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TITLE: A Phase 2 proof of concept study of nivolumab and ipilimumab in children and young adults with relapsed or refractory IN11-negative cancers.

Coordinating Center: Dana-Farber / Boston Children's Cancer and Blood Disorders Center

Principal Investigator (PI):

[REDACTED]
Dana-Farber / Boston Children's Cancer and Blood Disorders Center

450 Brookline Avenue, [REDACTED]
Boston, MA 02215

[REDACTED]

[REDACTED]

[REDACTED]

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[REDACTED]	[REDACTED]
[REDACTED]	

[REDACTED]	[REDACTED]
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SCHEMA

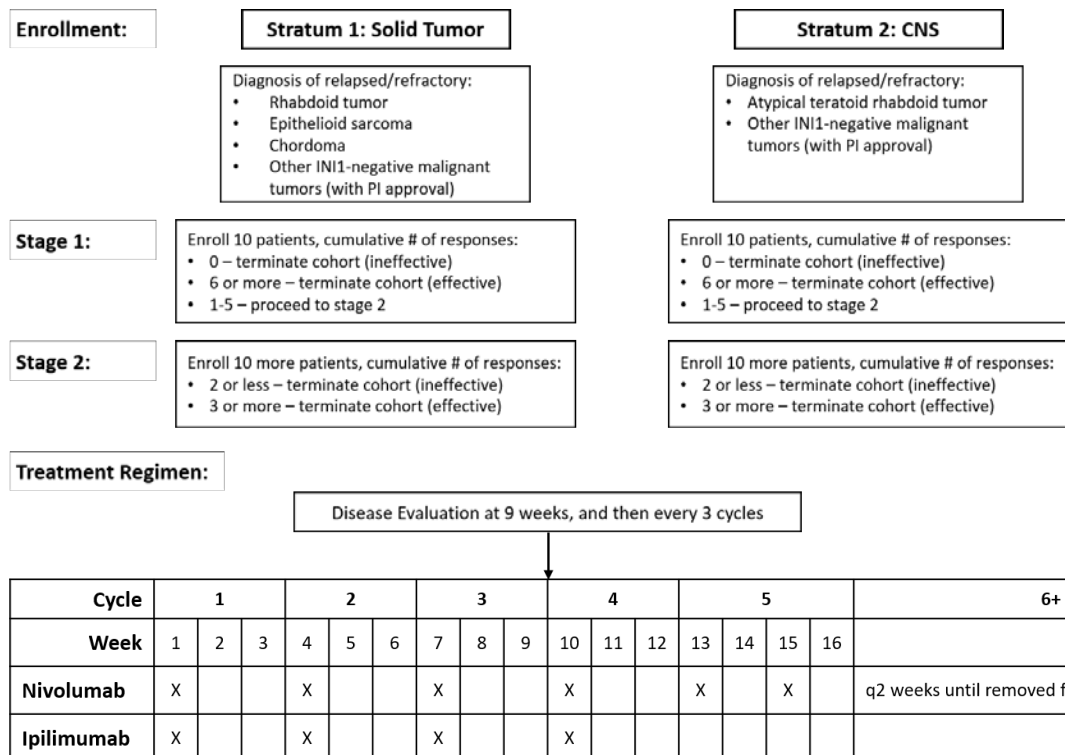


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1. OBJECTIVES

1.1 Study Design

This is a single arm, multi-center, phase 2, open-label study to evaluate the clinical activity of nivolumab in combination with ipilimumab in two parallel strata of patients aged 6 months to 40 years with relapsed or refractory INI1-negative cancers. The primary purpose of this trial is to evaluate the antitumor activity of nivolumab in combination with ipilimumab in two strata of patients with INI1-negative tumors as assessed by objective response rate (ORR) using a two-Stage design. Patients with INI1-negative relapsed or refractory extra-CNS solid tumors will be enrolled into Stratum 1 and objective responses will be assessed using Response Evaluation Criteria in Solid Tumors (RECIST), version 1.1. Patients with relapsed or refractory atypical teratoid rhabdoid tumor (ATRT) will be enrolled into Stratum 2 and objective responses will be assessed using the Response Assessment in Neuro-Oncology (RANO) criteria. An objective response is defined as a complete response (CR) or partial response (PR). Patients will be considered evaluable for the primary objective if they receive at least one dose of both nivolumab and ipilimumab, and have at least 1 post-baseline tumor assessment. In addition, patients will be considered evaluable if either of the following occurs: (1) Progressive disease while on therapy or (2) Death while on therapy. Patients inevaluable for response will be replaced.

The following two-stage design will be applied separately within the evaluable patients of Stratum 1, and within the evaluable patients of Stratum 2.

For stage 1 of the trial, 10 evaluable patients will be enrolled. If none have an objective response then the Stratum will be closed to accrual because of insufficient evidence of activity of the study treatment. If 6 or more patients have an objective response, then the Stratum will be closed to accrual, as it will be reasonable to conclude that there is sufficient activity of the combination treatment in the Stratum. If 1-5 patients have an objective response, then enrollment in the Stratum will continue into Stage 2. In Stage 2, an additional 10 patients will be enrolled for a total of 20 evaluable patients. If 2 or less of the 20 patients have an objective response then there is insufficient evidence of activity for further investigation of the study treatment in the Stratum. + If 3 or more of the patients have an objective response then it is reasonable to conclude that there is sufficient activity for further investigation of the study treatment in the Stratum.

Sample Size and Study Duration

Total accrual: Approximately 45 patients total

Accrual goal: Up to 20 evaluable patients in each stratum, for a total of up to 40 evaluable patients. The sample size is driven by the requirement of the two-stage design to address the Primary Objective. Assuming that up to 10% of patients could be inevaluable, up to 45 patients will be enrolled to obtain 40 evaluable patients. At an accrual rate of 1.5 patients per month, enrollment will be completed in 30 months.

Study duration: If the last patient enrolled is treated for 1 year, then the total study duration will be approximately 3.5 years.

The study design does not involve a dose escalation. Participants in both strata will receive combination therapy with nivolumab at a dose of 3mg/kg (maximum dose of 240mg) and

ipilimumab at a dose of 1mg/kg on day 1 of a 21-day cycle for 4 cycles. Starting with cycle 5, patients will receive nivolumab monotherapy at a dose of 3mg/kg (maximum dose 240mg) on day 1 and day 15 of a 28-day cycle. Patients will remain on treatment for up to 1 year if disease progression has not occurred. Patients with stable disease or confirmed response after 1 year of treatment could remain on study treatment beyond 1 year with approval from Principal Investigator.

Disease evaluation will take place after the first 3 cycles and then every 3 cycles until 12 months of treatment. Subjects will be followed up for toxicities and research assessments as detailed in the study calendar (Section 10).

1.2 Primary Objectives

The primary objective of the study is to estimate the objective response rate (ORR) of nivolumab in combination with ipilimumab separately in each of the two strata of children and young adults with INI1-negative cancers, as measured by RECIST 1.1 for Stratum 1 and RANO for Stratum 2 per local assessment.

1.3 Secondary Objectives

- 1.3.1 To estimate the progression-free survival (PFS) and overall survival (OS) rates of patients with INI1-negative cancers treated with nivolumab and ipilimumab in each stratum and across both strata
- 1.3.2 To estimate the disease control rate at 12 months in patients with INI1-negative cancers treated with nivolumab and ipilimumab in each stratum and across both strata
- 1.3.3 To describe the toxicities of nivolumab given in combination with ipilimumab in children and young adults with INI1-negative cancers

1.4 Exploratory Objectives

- 1.4.1 To describe biologic activity of study treatment as measured by correlative immunologic studies and to evaluate biomarkers of treatment response

2. BACKGROUND

2.1 Study Disease(s)

Several aggressive pediatric tumor types are characterized by INI1 negativity, including rhabdoid tumors, epithelioid sarcoma and chordoma.¹ In the pediatric setting, these cancers constitute a reasonable proportion of rare tumor diagnoses and are each associated with a poor prognosis with few novel treatment options available.²⁻⁷ Malignant rhabdoid tumors (MRTs) can arise in the brain, kidney, liver, and other soft tissues. These tumors are characterized by genetic alterations in the *SMARCB1* gene leading to bi-allelic inactivation of the INI1 protein.^{8,9} MRTs are aggressive tumors that are usually diagnosed in infants and young children, are highly resistant to treatment and are often fatal. Historically, the 5-year overall survival for children with MRTs is estimated to be between 17% and 33%.^{3,5} In a study from the SEER database of

229 patients with MRTs diagnosed between 1986 and 2005, the estimated 5-year-survival was 33%. Upfront treatment consists of surgical resection followed by intensive chemotherapy and radiation therapy, and currently there are no standard approaches for the treatment of relapsed or refractory MRTs irrespective of tumor location.^{2,7}

Additional INI1-deficient tumors include epithelioid sarcoma, chordoma, renal medullary carcinoma, and others.¹⁰⁻¹⁴ Epithelioid sarcoma is a rare tumor that typically occurs in the extremities of adolescents and young adults. Upfront treatment often consists of radical excisions or amputations as well as local radiation given the tendency for nodal metastatic spread. In the setting of relapse or recurrence there is no standard of care and prognosis is poor.^{13,15,16} Poorly differentiated chordomas with loss of INI1 expression are rare pediatric tumors which have been reported more recently and are associated with a dismal prognosis.^{11,17}

2.2 Study treatment

2.2.1 Nivolumab

Nivolumab is a potent humanized immunoglobulin G4 (IgG4) monoclonal antibody (mAb) with high specificity of binding to the programmed cell death 1 (PD-1) receptor, thus inhibiting its interaction with programmed cell death ligand 1 (PD-L1) and programmed cell death ligand 2 (PD-L2). Based on preclinical *in vitro* data, nivolumab has high affinity and potent receptor blocking activity for PD-1. Nivolumab has an acceptable preclinical safety profile and is in clinical development as an intravenous (IV) immunotherapy for advanced malignancies. Nivolumab is approved for the treatment of several types of cancer because of its mechanism of action to bind the PD-1 receptor on the T cell. For more details on specific indications refer to the Investigator Brochure.

The PD-1 receptor-ligand interaction is a major pathway hijacked by tumors to suppress immune control. The normal function of PD-1, expressed on the cell surface of activated T-cells under healthy conditions, is to down-modulate unwanted or excessive immune responses, including autoimmune reactions. PD-1 (encoded by the gene *PDCDI*) is an immunoglobulin (Ig) superfamily member related to cluster of differentiation 28 (CD28) and cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) that has been shown to negatively regulate antigen receptor signaling upon engagement of its ligands (PD-L1 and/or PD-L2).^{18,19}

The structure of murine PD-1 has been resolved.²⁰ PD-1 and its family members are type I transmembrane glycoproteins containing an Ig-variable-type (IgV-type) domain responsible for ligand binding and a cytoplasmic tail responsible for the binding of signaling molecules. The cytoplasmic tail of PD-1 contains 2 tyrosine-based signaling motifs, an immunoreceptor tyrosine-based inhibition motif, and an immunoreceptor tyrosine-based switch motif. Following T-cell stimulation, PD-1 recruits the tyrosine phosphatases, SHP-1 and SHP-2, to the immunoreceptor tyrosine-based switch motif within its cytoplasmic tail, leading to the dephosphorylation of effector molecules such as CD3 zeta (CD3ζ), protein kinase C-theta (PKCθ), and zeta-chain-associated protein kinase (ZAP70), which are involved in the CD3 T-cell signaling cascade.^{19,21-23} The mechanism by which PD-1 down-modulates T-cell responses is

similar to, but distinct from, that of CTLA-4, because both molecules regulate an overlapping set of signaling proteins.^{24,25}

Nivolumab monotherapy has been safely administered to pediatric patients including those with Hodgkin lymphoma biallelic mismatch repair deficiency.^{26,27} In a COG phase 1 trial (ADVL1412), nivolumab monotherapy was tolerable at a dose of 3mg/kg IV given every 14 days²⁸ Refer to the Investigator's Brochure for additional preclinical and clinical data.

2.2.2 Ipilimumab

Ipilimumab is a fully human monoclonal immunoglobulin IgG1 specific for human cytotoxic T-lymphocyte antigen 4 (CTLA-4), which is expressed on a subset of activated T cells. CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a monoclonal antibody (mAb) that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor-infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell (Treg) function, which may contribute to a general increase in T-cell responsiveness, including the anti-tumor response.

Ipilimumab has been approved for use in advanced melanoma in over 47 countries, including the United States, the European Union, and Australia. Ipilimumab is approved as adjuvant treatment of unresectable or metastatic melanoma in the US, including for pediatric patients age ≥ 12 .

In a phase 1 dose escalation study of ipilimumab in children, adolescents, and young adults with treatment refractory cancer, pediatric patients were treated with ipilimumab by IV infusion q3w for 4 doses. Eligible subjects who tolerated treatment and who obtained apparent clinical benefit continue to receive maintenance therapy q12w. Three subjects (aged 7, 10, and 11) received ipilimumab at 10 mg/kg and 2 experienced a DLT. One subject with neuroblastoma developed Grade 3 colitis and Grade 3 emesis on Cycle 1 Day 8 that were found to be concurrent with norovirus in stool. Symptoms resolved quickly with corticosteroids. A second subject with spindle cell sarcoma developed Grade 3 transaminitis in Week 4 that resolved without immunosuppression. The third subject tolerated 10 mg/kg without any significant toxicities. Because 2 of 3 subjects developed DLTs at 10 mg/kg, 5 mg/kg is being explored as the monotherapy MTD for subjects < 12 years old.²⁹

Ipilimumab has been developed in combination with other therapies, most commonly nivolumab. This combination has FDA approval for unresectable or metastatic melanoma, untreated intermediate and poor risk renal cell carcinoma, and MSI high/mismatch repair deficient colorectal carcinoma. To date, the safety profile of nivolumab and ipilimumab combination therapy is consistent with the mechanisms of action of nivolumab and ipilimumab. The nature of the AEs is similar to that observed with either agent used as monotherapy; however, both frequency and severity of most AEs are increased with the combination.

Children's Oncology Group trial ADVL1412 also evaluated nivolumab with ipilimumab in children with relapsed/refractory cancer. The recommended phase 2 dose of the combination was nivolumab 3mg/kg IV and ipilimumab 1mg/kg every 21 days for 4 doses and then

nivolumab monotherapy every 14 days.²⁸ This dosing strategy will be used in this trial. Drugs alone or in combination were safe, with toxicities similar to those reported on adult studies. Common toxicities included anemia, elevated liver enzymes, rash, fatigue, and nausea, generally Grade 1.

2.3 Rationale

Available evidence suggests a low rate of PD-L1 and CTLA-4 expression in pediatric cancers and a low rate of response to immune checkpoint blockade.³⁰ Recently published data and clinical experience with patients treated at Dana-Farber Cancer Institute suggest that INI1-deficient tumors may be an important exception to this pattern. The presence of PD-L1/PD-1 and CTLA-4 expression and response to immune checkpoint inhibitor therapy has, in lung cancer and melanoma, been correlated with high tumor mutational burden.^{31,32} INI1-deficient cancers in children have, of all cancers, amongst the lowest mutational burden.³³⁻³⁵ In a recent study of MRTs 50% (8/16) of cases showed membranous expression of PD-L1 in 10-70% of tumor cells.³³ In addition, three pediatric patients treated at Dana-Farber Cancer Institute with INI1-deficient tumors (rhabdoid tumor, epithelioid sarcoma, and chordoma) have had PD-L1 positivity by immunohistochemistry (IHC). Recently, responses to immune checkpoint blockade in patients with INI1-negative tumors of multiple histologies have been reported. One pediatric patient with INI1-negative malignant rhabdoid tumor enrolled on a clinical trial of atezolizumab was reported to have a response.^{36,37} Furthermore, there is a published report of a 24-year-old young adult with metastatic INI1-negative epithelioid sarcoma progressing on pazopanib who had a partial response to nivolumab given with pazopanib.³⁸ Another young adult patient with recurrent INI1-negative renal medullary carcinoma had a complete response to nivolumab lasting greater than nine months despite low tumor mutational burden.³⁹ Two subsequent patients with INI1-negative renal medullary carcinoma treated with nivolumab did not have durable responses.⁴⁰ With the hypothesis that the combination of anti-PD1 and anti-CTLA4 checkpoint inhibitor therapy would result in more potent antitumor effect compared to single-agent nivolumab, a single-arm phase II trial of nivolumab plus ipilimumab in adults with INI1-negative renal medullary carcinoma is now open [NCT03274258].⁴¹

Further studies are ongoing to understand the mechanism between INI1 loss and response to immune checkpoint blockade, but sufficient clinical data are available now to test the hypothesis that INI1 loss predicts clinical benefit to immune checkpoint inhibition. This clinical trial offers the opportunity to determine whether there is a clinical benefit to immune checkpoint inhibition in pediatric and young adult patients with highly aggressive tumors associated with a poor prognosis.

2.4 Correlative Studies Background

Response to immune checkpoint blockade has been associated with high mutational burden tumors. We hypothesize that INI1-deficient tumors are an important exception to this pattern. Response has also been associated with an inflamed tumor microenvironment, characterized by activated CD8⁺ T cells. We anticipate that INI1 deficient tumors are characterized by an increase in baseline CD8⁺ T cell infiltration and that treatment with immune checkpoint blockade will lead to activation of those T cells correlating with circulating inflammatory cytokines and

phenotypically activated T cells. Tumor immune microenvironment will be analyzed by multiplex IHC and/or single cell RNASeq, and circulating immune microenvironment will be analyzed for cytokines and immune populations by luminex, flow cytometry, and/or CyTOF. Blood samples will be collected to isolate circulating tumor DNA (ctDNA) by next-generation sequencing approaches.

3. PARTICIPANT SELECTION

3.1 Eligibility Criteria

3.1.1 All participants must have one of the following histologically confirmed tumors at original diagnosis or relapse:

- Stratum 1
 - Malignant rhabdoid tumor (MRT)
 - Rhabdoid tumor of the kidney (RTK)
 - Epithelioid sarcoma
 - Chordoma (poorly differentiated or de-differentiated)
 - Other INI1-negative or SMARCA4-deficient malignant tumors (with PI approval)
- Stratum 2
 - Atypical teratoid rhabdoid tumor (ATRT)
 - Other INI1-negative or SMARCA4-deficient primary CNS malignant tumors (with PI approval)

3.1.2 All participants must have tumor assessment at original diagnosis or relapse showing the following:

- Loss of INI1 confirmed by immunohistochemistry (IHC), OR Molecular confirmation of tumor bi-allelic *SMARCB1* (INI1) loss or mutation when INI1 IHC is equivocal or unavailable; OR,
- Loss of SMARCA4 confirmed by IHC or molecular confirmation of tumor bi-allelic SMARCA4 loss or mutation when SMARCA4 is equivocal or unavailable

3.1.3 Relapsed or refractory disease and no standard treatment options as determined by locally or regionally available standards of care and treating physician's discretion

3.1.4 Measurable disease as defined by

- RECIST v1.1 for Stratum 1 (see Section 11.1); OR,
- RANO for Stratum 2 (see Section 11.2)

Note: RECIST v1.1 may be used for disease evaluation for Stratum 2 (CNS-primary tumor) patients whose only measurable disease is extra-cranial in location.

3.1.5 Age ≥ 6 months and ≤ 40 years

3.1.6 Karnofsky performance status $\geq 50\%$ for participants ≥ 16 years of age and Lansky

performance status $\geq 50\%$ for participants <16 years of age (see Appendix A)

3.1.7 Participants must have fully recovered from the acute toxic effects of all prior anti-cancer therapy. Participants must meet the following minimum washout periods prior to first day of study treatment:

3.1.7.1 Myelosuppressive chemotherapy: At least 14 days after the last dose of myelosuppressive chemotherapy

3.1.7.2 Radiotherapy

- At least 14 days after local palliative XRT (small port)
- At least 90 days must have elapsed after prior TBI, craniospinal XRT or if $>50\%$ radiation of pelvis
- At least 42 days must have elapsed if other substantial BM radiation
- At least 42 days must have passed since last radionuclide therapy (e.g. samarium or radium)

3.1.7.3 Small molecule biologic therapy: At least 7 days following the last dose of a non-monoclonal biologic agent

3.1.7.4 Monoclonal antibody: At least 21 days after the last dose

3.1.7.5 Myeloid growth factors: At least 14 days following the last dose of long-acting growth factor (e.g. Neulasta) or 7 days following short-acting growth factor

3.1.7.6 Stem Cell or Autologous T Cell Infusion: At least 42 days must have elapsed after stem cell or autologous T cell infusion

3.1.8 Participants must have adequate organ function as defined below

3.1.8.1 Bone Marrow Function

- Absolute neutrophil count $\geq 500/\mu\text{L}$
- Platelets $\geq 50,000/\mu\text{L}$ and transfusion independent, defined as not receiving a platelet transfusion for at least 7 days prior to CBC documenting eligibility

3.1.8.2 Hepatic Function

- Total bilirubin $\leq 1.5 \times$ upper limit of normal for age
- ALT (SGPT) $\leq 3 \times$ upper limit of normal (for the purpose of this study, the ULN for ALT is 45 U/L)

3.1.8.3 Renal function

- A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)

	Male	Female
6 months to 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

OR

- Creatinine clearance ≥ 70 mL/min/1.73 m² for participants with creatinine levels above institutional normal
- 3.1.9 Adequate Pulmonary Function Defined as:
- No evidence of dyspnea at rest, no exercise intolerance due to pulmonary insufficient and a pulse oximetry > 92% while breathing room air
- 3.1.10 Adequate pancreatic function defined as
- Serum lipase $\leq$ ULN at baseline
- 3.1.11 Negative B-HCG pregnancy test (urine or serum) in females of childbearing potential. Must be drawn or repeated within 24 hours prior to initial administration of nivolumab.
- 3.1.12 Women of childbearing potential (WOCBP) receiving nivolumab agree to adhere to contraception for a period of 5 months after the last dose of nivolumab. Men receiving nivolumab and who are sexually active with WOCBP will agree to adhere to contraception for a period of 7 months after the last dose of nivolumab.
- 3.1.13 Ability to understand and/or the willingness of the patient (or parent or legally authorized representative, if minor) to provide informed consent, documented using an institutionally approved informed consent procedure.

3.2 Exclusion Criteria

- 3.2.1 Participants who are receiving any other investigational agents.
- 3.2.2 Corticosteroids: If used to modify immune adverse events related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid. CNS subjects receiving corticosteroids for neurologic symptom relief must be at stable or decreasing doses for at least 7 days prior to the first day of study treatment. For all patients, corticosteroid doses of up to 0.12 mg/kg/day prednisone equivalent may be approved after consultation with the Principal Investigator. Treatment with topical, inhaled or ophthalmic corticosteroid is acceptable.
- 3.2.3 Participants with a known history of HIV, hepatitis B, and/or hepatitis C (testing

not required as part of screening).

- 3.2.4 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection or any other concurrent disease which in the judgment of the Investigator would make the subject inappropriate for enrollment on this study.
- 3.2.5 Has a history of (non-infectious) pneumonitis that required steroids or has current pneumonitis.
- 3.2.6 Has active autoimmune disease that has required systemic treatment in the past 12 months, or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with vitiligo or resolved childhood asthma/atopy are exceptions. Intermittent use of bronchodilators or local steroid injections are not excluded. Replacement therapy (e.g. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Autoimmune diagnoses not listed must be approved by the Principal Investigator.
- 3.2.7 Patients who have received prior solid organ transplantation are not eligible.
- 3.2.8 Pregnancy or Breast-Feeding: Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogenic adverse events as there is yet no available information regarding human fetal or teratogenic toxicities. Pregnancy tests must be obtained in girls who are post-menarchal. Women of childbearing potential (WOCBP) receiving nivolumab will be instructed to adhere to contraception for a period of 5 months after the last dose of nivolumab. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 7 months after the last dose of nivolumab.
- 3.2.9 Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2 or anti-CTLA4 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g. OX-40, CD137)
- 3.2.10 Participants who have received live / attenuated vaccine within 30 days of first dose of study treatment.

3.3 Inclusion of Children and Minorities

Both male and female children 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 any protocol-specific therapy or intervention. Any participant not registered to the protocol before protocol-specific therapy or intervention begins will be considered ineligible and registration will be denied.

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

4.2 Registration Process for DF/HCC Institutions

Applicable DF/HCC policy (REGIST-101) must be followed.

4.3 General Guidelines for Other Investigative Sites

Eligible participants will be entered on study centrally at the Dana-Farber Cancer Institute by the Study Coordinator. All sites should email the DFCI Study Coordinator, and the study team mailbox [REDACTED] to verify slot availability.

Following registration, participants should begin protocol therapy within 5 days. Issues that would cause treatment delays should be discussed with the Overall PI. If the subject does not receive protocol therapy following registration, the subject must be taken off-study in the CTMS (OnCore) with an appropriate date and reason entered.

4.4 Registration Process for Other Investigative Sites

To register a participant, the following documents should be completed by the participating site and e-mailed to the Study Coordinator:

- Copy of eligibility source documentation, including confirmation of INI1/SMARCA4 loss by IHC or *SMARCB1/SMARCA4* mutation/loss
- Copy of required laboratory tests including:
 - CBC with differential
 - Serum chemistry (total bilirubin, creatinine, SGOT [AST], SGPT [ALT], amylase, lipase), B-HCG pregnancy test (serum or urine)

- Creatinine clearance for participants with creatinine levels above institutional normal
- Signed informed consent document
- HIPAA authorization form (if separate from the informed consent document)
- Completed Eligibility Checklist

The participating site will then e-mail the Study Coordinator to verify eligibility. The Study Coordinator will follow DF/HCC policy (REGIST-101) and register the participant on the protocol. The Study Coordinator will fax or e-mail the participant study number, and if applicable the dose treatment level, to the participating site. The Study Coordinator will also contact the participating site and verbally confirm registration.

5. TREATMENT AND/OR IMAGING PLAN

5.1 Treatment Regimen and Agent Administration

Treatment will be administered on an outpatient basis unless the participant is hospitalized for other reasons and meets criteria to receive study treatment. Expected toxicities and potential risks for nivolumab and ipilimumab are described in Section 6 and Section 7.

Treatment will be given in cycles. Cycles 1-4 will be 3 weeks (21 days) in length to coincide with combination nivolumab and ipilimumab administration. Cycles 5 and subsequent cycles will be 4 weeks (28 days) in length to coincide with nivolumab monotherapy administration.

Nivolumab (3mg/kg with a maximum dose of 240mg) will be given as an IV infusion over 30 minutes (hour 0) on day 1 of cycles 1-4. For cycle 5 and subsequent cycles, nivolumab (3mg/kg with a maximum dose of 240mg) will be given as an IV infusion over 30 minutes (hour 0) on day 1 and 15 until the patient comes off therapy (Section 5.4).

Ipilimumab (1mg/kg) will be given as an IV infusion over 90 minutes (at hour 1.0) on day 1 of cycles 1-4 for a total of 4 doses. Ipilimumab infusion should be started no sooner than 30 minutes after completion of the nivolumab infusion.

Drug doses should be adjusted based on the patient's actual weight in kilograms measured within 7 days prior to the beginning of each cycle.

At the end of the study period, Bristol-Myers Squibb Company will not continue to supply study drug to subjects/investigators unless the Sponsor chooses to extend their study. The Investigator is responsible to ensure that the subject receives appropriate standard of care or other appropriate treatment in the independent medical judgement of the Investigator to treat the condition under study.

Disease reevaluation will take place at the end of Cycle 3 and then every 3 cycles until month 12 or the patient comes off study.

Disease Evaluation at the end of Cycle 3 and then every 3 cycles																
Cycle	1			2			3			4			5			6+
Week	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16
Nivolumab	X			X			X			X			X		X	
Ipilimumab	X			X			X			X						
																q2 weeks until removed from study or 1 year

5.2 Pre-Treatment Criteria

5.2.1. Cycle 1, Day 1

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility (see Section 3.1) must be no older than seven (7) days at the start of therapy. Laboratory tests need not be repeated if therapy starts within seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are older than 7 days, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy.

5.2.2. Criteria to Start Subsequent Cycles or Administer Day 15 Nivolumab (Cycles 5+)

- Absolute Neutrophil Count $\geq 500/\mu\text{L}$ off growth factor
- Platelet count $\geq 50,000/\mu\text{L}$ and transfusion independent (no platelet transfusion for at least 7 days)
- No systemic corticosteroid therapy, other than replacement therapy for adrenal insufficiency or transfusion premedication
- Does not meet criteria for delay or permanent discontinuation as outlined in section 6.1
- No therapy with another investigational agent
- No uncontrolled active infection
- Negative B-HCG pregnancy test in females of childbearing potential

5.3 General Concomitant Medication and Supportive Care Guidelines

- Short term use of systemic steroids, such as for blood or platelet transfusion reactions, hives, or other acute allergic reaction is allowed. Steroid replacement dosing for adrenal insufficiency and stress-dose steroid dosing is allowed.
- Systemic glucocorticoids may be used to modulate symptoms from an adverse event of suspected immunologic etiology. Steroid treatment should be completed at least 14 days prior to resuming study-related treatments.

- Any live / attenuated vaccine (e.g. varicella, zoster, yellow fever, rotavirus, oral polio and measles, mumps, rubella (MMR)) is prohibited during treatment and until 100 days post last dose of study treatment.

5.4 Duration of Study Treatment and 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 for 14 cycles (12 months)* or 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 medication regimen and/or documentation requirements
- Participant or parent/legal guardian 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
- Pregnancy

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

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

*Patients with stable disease or confirmed response after 1 year of treatment could remain on study treatment beyond 1 year with approval from Principal Investigator.

5.5 Duration of Follow Up

Participants who are off protocol therapy will be followed as described in Section 10 until they meet Criteria for Taking a Participant Off Study (see section 5.6 below). Participants removed from protocol therapy for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event or they meet Criteria for Taking a Participant Off Study, whichever is longer.

5.6 Criteria for Taking a Participant Off Study

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

- Completed 2 years of follow up after last dose of protocol therapy
- Participant did not receive protocol treatment after study enrollment

- Found to be ineligible, including participants who have repeat organ function laboratory studies obtained within 7 days of Cycle 1, Day 1 that do not meet entry eligibility requirements
- 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). In addition, the study team will ensure the participant's status is updated in OnCore in accordance with REGIST-OP-1.

6. DOSING DELAYS/DOSE MODIFICATIONS AND EXPECTED TOXICITIES

6.1 Dose Modification/Delays

Dose delays will be made as indicated in the following text. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for dose delays and dose modifications. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website

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

All adverse events experienced by participants will be collected from the time of the first vaccination, through the study and until the final study visit. Participants continuing to experience toxicity at the end of study/off-study visit will be contacted for additional assessments until the toxicity has resolved or is deemed irreversible.

Nivolumab and ipilimumab are associated with immune-related adverse reactions. With appropriate medical therapy, immune-related adverse reactions resolve in most cases. In order to standardize the management of AEs for all subjects, treatment management algorithms are included in Appendix C, Immune-Mediated Adverse Reactions Management Guide.

There will be no dose reductions to nivolumab or ipilimumab, only treatment delays or permanent discontinuation.

Dosing of nivolumab and ipilimumab will be delayed for the following criteria:

- AST/ALT $> 3 \times$ ULN
- Total bilirubin $> 1.5 \times$ ULN
- Creatinine $> 1.5 \times$ ULN or GFR < 40 mL/min/1.73 m²
- ANC < 500 /uL
- Platelets < 50000 /uL
- Glucose > 160 mg/dL (8.9mmol/L) (fasting) or > 200 mg/dL (11.1 mmol/L) (non-fasting)
- Any $\geq$ Grade 2 non-skin, non-hematological nivolumab/ipilimumab-related adverse event, with the following exceptions:

- Grade 2 fatigue
 - Grade 2 lab abnormalities (with the exception of ALT/AST, total bilirubin, creatinine, fasting glucose as noted above)
 - Grade 2 hypothyroidism or thyroiditis
 - Grade 3 or 4 fever and neutropenia
- Any $\geq$ Grade 3 skin nivolumab/ipilimumab related AE
- Any $\geq$ Grade 3 nivolumab/ipilimumab - related laboratory abnormality with the following exceptions:
 - Grade $\geq$ 3 lymphopenia
 - Any $\geq$ Grade 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis
 - Isolated grade 3 or 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management
- Any AE, laboratory abnormality, or inter-current illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Subjects who require delay during study treatment, should be evaluated weekly or more frequently if clinically indicated and resume dosing when re-treatment criteria are met.

Subjects may resume treatment with study drug when the nivolumab or ipilimumab-related AE(s) resolve to grade ≤ 1 or baseline value, with the following exceptions:

- Subjects may resume treatment in the presence of grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin adverse event
- Treatment-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed.
- Treatment-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment, which includes grade 2 hyperglycemia, hypothyroidism and thyroiditis.

Subjects should be permanently discontinued if AE does not resolve within 12 weeks of last dose or corticosteroids cannot be reduced to $\leq 0.5\text{mg/kg}$ prednisone or equivalent per day within 12 weeks.

6.2 Infusion Reactions

Nivolumab and ipilimumab may cause severe or life-threatening infusion-reactions including severe hypersensitivity or anaphylaxis. Signs and symptoms usually develop during or shortly after drug infusion and generally resolve completely within 24 hours of completion of infusion. Monitor patients for signs and symptoms of infusion-related reactions from the start of each infusion until at least 30 minutes after the end of the infusion, in an area containing resuscitation equipment and medications necessary for advanced life support and cardiopulmonary resuscitation. Toxicity management

guidelines on drug-related infusion reactions are provided in **Table 2**.

Table 2. Infusion Reaction Dose modification and Treatment Guidelines

NCI CTCAE Grade	Treatment	Premedication at Subsequent Dosing
Grade 1 Mild reaction; infusion interruption not indicated; intervention not indicated	Monitor vital signs as medically indicated until the participant is deemed medically stable in the opinion of the investigator.	Participant may be premedicated at least 30 minutes before infusion of nivolumab or ipilimumab with: Diphenhydramine 1mg/kg (max 50 mg) PO (or equivalent dose of antihistamine) and/or Acetaminophen 12.5mg/kg PO (or equivalent dose of analgesic)
Grade 2 Moderate reaction; requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs	Stop Infusion. Begin IV normal saline, and treat subject with diphenhydramine 1mg/kg (max 50 mg) IV (or equivalent) and/or acetaminophen 12.5mg/kg; monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If symptoms resolve within 1 hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate. Otherwise dosing will be held until symptoms resolve and the participant should be premedicated for the next scheduled dose. If symptoms recur, then no further nivolumab or ipilimumab will be administered at that visit.	Participant may be premedicated at least 30 minutes before infusion of nivolumab or ipilimumab with: Diphenhydramine 1mg/kg (max 50 mg) PO (or equivalent dose of antihistamine). and/or Acetaminophen 12.5mg/kg PO (or equivalent dose of analgesic). If necessary, corticosteroids (1-2mg/kg methylprednisolone or equivalent) may be used.

Grades 3 or 4 Grade 3: Severe reaction; prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae Grade 4: Life-threatening; urgent intervention indicated	Stop Infusion. Begin IV normal saline and treat as follows: Investigators should follow institutional guidelines for the treatment of anaphylaxis. Recommended bronchodilators, epinephrine IM at a dose of 0.01mg/kg (max 0.3mg for prepubertal child, maximum 0.5mg for adolescent) every 5-15 minutes as needed for anaphylaxis Subject should be monitored until symptoms resolve and the investigator is comfortable that the symptoms will not recur. Participant is permanently discontinued from further nivolumab or ipilimumab treatment.	No subsequent dosing
Appropriate resuscitation equipment should be available at the bedside and a physician readily available during the period of drug administration.		

6.3 Toxicity-Related Treatment Discontinuation

In addition to the nivolumab/ipilimumab discontinuation criteria listed in **Table 2** above, permanent discontinuation of these drugs should be considered for any severe or life-threatening treatment-related AEs, including, but not limited to, any of the following (the IND Sponsor and BMS must be notified in the event of these AEs):

- Any grade 2 treatment-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within 2 weeks of starting therapy OR requires systemic treatment
- Any grade 3 non-skin, drug-related AE lasting > 7 days, with the following exceptions:
 - Grade 3 treatment-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
 - Grade 3 treatment-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
 - Grade 3 treatment-related laboratory abnormalities do not require treatment discontinuation except:
 - Grade 4 treatment-related thrombocytopenia > 7 days OR that is associated with bleeding requires discontinuation
 - Any treatment-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
 - Total bilirubin > 5 × ULN
 - Concurrent AST or ALT > 3 × ULN **and** total bilirubin > 2 × ULN

- Any grade 4 treatment-related AE or laboratory abnormality, except for the following events which do not require discontinuation:
 - Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations, or radiographic signs of pancreatitis.
 - Isolated grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset.
 - Grade 4 lymphopenia and leukopenia.
 - Grade 4 treatment-related endocrinopathy adverse events, such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the IND Sponsor.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

7.1 Introduction to Adverse Event Reporting

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

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs (Section 7.2 and 7.3) and the characteristics of an observed AE (Section 7.4) will determine whether the event requires expedited reporting **in addition** to routine reporting.

7.2 Adverse Event List for Ipilimumab

The following adverse events are the most commonly seen adverse events with ipilimumab treatment (see also current version of the package insert and Investigator Brochure). The following list was obtained from the Comprehensive Adverse Events and Potential Risks list (CAEPR), Version 2.10, March 29, 2019.

Likely (>20%)

- Diarrhea
- Nausea
- Fatigue
- Rash

Less Likely (<=20%)

- Atrial fibrillation
- Hearing loss

- Adrenal insufficiency
- Hyperthyroidism/Hypothyroidism
- Hypophysitis
- Hypopituitarism
- Testosterone Deficiency
- Uveitis, Other eye disorders (episcleritis)
- Abdominal Pain, Constipation
- Colitis/ Enterocolitis
- Esophagitis
- Pancreatitis
- Vomiting
- Chills/ Fever
- Hepatitis
- Autoimmune disorder
- Infusion related reaction
- Transaminitis
- Neutropenia
- Anorexia/Weight loss
- Dehydration
- Hyperglycemia
- Arthritis/ Arthralgia
- Myositis
- Guillain-Barre Syndrome
- Headache
- Myasthenia Gravis
- Acute kidney injury
- Pneumonitis
- Pruritis
- Skin disorder (Sweet's Syndrome)
- Urticaria
- Hypotension

Rare but Serious (<3%)

- Blood and lymphatic system autoimmune disorders (ie acquired hemophilia)
- Myocarditis
- Pericardial effusion
- Colonic perforation
- Ileus
- Systemic inflammatory response syndrome
- Multi-organ failure
- Aseptic Meningitis
- Lymphopenia
- Muscle weakness
- Ataxia
- Neuropathy
- Encephalitis
- Respiratory failure

- Erythema multiforme
- Stephens- Johnson Syndrome
- Toxic epidermal necrolysis

7.3 Adverse Event List for Nivolumab

The following adverse events are the most commonly seen adverse events with nivolumab treatment (see also current version of the package insert and Investigator Brochure). The following list was obtained from the Comprehensive Adverse Events and Potential Risks list (CAEPR), Version 2.4, December 2, 2020.

Likely (>20%)

- Fatigue

Less Likely (<=20%)

- Anemia
- Adrenal insufficiency
- Hypophysitis
- Hyperthyroidism/Hypothyroidism
- Uveitis
- Abdominal Pain
- Colitis
- Diarrhea
- Dry mouth
- Nausea/vomiting
- Pancreatitis
- Fever
- Injection site reaction / infusion related reaction
- Transaminitis
- Hyperbilirubinemia
- Creatinine increased
- Lipase increased
- Amylase increased
- Neutropenia
- Lymphopenia
- Thrombocytopenia
- Anorexia/Weight loss
- Arthralgia
- Pleural Effusion
- Pneumonitis
- Pruritis
- Rash
- Skin disorder (Sweet's Syndrome)
- Skin hypopigmentation (Vitiligo)

Rare but Serious (<3%)

- Cardiomyopathy

- Myocarditis
- Pericardial effusion/tamponade
- Pericarditis
- Blurred vision
- Optic neuritis
- Dry eye
- Graves ophthalmopathy
- Vogt-Koyanagi-Harada disorder
- Colonic perforation
- Enterocolitis
- Gastritis
- Mucositis
- Immune-mediated hepatitis
- Cytokine Release Syndrome
- Sarcoidosis
- Autoimmune disorder
- Hyperglycemia
- Diabetes mellitus/Diabetic Ketoacidosis
- Polymyositis / Myositis
- Rhabdomyolysis
- Encephalopathy
- Encephalitis/meningoencephalitis
- Meningoradiculitis
- Guillain-Barre Syndrome
- Facial nerve disorder
- Myasthenia Gravis
- Neuropathy
- Reversible posterior leukoencephalopathy syndrome
- Acute Kidney Injury
- Nephritis
- Bronchiolitis obliterans with organizing pneumonia
- Respiratory failure
- Erythema multiforme
- Bullous pemphigoid
- Stevens- Johnson Syndrome
- Toxic epidermal necrolysis
- Allergic reaction

7.4 Adverse Event Characteristics

Investigators are to provide the following adverse event characteristics for all adverse events experienced from enrollment until 30 days after last dose study treatment. In addition, investigators are to provide the following adverse event characteristics for **serious adverse events only** until 100 days after the last dose of study treatment.

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a

copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site

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

- **Attribution of the AE:**
 - Definite – The AE *is clearly related* to the study treatment.
 - Probable – The AE *is likely related* to the study treatment.
 - Possible – The AE *may be related* to the study treatment.
 - Unlikely – The AE *is doubtfully related* to the study treatment.
 - Unrelated – The AE *is clearly NOT related* to the study treatment.
- **Serious adverse event (SAE):** An AE is classified as “serious” (SAE) if it meets any of the following criteria:

Death of Patient	An event that results in the death of a patient.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization	An event that occurs while the study patient is hospitalized and prolongs the patient’s hospital stay.
Congenital Anomaly	An anomaly detected at or after birth or any anomaly that result in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study patient. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, or accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An <u>important medical event</u> that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the patient and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of patient, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. NOTE: All Grade 3-5 infusion-related reactions are considered serious and require expedited reporting.

An AE that meets none of the above criteria is considered “non-serious”.

Note: Seriousness is independent of attribution or expectedness of the AE.

- **Expectedness of the AE:** In addition to term, grade, attribution, and seriousness, adverse events that have the potential to qualify for expedited reporting (see Section 7.6) are to be designated as “expected” or “unexpected”. For the purposes of expedited reporting to DF/HCC, the adverse events listed in Sections 7.2 and 7.3 are to be considered expected.

7.5 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the toxicity case report forms. AE collection will begin following the participant’s written consent to participate in the study. **AEs that also meet criteria for expedited reporting (see Section 7.6) must also be reported in routine study data submissions.**

All non-serious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 30 days following the last dose of study treatment. **Furthermore, all serious adverse events should be collected for a minimum of 100 days following the last dose of study treatment.** Non-serious AEs ongoing at the end of the 30-day follow up period if attributed as related to study treatment should be followed until the event stabilizes, resolves, or is no longer of clinical concern (eg. patient started new treatment).

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported as such.

The following laboratory abnormalities should be documented and reported appropriately:

- any laboratory test result that is clinically significant or meets the definition of an SAE
- any laboratory abnormality that required the participant to have study drug discontinued or interrupted
- any laboratory abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

7.6 Expedited Adverse Event Reporting

7.6.1 Criteria for Expedited Adverse Event Reporting

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

Investigators must report to the Overall PI in an expedited manner any adverse events (AE) that occurs after the initial dose of study treatment, during treatment, or within 100 days of the last dose of treatment if they meet any of the following criteria:

- Serious adverse event, including Grade 5 adverse events
- Pregnancy in a female participant treated with protocol therapy

Investigators must report to the Overall PI in an expedited manner any adverse events (AE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment if they meet any of the following criteria:

- Other adverse events that meet DFCI Institutional Review Board Adverse Event Reporting policy for expedited reporting:

Note: Grade 2 and Grade 3 laboratory abnormalities that are considered by the investigator to be clinically insignificant and do not require therapy, or adjustment in prior therapy, do not need to be reported to the Overall Principal Investigator or the DFCI IRB.

Regardless of treating institution, these expedited reports will be submitted to the Overall Principal Investigator using a DF/HCC AE Reporting form.

The treating institution must notify the Overall Principal Investigator by phone or email of any serious adverse event within 24 hours of learning of the event, with a formal written report within 3 business days.

If the investigator believes that an SAE is not related to study treatment, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

For non-serious AE's that nevertheless meet the definition below for DF/HCC reportable AEs, the following timelines apply for submission of a DF/HCC AE Reporting form to the Overall Principal Investigator.

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 <u>24 business hours</u> of learning of the event.					
**Please follow these reporting timelines only if the event qualifies as <u>non-serious</u> . The treating institution must notify the Overall Principal Investigator by phone or email of any <u>serious adverse event</u> within 24 hours of learning of the event, with a formal written report within 3 business days.					

7.6.2 Guidelines for Multicenter Expedited AE Reporting

For multi-institution studies where a DF/HCC investigator is serving as the Overall Principal Investigator, each participating institution **must** abide by the reporting requirements set by the DF/HCC. This applies to any adverse event meeting the criteria for expedited reporting as

defined in section 7.6.1.

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

Other investigative sites will report expedited AEs to their respective IRB according to the local IRB's policies and procedures in reporting adverse events. These sites will also complete a DF/HCC AE Reporting form to the Overall PI within the timeframes detailed above. The Overall PI will then submit the DF/HCC AE Reporting form from outside institutions to the DFCI OHRS according to DFCI IRB policies and procedures in reporting adverse events. Outside sites should also provide the Overall PI with a copy of any local AE reporting form required to be submitted to their local IRB.

7.6.3 Protocol-Specific Expedited Adverse Event Reporting Exclusions

Unless the adverse event meets the definition of serious, the following grade 2 adverse events do not require expedited reporting to the Overall Principal Investigator or the DFCI IRB: nausea; vomiting; fatigue; anemia; anorexia; headache; constipation; and diarrhea. Planned hospitalizations do not require expedited adverse event reporting.

These AEs still must be reported through the routine reporting mechanism (i.e. case report form).

7.7 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 Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.8 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.

7.9 Reporting to Bristol-Myers Squibb (BMS)

7.9.1 SAE Reporting to Bristol-Myers Squibb

The Overall Principal Investigator or designee will report any serious adverse events from time of consent until 100 days after last dose of study treatment (regardless of expectedness or attribution) to Bristol-Myers Squibb. The initial report must be within 24 hours of notification of such events. If only limited information is initially available, a follow-up report is required. All serious adverse events should be followed to resolution or stabilization.

Initial and follow-up safety reports will utilize the DF/HCC AE Reporting form and will be sent electronically to: [REDACTED] Please include the BMS Protocol number and

country of origin, and laboratory data on the SAE form or on the cover sheet with the SAE form transmission.

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

7.9.2 Other AE Reporting to BMS

AEs that require treatment discontinuation (see Section 6.3) must also be reported to BMS.

7.9.3 AE database reconciliation

The Sponsor will reconcile the clinical database AE cases (case level only) transmitted to BMS Global Pharmacovigilance [REDACTED]

- The Investigator will request from BMS GPV&E, [REDACTED] the SAE reconciliation report and include the BMS protocol number every 3 months and prior to data base lock or final data summary
- GPV&E will send the investigator the report to verify and confirm all SAEs have been transmitted to BMS GPV&E.
- 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 [REDACTED]

7.9.4 Reporting Pregnancy to Bristol-Myers Squibb

Any pregnancy in a female participant treated with study treatment will be reported to BMS in an expedited manner following the same guidelines used for reporting SAEs (section 7.9.1). The Overall PI must immediately notify [REDACTED] of this event via either the CIOMS, MedWatch or appropriate Pregnancy Surveillance Form in accordance with SAE reporting procedures.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant. Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the approved site SAE form. A BMS Pregnancy Surveillance Form may be provided upon request.

7.10 External Safety Reports Received from Bristol-Myers Squibb

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

Other important findings which may be reported by BMS as an Expedited Safety Report (ESR) include: increased frequency of a clinically significant expected SAE, an SAE considered

associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor or BMS decision to end or temporarily halt a clinical study for safety reasons.

Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.

8. PHARMACEUTICAL INFORMATION

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9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

Biologic responses to immune checkpoint blockade will be assessed by laboratory and histologic analyses of blood and tumor tissue before, during and after therapy, when available. All correlative studies are optional but encouraged. We anticipate that INI1 deficient tumors are characterized by an increase in baseline CD8⁺ T cell infiltration and that treatment with immune checkpoint blockade will lead to activation of those T cells correlating with circulating inflammatory cytokines and phenotypically activated T cells.

Tumor tissue, when available, will be analyzed for numbers and proportions of CD4⁺ T cells, CD8⁺ T effectors, FoxP3⁺ Tregs, macrophages, and myeloid derived suppressor cells (MDSCs), along with tumor and immune expression of PD-L1 and T cell expression of PD-1, by multiplex IHC, flow cytometry, and/or single cell RNASeq. The local production of relevant cytokines and chemokines will also be examined using RT PCR and commercially available Luminex assays.

Serum and circulating mononuclear cells will be frozen prior to therapy initiation and at regular intervals thereafter. These longitudinal samples will be analyzed for immune cell numbers and subsets. We will use multi-color flow cytometry methods (5 or 9 color), and where feasible CyTOF analysis or single cell RNASeq, to investigate immune cell subsets. These phenotypic measurements will be complemented with functional studies. The systemic production of relevant cytokines and chemokines will be examined using commercially available Luminex assays.

Blood samples will be collected to isolate circulating tumor DNA (ctDNA) by next-generation sequencing approaches.

9.1 Laboratory Correlative Studies

Please refer to manual of operations for additional sample handling and shipping instructions

Tissue immune microenvironment by multiplex IHC

- 10 unstained FFPE slides from tumor diagnostic procedure or any clinically indicated biopsy/resection of tumor while on therapy
- [REDACTED]

Tumor immune microenvironment by single cell RNA Sequencing

- 25 mg frozen tumor tissue, archival, or frozen in cryovial at -80 degrees as soon as possible after any clinically indicated biopsy/resection of tumor while on therapy

- [REDACTED]

Peripheral immune microenvironment cytokine analysis and flow cytometry/CyTOF

- 10ml in EDTA tube sent at room temperature

- [REDACTED]

Peripheral blood for circulating tumor DNA (ctDNA)

- 5-10ml in Streck Cell-Free DNA BCT tube

- [REDACTED]

- Please refer to manual of operations for additional sample handling and shipping instructions

10. STUDY CALENDAR

For patients starting therapy baseline evaluations are to be conducted within 7 days prior to start of protocol therapy. Imaging studies must be done ≤ 28 days prior to the start of therapy. In the event that the participant's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of therapy.

	Screening	Cycle 1			Cycle 2	Cycle 3	Cycle 4	Cycle 5 and Subsequent Cycles		End of Therapy ^d	Surgery or Biopsy	
Day		D1	D8	D15	D1	D1	D1	D1	D15			
<i>Nivolumab</i>		X			X	X	X	X	X ^a			
<i>Ipilimumab</i>		X			X	X	X					
Informed consent	X											
Demographics	X											
Medical history	X	X			X	X	X	X	X ^e			
Concurrent meds	X	X										
Physical exam	X	X			X	X	X	X	X ^e	X		
Vital signs	X	X			X	X	X	X	X ^e	X		
Pulse oximetry	X											
Height	X				X	X	X	X		X		
Weight	X	X			X	X	X	X	X ^e	X		
Performance status	X	X			X	X	X	X		X		
CBC w/diff, plts	X	X	X	X	X	X	X	X	X ^e	X		
Serum chemistry ^b	X	X			X	X	X	X	X ^e	X		
B-HCG ^c	X	X			X	X	X	X				
TSH ^f	X				X	X	X	X				
Adverse events	X	X								Through 30 days post last study treatment dose		
Serious adverse events	X	X								Through 100 days post last study treatment dose		
Tumor evaluation ^g	X						X	Tumor evaluations are repeated every 3 cycles. Please refer to Section 11 for details of disease evaluation.				
Blood for correlative studies ^h		X			X		X	To be repeated every 3 cycles		X	X	
Tumor tissue ⁱ	X										X	
Surgical Pathology Report(s) (redacted) and molecular report(s)	X										X	
OBTAIN OTHER STUDIES AS NEEDED FOR GOOD PATIENT CARE.												
a: Continuing q2 weeks while patient remains on study, or 12 months of therapy.												
b: Albumin, alkaline phosphatase, total bilirubin, bicarbonate, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus,												

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magnesium, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, amylase, lipase. c: Serum or urine pregnancy test within 24 hours of administration of study drug (women of childbearing potential). d: Off-study evaluation. e: Then every 2 weeks (+/- 2 days) in conjunction with nivolumab administration. f: Free T4 should also be measured for patients with an abnormal TSH level. Please refer to Appendix C for guidance on the management of patients who develop endocrinopathy adverse events. g: At the end of Cycle 3 and then every 3 cycles thereafter (within 10 days prior to planned start of subsequent cycle). Evaluations should include CT or MRI of all lesions. Use the same imaging modality for all disease evaluations. For lung metastases, chest CT is recommended. For soft tissue lesions, CT or MRI may be used. Participants who have a response (CR or PR) on any evaluation will have confirmatory imaging 4 weeks after the evaluation upon which the response was detected (additional imaging time point). h. Blood for correlative studies (EDTA and Streck tubes) should occur pre-dose on Day 1 of Cycle 1, 2, 4 and every 3 cycles thereafter i. Frozen/archival and/or unstained FFPE as outlined in section 9.	
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Assessments must be performed prior to administration of any study treatment. Study assessments and agents should be administered within $\pm$ 3 days of the protocol-specified date, unless otherwise noted.

End of Therapy: End of Therapy visit should occur within 30 days inclusive from the date the patient is taken off of protocol therapy.

Follow-up: After participants meet off-protocol therapy criteria and complete the end of therapy observations in the above table, they will enter follow-up. Participants will remain in follow-up until two years from last dose of study treatment or death, whichever occurs first. During follow-up, participants will undergo disease evaluations according to a schedule determined by their treating physician. Disease and vital status will be collected every 6 months during the follow-up period.

11. MEASUREMENT OF EFFECT

Note: RECIST v1.1 criteria may be used for disease evaluation for in Stratum 2 (CNS-primary tumor) patients whose only measurable disease is extra-cranial in location.

11.1 Antitumor Effect – Stratum 1 – RECIST v1.1

For the purposes of this study, participants should be re-evaluated for response every 3 cycles (which is 9 weeks for the first 3 cycles and 12 weeks starting with cycle 4). In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

Response and progression for patients in Stratum 1 will be evaluated in this study using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

Definitions

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

Evaluable Non-Target Disease Response. Participants who have lesions present at baseline that are evaluable but do not meet the definitions of measurable disease, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray or ≥ 10 mm with CT scan, MRI, or calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area are not considered measurable or evaluable unless that site meets criteria for progression after completion of radiation.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a

lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

‘Cystic lesions’ thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow up.

Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions. Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥ 10 mm in diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung; however, CT is preferable.

Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

- (a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
- (b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

(c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A ‘positive’ FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound. Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure from CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy. The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers. Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a participant to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology. These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

Response Criteria

- Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Pseudoprogression: Exceptions for Delayed Response

Subjects in whom the magnitude of increase in tumor size is >20% but <40%, may remain on study for up to 12 weeks after start of protocol therapy if the following criteria are met. Lesions < 10 mm will not be considered new lesions; new lesions ≥ 10 mm of longest diameter must be included in the total tumor burden.

- In the judgment of the treating clinician, the subject does not show evidence for rapid disease progression or the subject has shown evidence for clinical benefit.
- There is no decrease in performance status.
- The subject is tolerating the study treatment.
- Continued study treatment will not delay an imminent intervention required to prevent serious complications.

For subjects who remain on study despite increase in tumor size > 20%, imaging to include target lesions must occur every cycle if clinically indicated, or if “pseudoprogression” appears based on inflammatory response, or sarcoid granuloma is present, and the same radiographic and clinical criteria must be met in order to remain on study. If tumor size subsequently diminishes to < 20% increase from baseline, the subject may be followed according to the standard protocol guidelines which will involve less frequent imaging. The decision to continue treatment beyond radiographic evidence for disease progression should be discussed with the study PI

and documented in the study record.

Subjects who develop worsening radiographic findings >6 months from start of immunotherapy are expected to have a low likelihood of ultimately deriving benefit from the therapy and should be considered PD based on imaging if they have a 50% increase in size of the target lesion or if new lesions appear. Subjects who experience significant clinical decline or those who have radiographic progression on the 3-month follow up scan should be classified as confirmed PD and the date of progression should be entered as the first MRI that showed progressive disease.

- **Evaluation of Non-Target Lesions**

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of “non-target” lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

- **Evaluation of New Lesions**

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some ‘new’ bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

- Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Participants with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	
* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion. ** Only for non-randomized trials with response as primary endpoint. *** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression. <u>Note:</u> Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as “<i>symptomatic deterioration</i>.” Every effort should be made to document the objective progression even after discontinuation of treatment.				

For Participants with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* ‘Non-CR/non-PD’ is preferred over ‘stable disease’ for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign		

this category when no lesions can be measured is not advised
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Response Review

Participants with confirmed objective response (partial response or better) may have de-identified imaging studies requested by the coordinating center for central confirmation of response. Imaging studies that could be requested include baseline scans, initial scans documenting response, and second set of scans confirming response.

11.2 Antitumor Effect – Stratum 2 – RANO

For the purposes of this study, participants should be re-evaluated for response every 3 cycles (which is 9 weeks for the first 3 cycles and 12 weeks starting with cycle 4). In addition to a baseline scan, confirmatory scans should also be obtained 4 weeks following initial documentation of objective response.

Response and progression for patients in Stratum 2 will be evaluated in this study using the Response Assessment in Neuro-Oncology criteria (*J Clin Oncol* 28(11):1963-1972, 2010). *Note: RECIST v1.1 (Section 11.1) may be used for disease evaluation for Stratum 2 (CNS-primary tumors) patients whose only measurable disease is extra-cranial in location.*

Measurable disease is defined as bi-dimensionally contrast-enhancing or enhancing lesions with clearly defined margins by magnetic resonance imaging (MRI) scan, with 2 perpendicular diameters of at least 10 mm, visible on two or more axial slices that are preferably, at most, 5 mm apart with 0 mm skip.

Non-measurable disease is defined as either uni-dimensionally measurable lesions, masses with margins not clearly defined, or lesions with maximal perpendicular diameters less than 10 mm. All measurable and non-measurable lesions must be assessed using the same techniques as at baseline.

Complete response (CR): Requires all of the following:

- Complete disappearance of all enhancing measurable and non-measurable disease sustained for at least 4 weeks
- No new lesions
- Stable or improved non-enhancing (T2/fluid-attenuated inversion recovery [FLAIR]) lesions
- Subjects must be off corticosteroids (or on physiologic replacement doses only)
- Stable or improved clinically

Note: Subjects with non-measurable disease only cannot have a CR; the best response possible is SD.

Partial response (PR): Requires all of the following:

- $\geq 50\%$ decrease compared with baseline, in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks
- No progression of non-measurable disease; no new lesions

- Stable or improved non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan
- Corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan
- Stable or improved clinically

Note: Subjects with non-measurable disease only cannot have a PR; the best response possible is SD.

Stable disease (SD): Requires all of the following:

- Does not qualify for CR, PR, or progression
- Stable non-enhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan

In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression (PD) on neuro-imaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of PD, the last scan considered to show SD will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.

Note: Stable doses of corticosteroids include subjects not on corticosteroids.

Disease progression (PD): PD is defined by any of the following:

- $\geq 25\%$ increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids
- Significant increase in T2/FLAIR non-enhancing lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy not caused by co-morbid events (e.g., radiation therapy, demyelination, ischemic injury, infection, seizures, post-operative changes, or other treatment effects)
- Any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (e.g., seizures, medication adverse effects, complications of therapy, cerebrovascular events, infection) or changes in corticosteroid dose
- Failure to return for evaluation as a result of death or deteriorating condition
- Clear progression of non-measurable disease

Pseudoprogession: Exceptions for Delayed Response:

Subjects in whom the magnitude of increase in tumor size is $>20\%$ but $<40\%$, may remain on study for up to 12 weeks after start of protocol therapy if the following criteria are met.

- In the judgment of the treating clinician, the subject does not show evidence for rapid disease progression or the subject has shown evidence for clinical benefit.
- There is no decrease in performance status nor significant neurological decline (defined as CTCAE grade 3 or higher). Subject is tolerating the study treatment.
- Continued study treatment will not delay an imminent intervention required to prevent serious complications.

For subjects who remain on study despite increase in tumor size $> 20\%$, imaging to include target lesions must occur every cycle if clinically indicated, or if “pseudoprogession” appears

based on inflammatory response, and the same radiographic and clinical criteria must be met in order to remain on study. If tumor size subsequently diminishes to < 20% increase from baseline, the subject may be followed according to the standard protocol guidelines which will involve less frequent imaging. The decision to continue treatment beyond radiographic evidence for disease progression should be discussed with the study PI and documented in the study record.

Subjects who develop worsening radiographic findings >6 months from start of immunotherapy are expected to have a low likelihood of ultimately deriving benefit from the therapy and should be considered PD based on imaging if they have a 50% increase in size of the target lesion or if new lesions appear. Subjects who experience significant clinical decline or those who have radiographic progression on the 3 month follow up scan should be classified as confirmed PD and the date of progression should be entered as the first MRI that showed progressive disease.

Summary of RANO Response Criteria

Criterion	CR	PR	SD	PD
T1 gadolinium enhancing disease	None	≥50% decrease	<50% decrease but <25% increase	≥25% increase ^a
T2/FLAIR	Stable or decrease	Stable or decrease	Stable or decrease	Increase
New Lesion	None	None	None	Present
Corticosteroids	None	Stable or decreasing dose	Stable or decreasing dose	NA ^b
Clinical Status	Stable or increase	Stable or increase	Stable or increase	Decrease
Requirement for Response	All	All	All	Any
Abbreviations: CR, complete response; FLAIR, fluid-attenuated inversion recovery; NA, not applicable; PD, progressive disease; PR, partial response; RANO, Response Assessment in Neuro-Oncology; SD, stable disease ^a Progression occurs when this criterion is present. ^b Increase in corticosteroids alone will not be taken into account in determining progression in the absence of persistent clinical deterioration.				

11.3 Antitumor Effect – Both Strata

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is

objectively documented, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

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

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

12. DATA REPORTING / REGULATORY REQUIREMENTS

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

12.1 Data Reporting

12.1.1 Method

Data will be captured using the electronic data capture system, InForm. The DFCI Office of Data Quality (ODQ) will perform quality checks on the data for this study.

12.1.2 Timelines for Data Submission

Data should be submitted to InForm according to the following timelines.

Form	Submission Timeline
Eligibility Checklist	Complete prior to registration
On Study Form	Within 14 days of registration
Toxicity Log (Baseline Adverse events)	Within 14 days of registration
Baseline Disease Assessment Form	Within 14 days of registration
Reporting Period Forms	Cycle 1: Within 5 business days of the last day of the cycle Other Cycles: Within 10 days of the last day of the cycle
Toxicity Log	Cycle 1: Within 5 business days of the last day of the cycle

	Other Cycles: Within 10 business days of the last day of the cycle
Response Assessment Form	Within 14 days of the completion of cycles in which disease evaluated
Off Protocol Therapy Form	Within 14 days of completing treatment
Follow-up Form	Within 14 days of the protocol defined follow up visit
Off Study Form	Within 14 days of being taken off study for any reason
Outcome Form	Within 14 days of being taken off study for any reason

12.1 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; DLT information; all grade 2 or higher unexpected adverse events that have been reported; summary of all deaths occurring within 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.

12.2 Multi-Center Guidelines

“This protocol will adhere to DF/HCC Policy MULTI-100 and the 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 B.”

13. STATISTICAL CONSIDERATIONS

This is a single arm, multi-center, phase 2, open-label study to evaluate the clinical activity of nivolumab in combination with ipilimumab in two parallel strata of patients aged 1-30 with relapsed or refractory INI1-negative cancers. A two-stage design will be used to evaluate the efficacy of the combination therapy.

13.1 Evaluability

To be evaluable for the analysis of the primary objective using the two-stage design, a patient

must meet eligibility criteria, receive at least one dose of both nivolumab and ipilimumab, and have at least one post-baseline tumor assessment. . In addition, patients will be considered evaluable if either of the following occurs:

- 1) Progressive disease while on therapy (note: if the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, it is permissible to opt not to confirm this finding radiographically); or,
- 2) Death while on therapy.

Patients inevaluable for response will be replaced.

13.2 Study Design/Endpoints

The primary endpoint for Stratum 1 is best overall response based on RECIST v1.1 per local assessment. The primary endpoint for Stratum 2 is best overall response based on RANO per local assessment. Each evaluable patient will be classified as either a responder (CR or PR) or a non-responder (<PR).

For Secondary Objective 1, the endpoints are progression-free survival (PFS) and overall survival (OS). PFS time will be calculated as the time from study enrollment until the first occurrence of disease progression, relapse or death due to disease. Participants alive without disease progression are censored at date of last disease evaluation. OS time will be calculated as the time from study enrollment until death from any cause. Participants who are alive will be censored on the date of last contact.

For Secondary Objective 2, the endpoint is stable disease or better at 12 months from study enrollment. This is a binary endpoint which is equivalent to categorizing a patient as having a) an event at or before 12 months; or, b) no event (SD or better) by 12 months.

The endpoint for Secondary Objective 3 is the occurrence of a toxicity (Grade 3-5 per CTCAE version 5.0.).

For Exploratory Objective 1, the endpoint is a patient's best overall response.

13.3 Sample Size, Accrual Rate and Study Duration

Total accrual: Up to approximately 45 patients across both Stratum

Accrual goal: Up to 20 evaluable patients in each Stratum, for a total of up to 40 evaluable patients. The sample size is driven by the requirement of the two-stage design to address the Primary Objective. Assuming that up to 10% of patients could be inevaluable, up to 45 patients may be enrolled to obtain 40 evaluable patients. At an accrual rate of 1.5 patients per month, enrollment will be completed in 30 months.

Study duration: If the last patient enrolled is treated for 1 year, then the total study duration will be approximately 3.5 years.

13.4 Stratification Factors

For descriptive purposes, and to identify subgroups to be included in particular study objectives, patients will be classified as either:

Stratum 1 – patients with extracranial INI1-negative solid tumors

Stratum 2 – patients with intracranial INI1-negative tumors

13.5 Interim Monitoring Plan

We will perform interim monitoring for the primary endpoint, “best overall response” by applying a two-stage design to the evaluable patients, separately in Stratum 1 and in Stratum 2. Within a given stratum, accrual will be suspended at the end of stage 1 to determine whether there is justification to proceed to stage 2. Toxicity will be monitored on an ongoing basis.

13.6 Analysis of Primary Endpoints

To address the primary objective, the following two-stage design will be applied to the analysis of the primary endpoint, best overall response. This two-stage design will be applied separately within the evaluable patients of Stratum 1, and within the evaluable patients of Stratum 2.

Two-stage design for a given Stratum

Stage 1 – Enroll 10 evaluable patients. If 0 have an objective response (CR or PR), then the Stratum will be closed to accrual because insufficient evidence of activity of the study treatment. If 1-5 patients have an objective response, then enrollment in the Stratum will be continued to Stage 2. If 6 or more participants have an objective response, then the Stratum will be closed to accrual, as it will be reasonable to conclude that there is sufficient activity of the combination treatment in the Stratum.

Stage 2 – Enroll an additional 10 patients for a total of 20 evaluable patients. If 2 or less of the 20 patients have an objective response, then there is insufficient evidence of activity for further investigation of the study treatment in the Stratum. If 3 or more of the 20 patients have an objective response, then it is reasonable to conclude that there is sufficient activity for further investigation of the study treatment in the Stratum.

Under the null hypothesis of a true response rate that does not exceed 5%, the two-stage design will control type I error to be no more than 0.07. Under the alternative hypothesis of a true response rate that is at least 25%, type II error will be no more than 0.12. If accrual is stopped at the first stage for a given stratum because the agent is considered effective, the lower bound of a 95% confidence interval for the response rate will be 25%. See Chang et al for details on calculation of the operating characteristics⁴².

13.7 Analysis of Secondary Endpoints

Secondary Objective 1 – Kaplan-Meier curves of PFS and OS will be generated, using standard errors according to the methods of Greenwood, overall and separately for Stratum 1 and Stratum 2.

Secondary Objective 2 – We will calculate the proportion of participants who are progression-free at 12 months, as the total number progression-free at 12 months divided by the number of evaluable patients, and place an exact two-sided binomial 95% confidence interval on this proportion.

Secondary Objective 3 – In the overall cohort, the number and proportion of CTCAE Grade 3-5 adverse events will be tabulated by type and grade. Within a given patient, a given adverse event will be counted only once at the highest grade. Listings of all the Grade 3-5 adverse events will be generated.

13.8 Analysis of Exploratory Endpoints

The analyses of the biology correlates are exploratory. Descriptive statistics will be generated, in accordance with the type of measure (frequency tabulations for categorical measures, confidence intervals on proportions, minimum/maximum/quartiles for continuous measures).

13.9 Reporting and Exclusions

13.9.1 Evaluation of Toxicity

All participants who are eligible and receive at least one dose of study treatment with both nivolumab and ipilimumab are evaluable for toxicity.

13.9.2 Evaluation of the Primary Efficacy Endpoint

All evaluable patients (as defined in Section 13.1) will be evaluable for the primary efficacy endpoint.

PUBLICATION PLAN

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

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APPENDIX A: PERFORMANCE STATUS CRITERIA**Performance Status Criteria**

Karnofsky and Lansky performance scores are intended to be multiples of 10

ECOG (Zubrod)		Karnofsky		Lansky*	
Score	Description	Score	Description	Score	Description
0	Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease	100	Fully active, normal.
		90	Able to carry on normal activity, minor signs or symptoms of disease.	90	Minor restrictions in physically strenuous activity.
1	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.	80	Active, but tires more quickly
		70	Cares for self, unable to carry on normal activity or do active work.	70	Both greater restriction of and less time spent in play activity.
2	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	Required occasional assistance, but is able to care for most of his/her needs.	60	Up and around, but minimal active play; keeps busy with quieter activities.
		50	Requires considerable assistance and frequent medical care.	50	Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.	40	Mostly in bed; participates in quiet activities.
		30	Severely disabled, hospitalization indicated. Death not imminent.	30	In bed; needs assistance even for quiet play.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.	20	Often sleeping; play entirely limited to very passive activities.
		10	Moribund, fatal processes progressing rapidly.	10	No play; does not get out of bed.

*The conversion of the Lansky to ECOG scales is intended for NCI reporting purposes only.

DF/HCC Protocol #: 20-041

Version Date: v4.0 October 12, 2023

APPENDIX B: MONITORING PLAN

DF/HCC Protocol #: 20-041

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

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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 Policies and Operations..

2 GENERAL ROLES AND RESPONSIBILITIES

For DF/HCC Multi-Center Protocols, the following general responsibilities apply, in addition to those outlined in DF/HCC Policies for Sponsor-Investigators:

2.1 External Site

An External Site is 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 External Site acknowledges the DF/HCC Sponsor as having the ultimate authority and responsibility for the overall conduct of the study.

Each External Site is expected to comply with all applicable DF/HCC requirements stated within this Data and Safety Monitoring Plan and/or the protocol document..

The general responsibilities for each External Site 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 IRB of record. For studies under a single IRB, the Coordinating Center will facilitate any study-wide submissions..
- Maintain regulatory files as per ICH GCP and federal requirements.
- Provide the Coordinating Center with regulatory documents or source documents as requested.
- Participate in protocol training prior to enrolling participants and throughout the trial as required.
- Update Coordinating Center with research staff changes on a timely basis.
- Register participants through the Coordinating Center prior to beginning research related activities when required by the sponsor.
- Submit Serious Adverse Event (SAE) reports to sponsor, Coordinating Center, and IRB of record as applicable, in accordance with DF/HCC requirements.

- Submit protocol deviations and violations to the Sponsor, Coordinating Center, and IRB of record as applicable..
- Order, store and dispense investigational agents and/or other protocol mandated drugs per federal guidelines and protocol requirements.
- Participate in any quality assurance activities 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.
- Notify the sponsor immediately of any regulatory authority inspection of this protocol at the External Site.

3 DF/HCC REQUIREMENTS FOR MULTI-CENTER PROTOCOLS

Certain DF/HCC Policy requirements apply to External Sites participating in DF/HCC research. 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 Revisions and Closures

The External Sites will receive notification of protocol revisions and closures from the Coordinating Center. When under a separate IRB, it is the individual External Site's responsibility to notify its IRB of these revisions.

- **Protocol revisions:** External Sites will receive written notification of protocol revisions from the Coordinating Center. All protocol revisions should be IRB approved and implemented within a timely manner from receipt of the notification.
- **Protocol closures and temporary holds:** External Sites 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 External Sites on an ongoing basis about protocol accrual data so that they will be aware of imminent protocol closures.

3.2 Informed Consent Requirements

The DF/HCC approved informed consent document will serve as a template for the informed consent for External Sites. The External Site 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 External Site upon request.

External Sites must send their version of the informed consent document to the Coordinating Center for sponsor review and approval. If the HIPAA authorization is a separate document, please submit to the sponsor for the study record. Once sponsor approval is obtained, the External site may submit to their IRB of record, as applicable. In these cases, 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 External Site will identify the appropriate members of the study team who will be obtaining consent and signing the consent form for protocols. External Sites 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.

3.3 IRB Re-Approval

Verification of IRB re-approval for the External Sites 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 for the External Site on or before the anniversary of the previous approval date.

3.4. 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 protocol case number be used for all participant specific documents. Participant initials may be included or retained for cross verification of identification.

3.5. Participant Registration and Randomization

To register a participant, the following documents should be completed by the External Site and e-mailed to the Coordinating Center study coordinator, PI and study team at [REDACTED]

Please include:

- Copy of eligibility source documentation, including confirmation of INI1 loss by IHC or *SMARCB1* mutation/loss
- Copy of required laboratory tests including:
 - CBC with differential
 - Serum chemistry (total bilirubin, creatinine, SGOT [AST], SGPT [ALT], amylase, lipase), B-HCG pregnancy test (serum or urine)
 - Creatinine clearance for participants with creatinine levels above institutional normal
- Signed informed consent document
- HIPAA authorization form (if separate from the informed consent document)
- Completed Eligibility Checklist

The Coordinating Center will review the submitted documents in order to verify eligibility and consent. To complete the registration process, the Coordinating Center will:

- Register the participant on the study with the DF/HCC Clinical Trial Management System (CTMS).

- Upon receiving confirmation of registration, the Coordinating Center will inform the External Site and provide the study specific participant case number, and, if applicable, assigned treatment and/or dose level.

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. External Sites should submit all de-identified subsequent communication and documents to the Coordinating Center, using this case number to identify the subject.

5.2.1. 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 External Site receives confirmation of the participant's registration from the Coordinating Center. The DF/HCC Sponsor and IRB of record must be notified of any violations to this policy.

5.2.2. Eligibility Exceptions

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

A Protocol Exception is defined as: Any protocol deviation that relates to the eligibility criteria, e.g. enrollment of a participant who does not meet all inclusion/exclusion criteria.

To request protocol exception, email the study coordinator and the PI with your request. The PI and/or study coordinator will confirm via email whether or not they will apply for a protocol exception to the IRB. A confirmatory email is **not** permission to continue enrollment procedures. If the PI feels an exception is merited in this case, the study team will obtain IRB approval and email the requesting study team with a copy of the IRB approval.

3.5. Data Management

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

3.5.1. Data Forms Review

Data submissions are monitored for timeliness and completeness of submission. 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.

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

3.6. Protocol Reporting Requirements

3.6.1. 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 and to the IRB of record.

3.6.2. Reporting Procedures

Requests to deviate from the protocol require approval from the IRB of record and the sponsor.

All protocol violations must be sent to the Coordinating Center in a timely manner. The Coordinating Center will provide training for the requirements for the reporting of violations.

3.6.3. Guidelines for Processing IND Safety Reports

The DF/HCC Sponsor will review all IND Safety Reports per DF/HCC requirements, and ensure that all IND Safety Reports are distributed to the External Sites as required by DF/HCC Policy. External Sites will review/submit to the IRB according to their institutional policies and procedures.

4. MONITORING: QUALITY CONTROL

The Coordinating Center, with the aid of the DF/HCC Office of Data Quality, provides quality control oversight for the protocol.

4.4. Ongoing Monitoring of Protocol Compliance

The External Sites may be required to submit participant source documents to the Coordinating Center for monitoring. External Sites may also be subject to on-site monitoring conducted by the Coordinating Center.

The Coordinating Center will implement ongoing monitoring activities to ensure that External Sites are complying with regulatory and protocol requirements, data quality, and participant safety. Monitoring practices may include but are not limited to source data verification, and review and analysis of eligibility requirements, informed consent

procedures, adverse events and all associated documentation, review of study drug administration/treatment, regulatory files, protocol departures reporting, pharmacy records, response assessments, and data management.

External Sites will participate in regular (approximately monthly) Coordinating Center initiated teleconferences. In addition, communications to update external sites on protocol progress and share important announcements will be distributed regularly.

Remote monitoring will occur on a regular basis, approximately every 6-12 months. The Coordinating Center will request source documentation from participating Institutions as needed to complete monitoring activities. Participating Institutions will be asked to forward copies of participants' medical record and source documents to the Coordinating Center to aid in source documentation verification.

On-site monitoring will occur at least once per site. Participating Institutions will be required to provide access to participants' complete medical record and source documents for source documentation verification during the on-site visit. In addition, upon request from a monitor or auditor, Participating Institutions should provide access to regulatory documents, pharmacy records, local policies related to the conduct of research, and any other trial-related documentation maintained by the participating site. If there are concerns for protocol compliance, issues that impact subject safety or the integrity of the study are found, or trends identified based on areas of need, additional monitoring visits may be scheduled.

4.5. 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 External Sites that are unable to comply with the protocol, DF/HCC Sponsor requirements or federal and local regulations.

4.6. Accrual Monitoring

Prior to extending a protocol to an external site, the DF/HCC Sponsor will establish accrual requirements for each External Site. Accrual will be monitored for each External Site by the DF/HCC Sponsor or designee. Sites that are not meeting their accrual expectations may be subject to termination. The minimum accrual expectation for Participating Institutions is 0-1 accruals/year given that the rarity of the diseases included in this study. Sites that are not meeting their accrual expectations may be subject to termination.

5. AUDITING: QUALITY ASSURANCE

5.4. DF/HCC Internal Audits

All External Sites 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.

5.5. Audit Notifications

It is the External Site'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.

5.6. 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 IRB as applicable.

5.7. External Site Performance

The DF/HCC Sponsor and the IRB of record are charged with considering the totality of an institution's performance in considering institutional participation in the protocol.

External Sites 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 put on hold or closed.

APPENDIX C: IMMUNE RELATED ADVERSE EVENT MANAGEMENT

DF/HCC Protocol #: 20-041

Dana-Farber/Harvard Cancer Center Immune Related Adverse Event Management

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. The guidance applies to all immuno-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

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 v5)	Management	Follow-up
Grade 1 <u>Diarrhea:</u> < 4 stools/day over baseline; <u>Colitis:</u> asymptomatic	- Continue I-O therapy per protocol - Symptomatic treatment	- Close monitoring for worsening symptoms. - Educate patient to report worsening immediately <u>If worsens:</u> - Treat as Grade 2 or 3/4
Grade 2 <u>Diarrhea:</u> 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL <u>Colitis:</u> abdominal pain; blood in stool	- Delay I-O therapy per protocol - Symptomatic treatment	<u>If improves to grade 1:</u> - Resume I-O therapy per protocol <u>If persists > 5-7 days or recurs:</u> 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. <u>If worsens or persists > 3-5 days with oral steroids:</u> - Treat as grade 3/4
Grade 3-4 <u>Diarrhea (G3):</u> ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL <u>Colitis (G3):</u> 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	<u>If improves:</u> - Continue steroids until grade 1, then taper over at least 1 month <u>If persists > 3-5 days, or recurs after improvement:</u> - 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

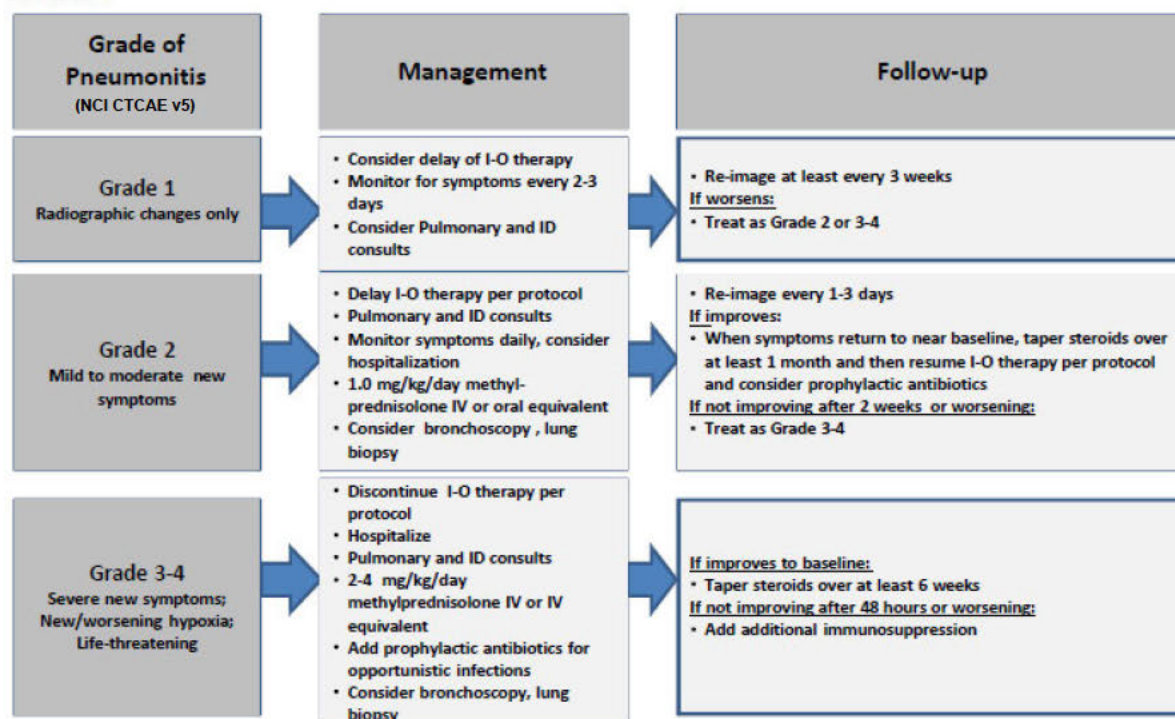
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.

Grade of Creatinine Elevation (NCI CTCAE v5)	Management	Follow-up
Grade 1 Creatinine > ULN and > than baseline but ≤ 1.5x baseline	- Continue I-O therapy per protocol - Monitor creatinine weekly	<u>If returns to baseline:</u> - Resume routine creatinine monitoring per protocol <u>If worsens:</u> - Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	- Delay I-O therapy per protocol - Monitor creatinine every 2-3 days 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent - Consider renal biopsy with nephrology consult	<u>If returns to Grade 1:</u> - Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol <u>If elevations persist > 7 days or worsen:</u> - Treat as Grade 4
Grade 4 Creatinine > 6x ULN	- Discontinue I-O therapy per protocol - Monitor creatinine daily 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent - Consult nephrologist - Consider renal biopsy	<u>If returns to Grade 1:</u> Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

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.

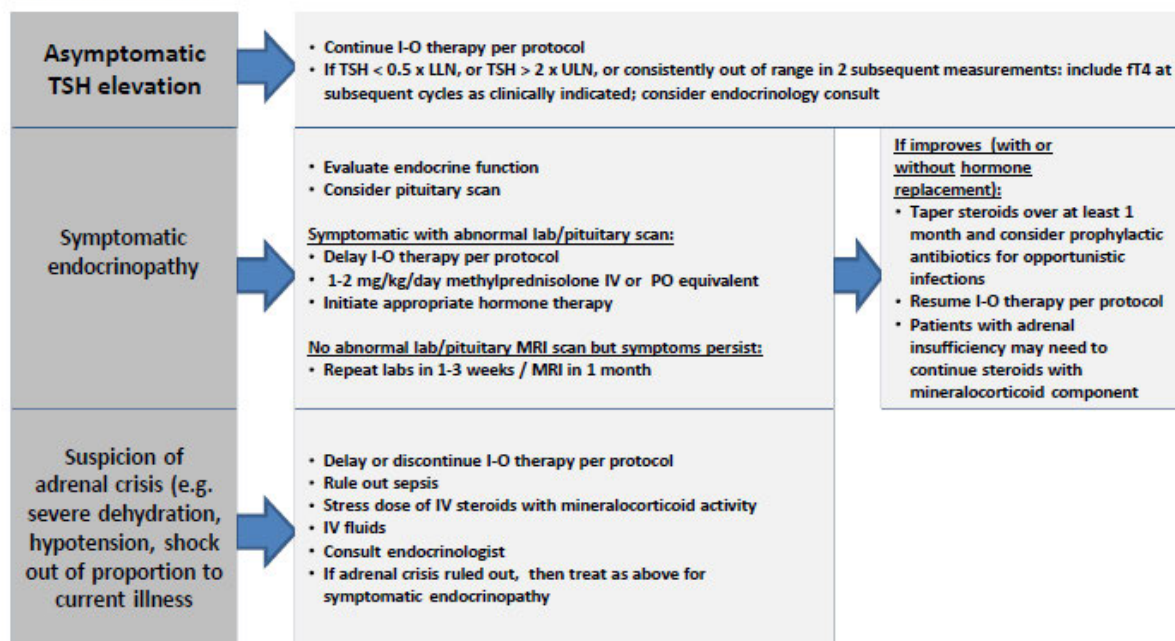
Grade of Liver Test Elevation (NCI CTCAE v5)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN <u>and/or</u> T. bili > ULN to 1.5 x ULN	Continue I-O therapy per protocol	- Continue LFT monitoring per protocol <u>If worsens:</u> - Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN <u>and/or</u> T. bili > 1.5 to ≤ 3 x ULN	- Delay I-O therapy per protocol - Increase frequency of monitoring to every 3 days	<u>If returns to baseline:</u> - Resume routine monitoring, resume I-O therapy per protocol <u>If elevations persist > 5-7 days or worsen:</u> 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN <u>or</u> T.bili > 3 x ULN	- Discontinue I-O therapy* - Increase frequency of monitoring to every 1-2 days 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent* - Add prophylactic antibiotics for opportunistic infections - Consult gastroenterologist	<u>If returns to grade 2:</u> - Taper steroids over at least 1 month <u>If does not improve in >3-5 days, worsens or rebounds:</u> - Add mycophenolate mofetil 1 g BID - If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

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.

*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Endocrinopathy Adverse Event Management Algorithm

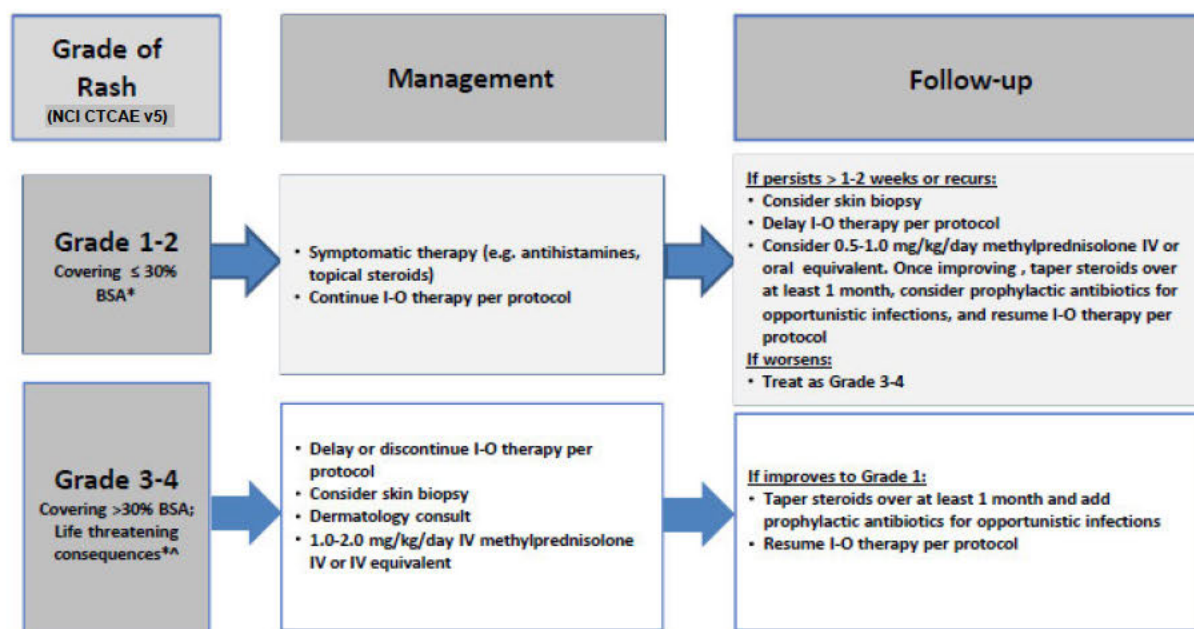
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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.



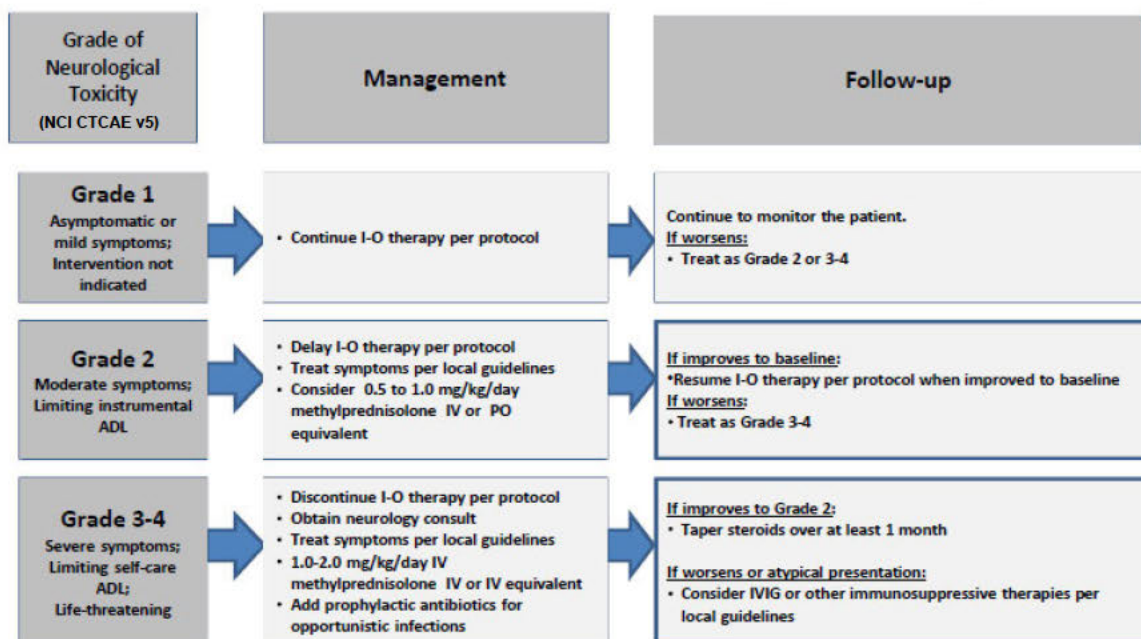
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

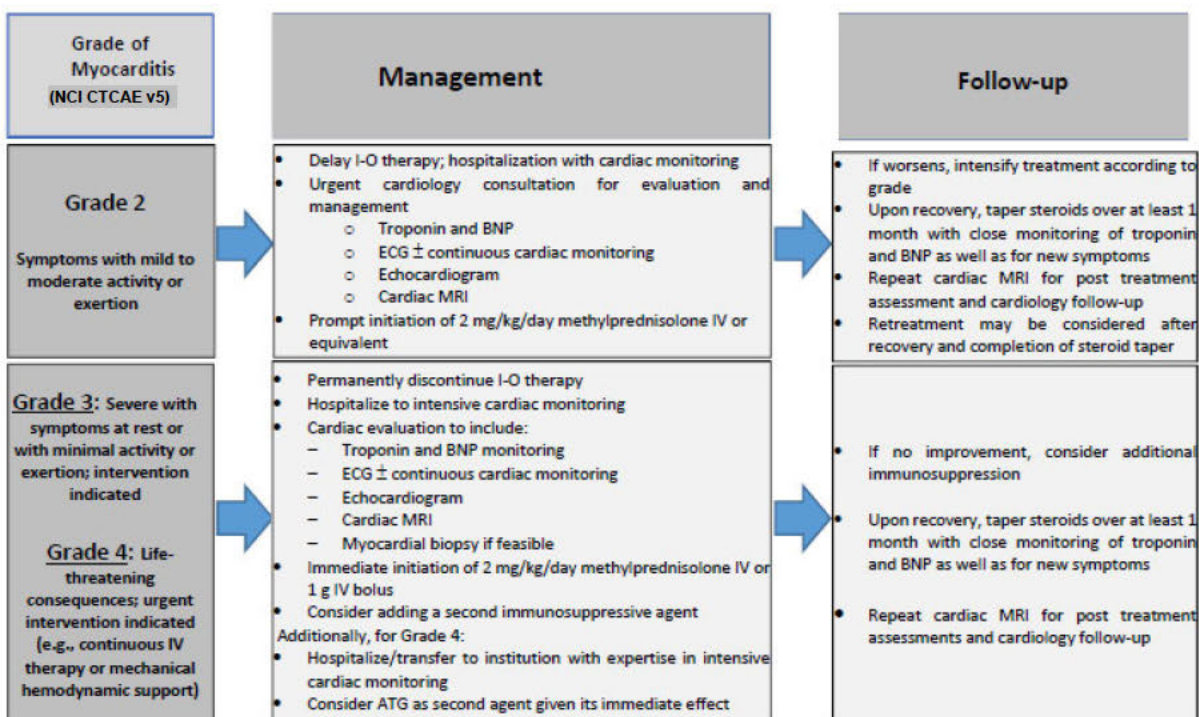
Neurological Adverse Event Management Algorithm

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.

Myocarditis Adverse Event Management Algorithm



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, 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.

Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.

ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging