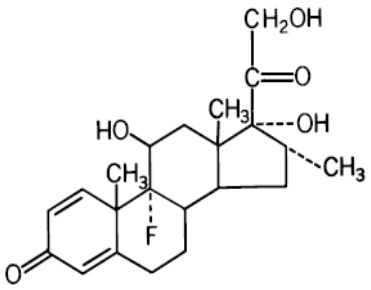
Per institutional practice.

8.4 Dexamethasone

8.4.1 Description

Dexamethasone is a synthetic adrenocortical steroid. Corticosteroids are naturally occurring chemicals produced by the adrenal glands located above the kidneys. Corticosteroids affect the function of many cells within the body and suppress the immune system. Corticosteroids also block inflammation and are used in a wide variety of inflammatory diseases affecting many organs. The molecular weight for dexamethasone is 392.47. It is designated chemically as 9-fluoro-11β,17,21-trihydroxy-16α-

methylpregna-1,4-diene-3,20-dione. Dexamethasone is stable in air and almost insoluble in water. The empirical formula is $C_{22}H_{29}FO_5$ and the structural formula is:



8.4.2 Form

Dexamethasone is a white to practically white, odorless, crystalline powder. It is available in 2 or 4 mg tablets (commercially) for oral administration.

8.4.3 Storage and Stability

Dexamethasone will be stored according to institutional practice.

8.4.4 Compatibility

As dexamethasone is an oral drug, this is not applicable.

8.4.5 Handling

Dexamethasone will be handled according to institutional practice.

8.4.6 Availability

Commercial supplies of dexamethasone will be used for this study.

8.4.7 Preparation

Not applicable.

8.4.8 Administration

Dexamethasone will be administered according to institutional practice and according to Section 5.

8.4.9 Ordering

Commercial supplies of dexamethasone will be used for this trial.

8.4.10 Accountability

Per institutional practice.

8.4.11 Destruction and Return

Per institutional practice.

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

This trial will provide samples from participants with relapsed disease who are uniformly treated to comprehensively characterize the MM genome and transcriptome (via expression profiling and/or sequencing), to define molecular events driving progression of MM, as well as to identify novel therapeutic targets and biomarkers. The findings from these correlative studies will be hypothesis generating.

Analysis will include genotyping by the Snapshot platform at Massachusetts General Hospital.

An additional aim is to evaluate biomarkers that may correlate with response to nivolumab in combination with ixazomib and dexamethasone. These biomarkers may include PD-L1 expression on myeloma cells and tumor stroma and PD1 expression on CD4 T cells, T- and B- cell subsets assessed by flow cytometry, expression profiling of PBMCs and tumor cells, and T cells phenotyping including expression of other co-stimulatory molecules e.g. OX40 and 4-1BB. These biomarkers may be assessed before and over the course of treatment.

Streck tubes will be provided to each site for collection of peripheral blood and bone marrow aspirates. Sites will be responsible for the standard purple top (EDTA) tubes as well a shipment of samples.

9.1 Bone Marrow Aspirate

Collection of bone marrow aspirate for exploratory analysis is recommended. Refer to Section 10.1. Study Calendar for Research Samples for collection schedule. There is a ± 10 day window for obtaining these samples. Specimens will be shipped (via traceable carrier) to and subsequently processed, analyzed, and stored at Massachusetts General Hospital or Dana Farber Cancer Institute. Participating sites are responsible for shipment of specimens.

9.1.1 Sample Instructions

9.1.1.1 *Bone Marrow Aspirate Specimens Required*

The following should be collected per the Study Calendar for Research Samples. Specimens must be collected on Mondays, Tuesdays, Wednesdays or Thursdays for same-day shipment (FEDEX). Samples should be shipped with a fridge pack (preferably NanoCool 2-8°C systems and NOT dry ice) and Fed-Ex

priority overnight (OR by courier service if patient treated at MGH).

For Bone Marrow aspirate:

- 2 purple top tubes (EDTA) (10 mL each)

Tubes may be filled roughly one third to half way with bone marrow aspirate.

9.1.1.2 *Processing Information*

There is no required processing for bone marrow samples at each participating site prior to shipment.

9.2 Peripheral Blood Samples

Refer to Section 10.1. Study Calendar for Research Samples for collection schedule. There is a ± 10 day window for obtaining these samples. Specimens will be shipped (via traceable carrier) to and subsequently processed, analyzed, and stored at Massachusetts General Hospital or Dana-Farber Cancer Institute.

9.2.1 Sample Instructions

9.2.1.1 *Peripheral Blood Specimens Required*

The following should be collected per the Study Calendar for Research Samples. Specimens must be collected on Mondays, Tuesdays, Wednesdays or Thursdays for same-day shipment (FEDEX). Samples should be shipped with a fridge pack (preferably NanoCool 2-8°C systems and NOT dry ice) and Fed-Ex priority overnight (OR by courier service if patient treated at MGH).

For Peripheral Blood samples:

- 2 purple top tubes (EDTA) (10 mL each)
- 1 Streck Cell-Free DNA BCT tube, 10 mL

9.2.1.2 *Processing Information*

There is no required processing for peripheral blood samples at each participating site prior to shipment.

9.3 Shipping Instructions

Refer to table below for shipping destination of samples.

Bone marrow and peripheral blood samples must be shipped on the day of collection and cannot be batched. Samples should be shipped with a fridge pack (preferably NanoCool 2-8°C systems and NOT dry ice) and Fed-Ex priority overnight (OR by courier service if patient treated at MGH). Participating sites are responsible for shipment of specimens.

Prior to shipping any samples, please notify the Coordinating Center of the pending shipment and the

samples included. For sites outside of Massachusetts, ship Monday, Tuesday, Wednesday, or Thursdays as shipments cannot be received on weekends and/or on holidays. For sites in Massachusetts, Friday sample collection is permitted if samples arrive at the respective destination by noon.

Label all specimens with the following:

- Protocol Number
- Subject Initials
- Subject study number
- Visit at which sample was drawn (screening, cycle number and day, complete response assessment (yes/no), etc.)
- Date sample drawn (mm/dd/yyyy)
- Time sample drawn (24 hour clock)
- Type of sample

Sites must maintain a detailed log of all specimens obtained to include the information above as well as dates shipped and confirmation of receipt.

An inventory sheet including a complete list of samples shipped (participant number, time point, study #, etc.) must accompany each shipment. Please sign and date the form and retain a copy for site record maintenance. Please send an electronic copy of the sample list by email or fax to the Coordinating Center. The listing must also include a contact name, address and phone number of the person who is responsible for the shipment.

Bone marrow and peripheral blood correlative samples

	Purple top	**Purple top**	**Streck cell-free DNA BCT tube (brown tiger)**	**Destination**
ALL SITES				
Bone marrow	2			Lohr laboratory
Peripheral blood	2		1	
DF/HCC SITES (SCREENING ONLY)				
Bone marrow		1		MGH flow cytometry
Peripheral blood		1		

Lohr laboratory

Attention: Tushara Vijaykumar
Dana-Farber Cancer Institute
DA-542
1 Jimmy Fund Way
Boston, MA 02115

Email: *Tushara_Vijaykumar@dfci.harvard.edu*
Phone: 312-662-2799

Please alert Tushara Vijaykumar and the Coordinating Center by e-mail when samples are being sent.

MGH flow cytometry

Attention: Kathleen Mary Ellen Gallagher, PhD
Immune Monitoring Laboratory
3rd floor
MGH Cancer Center
149 13th Street
Charlestown, MA 02129
Email: *KGALLAGHER19@mgh.harvard.edu*
Phone: 617-643-5152

Please alert Dr. Gallagher and the Coordinating Center by e-mail when samples are being sent.

10. Study Calendar

Screening evaluations are to be conducted within 21 days prior to initiation of protocol therapy. Baseline assessments are to be conducted on Cycle 1 Day 1 of treatment. With the exception of hematology, screening assessments that are performed within 7 days of Cycle 1 Day 1 do not need to be repeated at baseline. Unless otherwise specified, drug administration and assessments have a ± 3 day window (or longer, after discussion with the PI). However, all assessments must be performed prior to administration of any study medication.

Procedure	Screening [a]	Cycle 1-2			Cycle 3+			End of treatment	Follow up
		Day 1	Day 8	Day 15	Day 1	Day 8	Day 15		
Informed consent	X								
Inclusion/exclusion criteria	X								
Complete medical history	X								
Vital signs, height, weight, BSA [c]	X	X	X	X	X	X	X	X	X
Physical examination	X	X			X			X	X
ECOG performance status	X	X			X			X	X
Adverse events		X	X	X	X	X	X	X	X
12-lead EKG	X								
Chest X-ray	X								
CBC with differential	X	X	X	X	X	X*	X	X	X
Coagulation [d]	X								
Chemistry [e]	X	X	X	X	X	X*	X	X	X
Calculated creatinine clearance†	X	X			X				
HIV, hepatitis B, hepatitis C testing [f]	X								
Pregnancy test [g]	X	X			X				
Pregnancy counseling	X	X			X			X	

Thyroid function [h]	X				X			X	
Monoclonal protein studies and B2M [i]	X	X			X			X	X
Skeletal survey	X								
Evaluation of soft tissue plasmacytomas [j]	X								
Bone marrow aspirate (and biopsy)[k]	X								

†Calculated by Cockroft-Gault equation.

*CBC with differential and chemistry studies to be performed on cycles 3-8.

a. Assessments required at screening visit, except for hematology, do not have to be repeated if performed ≤ 7 days prior to C1D1 unless otherwise specified. To take into account scheduling conflicts (e.g., over public holidays), a ±3 day window will be allowed for all assessments, unless otherwise specified.
b. End of treatment visit should occur within 28 days of discontinuation of treatment.
c. Height required at baseline only. BSA and weight according to institutional practice. Note vital sign measurements.
d. Coagulation profile includes prothrombin time (PT) or International Normalized Ratio (INR), activated partial thromboplastin time (aPTT), and fibrinogen. Evaluation should be performed at screening visit and may be repeated at the investigator's discretion, if medically indicated. If participant is receiving warfarin, then coagulation parameters should be monitored more frequently, per investigator's discretion
e. Chemistry includes the following parameters: complete metabolic panel (includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, magnesium, phosphorus, AST, ALT, alkaline phosphatase, total bilirubin, direct bilirubin), as per local institutional practice, and LDH. If total bilirubin > ULN, direct and indirect bilirubin should be performed as per institutional practice.
f. Testing for hepatitis B, hepatitis C, and HIV per local institutional practice. In participants who have a prior history of hepatitis C and are viral load negative, participants should undergo hepatitis C viral load testing monthly for the first six months and then every three months while on the trial medications.
g. Females of reproductive potential must have one negative pregnancy test at screening (serum or urine).
h. Thyroid function includes thyroid stimulating hormone (TSH) and free T4 (thyroxine). To be performed at screening and cycle 3, 6, 9, etc. and end of treatment.
i. IgG, IgA, IgM, serum protein electrophoresis and immunofixation, 24 hour urine protein electrophoresis and immunofixation, and serum free light chains as well as β2-microglobulin
j. Soft tissue plasmacytomas(s): If present, must be assessed by clinical examination and MRI or CT at screening. Assessment of the lesion(s) by MRI or CT is also required at the end of Cycle 4, at time of complete response (CR) if it is achieved, and when medically indicated during treatment. Participants who have soft tissue plasmacytomas at baseline and who discontinue for reasons other than disease progression will have clinical examination assessment of plasmacytoma every 3 months in follow-up and until disease progression or death.
k. Bone marrow aspiration and biopsy to be evaluated for morphology and for cytogenetics by standard banding and FISH, including marrow karyotype if possible. Suggested probes include, at a minimum, del 13q14, t(4:14), t(11;14), t(14:16), and del 17p. After baseline, bone marrow sampling to confirm CR and at the end of cycle 4 for all participants. Biopsy may be deferred at investigator's discretion.

10.1 Study Calendar for Research Samples

Procedure	Screening	C3D1	C5D1	End of study or disease progression

Bone marrow aspirate	X†		X*	X
Peripheral blood	X†	X	X	X

*May be performed earlier to confirm complete response

11. Measurement of Effect

11.1 Definitions

11.1.1 Evaluable for Toxicity

All participants who receive at least one dose of study treatment will be evaluable for toxicity from the time of their first treatment.

11.1.2 Evaluable for Response

All participants who receive at least one complete cycle of treatment or who discontinue due to death or disease progression prior to completing one cycle will be included in a response evaluation. Responses will be classified according to the definitions stated below.

11.1.3 Measurable Disease

Measurable disease is disease that can be measured either by serum, 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 (or quantitative IgA ≥1000 mg/dL)
- Urine M-protein ≥ 200 mg/24 h
- Involved serum FLC level ≥ 100 mg/L, provided serum FLC ratio is abnormal

11.1.4 Methods for Evaluation of Measurable Disease

All baseline evaluations should be performed within 7 days of Cycle 1, Day 1 of therapy. Response will be assessed by serum M-protein quantification using protein electrophoresis and immunofixation from serum and 24-hour urine collection and protein electrophoresis and immunofixation. Serum free light chain testing will be performed. In addition, bone marrow aspiration will be performed when indicated to confirm response and to differentiate between CR and stringent CR.

11.1.5 Response Criteria

Disease response will be assessed using the International Myeloma Working Group Response Criteria (IMWG) (Kumar et al., 2016b). All response categories require one confirmation. Bone marrow aspirate and/or biopsy findings do not require confirmation.

11.1.5.1 *International Myeloma Working Group Response Criteria*

Response	IMWG criteria
sCR	CR as defined below plus: Normal FLC ratio and Absence of clonal cells in bone marrow by immunohistochemistry or 2-4 color flow cytometry
CR	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and < 5% plasma cells in bone marrow. In patients with only FLC measurable disease, a normal FLC ratio of 0.26-1.65.
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h. In patients with only FLC measurable disease, > 90% decrease in the difference between involved and uninvolved FLC.
PR	≥ 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥ 90% or to < 200 mg/24 h If the serum and urine M-protein are unmeasurable a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are not measurable, and serum free light assay is also not measurable, ≥ 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
MR	≥25% but ≤49% reduction of serum M-protein and reduction in 24-h urine M-protein by 50–89%. In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also require
Stable Disease	Not meeting criteria for CR, VGPR, PR, or progressive disease
Progressive disease	Increase of ≥ 25% from lowest response value in any one of the following: Serum M-component (the absolute increase must be ≥ 0.5 g/dL) and/or Urine M-component (the absolute increase must be ≥ 200 mg/24 h) and/or Only in patients without measurable serum and urine M-protein, the absolute increase in FLC must be >10 mg/dL (100 mg/L) Only in patients without measurable serum and urine M-protein and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute % must be ≥ 10%) Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder

11.2 Duration of Response and Endpoint Definitions

Overall survival (OS) is defined as the time from registration to death due to any cause or censored at date last known alive.

Duration of overall response is measured as the time from initiation of first response to first documentation of disease progression or death. Patients who have not progressed or died are censored at the date last known progression-free.

Duration of overall complete response is measured as the time from initiation of CR to first documentation of disease progression or death. Patients who have not progressed or died are censored at the date last known progression-free.

Progression-free survival (PFS) is defined as the time from randomization to the disease progression or death from any cause. Patients who have not progressed or died are censored at the date last known progression-free.

11.3 Response Review

Disease response assessments will be performed locally by the investigator and by the overall PI. Central review of disease response assessments is not planned for this trial.

12. DATA REPORTING AND REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.

12.1 Data Reporting

12.1.1 Method

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

12.1.2 Responsibility for Data Submission

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

12.2 Data Safety Monitoring

The DF/HCC Data and Safety Monitoring Committee (DSMC) will review and monitor toxicity and accrual data from this study. The committee is composed of clinical specialists with experience in oncology and who have no direct relationship with the study. Information that raises any questions about participant safety will be addressed with the Overall PI and study team.

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

12.3 Multicenter Guidelines

This protocol will adhere to the policies and requirements of the DF/HCC Multi-Center Data and Safety Monitoring Plan. The specific responsibilities of the Overall PI, Coordinating Center, and Participating Institutions and the procedures for auditing are presented in Appendix C.

- The Overall PI/Coordinating Center is responsible for distributing all IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.
- Mechanisms will be in place to ensure quality assurance, protocol compliance, and adverse event reporting at each site.
- Except in very unusual circumstances, each participating institution will order the study agent(s) directly from supplier. A participating site may order the agent(s) only after the initial IRB approval for the site has been forwarded to the Coordinating Center.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

The primary endpoint is to estimate the objective response rate of the combination of nivolumab with ixazomib and dexamethasone. All participants enrolled who have received at least one cycle of treatment or who discontinue treatment due to death or disease progression before completing one cycle will be evaluable for this endpoint. All participants who receive any amount of study drug will be evaluable for toxicity. Participants who do not complete one cycle may be replaced.

The objective response rate (complete response and partial response) and the proportion of participants with a CR (or better), VGPR, PR, or MR will be reported.

The ORR for ixazomib given weekly in a phase I trial was 27% when given at the MTD (Kumar et al., 2014). The ORR for the combination of ixazomib, cyclophosphamide, and dexamethasone in a phase II trial of relapsed or refractory disease was 48% (Kumar et al., 2019). In this more refractory patient population, all with prior exposure to immunomodulatory drug, proteasome inhibitor, and anti-CD38 monoclonal antibody and three prior lines of treatment, an objective response rate of 40% will be

considered promising and 20% will be considered non-promising.

Simon's two-stage design will be used. In the first stage, 13 participants will be accrued. If there are 3 or fewer responses in these 13 participants, the study will be stopped. Otherwise, up to 30 additional participants will be accrued to obtain a total of 43 evaluable participants. The treatment will be considered promising if 13 or more responses are observed in 43 participants. The probability of concluding the treatment is effective is 0.8 assuming a true response rate of 40% and < 0.05 assuming a true response rate of 20%. The probability of stopping early in the first stage if the treatment is true response rate is 20% is 0.7473.

Toxicity will be summarized on all participants treated.

The 90% two-stage exact binomial confidence interval will be reported.

Secondary endpoints include progression-free survival (PFS) and correlative studies. PFS (defined in section 11.4) will be estimated using the Kaplan-Meier method. The clonal evolution and clonal heterogeneity will be summarized using descriptive statistics. Exploratory analyses will be performed to correlate these endpoints with response, however, it is recognized that these analyses have limited power.

13.1.1 Stopping Rules

Unacceptable toxicity will be defined as grade 4 or higher treatment-related adverse event, excluding lymphopenia.

After the safety run in phase (see above, Section 5), the rate of unacceptable toxicity will be assessed at two interim analyses. Stopping boundaries were derived using the power family method (with rho=0.1) for a two-stage group sequential design for a binomial test of proportion with null and alternative rates of unacceptable toxicities of 0.05 and 0.2, respectively. After 13 patients have each completed 1 treatment cycle, the study will stop if 3 or more patients have experienced unacceptable toxicities. If the true toxicity rate is 0.05 or less, the probability of stopping at stage 1 is 0.06. If the true toxicity rate is 0.2 or more, the probability of stopping at stage 1 is 0.41. If the study continues past the first interim safety analysis, the second assessment will occur after 26 patients have completed 1 treatment cycle. If 5 or more of 26 patients have experienced unacceptable toxicities, the study will stop. If the true toxicity rate is 0.05 or less, the probability of stopping at stage 2 is 0.10. If the true toxicity rate is 0.2 or more, the probability of stopping at stage 2 is 0.70.

13.2 Sample Size, Accrual Rate, and Study Duration

A total of up to 50 patients may be enrolled to obtain 43 evaluable participants. We expect 2-3 years of active accrual (estimated accrual between 15-20/year). Up to an additional 6 months of follow up will be required on the last participant accrued. The overall study duration is expected to be a maximum of 3 years, and 2 years of follow-up of participants.

Due to the small sample size for the protocol, specific accrual targets have not been set for ethnicity or

gender. Women, minorities, and members of other underrepresented populations will have equal consideration for participation in this trial.

13.3 Stratification Factors

There are no stratification factors in this study.

13.4 Interim Monitoring Plan

Involvement in this study as a participating investigator implies acceptance of potential audits or inspections, including source data verification, by representatives designated by the PI and as described in the Data and Safety Monitoring Plan. The purpose of these audits or inspections is to examine study-related activities and documents to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported in accordance with the protocol, institutional policy, Good Clinical Practice (GCP), and any applicable regulatory requirements.

13.5 Reporting and Exclusions

13.5.1 Evaluation of Toxicity

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

13.5.2 Evaluation of the Primary Efficacy Endpoint

All participants who have completed at least one cycle of treatment will be assessed for response to treatment.

14. PUBLICATION PLAN

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

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16. APPENDICES

Appendix A: Performance Status Criteria

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

Appendix B. Nivolumab Adverse Event Management Algorithms

GI Adverse Event Management Algorithm

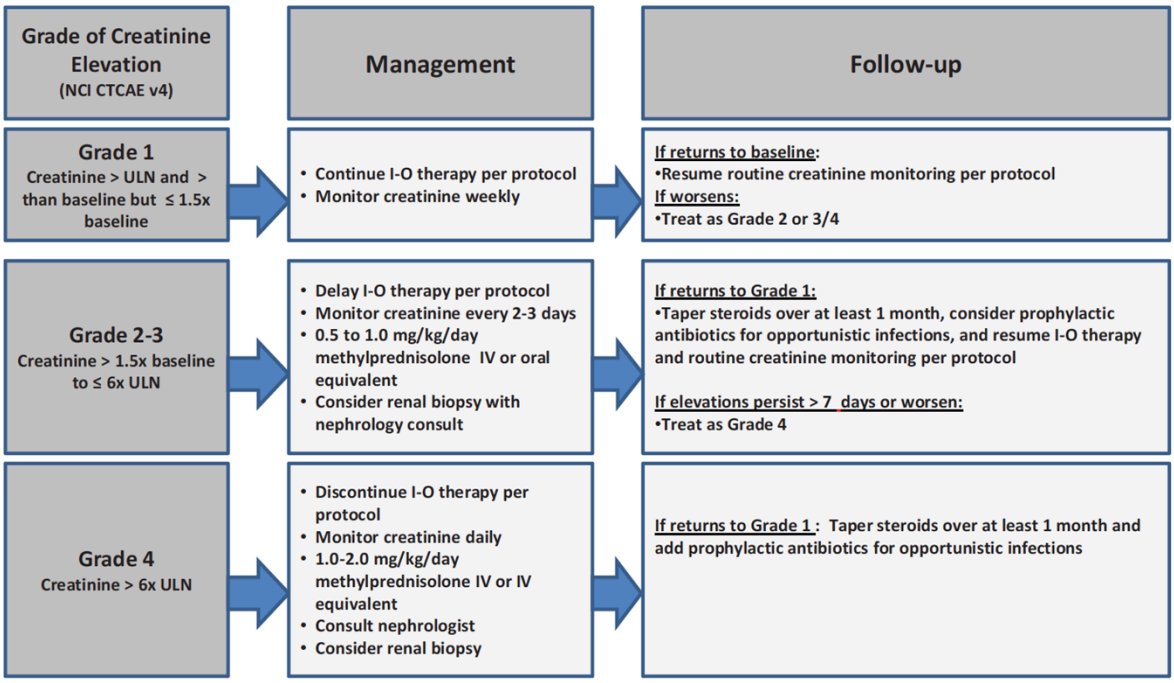
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Renal Adverse Event Management Algorithm

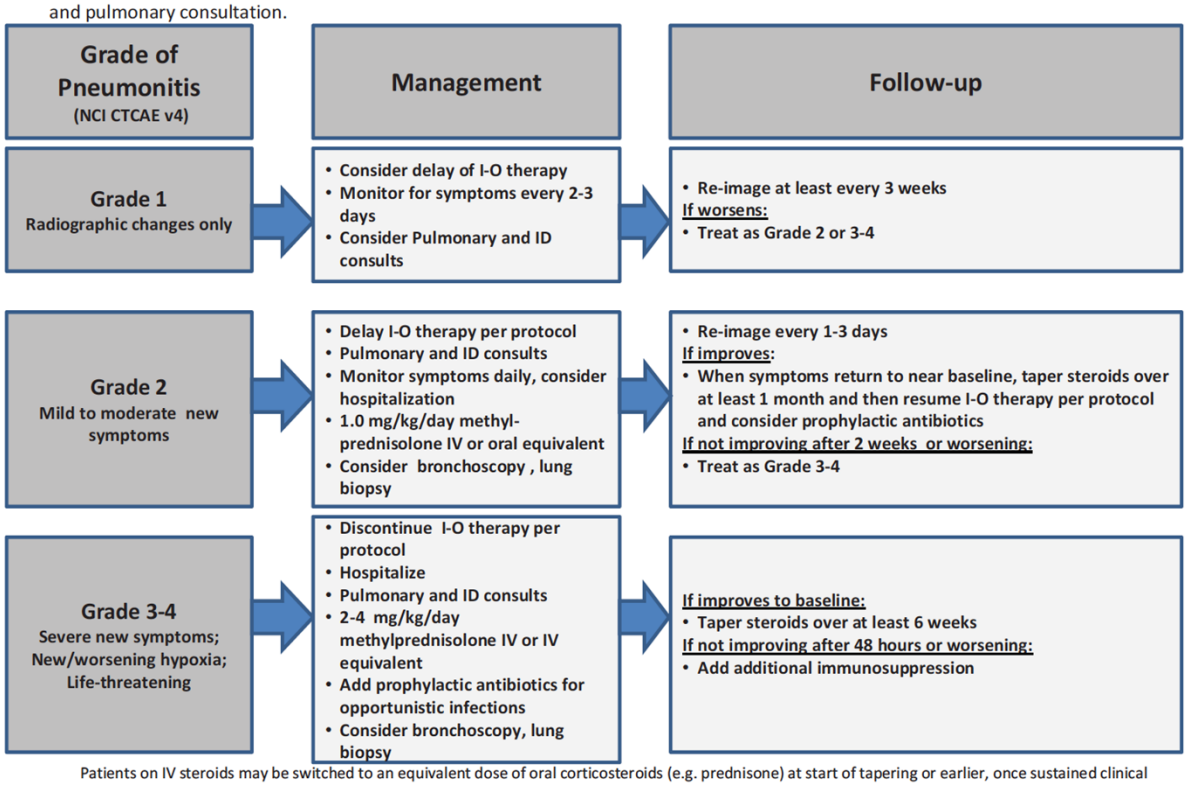
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pulmonary Adverse Event Management Algorithm

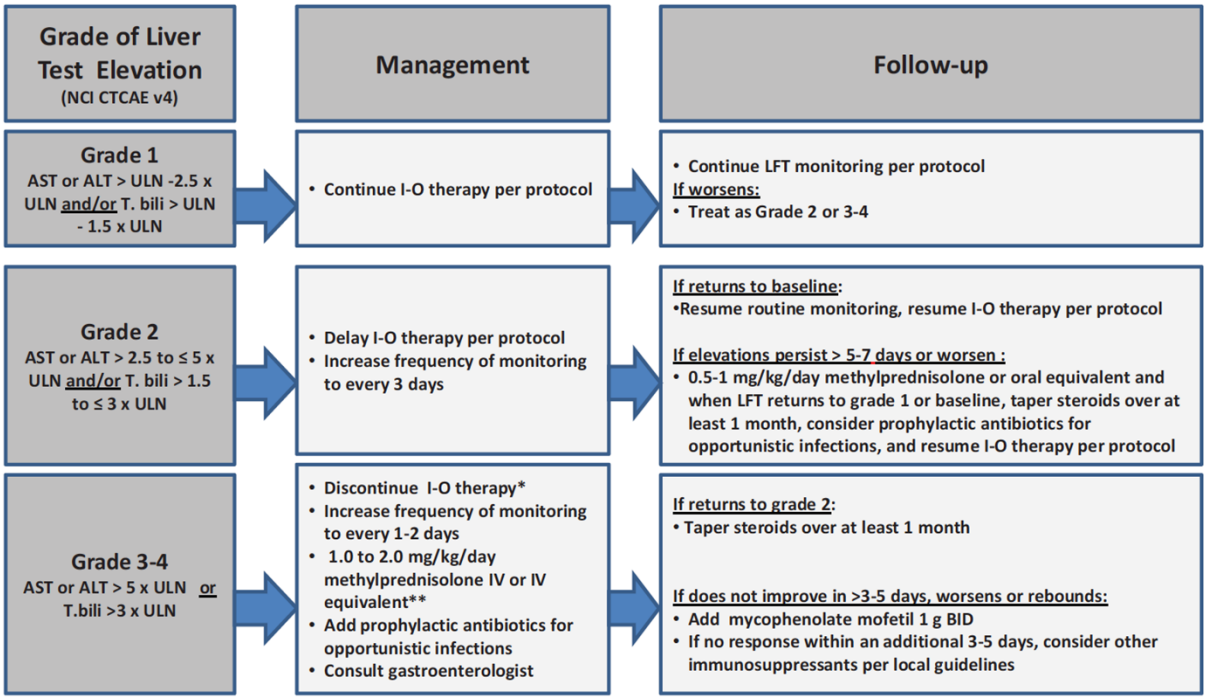
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Hepatic Adverse Event Management Algorithm

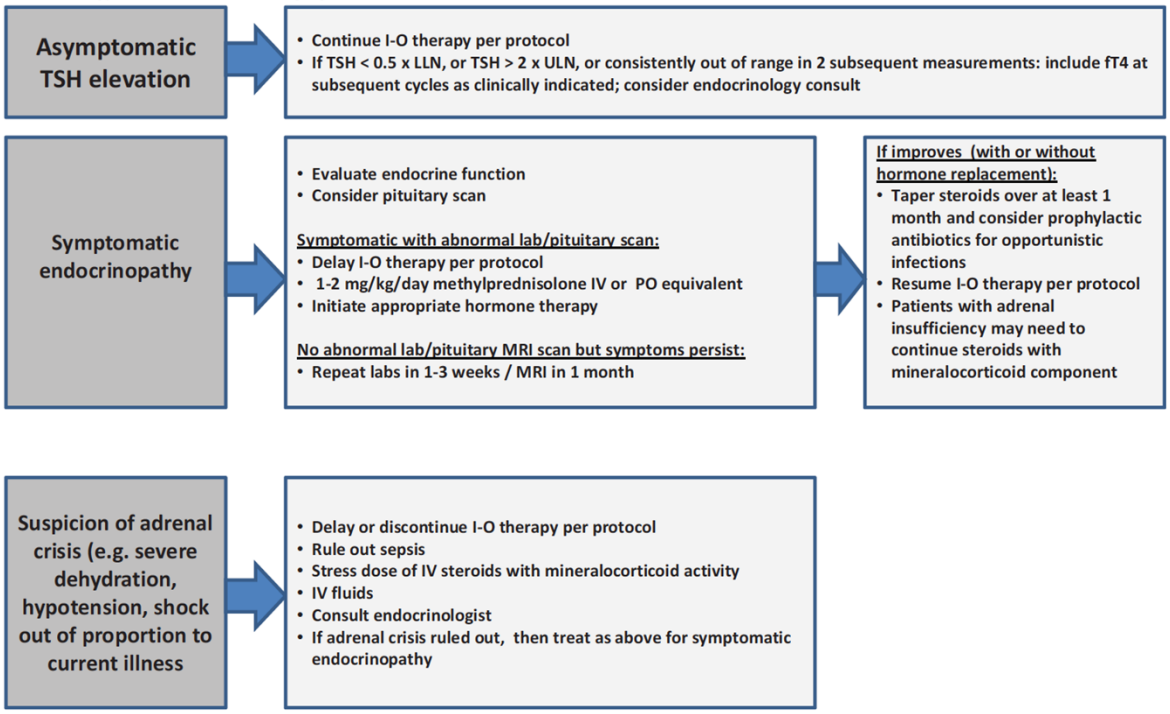
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**
****The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Endocrinopathy Adverse Event Management Algorithm

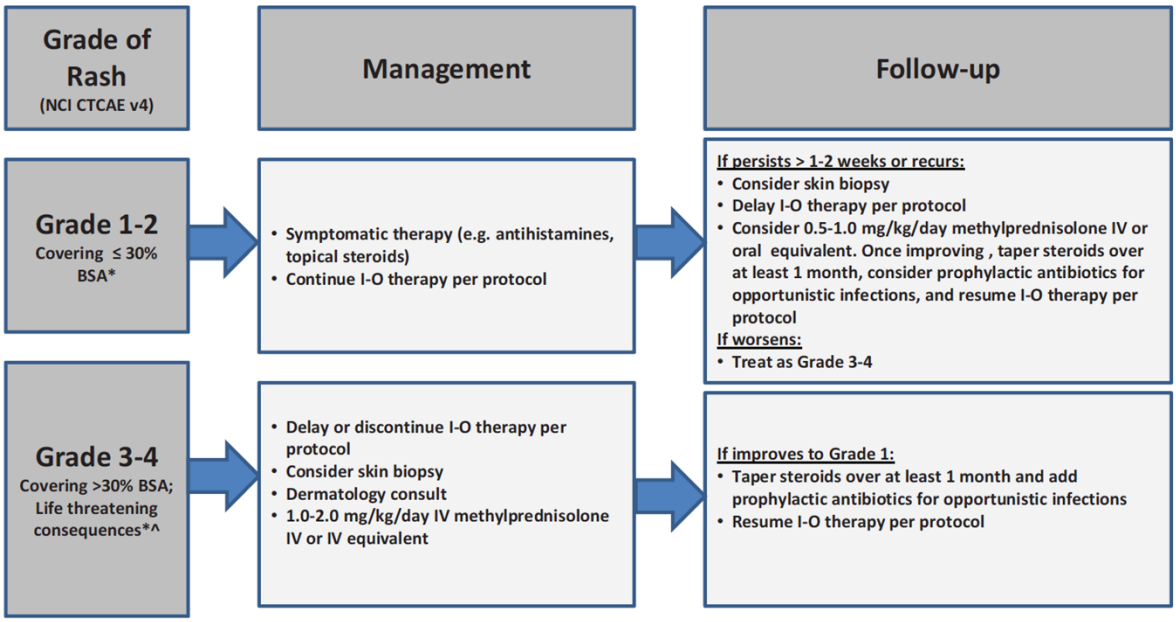
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

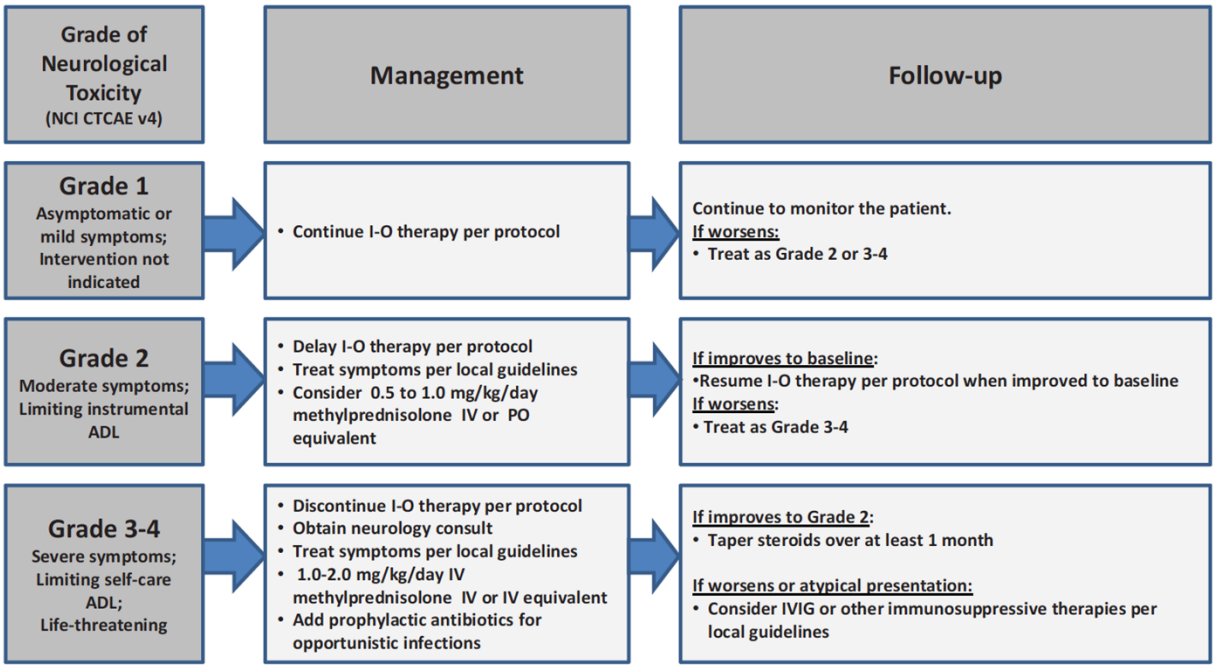
Skin Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

Neurological Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Appendix C: Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan

1. INTRODUCTION

The Dana-Farber/Harvard Cancer Center Multi-Center Data and Safety Monitoring Plan (DF/HCC DSMP) outlines the procedures for conducting a DF/HCC Multi-Center research protocol. The DF/HCC DSMP serves as a reference for any sites external to DF/HCC that are participating in a DF/HCC clinical trial.

1.1. Purpose

To establish standards that will ensure that a Dana-Farber/Harvard Cancer Center Multi-Center protocol will comply with Federal Regulations, Health Insurance Portability and Accountability Act (HIPAA) requirements and applicable DF/HCC Standard Operating Procedures, and Cancer Therapy Evaluation Program (CTEP) Multi-Center Guidelines.

1.2. Multi-Center Data and Safety Monitoring Plan Definitions

DF/HCC Multi-Center Protocol: A research protocol in which one or more outside institutions are collaborating with Dana-Farber/Harvard Cancer Center where a DF/HCC investigator is the sponsor. DF/HCC includes Dana-Farber/Partners Cancer Care (DF/PCC) Network Clinical Trial Affiliates.

Lead Institution: One of the Dana-Farber/Harvard Cancer Center consortium members (Dana-Farber Cancer Institute (DFCI), Massachusetts General Hospital (MGH), Beth Israel Deaconess Medical Center (BIDMC), Boston Children's Hospital (BCH), Brigham and Women's Hospital (BWH) responsible for the coordination, development, submission, and approval of a protocol as well as its subsequent amendments per the DFCI IRB and applicable regulatory guidelines (CTEP, Food and Drug Administration (FDA), Office of Biotechnology Activities (OBA) etc.). The Lead Institution is typically the home of the DF/HCC Sponsor. The Lead Institution also typically serves as the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Sponsor: The person sponsoring the submitted Multi-Center protocol who takes responsibility for initiation, management and conduct of the protocol at all research locations. In applicable protocols, the DF/HCC Sponsor will serve as the single liaison with any regulatory agencies (i.e. FDA, OBA etc.). The DF/HCC Sponsor has ultimate authority over the protocol and is responsible for the conduct of the study at DF/HCC and all Participating Institutions. In most cases the DF/HCC Sponsor is the same person as the DF/HCC Overall Principal Investigator; however, both roles can be filled by two different people.

Participating Institution: An institution that is outside the DF/HCC and DF/PCC consortium that is collaborating with DF/HCC on a protocol where the sponsor is a DF/HCC Investigator. The Participating Institution acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Coordinating Center: The entity that provides administrative support to the DF/HCC Sponsor in order that he/she may fulfill the responsibilities outlined in the protocol document and DSMP, and as specified in applicable regulatory guidelines. In general, the Lead Institution is the Coordinating Center for the DF/HCC Multi-Center Protocol.

DF/HCC Office of Data Quality (ODQ): A group within DF/HCC responsible ensuring high-quality standards are used for data collection and the ongoing management of clinical trials, auditing, and data and safety monitoring. ODQ also coordinates quality assurance efforts related to multi-center clinical research.

DF/HCC Research Informatics for Operations (RIO): A group within DF/HCC responsible for providing a comprehensive data management platform for managing clinical trial data.

2. GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the DF/HCC Sponsor, the Coordinating Center, and the Participating Institutions are expected to adhere to the following general responsibilities:

2.1. DF/HCC Sponsor

The DF/HCC Sponsor, Andrew Yee, MD will accept responsibility for all aspects of conducting a DF/HCC Multi-Center protocol which includes but is not limited to:

- Oversee the coordination, development, submission, and approval of the protocol as well as subsequent amendments.
- Ensure that the investigators, study team members, and Participating Institutions are qualified and appropriately resourced to conduct the protocol.
- Include the Multi-Center Data and Safety Monitoring Plan as an appendix to the protocol.
- Ensure all Participating Institutions are using the correct version of the protocol.
- Ensure that each participating investigator and study team member receives adequate protocol training and/or a Site Initiation Visit prior to enrolling participants and throughout trial's conduct as needed.
- Ensure the protocol will be provided to each participating site in a language understandable to all applicable site personnel when English is not the primary language.
- Ensure appropriate procedures are in place for the shipment, handling, storage dispensing and accountability of all investigational product.
- Monitor progress and overall conduct of the study at all Participating Institutions.
- Ensure all DFCI Institutional Review Board (IRB), DF/HCC and other applicable (i.e. FDA, OBA) reporting requirements are met.
- Review data and maintain timely submission of data for study analysis.
- Act as the single liaison with FDA (investigator-held IND trials) or OBA (gene therapy trials), as applicable.

- Ensure compliance with all requirements as set forth in the Code of Federal Regulations, applicable DF/HCC requirements, HIPAA requirements, and the approved protocol.
- Commit to the provision that the protocol will not be rewritten or modified by anyone other than the DF/HCC Sponsor.
- Identify and qualify Participating Institutions and obtain accrual commitments prior to extending the protocol to that site.
- Monitor accrual and address Participating Institutions that are not meeting their accrual requirements.

2.2. Coordinating Center

The general responsibilities of the Coordinating Center may include but are not limited to:

- Assist in protocol development.
- Maintain FDA or OBA correspondence, as applicable.
- Review registration materials for eligibility and register participants from Participating Institutions in the DF/HCC clinical trial management system (CTMS).
- Distribute protocol and informed consent document updates to Participating Institutions as needed; obtain protocol signature pages from participating sites.
- Review and approve Participating Site informed consent forms
- Conduct and document initial and ongoing protocol training
- Oversee the data collection process from Participating Institutions.
- Maintain documentation and cumulative reports of Serious Adverse Event (SAE) reports and Deviations/Violations across all sites and provide to the DF/HCC Sponsor for timely review and submission to the DFCI IRB, as necessary.
- Distribute serious adverse events reported to the DF/HCC Sponsor that fall under the DFCI IRB Adverse Event Reporting Policy to all Participating Institutions.
- Provide Participating Institutions with information regarding DF/HCC requirements that they will be expected to comply with.
- Carry out approved protocol monitoring plan either by on-site or remote monitoring and maintain logs of all monitoring activities.
- Ensure adequate source documentation is maintained and study documents are securely stored as per regulatory requirements.
- Maintain essential regulatory documents of all Participating Institutions which includes but is not limited to the following: local IRB approvals/notifications from all Participating Institutions, confirmation of Federalwide Assurances (FWAs) for all sites, all SAE submissions, Screening Logs for all sites, IRB approved consents for all sites, and protocol training documentation
- Conduct regular communications with all Participating Institutions (conference calls, emails, etc.) and maintain documentation all relevant communications.

2.3. Participating Institution

Each Participating Institution is expected to comply with all applicable federal regulations and DF/HCC requirements, the protocol and HIPAA requirements.

The general responsibilities for each Participating Institution may include but are not limited to:

- Document the delegation of research specific activities to study personnel.
- Commit to the accrual of participants to the protocol.
- Submit protocol and/or amendments to their local IRB of record.
- Maintain regulatory files as per sponsor requirements.
- Provide the Coordinating Center with regulatory documents, including enrollment log, biospecimen log, violation/deviation log, or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required (i.e. teleconferences).
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities.
- Submit Adverse Event (SAE) reports to local IRB per institutional requirements and to the Coordinating Center, in accordance with DF/HCC or other sponsor requirements.
- Submit protocol deviations and violations to local IRB per institutional requirements and to the DF/HCC Sponsor in accordance with DF/HCC requirements.
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Have office space, office equipment, and internet access that meet HIPAA standards.
- Participate in any quality assurance activities, including onsite and remote monitoring visits, and meet with monitors or auditors at the conclusion of a visit to review findings.
- Promptly provide follow-up and/or corrective action plans for any monitoring queries or audit findings.

3. DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

The following section will clarify DF/HCC Requirements and further detail the expectations for participating in a DF/HCC Multi-Center protocol.

3.1. Protocol Distribution

The Coordinating Center will distribute the final DFCI IRB approved protocol and any subsequent amended protocols to all Participating Institutions.

3.2. Protocol Revisions and Closures

The Participating Institutions will receive notification of protocol revisions and closures from the Coordinating Center. It is the individual Participating Institution's responsibility to notify its IRB of these revisions.

- **Non life-threatening revisions:** Participating Institutions will receive written notification of protocol revisions regarding non life-threatening events from the Coordinating Center. Non-life-threatening protocol revisions must be IRB approved and implemented within 90 days from receipt of the notification.

- **Revisions for life-threatening causes:** Participating Institutions will receive immediate notification from the Coordinating Center concerning protocol revisions required to protect lives with follow-up by fax, mail, e-mail, etc. Life-threatening protocol revisions will be implemented immediately followed by IRB request for approval.

- **Protocol closures and temporary holds:** Participating Institutions will receive notification of protocol closures and temporary holds from the Coordinating Center. Closures and holds will be effective immediately. In addition, the Coordinating Center, will update the Participating Institutions on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.3. Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for Participating Institutions. The Participating Institution consent form must follow the consent template as closely as possible and should adhere to specifications outlined in the DF/HCC Guidance Document on Model Consent Language for Investigator-Sponsored Multi-Center Trials. This document will be provided separately to each Participating Institution upon request.

Participating Institutions are to send their version of the informed consent document and HIPAA authorization, if a separate document, to the Coordinating Center for review and approval prior to submission to their local IRB. The approved consent form must also be submitted to the Coordinating Center after approval by the local IRB for all consent versions.

The Principal Investigator (PI) at each Participating Institution will identify the physician members of the study team who will be obtaining consent and signing the consent form for therapeutic protocols. Participating institutions must follow the DF/HCC requirement that for all interventional drug, biologic, or device research, only attending physicians may obtain initial informed consent and any re-consent that requires a full revised consent form.

3.4. IRB Documentation

The following must be on file with the Coordinating Center prior to site activation or receipt of any investigational product:

- Initial approval letter of the Participating Institution's IRB.
- Copy of the Informed Consent Form(s) approved by the Participating Institution’s IRB.

- Participating Institution's IRB approval for all amendments.
- Annual approval letters by the Participating Institution's IRB.

3.5. IRB Re-Approval

Verification of IRB re-approval from the Participating Institutions is required in order to continue research activities. There is no grace period for continuing approvals.

The Coordinating Center will not register participants if a re-approval letter is not received from the Participating Institution on or before the anniversary of the previous approval date.

3.6. Participant Confidentiality and Authorization Statement

In 1996, congress passed the first federal law covering the privacy of health information known as the Health Insurance Portability and Accountability Act (HIPPA). Any information, related to the physical or mental health of an individual is called Protected Health Information (PHI). HIPAA outlines how and under what circumstances PHI can be used or disclosed.

In order for covered entities to use or disclose protected health information during the course of a study, the study participant must sign an authorization statement. This authorization statement may or may not be separate from the informed consent document. The Coordinating Center, with the approval from the DFCI IRB and will provide a consent template, with information regarding authorization for the disclosure of protected health information.

The DF/HCC Sponsor will use all efforts to limit its use of protected health information in its trials. However, because of the nature of these trials, certain protected health information must be collected. DF/HCC has chosen to use authorizations, signed by the participant in the trial, rather than limited data sets with data use agreements.

3.6.1. DF/HCC Multi-Center Protocol Confidentiality

All documents, investigative reports, or information relating to the participant are strictly confidential. Whenever reasonably feasible, any participant specific reports (i.e. Pathology Reports, MRI Reports, Operative Reports, etc.) submitted to the Coordinating Center should be de-identified. It is recommended that the assigned DF/HCC case number (as described below) be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.7. DF/HCC Multi-Center Protocol Registration Policy

All participants must be registered with DF/HCC prior to conducting any research-related procedures.

Please refer to protocol section 4.0: Registration Procedures

3.7.1. Initiation of Therapy

Participants must be registered with the DF/HCC CTMS before the initiation of treatment or other protocol-specific interventions. Treatment and other protocol-specific interventions may not be initiated until the Participating Institution receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and DFCI IRB must be notified of any violations to this policy.

3.7.2. Eligibility Exceptions

No exceptions to the eligibility requirements for a protocol without DFCI IRB approval will be permitted. All Participating Institutions are required to fully comply with this requirement. The process for requesting an eligibility exception is defined below.

3.7.3. DF/HCC Protocol Case Number

At the time of registration, the following identifiers are required for all subjects: initials, date of birth, gender, race and ethnicity. Once eligibility has been established and the participant successfully registered, the participant is assigned a unique protocol case number. Participating Institutions should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

3.7.4. Protocol Deviations, Exceptions and Violations

Federal Regulations require an IRB to review proposed changes in a research activity to ensure that researchers do not initiate changes in approved research without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the participant. DF/HCC requires all departures from the defined procedures set forth in the IRB approved protocol to be reported to the DF/HCC Sponsor, who in turn is responsible for reporting to the DFCI IRB.

For reporting purposes, DF/HCC uses the terms "violation", "deviation" and "exception" to describe departures from a protocol. All Participating Institutions must adhere to these requirements for reporting to the DF/HCC Sponsor and will follow their institutional policy for reporting to their local IRB.

3.7.5. Definitions

Protocol Deviation: Any departure from the defined procedures set forth in the IRB-approved protocol which is *prospectively approved* prior to its implementation.

Protocol Exception: Any protocol deviation that relates to the eligibility criteria, e.g.

enrollment of a participant who does not meet all inclusion/exclusion criteria.

Protocol Violation: Any protocol departure that was not *prospectively approved* by the IRB prior to its initiation or implementation.

3.7.6. Reporting Procedures

DF/HCC Sponsor: is responsible for ensuring that clear documentation is available in the medical record and/or regulatory documents to describe all protocol exceptions, deviations and violations. The DF/HCC Sponsor will also be responsible for ensuring that all protocol violations/deviations are promptly reported per DFCI IRB guidelines.

Participating Institutions: Protocol deviations require prospective approval from the DFCI IRB. The Participating Institution must submit the deviation request to the Coordinating Center who will then submit the deviation request to the DFCI IRB. Upon DFCI IRB approval the deviation is submitted to the Participating Institution IRB, per institutional policy. A copy of the Participating Institution's IRB report and determination will be forwarded to the Coordinating Center within 10 business days after the original submission. The deviation may not be implemented without all required approvals

All reportable protocol violations must be sent to the Coordinating Center in a timely manner. Participating sites must also maintain a log of all minor violations and submit the log to the Coordinating Center each month. The Coordinating Center will provide training for the requirements for the reporting of violations.

Coordinating Center: Upon receipt of the violation/deviation report from the Participating Institution, the Coordinating Center will submit the report to the DF/HCC Sponsor for review. Subsequently, the Participating Institution's IRB violation/deviation report will be submitted to the DFCI IRB for review per DFCI IRB reporting guidelines.

3.8. Safety Assessments and Toxicity Monitoring

The study teams at all participating institutions are responsible for protecting the safety, rights and well-being of study participants. Recording and reporting of adverse events that occur during the course of a study help ensure the continuing safety of study participants.

All participants receiving investigational agents and/or other protocol mandated therapy will be evaluated for safety. The safety parameters include all laboratory tests and hematological abnormalities, physical examination findings, and spontaneous reports of adverse events reported by participants. All toxicities encountered during the study will be evaluated according to the NCI criteria specified in the protocol. Life-threatening toxicities must be reported immediately to the DF/HCC Sponsor via the Coordinating Center.

Additional safety assessments and toxicity monitoring will be outlined in the protocol.

3.8.1. Guidelines for Reporting Serious Adverse Events

Guidelines for reporting Adverse Events (AEs) and Serious Adverse Events (SAEs) are detailed in protocol section 7: Adverse Events: List and Reporting Requirements.

Participating Institutions must report the SAEs to the DF/HCC Sponsor and the Coordinating Center following the DFCI IRB Adverse Event Reporting Policy.

The Coordinating Center will maintain documentation of all Participating Institution Adverse Event reports and be responsible for communicating to all participating investigators, any observations reportable under the DFCI IRB Reporting Requirements. Participating Institutions will review and submit to their IRB according to their institutional policies and procedures

3.8.2. Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports and ensure that all IND Safety Reports are distributed to the Participating Institutions. Participating Institutions will review /submit to the IRB according to their institutional policies and procedures.

3.9. Data Management

DF/HCC RIO develops case report forms (CRF/eCRFs) in InForm for use with the protocol. These forms are designed to collect data for each study. DF/HCC RIO provides a web-based training for all eCRF users.

3.9.1. Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. Data should be entered promptly and completely after each assessment, but no later than 2 weeks after the completion of a study visit/timepoint. If study forms are received with missing or questionable data, the submitting institution will receive a written or electronic query from the DF/HCC Office of Data Quality, Coordinating Center, or designee.

Responses to all queries should be completed and submitted within 14 calendar days.

Responses may be returned on the written query or on an amended paper case report form, or in the case of electronic queries, within the electronic data capture (eDC) system. In the case of a written query for data submitted on a paper case report form, the query must be attached to the specific data being re-submitted in response.

If study forms are not submitted on schedule, the Participating Institution will periodically receive a Missing Form Report from the Coordinating Center noting the missing forms.

4. REQUISITIONING INVESTIGATIONAL DRUG

The ordering of investigational agent is specified in the protocol section 8: Pharmaceutical Information.

Participating Institutions should order their own agent regardless of the supplier. (i.e., NCI or a pharmaceutical company.)

If the agent is commercially available, check with the local Director of Pharmacy and/or the Research Pharmacy to ensure that the agent is in stock. If the agent is not stocked, ensure that the agent can be ordered once the protocol is approved by the local IRB.

If the agent is investigational, ensure that the pharmacy will be able to receive and store the agent according to state and federal requirements. The local IRB should be kept informed of who will supply the agent (i.e., NCI or a pharmaceutical company) so that any regulatory responsibilities can be met in a timely fashion.

5. MONITORING: QUALITY CONTROL

The quality control process for a clinical trial requires verification of protocol compliance and data accuracy. The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

Ongoing Monitoring of Protocol Compliance

Participating Institution will be subject to on-site and remote monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that Participating Institutions are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring will occur before the clinical phase of the protocol begins, continue during protocol performance and through study completion. Monitoring practices include but are not limited to; source data verification and review and analysis of the following: eligibility requirements of all participants, informed consent procedures, adverse events and all associated documentation, study drug administration/treatment, regulatory files, protocol departures, pharmacy records, tissue and biospecimen sample logs, response assessments, and data management.

All DF/HCC site and Participating Institutions will undergo on-site monitoring by the Coordinating Center within 3 months of completion of C1 for the first patient; Combination on-site and remote monitoring will occur every 4-6 months thereafter with at least 1 on-site visit every 12 months. Remote monitoring may be done in lieu of on-site monitoring if site accrual is low or current participants are off-treatment. Once all site participants are off treatment and have completed the post-treatment assessment, remote monitoring will be conducted annually for confirmation of long-term follow-up data and regulatory documentation.

For remote monitoring visits, Participating Institutions will be asked to provide remote electronic medical record access to the monitor or will be required to forward redacted copies of participants' medical record and source documents to the Coordinating Center to aid in source data verification. The participants and CRFs to be reviewed at the visit will be communicated at least 2 weeks in advance of the scheduled monitoring visit. Source documentation can be provided to the Coordinating Center via an encrypted memory stick or via a secure file transfer system. During remote monitoring visits, the Site Specific File will be reviewed in lieu of the site regulatory binder.

On-Site Monitoring will be scheduled several weeks in advance and will be conducted over a 2-3 day period. During an on-site monitoring visit 2-4 participants will be monitored. Source documentation verification (SDV) will be conducted by having access to participants' complete medical record and source documents. Participating Institutions will be expected to coordinate the necessary resources for the monitor, including a desk, access to all participant medical and research records (electronic and hard copy), the regulatory binders and access to a photocopier. The Participating Institution will also be asked to assist in scheduling a pharmacy visit and a brief exit interview on the final day of the visit with the Study Coordinator and the Site investigator.

All Participating Institutions will be required to participate in monthly Coordinating Center initiated teleconferences. Once all participants have completed treatment, teleconferences will be scheduled as needed.

5.1. Monitoring Reports

The DF/HCC Sponsor will review all monitoring reports to ensure protocol compliance. The DF/HCC Sponsor may increase the monitoring activities at Participating Institutions that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

5.2. Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each participating institution. Accrual will be monitored for each participating institution by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination.

The **minimum** accrual per participating site is 3-5 participants annually in consideration of the regulatory and monitoring cost and effort of overseeing each site.

Participating sites will be required to submit current Screening and Enrollment logs to the Coordinating Center each month.

6. AUDITING: QUALITY ASSURANCE

Auditing is a method of Quality Assurance and involves the systematic and independent examination of all trial related activities and documents. Audits determine if evaluated activities were appropriately conducted and whether data was generated, recorded and analyzed, and accurately reported per the protocol, applicable policies, and the Code of Federal Regulations (CFR).

6.1. Audit Plan: NCI Sponsored Trials

Not applicable

6.2. DF/HCC Internal Audits

All Participating Institutions are subject to audit by the DF/HCC Office of Data Quality (ODQ). Typically, approximately 3-4 participants would be audited at the site over a 2-day period. If violations which impact participant safety or the integrity of the study are found, more participant records may be audited.

6.3. Audit Notifications

It is the Participating Institution's responsibility to notify the Coordinating Center of all external audits or inspections (e.g., FDA, EMA, NCI) that involve this protocol. All institutions will forward a copy of final audit and/or re-audit reports and corrective action plans (if applicable) to the Coordinating Center, within 12 weeks after the audit date.

6.4. Audit Reports

The DF/HCC Sponsor will review all final audit reports and corrective action plans, if applicable. The Coordinating Center, must forward any reports to the DF/HCC ODQ per DF/HCC policy for review by the DF/HCC Audit Committee. For unacceptable audits, the DF/HCC Audit Committee would forward the final audit report and corrective action plan to the DFCI IRB as applicable.

6.5. Participating Institution Performance

The DF/HCC Sponsor and the DFCI IRB are charged with considering the totality of an institution's performance in considering institutional participation in the protocol. Participating Institutions that fail to meet the performance goals of accrual, submission of timely and accurate data, adherence to protocol requirements, and compliance with state and federal regulations, may be recommended for a six-month probation period. Such institutions must respond with a corrective action plan and must demonstrate during the probation period that deficiencies have been corrected, as evidenced by the improved performance measures. Participating Institutions that fail to demonstrate significant improvement will be considered by the DF/HCC Sponsor for revocation of participation. A DF/HCC Sponsor and/or the DFCI IRB may terminate a site's participation if it is determined that a site is not fulfilling its responsibilities as described above.