

NU Study Number: NU 15H13
BMS Study Number: CA209-613

Phase Ib Study of Nivolumab and Dasatinib in Patients with Relapsed/Refractory Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ ALL)

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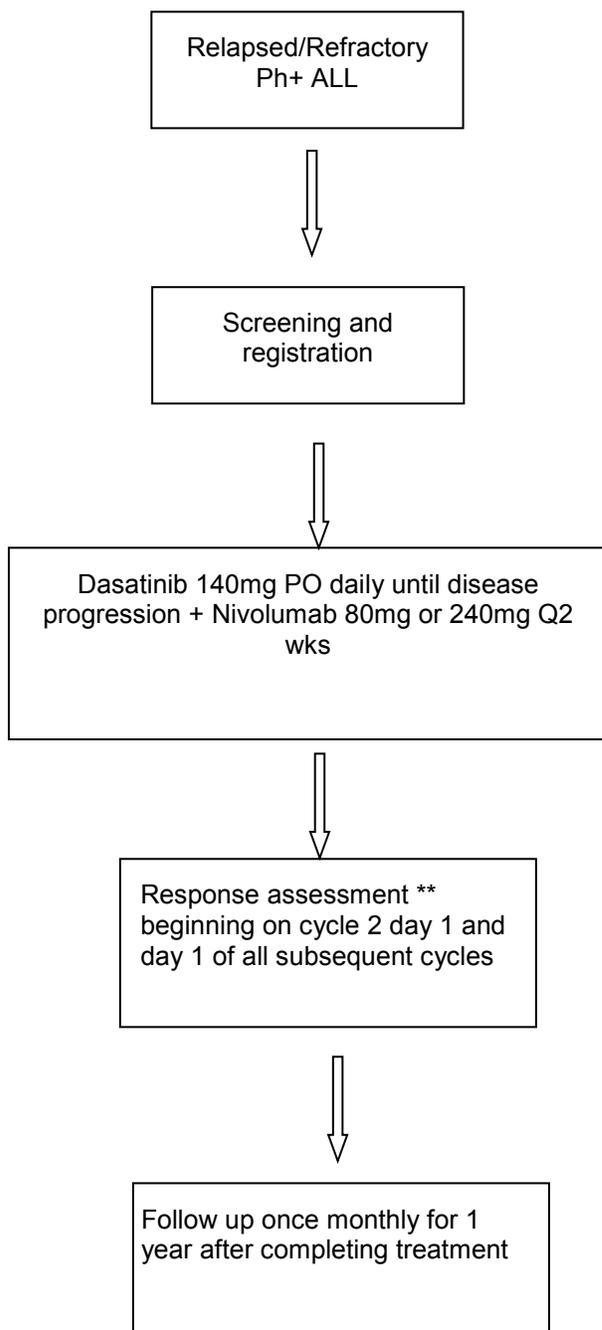
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LIST OF ABBREVIATIONS

AE	Adverse Event
ALL	Acute Lymphoblastic Leukemia
ALT	Alanine Aminotransferase
ANC	Absolute Count
AST	Aspartate Aminotransferase
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CMP	Comprehensive Metabolic Panel
CR	Complete Response
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose Limiting Toxicity
DMC	Data Monitoring Committee
DSMB	Data and Safety Monitoring Board
ECOG	Eastern Cooperative Oncology Group
FOCBP	Females of Child-Bearing Potential
H&PE	History & Physical Exam
IV (or iv)	Intravenously
MTD	Maximum Tolerated Dose
NCI	National Cancer Institute
ORR	Overall Response Rate or Objective Response Rate
OS	Overall Survival
PBMCs	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
Ph+	Philadelphia positive
PI	Principal Investigator
PFS	Progression Free Survival
PO (or p.o.)	Per os/by mouth/orally
PR	Partial Response
SAE	Serious Adverse Event
SD	Stable Disease
QTc	QT interval corrected
WBC	White Blood Cells

STUDY SCHEMA



- *Cycle length = 28 days
- Patients may continue treatment until disease progression, unacceptable toxicity, or withdrawal from the study for other reasons
- **Response assessment will consist of peripheral blood draw and bone marrow biopsy. If patient has documented molecular remission, subsequent bone marrow biopsies will be deferred to the treating physician and patient will be monitored by peripheral blood PCR for BCR-ABL

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STUDY SUMMARY

Title	Phase 1b Study of Nivolumab and Dasatinib in Patients with Relapsed/Refractory Philadelphia Chromosome Positive Acute Lymphoblastic Leukemia (Ph+ ALL)
Short Title	Nivolumab and dasatinib in relapsed/refractory Ph+ ALL
Version	June 2 September 2, 2016 (Amendment 2)
Study Design	Phase 1b, open label, modified 3+3 dose de-escalation design
Study Center(s)	Robert H. Lurie Comprehensive Cancer Center of Northwestern University
Objectives	<p>Primary objective: To determine the maximally tolerated dose (MTD) of nivolumab when given in combination with dasatinib in patients with relapsed/refractory Ph+ ALL.</p> <p>Secondary objectives:</p> <ul style="list-style-type: none"> • To evaluate the toxicities and tolerability of nivolumab and dasatinib in patients with relapse/refractory Ph+ ALL • Rate of complete hematologic remission • Rate of MRD negativity or molecular remission • To study the pharmacokinetics of nivolumab and dasatinib • To evaluate PD1 expression levels and saturation in the peripheral blood and bone marrow • To measure peripheral T-cell levels and activation in response to treatment
Sample Size	6-12 patients will be enrolled across all the dose de-escalation cohorts, and an additional 10 evaluable patients will be enrolled in the dose expansion cohort. Up to a total of 25 patients will be enrolled to allow for 22 evaluable patients.
Diagnosis & Key Eligibility Criteria	Adults with Ph+ ALL who have primary refractory ALL based on failure to achieve a hematologic or molecular remission after induction therapy with dasatinib and steroids or dasatanib and chemotherapy, or have relapsed after treatment with a tyrosine kinase inhibitor with or without chemotherapy. Patients who have previously been treated with drugs targeting checkpoint pathways or T-cell co-stimulation, or who have a severe intolerance to prior tyrosine kinase inhibitors will be excluded.

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<p>Treatment Plan</p>	<p>The safety lead-in phase will begin in a standard 3+3 design with enrollment of 3 patients to cohort 1 to receive dasatinib 140mg PO daily and nivolumab 240mg IV once every 2 weeks, beginning on day 8 and day 22 of the first cycle. This will allow for a lead in phase during cycle one with single agent dasatinib to assess T-cell subsets prior to the addition of nivolumab. Starting with cycle 2, nivolumab will be given on day 1 and day 15 of each cycle. If ≤ 1 patients experiences a dose-limiting toxicity (DLT), an additional 3 patients will be enrolled to cohort 1. If 0 or 1 DLTs occur in 6 patients, 10 additional patients will be enrolled onto the dose expansion cohort with nivolumab 240mg IV every 2 weeks and dasatinib 140mg PO daily. If 2 or more patients of the initial 6 patients from cohort 1 experience a DLT, 3 additional patients will be enrolled at a de-escalated dose of nivolumab 80mg IV every 2 weeks with dasatinib 140mg PO daily. If ≤ 1 patient experiences a DLT, an additional 3 patients will be enrolled to cohort 2. If 0 or 1 DLTs occur in 6 patients, 10 additional patients will be enrolled to the dose expansion phase at the de-escalated dose of nivolumab 80mg every 2 weeks. Enrolled patients will be treated in repeating 28-day cycles until disease progression, unacceptable toxicity, or withdrawal from the study for other reasons.</p>
<p>Statistical Methodology</p>	<p>This is a phase Ib design where up to 6 patients will be treated at each dose level. For each dose, three patients will be initially treated. If 2 or 3 patients at dose level 1 experience a DLT, then the dose will be de-escalated. If 0 or 1 of 3 patients has a DLT, then an additional 3 patients will be added to this dose. If 1 of 6 have a DLT, then the dose will be chosen as the dose for the expansion cohort. If 2 or 3 of 6 have a DLT, then the de-escalation dose is the MTD, provided 6 patients have been treated at that dose and have had 1 or fewer DLTs. This 3+3 component of the design has a 95% chance (64%, 30%) of declaring acceptable toxicity when the true toxicity rate for that dose is 10% (30%, 50%). With two doses, the expected sample size in the dose finding portion of the study will be between 6 and 12. Up to 10 additional patients will be enrolled at any dose found to be acceptable in the 3+3 component. While it is theoretically possible to expand each dose with 10 patients so that the possible maximum sample size is 32, it is expected that the dose expansion will occur only at the MTD so that the total expected sample size is 16-22 patients Toxicity profile will be presented by rate of overall toxicity and rates of > grade 3 toxicities analyzed separately and combined. AEs will be summarized and accompanied by 95% confidence intervals using binomial distribution. Patients' characteristics will be summarized using mean, median, and standard deviation for continuous variables, and tables for discrete variables. We will descriptively report observed secondary and exploratory endpoints, including rates of complete hematologic and molecular remission after 3 cycles of nivolumab and dasatinib, duration of remission, progression free survival, overall survival, 30-day mortality rate, and the outcomes for patients that go on to HSCT vs those that do not receive further therapy. Rates will be estimated using exact binomial probabilities and 95% confidence intervals. Molecular remission will be estimated using an exact binomial confidence interval. PFS and OS will be estimated using Kaplan-Meier curves. T cell levels after treatment will be assessed using the paired t-test or the signed rank test. Levels of PD1 expression will be compared with responders versus non-responders using a Wilcoxon rank sum test. Basic pharmacokinetic parameters will be calculated and summarized using means, medians and ranges.</p>

1.0 INTRODUCTION – BACKGROUND & RATIONALE

1.1 Disease Background

Acute lymphoblastic leukemia (ALL) is a rare disease, representing only approximately 20% of all leukemia diagnosed in adults. The Philadelphia chromosome [t(9;22)(q34;q11)] resulting in the BCR-ABL oncogene fusion is the most common cytogenetic abnormality in adult ALL. The incidence of Philadelphia chromosome positive ALL (Ph+ ALL) increases with age and is associated with lower remission rates and a poor prognosis. Among patients over 60 years old, approximately 50% have the Philadelphia chromosome at diagnosis.¹ The introduction of tyrosine kinase inhibitor (TKI) therapy targeted against the BCR-ABL kinase, such as imatinib and dasatinib, has resulted in improved hematologic remission rates of 80-90% both in combination with chemotherapy and when used with steroids.^{2,3,4,5,6,7} However, it has been reported that only 20-50% achieve molecular remissions when treated with TKI and steroids. Further, patients that do not achieve molecular remission are at higher risk for relapse.^{7,8} For both elderly patients that cannot tolerate intensive multi-agent chemotherapy and younger patients that would like to mitigate the use of these agents and their associated toxicities, it would be attractive to optimize the efficacy of TKIs. Because immunotherapies such as the graft-versus-leukemia effect of hematopoietic stem cell transplant (HSCT) and antibodies have demonstrated efficacy in ALL as monotherapies, adding an immunotherapy to TKI therapy may provide further benefit.

1.2 Intervention Background & Overview

Dasatinib is an FDA-approved second-generation TKI that inhibits the BCR-ABL kinase as well as the SRC family kinase. The SRC kinase is thought to drive an alternate signaling pathway in imatinib-resistant ALL. Dasatinib demonstrated a 325-fold greater potency for inhibiting growth of ALL cells compared to imatinib *in vitro*,⁹ and is active against Ph+ ALL cells with imatinib-resistant *ABL* kinase domain mutations.¹⁰ Dasatinib has shown activity in patients with relapsed or refractory Ph+ ALL who could not tolerate or were resistant to imatinib.¹¹ Additionally, dasatinib is known to cross the blood brain barrier and is effective in central nervous system leukemia in preclinical xenograft models and in a small group of patients with Ph+ ALL with CNS involvement.¹² Thus, dasatinib may be more beneficial than imatinib in Ph+ ALL.

The Italian GIMEMA LAL1205 study investigated dasatinib 70 mg PO twice daily with steroids as frontline treatment for 53 adult Ph+ ALL patients with a median age of 54 years. All patients achieved a complete hematologic response (CHR), with no induction deaths. BCR-ABL transcript levels decreased rapidly during induction therapy, and the percentage of patients achieving a molecular remission (BCR-ABL levels < 0.001%) increased from 23% at day 22 to 52% at day 85. At 20 months, the overall survival (OS) was 69% and disease free survival (DFS) was 51%. Notably, BCR-ABL levels < 0.001% at day 85 correlated with improved DFS.⁷ These results with dasatinib without any cytotoxic chemotherapy are encouraging, but demonstrated that single-agent dasatinib is not sufficient to cure this disease. In the subsequent trial, GIMEMA LAL1509, if patients did not achieve complete molecular response after a prolonged 84 day induction with dasatinib 140 mg daily and steroids, they received more intensive multi-agent chemotherapy and/or an allogeneic hematopoietic stem cell transplantation. At day 85, 58/60 (97%) patients achieved a complete hematologic remission, however only 11 (18.6%) patients achieved a complete molecular remission (CMR) with TKI plus steroid induction, once again demonstrating the need for additional post-remission therapy.⁸ No deaths occurred during induction in either trial, confirming dasatinib is well tolerated in Ph+ ALL and can likely be safely combined with immunotherapies.

Programmed death (PD)-1 is a T-cell surface receptor that leads to T-cell inactivation and down regulation of cellular immune response upon binding the PD-1 or PD-2 ligand (PD-L1, PD-L2) in order to serve as a checkpoint in the immune system. PD-L1 is expressed

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on malignant cells and also at low levels on most normal hematopoietic cells in patients with a variety of hematologic malignancies including lymphoma, multiple myeloma, and chronic and acute leukemia.^{13,14,15,16} The co-expression of PD-L1 by malignant cells and normal cells in the tumor microenvironment has been shown to prevent the host immune response from exerting a beneficial impact on the tumor. Therefore, blockade of PD-1 may significantly enhance anti-tumor immunity resulting in durable responses.

Nivolumab is a fully human antibody against the PD-1 receptor that selectively blocks the interaction between PD-1 and its ligands PD-L1 and PD-L2. By inhibiting this interaction, nivolumab can enhance T-cell function, which may result in anti-tumor activity. In a phase 1 study in solid tumors, nivolumab demonstrated a tolerable safety profile and objective responses.¹⁷ The subsequent trial in advanced melanoma, non-small-cell lung cancer, castration-resistant prostate cancer, renal-cell and colorectal cancer treated patients at a dose of 0.1 to 10.0 mg/kg every 2 weeks. No maximum tolerated dose (MTD) was reached and the drug was well-tolerated. Common treatment-related adverse events (AE) included fatigue, rash, diarrhea, pruritus, decreased appetite, and nausea, however only 5% of patients discontinued therapy related to an AE. All dose levels demonstrated anti-tumor activity.¹⁸ In an ongoing trial of nivolumab in relapsed/refractory lymphoid malignancies, the safety profile has been similar to that observed in solid tumors. While single agent nivolumab is highly active in Hodgkin lymphoma with an overall response rate of 87%, in non-Hodgkin lymphomas response rates were only 17-28% and multiple myeloma patients did not respond.^{19,20} This suggests that anti-PD1 therapies may be best used in combination with other targeted therapies in lymphoid malignancies.

1.3 Rationale for the Current Study

Dasatinib has immunomodulatory properties that may make it the ideal TKI to combine with immunotherapy. Data from patients with chronic myeloid leukemia (CML) treated with dasatinib demonstrated that approximately 30-50% developed a marked and persistent lymphocytosis due to expansion of large granular lymphocytes (LGL) with clonal T-cell receptor (TCR) delta or gamma gene rearrangements.^{21,22,23} Rapid mobilization and expansion of cytotoxic T lymphocytes has also been observed with dasatinib.²⁴ Further, clonal LGL lymphocytosis may be associated with response to dasatinib.²¹ Similarly, natural killer cell and LGL expansion has been observed in Ph+ ALL patients treated with dasatinib and is associated with optimal molecular response.²⁵ The mechanism of action for this T-cell expansion with dasatinib is not completely understood, but suggests that it may play an important role in its anti-leukemia activity that should be exploited further to improve efficacy. We therefore propose a phase 1b clinical trial of nivolumab given in combination with dasatinib in patients with Ph+ ALL that have not achieved a complete hematologic remission or molecular remission after induction therapy with dasatinib and steroids or have relapsed after treatment with a TKI with or without chemotherapy. The study design will be a phase 1b, open-label 3+3 design with the starting dose of nivolumab at 240mg given IV every 2 weeks. The safety and efficacy of 240mg as a flat dose is expected to be similar to the 3mg/kg dosing currently FDA approved for use in lung cancer and melanoma given that across tumor types, nivolumab has been shown to be safe and well-tolerated up to a dose level of 10mg/kg with relatively similar efficacy. A flat dose of 240mg is therefore being investigated. This will be given with dasatinib at a dose of 140mg PO daily, which is also the dose currently approved for treatment of Ph+ALL and CML. In the event of unexpected toxicity, patients will be enrolled to a dose level -1 with a nivolumab dose of 80mg every 2 weeks with the same dasatinib dose. The primary endpoint will be the incidence of dose-limiting toxicity when nivolumab is used in combination with dasatinib in relapsed/refractory Ph+ ALL.

1.4 Exploratory Studies

As described above, both dasatinib and nivolumab have demonstrated the ability to modulate the immune system and expand T cells as single agents. We therefore hypothesize that nivolumab and dasatinib will act synergistically to increase T cell levels and activation, and induce lysis of ALL blast cells.

2.0 OBJECTIVES & ENDPOINTS

2.1 Primary Objective & Endpoint

4.1.42.1.1 Primary Objective:

- To determine the maximum tolerated dose (MTD) of nivolumab when given in combination with dasatinib in patients with relapsed/refractory Ph+ ALL. The MTD will be defined as the highest dose level at which ≤ 1 DLT occurs in 6 patients.

4.1.22.1.2 Primary Endpoint:

- The incidence of dose-limiting toxicity (DLT), as defined in section 4.3.1, assessed by the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03.

2.2 Secondary Objectives & Endpoints

4.1.32.2.1 Secondary Objectives:

- To evaluate the toxicities and safety profile of nivolumab and dasatinib in patients with relapsed/refractory Ph+ ALL
- To determine the rate of complete hematologic remission (CR) after three cycles of nivolumab and dasatinib.
- To determine the rate of molecular remission after three cycles of nivolumab and dasatinib.
- To study the pharmacokinetics of nivolumab and dasatinib.
- To evaluate PD1 expression levels and saturation in the peripheral blood and bone marrow.
- To measure peripheral T-cell levels and activation in response to treatment.

4.1.42.2.2 Secondary Endpoints:

- The number, frequency, and severity of adverse events (as defined by the NCI Common Terminology Criteria for Adverse Events or CTCAE version 4.03) will be recorded from consent until 30 days after treatment (100 days for SAE's).
- Clinical response defined as complete remission (CR) rate and/or molecular remission after three cycles of nivolumab and dasatinib.
- PD1 expression levels and saturation in the peripheral blood and bone marrow before and after treatment. T cell levels and activation will be measured in the peripheral blood after treatment.

2.3 Exploratory Objectives & Endpoints

4.1.52.3.1 Exploratory Objectives:

- To evaluate the 30 day mortality rate, overall survival (OS), progression free survival (PFS), and duration of remission (DOR) one year after treatment with nivolumab when given in combination with dasatinib in patients with relapsed/refractory Ph+ ALL.
- To compare the OS between patients who receive a hematopoietic stem cell transplant and those who receive no further therapy following remission.

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- To evaluate for resistance mutations at the time of disease progression.
Endpoint: Presence of resistance mutations based on molecular analysis of the bone marrow aspirate at the time of disease progression.

3.0 PATIENT ELIGIBILITY

The target population for this study is patients with relapsed or refractory Ph+ ALL. This will be a multi-center trial conducted at The Robert H. Lurie Comprehensive Cancer Center of Northwestern University. Northwestern University will serve as the lead site and coordinating center for this study.

A total of up to 25 patients will be needed for this trial for 16-22 evaluable patients. Approximately 6 potentially eligible patients are seen per month, and it is anticipated that at least 2 per month will be accrued. Potential patients may be referred to the Principal Investigator (PI) at Northwestern University, Dr. Shira Dinner at 312-695-6180.

Eligibility will be evaluated by the study team according to the following criteria. Eligibility waivers are not permitted. Subjects must meet all of the inclusion and none of the exclusion criteria to be registered to the study. Study treatment may not begin until a subject is registered. Please refer to Section 11 for complete instructions regarding registration procedures.

3.1 Inclusion Criteria

- 3.1.1 Patients must have a histologically confirmed diagnosis of Ph+ ALL.
- 3.1.2 Detection of one of the following must be present:
 - t(9;22)(q34;q11) or 3-way variant by metaphase cytogenetics
 - BCR-ABL positive status by molecular analysis with qualitative PCR or FISH
- 3.1.3 Patients must have primary refractory ALL based on failure to achieve a hematologic or molecular remission after induction therapy with dasatinib and steroids or dasatinib and chemotherapy, or have relapsed after treatment with a tyrosine kinase inhibitor with or without chemotherapy.
 - *Note: Prior course of dasatinib and steroid induction therapy should have included dasatinib 140mg PO daily on days 1-84 and prednisone 60mg/m² (capped at 120mg, or equivalent steroid dose) on days 1-28. If patients were unable to tolerate full steroid dose during induction therapy they will still be eligible.*
 - *Note: Patients with refractory or relapsed disease in the central nervous system will be eligible.*
- 3.1.4 Prior chemotherapy or TKI treatment, aside from dasatinib, must be ≥ 7 days before first investigational agent dose.
- 3.1.5 Patients must be age ≥ 18 years.
- 3.1.6 Patients must exhibit an ECOG performance status of 0-2
- 3.1.7 Patients must have adequate organ function prior to registration, as defined below:
 - ALT and AST $< 2 \times$ institutional upper limit of normal (IULN). Total bilirubin $< 2.0 \times$ IULN (unless Gilbert syndrome has been diagnosed). If leukemia infiltration of the liver is suspected to be causing liver function abnormalities the patient will still be eligible with PI approval
 - Creatinine $< 2 \times$ IULN, Creatinine clearance >40 mL/min (measured by Cockcroft-Gault)

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- 3.1.8 Females of child-bearing potential (FOCBP) must have a negative pregnancy test within 7 days of registration.

Note: A FOCBP is any woman (regardless of sexual orientation, having undergone a tubal ligation, or remaining celibate by choice) who meets the following criteria:

- Has not undergone a hysterectomy or bilateral oophorectomy
- Has had menses at any time in the preceding 12 consecutive months (and therefore has not been naturally postmenopausal for > 12 months)

- 3.1.9 Women must not be breastfeeding at the time of study registration.

- 3.1.10 Women and men of reproductive potential should agree to use two effective means of birth control as dictated in Appendix 3.

- For women, contraception should continue for 23 weeks after the last dose of nivolumab and 12 weeks after the last dose of dasatinib to allow complete clearance of drug and its principal metabolites from the body.
- For men, contraception should continue for 31 weeks after nivolumab and 12 weeks after dasatinib.

- 3.1.11 Patients must have the ability to understand and the willingness to sign a written informed consent prior to registration on study.

3.2 Exclusion Criteria

- 3.2.1 Patients may not be receiving any other investigational agents within 5 half-lives of the drug (if known). If the half-life is not known, investigational agents should not be taken within two weeks.

- 3.2.2 Patients are not eligible if they have an intolerance to most recent prior TKI (other than dasatinib) at the lowest possible effective dose, defined as a Grade \geq 3 toxicity considered at least possibly related to that TKI. Patients are also excluded if they are intolerant or allergic to dasatinib and discontinued prior therapy due to a \geq Grade 2 treatment related adverse event.

- 3.2.3 Patients must not have a history of a grade 4 anaphylactic reaction to monoclonal antibody therapy or known hypersensitivity reactions to drugs formulated with polysorbate 90.

- 3.2.4 Patients must not have had any prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137 or anti-CTLA-4 antibody (or any antibody or drug specifically targeting T-cell costimulation or checkpoint pathways). For questions or uncertainties, please contact the PI or QAM.

- 3.2.5 Patients who have had allogeneic hematopoietic stem cell transplant (HSCT) are not eligible if they meet any of the following:

- transplant is within 2 months from C1D1
- Has clinically significant graft-versus-host disease requiring treatment
- Has \geq Grade 3 persistent non-hematological toxicity related to the transplant

- 3.2.6 Concomitant use of strong inhibitors of the CYP3A4 isoenzyme is not permitted. Must have wash-out period of 5 times the half-life of the compound before first dasatinib dose. Please see Appendix 2 for examples.

- 3.2.7 Concomitant use of QT prolonging agents strongly associated with Torsades de Pointes (See Section 4.5.2) is not permitted.

- 3.2.8 Patients who have a known dasatinib-resistant ABL-kinase mutation such as T315I are not eligible. For confirmation, please contact PI.
- 3.2.9 Patients who have any serious or uncontrolled medical disorder that would impair the ability of the subject to receive protocol therapy are not eligible. These include, but are not limited to:
- Active infection that is not well controlled
 - Known pleural or pericardial effusion at baseline
 - Clinically significant gastrointestinal disease or digestive dysfunction compromising absorption of dasatinib
 - Pulmonary arterial hypertension
 - Uncontrolled or significant cardiovascular disease, including:
 - Myocardial infarction within 6 months of enrollment date
 - Uncontrolled angina or congestive heart failure within 3 months of enrollment date
 - Left ventricular ejection fraction (LVEF) <40%
 - Significant cardiac conduction abnormality, including:
 - History of clinically significant ventricular arrhythmia (such as ventricular tachycardia, ventricular fibrillation, or Torsades de Pointes)
 - History of second or third degree heart block (except for second degree type 1)
 - QTc interval >500 msec, unless a cardiac pacemaker is present
 - Prior malignancy active within the previous 3 years, except for locally curable cancers that have been apparently cured, such as basal or squamous cell skin cancers, superficial bladder cancer, or carcinoma in situ of the prostate, cervix or breast.
 - Subjects with active, known or suspected autoimmune disease. (Note: Subjects with vitiligo, type I diabetes mellitus, hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll).
 - Psychiatric illness/social situations that would limit compliance with study requirements
 - Any other illness or condition that the treating investigator feels would interfere with study compliance or would compromise the patient's safety or study endpoints
- 3.2.10 Female patients who are pregnant or nursing are not eligible.
- 3.2.11 Patients are not eligible if they have a known positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute infection.
- Note: Patients with evidence of chronic hepatitis B infection will be allowed to enroll if on appropriate suppressive medications under the direction of a hepatologist and with PI approval.*
- 3.2.12 Patients who are known to be positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS) are not eligible.

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- 3.2.13 Patients must not have live vaccine therapies for prevention of infectious diseases within 28 days of first nivolumab dose.
- 3.2.14 Patients who are unable to swallow oral medication are not eligible.
- 3.2.15 Patients with active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including chronic prolonged systemic corticosteroids (defined as corticosteroid use of duration one month or greater), should be excluded. These include but are not limited to patients with a history of:
- immune related neurologic disease
 - multiple sclerosis
 - autoimmune (demyelinating) neuropathy
 - Guillain-Barre syndrome
 - myasthenia gravis
 - systemic autoimmune disease such as SLE
 - connective tissue diseases
 - scleroderma
 - inflammatory bowel disease (IBD)
 - Crohn's
 - ulcerative colitis
 - patients with a history of toxic epidermal necrolysis (TEN)
 - Stevens-Johnson syndrome
 - anti-phospholipid syndrome

NOTE: Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

4.0 TREATMENT PLAN

4.1 Overview

This will be a phase 1b dose de-escalation study of nivolumab and dasatinib in relapsed/refractory Ph+ ALL. Please refer to section 4.3 for the dose de-escalation details. Enrolled patients will be treated in repeating 28-day cycles until disease progression, unacceptable toxicity, or withdrawal from the study for other reasons. Response will be assessed via peripheral blood and bone marrow biopsies on day 1 of each cycle beginning with cycle 2. If a patient has a documented complete hematologic response and molecular remission based on PCR for BCR-ABL or cytogenetics, subsequent bone marrow biopsies may be done based on physician's discretion. These patients will be monitored by peripheral blood PCR for BCR-ABL on day 1 of each cycle after documentation of complete hematologic response and molecular remission.

4.2 Treatment Administration

Treatment Administration Summary						
Agent	Premedications	Dose	Route	Schedule	Cycle Length	Supportive Therapies
Dasatinib	None	140mg	PO before nivolumab	Daily	28 days	None
Nivolumab	None	240mg or 80mg	IV over 30 min after dasatinib	Every 2 weeks*		None

*Nivolumab will be administered on C1D8, C1D22, D1 and D15 of all subsequent cycles.

4.2.1 Dasatinib

Dasatinib is dosed at 140mg PO daily on a continuous 28-day cycle. Treatment with dasatinib will begin 7 days prior to starting nivolumab. ~~This 7 day period will be referred to as "Cycle 0".~~ On days where both dasatinib and nivolumab are administered, dasatinib administration should be immediately before nivolumab infusion is begun. Dasatinib should be taken the same time each day, with or without food. If the dose administration time is missed, the dose can be made up within the same day as long as the time between subsequent doses is at least 12 hours. If a day's dose is missed it should not be made up the next day (i.e. do not take more than one dose in any treatment day). If a dose is vomited it should not be made up. Any time the patient has a planned study visit, dasatinib should be taken in clinic after labs have been drawn (specifically for PK trough determinations) and immediately before nivolumab administration, when applicable. Patients will record dosing details in a diary provided each cycle. Dasatinib is commercially available for the treatment of Ph+ ALL and will not be supplied by the sponsor.

4.2.2 Nivolumab

The starting dose of nivolumab will be 240mg IV over 30 minutes with a dose de-escalation to 80mg in the event of increased toxicity as described in section 4.3. Nivolumab should be administered as an IV infusion on day 8 (\pm 3 days) and day 22 (\pm 3 days) of the first cycle, and day 1 (\pm 3 days) and day 15 (\pm 3 days) of all subsequent cycles starting with cycle 2. Nivolumab infusion should begin immediately after administration of dasatinib whenever possible. Please refer to section 4.4.3 for use of premedications. Missed doses of nivolumab will not be made up. Nivolumab will be provided by the clinical trial sponsor.

4.3 Phase I Dose De-Escalation Scheme

Following signed informed consent, the dose de-escalation phase will begin in a 3+3 design with enrollment of 3 patients to cohort 1 to receive dasatinib 140mg PO daily continuously in a 28-day cycle. Initially, 3 patients will be enrolled at the starting dose (level 1), and monitored until all 3 patients complete the DLT evaluation period (defined as cycle 1 or the first 28 days of treatment). Once all 3 patients complete the DLT period and toxicity data has been submitted, the Data Monitoring Committee (DMC) will review the data and confirm the presence or absence of any DLTs (defined below). The starting dose of nivolumab will be 240mg IV every 2 weeks, which is tolerable as a single agent and is within the range that has shown anti-tumor activity in solid tumors, and is the same dose and schedule used in global Phase 3 studies that are currently ongoing. If the first 3 patients do not experience a dose limiting toxicity (DLT), an additional 3 patients will be evaluated for DLT. If \leq 1 of these 6 patients experience a DLT, nivolumab 240mg will be determined to be the recommended dose for the expansion cohort, in which case, 10 additional patients will be enrolled to the dose expansion phase at the dose level 1 dose of nivolumab 240mg every 2 weeks. If 2 or more of the initial 6 patients or 5 or more of the total of 16 at that dose -experience a DLT the nivolumab dose will be reduced to 80mg. Three patients will then be entered at the 80mg dose (i.e. the dose level -1 cohort). If 0 or 1 patient has a DLT at the dose -1 cohort, the cohort will be expanded to 6 patients. If \leq 1 of these 6 patients experience a DLT, nivolumab 80mg will be determined to be the recommended dose for the expansion cohort, and 10 additional patients will be enrolled to the dose expansion phase at the de-escalated dose of nivolumab, 80mg every 2 weeks. If 2 or more of the initial 6 patients or 5 or more of the total of 16 patients at this dose experience a DLT the protocol will be suspended and reviewed by the primary investigator and sponsor to determine if it should be terminated or amended with further dose cohorts. Nivolumab will be administered once every 2 weeks, on day 1 and day 15 of each cycle.

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Dose De-Escalation Scheme			
Dose Level	Nivolumab	Dasatinib	# of Patients [^]
Level -1	80mg	140mg	3-6
Level 1*	240mg	140 mg	3-6

*Starting dose level
[^]A minimum of 3 patients will be treated per cohort; a total of 6 patients should be treated at whichever dose level is determined to be the MTD.

4.3.1 Definitions

- Patients will be evaluated for DLTs during the first 28 days at each dose level (DLT period).
- DLT observed during cycle 1 will be defined as any treatment-related grade 3 or greater nonhematologic toxicity defined by version 4.03 of the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE) that lasts for > 7 days, with the exception of transaminitis and elevated amylase or lipase that resolves to ≤ grade 2 by the next cycle.
- Patients missing 7 or more doses of dasatinib due to toxicity during cycle 1 will be considered to have experienced a dose limiting toxicity
- The MTD will be defined as the highest dose level at which ≤ 1 DLT occurs in 6 patients.
- The recommended phase II dose (RP2D) will be determined after careful review of all clinical data at the end of the dose de-escalation and expansion phase

4.4 Toxicity Management & Dose Delays/Modifications

Any patient who receives at least one dose of study therapy will be evaluable for toxicity endpoints. Each patient will be assessed for the development of toxicity according to the timeframe referenced in the Schedule of Events table. Toxicity will be assessed according to version 4.03 of the National Cancer Institute’s Common Terminology Criteria for Adverse Events (CTCAE).

General Principles:

- Investigators should, whenever possible, determine which medication is causing the toxicity and interrupt or dose reduce the offending drug as applicable. If the offending medication cannot be established, reduction of dasatinib is recommended.
- No dose modifications are permitted for nivolumab.
- Dose modifications for dasatinib should be made when dasatinib related toxicity is suspected.
- Following dose reduction for dasatinib, the dose should not be re-escalated unless there is a clear clinical benefit after discussion and agreement by the PI.
- When treatment is interrupted due to toxicity, the subject should be re-evaluated in approximately 1 week intervals until resolution of the toxicity.
- Withdrawal from the study is required for any delay in therapy >28 days during the DLT period. After the DLT period, subjects may be allowed to remain on study despite delays in treatment >28 days if approved by the PI and DMC.

4.4.1 Dasatinib Toxicity Management:

Table 4.4.1-1

Dose Modification Levels for Dasatinib Toxicities	
Starting Dose	140mg QD
Level -1	100mg QD
Level -2	80mg QD

Table 4.4.1-2

Toxicity	Grade/Description	Dasatinib
Hematologic Toxicities		
Thrombocytopenia or Neutropenia (after achieving complete hematologic remission or molecular remission)	Grade 1 or 2	Maintain dose level.
	Grade 3	**For both Grade 3 & 4, perform bone marrow biopsy to assess for relapsed disease** Interrupt until ANC $\geq 1.0 \times 10^9/L$ and platelets $\geq 50 \times 10^9/L$. Resume dasatinib at original dose if recovery occurs in ≤ 7 days. If >7 days, resume dasatinib at dose level -1. For 2 nd episode, resume at dose level -2 (see Table 4.4.1-1)
	Grade 4	Interrupt until ANC $\geq 1.0 \times 10^9/L$ and platelets $\geq 50 \times 10^9/L$. Resume dasatinib at dose level -1 if recovery occurs in ≤ 7 days. For 2 nd episode, reduce to dose level -2. If >7 days, discontinue dasatinib.
Non-hematologic Toxicities		
Pleural Effusion	Grade 1	For patients that are asymptomatic with incidental finding of pleural effusion on imaging treatment may be continued without dose reduction.
	\geq Grade 2	Hold both dasatinib and nivolumab until resolved to \leq grade 1. Dasatinib should then be resumed at dose level -1 if no prior reduction. If dasatinib has been previously reduced may resume at dose level -2. If event has not improved within 14 days thoracentesis, should be performed for therapeutic and diagnostic purposes. For 2 nd episode, resume at dose level -2 if dose has not already been reduced to this level. If patients are already receiving dose level -2 and 2 nd episode occurs treatment will be discontinued.
LFTs	\geq Grade 3	Interrupt until \leq Grade 1 or baseline and resume dasatinib at same dose level.
QTc _b >500 msec, confirmed by repeat ECG	n/a	Interrupt until \leq Grade 1. Eliminate drugs that prolong QTc, supplement K, Mg. Consider monitored re-challenge of dasatinib. NOTE: subject should be discontinued in the event of QTc _b >530 msec.
LVEF	Grade 2 (or decrease by $>10\%$ from baseline), confirmed by repeat Echo	Interrupt until \leq Grade 1 or baseline and resume dasatinib at same dose. For 2 nd episode, reduce one dose level. If \geq Grade 3, reduce by one dose level.
Other	Grade 1 or 2	Maintain dose level.
Other	Grade ≥ 3	Hold dose until resolved to \leq Grade 1 or baseline. Once resolved, resume at one dose level reduction. Unresolved (persisting > 2 weeks) or recurrent event: permanently discontinue.

4.4.2 Nivolumab Toxicity Management

Immunotherapy agents such as nivolumab are associated with AEs that can differ in severity and duration compared to other therapeutic classes of medications. Early recognition and management of AEs associated with nivolumab can mitigate severe toxicity. Corticosteroids are the primary therapy for drug-related AEs. Management algorithms have been developed to assist investigators in assessing and managing nivolumab associated AEs, which can be found in Appendix 1 of this protocol. The guidance provided in these algorithms should not replace the Investigator's medical judgment. Should a female patient become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

4.4.3 Nivolumab Related Infusion Reaction

Infusion reactions should be graded according to CTCAE v 4.03 allergic reaction/hypersensitivity. Treatment of infusion reactions should follow institutional standards with recommendations provided below. Reactions may manifest as fever, chills, headache, rash, pruritus, arthralgias, hypo-or hypertension, bronchospasm or other symptoms. Severe infusion reactions require immediate interruption of nivolumab and permanent discontinuation from further treatment. Appropriate supportive care including epinephrine, corticosteroids, antihistamines, bronchodilators and oxygen should be available in the event of an infusion reaction. Subjects should be premedicated with acetaminophen and diphenhydramine for future treatments following an infusion reaction.

- Grade 1 Infusion Reaction:
 - Infusion interruption not indicated
 - For future infusions, premedication with 50mg diphenhydramine and 325mg-1000mg acetaminophen at least 30 minutes prior to nivolumab is recommended

- Grade 2 Infusion Reaction:
 - Stop nivolumab infusion and begin infusion of normal saline
 - Treat with diphenhydramine 50mg IV and 325mg-1000mg acetaminophen or equivalents
 - Corticosteroids may be administered if indicated
 - When symptoms resolve, restart the infusion at 50% of the original infusion rate. If symptoms reoccur, discontinue remainder of infusion. Subsequent infusions should be administered over 2 hours with premedication of 50mg diphenhydramine and 325mg-1000mg acetaminophen at least 30 minutes prior to nivolumab. Up to 25mg of SoluCortef or equivalent may also be used.

- Grade 3 or 4 Infusion Reaction:
 - Immediately discontinue nivolumab infusion and begin infusion of normal saline
 - The following, or equivalents, should be used to manage such reactions, per institutional standards:
 - bronchodilators, epinephrine 0.2 to 1mg of a 1:1,000 solution SQ or 0.1 to 0.25mg of a 1:10,000 solution injected IV, diphenhydramine 50mg IV, and methylprednisolone 125mg IV as needed.
 - Nivolumab should be permanently discontinued

4.4.4 Nivolumab Discontinuation

Nivolumab treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for laboratory abnormalities, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies:
 - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
 - Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation
 - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
 - ❖ Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation
- Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:
 - AST or ALT > 5-10 x ULN for > 2 weeks
 - AST or ALT > 10 xULN
 - Total bilirubin > 5 x ULN
 - Concurrent AST or ALT > 3 xULN and total bilirubin > 2 x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events which do not require discontinuation:
 - Grade 4 neutropenia
 - Grade 4 lymphopenia or leukopenia
 - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis. The Medical Monitor should be consulted for Grade 4 amylase or lipase abnormalities.
 - 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 drug-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.

Any event that leads to interruption in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:

- Dosing interruptions to allow for prolonged steroid tapers to manage drug-related adverse events are allowed. Prior to re-initiating treatment in a subject with a dosing interruptions lasting > 6 weeks from the previous dose, the medical monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted. Periodic study visits to assess

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safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing interruptions.

- Dosing interruptions lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the medical monitor. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Medical Monitor must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing interruptions.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

4.5 Concomitant Medications/Treatments

4.5.1 Prohibited Treatments

4.5.1.1 Medications Associated with Immune Suppression

Medications associated with suppression of the immune system are prohibited while subjects are on active therapy with nivolumab during this study. See Appendix 1 for specific management of AE's requiring such medications. Prohibited medications include:

- Chronic systemic corticosteroids >10mg daily prednisone equivalent, with the following exceptions:
 - Patients may receive steroids for control of leukocyte count until cycle 1, day 5. Steroid should then be discontinued to avoid mitigating nivolumab efficacy.
 - Subjects are permitted the use of topical, ocular, intranasal, intra-articular, and inhalational corticosteroids.
 - Immunosuppressive doses (prednisone >10mg/day or equivalent) and/or physiologic replacement doses are permitted in the context of treating adverse events.
 - A brief course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) is permitted.
- Concurrent immunosuppressive agents or any immunotherapy
- Influenza vaccines containing live virus or other clinically indicated vaccinations for infectious diseases (eg, pneumovax, varicella, etc) may be permitted but must be discussed with the Principal Investigator and QAM and may require a study drug washout period prior to and after administration of the vaccine.
 - The inactivated seasonal influenza vaccine is permitted without restriction

4.5.1.2 Medications that Prolong the QT Interval

Medications associated with QT interval prolongation that are prohibited while subjects are on active therapy with dasatinib alone or dasatinib with nivolumab during this study include:

- quinidine, procainamide, disopyramide
- amiodarone, sotalol, ibutilide, dofetilide
- erythromycins, clarithromycin
- chlorpromazine, haloperidol, mesoridazine, thioridazine, pimozide

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- cisapride, bepridil, droperidol, methadone, arsenic, chloroquine, domperidone, halofantrine, levomethadyl, pentamidine, sparfloxacin, lidoflazine

Ideally, subjects enrolled in this study should not begin taking other medications known to prolong the QT interval. Further information on medications known to prolong the QT interval can be found at the following website:

<https://www.crediblemeds.org/pdftemp/pdf/CompositeList.pdf>. If in the opinion of the investigator, a potential QT interval prolonging medication (other than those listed above which are explicitly prohibited) is vital to a subject's care, then additional ECGs should be completed at the investigator's discretion.

4.5.2 Medications to Use with Caution

4.5.2.1 Use of Growth Factors

Growth factors such as G-CSF are not permitted during the first cycle (28 days), as these may mask potential DLTs. G-CSF may be used outside of this period (including pre-treatment) at the treating physician's discretion if there is concern for active infection or the patient has experienced infectious complications during prior cycles.

4.5.2.2 H2-Agonists, PPIs and Antacids

Histamine (H2) antagonists (eg, famotidine), proton pump inhibitors (eg, omeprazole), and aluminum hydroxide/magnesium hydroxide (eg, Maalox) may reduce the exposure to dasatinib. H2 antagonists and proton pump inhibitors are not recommended (but not prohibited) and aluminum hydroxide/magnesium hydroxide products should be administered at least 2 hours before or after dasatinib.

4.5.2.3 Antiplatelet Agents and Anticoagulants

Dasatinib may increase the likelihood of bleeding. Subjects undergoing surgical procedures, including dental procedures, should hold dasatinib 24 hours prior and 24 hours after the procedure. Caution should be used with concomitant medications that inhibit platelet function.

Anticoagulants should also be avoided in the setting of Grade 3 or 4 thrombocytopenia while subjects are on active dasatinib treatment.

4.5.2.4 Agents Affecting CYP3A4

Strong and moderately potent inhibitors of CYP3A4 should be avoided while subjects are on active dasatinib treatment as they may increase dasatinib concentrations. CYP3A4 inducers may decrease the concentration of dasatinib and should be used with caution as well. Alternative agents with less enzyme-inducing or inhibiting potential should be considered as indicated. See Appendix 2 for a list of agents affecting the CYP enzyme system. If use of an azole antifungal is necessary, it is recommended that an agent with the least inhibitory effect on CYP3A4 be selected if possible. The following azoles appear in order of strength of inhibition of CYP3A4 (high to low): voriconazole, itraconazole, posaconazole, and fluconazole. Fluconazole at doses of 200 mg or less is not thought to be a significant inhibitor of CYP3A4.

4.5.3 Permitted Concomitant Medications/Treatments

4.5.3.1 Supportive Care Management

- The use of hydroxyurea is permitted to keep the total WBC <50,000/mm³ with no maximal allowed dosage.
- Allopurinol may also be used in subjects with an elevated WBC in order to prevent or treat elevated uric acid.
- The use of growth factor support is prohibited during the first cycle (28 days), but acceptable outside this time period.

4.5.3.2 Supplementation and Prophylaxis

- Due to expected osteoclast inhibition with dasatinib, calcium supplementation is recommended to maintain serum calcium within the institutional normal range during dasatinib treatment. Vitamin D supplementation may also be appropriate for persistent hypocalcemia.
- Infectious complications are a known risk with dasatinib. Consideration should be given to the use of appropriate prophylactic therapy for subjects at high risk of infection.

4.6 Other Modalities or Procedures

Response will be assessed via peripheral blood and bone marrow biopsies on day 1 of each cycle beginning with cycle 2. If a patient has a documented complete hematologic response and is MRD negative (molecular remission) by PCR for BCR-ABL, subsequent bone marrow biopsies may be done based on physician's discretion. These patients will be monitored by peripheral blood PCR for BCR-ABL on day 1 of each cycle after documentation of complete hematologic response and MRD negativity. Subjects who achieve complete hematologic remission and/or molecular remission will be considered for eligibility for allogeneic hematopoietic stem cell transplant (HSCT), as per current standard of care for all patients with Ph + ALL. Timing of HSCT will depend on donor availability and medical stability of the subject, but will be pursued as soon as able upon confirmation of remission. Patients may continue to receive treatment on study until they proceed to HSCT.

4.7 Duration of Therapy

Patients may continue to receive treatment until any of the following occur:

- Disease progression
- Development of an inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Patient decides to withdraw from either study treatment or the whole study
- The treating investigator determines that the patient should be taken off treatment for any reason (i.e. changes in condition, inability to comply with study treatment or procedures)

4.8 Duration of Follow Up

Once patients finish treatment, they should return for monthly follow-up visits for up to one year. All patients should have the first end of treatment visit 30 days +/- 7 days after the last dose of nivolumab, or prior to starting another therapy, whichever comes first. Patients removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of the adverse event. Date of disease progression or death should be documented.

4.9 Removal of Subjects from Study Treatment and/or Study as a Whole

Patients can be taken off the study treatment and/or study as a whole at any time at their own request, or they may be withdrawn at the discretion of the investigator for safety, behavioral or administrative reasons. The reason(s) for discontinuation must be clearly documented on the appropriate eCRF and may include:

- Patient voluntarily withdraws from treatment (follow-up permitted)
- Patient withdraws consent (no follow-up permitted)
- Patient is unable to comply with protocol requirements
- Patient demonstrates disease progression
- Patient experiences unacceptable toxicity
- QTc value becomes >530 msec
- Treating physician determines that continuation on the study would not be in the patient's best interest
- Patient becomes pregnant
- Patient develops a second malignancy that requires treatment which would interfere with this study
- Patient becomes lost to follow-up (LTF)

Once off treatment, patients will be followed monthly according to table 5.0 for one year or until death, whichever occurs first. Patients who progress or start new treatment will continue follow-up survival.

4.10 Patient Replacement

Three patients within a dose level must be observed for one cycle (28 days) before accrual to the next dose level or expansion cohort may begin. If a patient is withdrawn from the study prior to completing 22 days of dasatinib and 2 doses of nivolumab therapy without experiencing a DLT prior to withdrawal, an additional patient may be added to that dose level with approval from the DMC, however these patients will still count towards overall accrual. Any patient who has received at least one dose of either study drug may not be replaced for overall accrual.

5.0 STUDY PROCEDURES

Table 5.0

Procedure	Screening	Cycle 1 (±3 days)					Cycle 2+ (±3 days)		End of Treatment ³	Follow up ¹⁶
	Day -21 to -1 ¹	D1	2	8	15	22	D1 ²	D15		
Signed ICF	X									
Medical history	X									
Physical exam ⁴	X	X		X	X	X	X	X	X	X
ECOG PS	X	X		X	X	X	X	X	X	
12-lead ECG ⁵	X				X				X	
Chest x-ray (or chest CT)	X									
CBC with differential ⁶	X ¹	X		X	X	X	X	X	X	X
Chemistry ⁷	X ¹	X		X	X	X	X	X	X	
Bone marrow assessment	X ⁸						X ⁹		X ⁹	
TSH	X	X					X			
Correlative & PK blood samples ¹⁰		X	X	X	X	X				
Adverse events ¹¹	X	X		X	X	X	X		X	X ¹¹
Concomitant medications	X	X		X	X	X	X		X	
Pregnancy Serum or Urine test	X ¹	X ¹								
LVEF ¹²	X									
Dasatinib administration ¹³		X	X	X	X	X	X	X		
Nivolumab infusion ¹⁴		X		X	X	X	X	X		
Molecular analysis ¹⁵	X						X			
Mutation analysis for T315 ¹⁷	X								X	
Survival Status										X

Table 5.0 Footnotes:

1. Protocol-specified screening procedures that are performed as part of standard of care and within 21 days of Day 1 of Cycle 1 may be used for screening purposes. Clinical laboratory studies and pregnancy test must be performed within the 7-day period before registration. A pregnancy test should also be confirmed as negative within 24 hours of starting treatment.

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2. If the study treatment is well tolerated and the patient experiences no leukemic progression, clinic visits will be scheduled every 28 days (+/- 3 days) at beginning of each cycle until disease progression or unacceptable toxicity.
3. The end-of-study visit should be scheduled 30 days (±7 days) within the 28-day period after the last dose of study drug and before starting any new anti-neoplastic therapy.
4. Includes vitals, weight, and height (baseline only). A complete physical examination will be performed at screening. All subsequent physical examinations will be disease-specific.
5. ECG is performed after the patient has been in a supine position for at least 5 minutes. It is performed at screening, C1D15 (pre-dose), and at the end-of-study visit. Additional ECGs may be performed as clinically indicated.
6. A CBC with a differential count will be performed every 7 days until remission, than at every cycle, and at the end of the study.
7. Serum chemistry studies will be performed at each visit. Chemistries will include, complete metabolic panel with transaminases and total bilirubin. The CMP should include: Glucose, BUN, Calcium, Total Protein, Albumin, ALT, AST, GFR, Sodium, Potassium, Chloride, Carbon Dioxide, Alk Phos, Creatinine, Magnesium, and total bilirubin.
8. Bone marrow aspiration and biopsy with evaluation of morphology, blast percentage, cytogenetics, and flow cytometry is required for all patients at screening. A T315I Mutation analysis is required at screening and the End of Treatment visit. **An aspirate sample must be preserved at every time point for correlative studies (see section 9.0 for details).**
9. Bone marrow aspiration and biopsy should be performed within 7 days of the beginning of every cycle, starting with Cycle 2.

After a molecular remission has been documented, a follow-up bone marrow assessment may be performed as clinically indicated. Bone marrow assessment must include morphologic assessment and flow cytometry, PCR for BCR-ABL, and cytogenetics per institutional standard to evaluate for MRD.

When obtaining bone marrow aspirates, samples must be preserved for correlative studies (see section 9.0 for details).
10. Blood samples for PK analysis will be collected on Cycle 1, day 2 (24 hours after Day 1 dasatinib dosing ± 2 hours) to assess dasatinib single agent levels. Both dasatinib and nivolumab levels will be assessed pre-dose on Cycle 1 Day 8, 15, & 22. Blood will be collected for analysis of T cell subsets before dosing on Cycle 1 days 1, 2, 8, 15, & 22. See section 9.0 for details.
11. AEs will be monitored from the time of consent until 30 days after completing study treatment (100 days for SAE's) throughout the study via safety-related assessments, observation, and patient reports.
12. Either ECHO or MUGA can be performed at investigator's discretion. However, the same imaging platform should be used throughout the study if repeat assessment is clinically indicated (i.e evaluation for pericardial effusion).
13. Dasatinib will follow continuous dosing at 140mg PO QD starting at Cycle 1 Day 1 until disease progression or unacceptable toxicity. Any time a patient has a scheduled study visit, he or she should take their dose of dasatinib in clinic, after labs and immediately before the nivolumab infusion, if applicable.
14. Nivolumab will be given IV over 30 minutes on C1D8, C1D22, and Days 1 & 15 of all subsequent cycles (+/- 3 days) until disease progression or unacceptable toxicity. The starting dose will be 240mg, with possible de-escalation to 80mg.
15. If patient achieves complete hematologic remission they will be assessed for molecular remission on bone marrow. After achieving a molecular remission on bone marrow aspirate, patients should then be followed with peripheral blood BCR-ABL PCR on day 1 of each cycle.
16. Patients will be followed monthly for up to one year after treatment discontinuation.
17. T315I Mutation testing will be performed as part of the bone marrow procedure.

6.0 ENDPOINT ASSESSMENT

6.1 Primary Endpoint

The primary endpoint is the incidence of dose-limiting toxicity (DLT), as defined in protocol section 4.3.1, as assessed by the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. Toxicity will be assessed weekly during cycle 1 of treatment. All patients that receive at least one dose of nivolumab will be considered evaluable for this endpoint.

6.2 Secondary and Exploratory Endpoints

The secondary endpoints are [the safety profile of the combination treatment](#), the pharmacokinetics of nivolumab and dasatinib, PD1 expression levels and saturation in the peripheral blood and bone marrow before and after treatment, as well as T cell levels and activation in the peripheral blood after treatment as defined in section 9.0 of the protocol.

[The number, frequency, and severity of adverse events \(as defined by the NCI CTCAE v4.03\) will be recorded from the time of consent until 30 days after treatment \(100 days for SAE's\).](#)

The pharmacokinetic profile of dasatinib and nivolumab will be studied by measuring the serum level of dasatinib 24 hours after the start of cycle 1, and both dasatinib and nivolumab serum levels on treatment days 8, 15, and 22 prior to treatment during cycle 1.

In order to address the effects of nivolumab on dasatinib's ability to induce T-cell expansion and activation, lymphocyte subpopulations, specifically T-cells, will be quantitatively measured on cycle 1 day 1, 8, 15, and 22. Bone marrow samples that are required for response assessment will also be used to characterize T-cell receptor clonal expansion/diversity.

Patients that receive at least one cycle of treatment will be evaluable for these endpoints.

Exploratory endpoints:

- The rate of complete hematologic remission and molecular remission after 3 cycles of nivolumab and dasatinib as defined in section 6.2.1
- Duration of remission as defined in section 6.2.4
- Progression free survival as defined in section 6.2.4
- Overall survival as defined in section 6.2.4
- 30-day mortality rate as defined in section 6.2.4
- The PFS and OS for patients that go on to HSCT vs those that do not receive further therapy after completing nivolumab and dasatinib.
- Monitoring for the presence of resistance mutations at the time of disease progression. Bone marrow samples at the end of treatment visit will be sent for molecular analysis to evaluate for mutations that increase resistance to tyrosine kinase therapies.

6.2.1 Response Definitions

Response to treatment will be defined per NCCN guidelines version 2.2015 as outlined below:

- **Complete Response (CR)**
 - No circulating blasts or extramedullary disease
 - No lymphadenopathy, splenomegaly, skin/gum infiltration / testicular mass / CNS involvement
 - Trilineage hematopoiesis (TLH) and <5% blasts

- Absolute neutrophil count (ANC) > 1,000/uL
- Platelets > 100,000/uL
- No recurrence for 4 weeks
- **CR with incomplete blood count recovery (CRi)**
 - Recovery of platelets but <100,000 or ANC is <1,000uL
- **Molecular remission:**
Real time quantitative polymerase chain reaction (RQ-PCR) negative for the BCR-ABL1 fusion gene
- **Overall response rate (ORR) = CR + CRi**
- **Refractory Disease:**
Failure to achieve CR at the end of induction
- **Progressive Disease (PD):**
Increase of at least 25% in the absolute number or circulating or bone marrow blasts or development of extramedullary disease
- **Relapsed Disease:** Reappearance of blasts in the blood or bone marrow (>5%) or in any extramedullary site after a CR

6.2.2 Central Nervous System (CNS) Disease

6.2.2.1 Classification of CNS status

- CNS-1: No lymphoblasts in CSF regardless of WBC count.
- CNS-2: WBC <5/mcL in CSF with presence of lymphoblasts.
- CNS-3: WBC ≥5/mcL in CSF with presence of lymphoblasts.

If the patient has leukemic cells in the peripheral blood and the LP is traumatic and WBC ≥5/mcL in CSF with blasts, then compare the CSF WBC/RBC ratio to the blood WBC/RBC ratio. If the CSF ratio is at least two-fold greater than the blood ratio, then the classification is CNS-3; if not, then it is CNS-2

6.2.2.2 Response Criteria for CNS Disease

- CNS remission: Achievement of CNS-1 status in a patient with CNS-2 or CNS-3 status at diagnosis.
- CNS relapse: New development of CNS-3 status or clinical signs of CNS leukemia such as facial nerve palsy, brain/eye involvement, or hypothalamic syndrome.

6.2.3 Response Criteria for Mediastinal Disease

- CR: Complete resolution of mediastinal enlargement by CT.
- CR Unconfirmed (CRu): Residual mediastinal enlargement that has regressed by >75% in the sum of the product of the greatest perpendicular diameters (SPD).
- PR: >50% decrease in the SPD of the mediastinal enlargement.
- PD: >25% increase in the SPD of the mediastinal enlargement.
- No Response (NR): Failure to qualify for PR or PD.
- Relapse: Recurrence of mediastinal enlargement after achieving CR or CRu.

6.2.4 Survival outcomes definitions:

- **Duration of remission (DOR)**
Duration of remission is defined as the time from achieving CR until the time of disease relapse as defined in section 6.2.1
- **Overall Survival (OS)**
OS is defined as the time from the initiation of study treatment until death from any cause.
- **Progression-Free Survival (PFS)**
PFS is defined as the time from the initiation of study treatment until the

- time of disease progression or relapse as defined in section 6.2.1.
- **30 day mortality rate:**
Number and percentage of patients that die within the first 30 days of initiating treatment.

7.0 ADVERSE EVENTS

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to Appendices for additional information). The level of risk attributed to this study requires High Intensity Monitoring, as outlined in the DSMP. In addition, the study will abide by all safety reporting regulations, as set forth in the Code of Federal Regulations.

7.1 Adverse Event Monitoring

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial (see Section 5 for timepoints). In addition, certain adverse events must be reported in an expedited manner to allow for optimal monitoring and patient safety and care.

All patients experiencing an adverse event, regardless of its relationship to study drug, will be followed until:

- the adverse event resolves or the symptoms or signs that constitute the adverse event return to baseline;
- any abnormal laboratory values have returned to baseline;
- there is a satisfactory explanation other than the study drug for the changes observed; or
- death

7.2 Definitions & Descriptions

7.2.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

Recording of AEs should be done in a concise manner using standard, acceptable medical terms. In general, AEs are not procedures or measurements, but should reflect the reason for the procedure or the diagnosis based on the abnormal measurement. Preexisting conditions that worsen in severity or frequency during the study should also be recorded (a preexisting condition that does not worsen is not an AE). Further, a procedure or surgery is not an AE; rather, the event leading to the procedure or surgery is considered an AE.

If a specific medical diagnosis has been made, that diagnosis or syndrome should be recorded as the AE whenever possible. However, a complete description of the signs, symptoms and investigations which led to the diagnosis should be provided. For example, if clinically significant elevations of liver function tests are known to be secondary to hepatitis, "hepatitis" and not "elevated liver function tests" should be recorded. If the cause is not known, the abnormal test or finding should be recorded as an AE, using appropriate medical terminology (e/g/ thrombocytopenia, peripheral edema, QT prolongation).

7.2.2 Severity of AEs

All non-hematologic adverse events will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. The CTCAE v4 is available at <http://ctep.cancer.gov/reporting/ctc.html>

If no CTCAE grading is available, the severity of an AE is graded as follows:

- Mild (grade 1): the event causes discomfort without disruption of normal daily activities.
- Moderate (grade 2): the event causes discomfort that affects normal daily activities.
- Severe (grade 3): the event makes the patient unable to perform normal daily activities or significantly affects his/her clinical status.
- Life-threatening (grade 4): the patient was at risk of death at the time of the event.
- Fatal (grade 5): the event caused death.

7.2.3 Serious Adverse Events (SAEs)

All SAEs, regardless of attribution, occurring from time of signed informed consent, through ~~30~~-100 days after the last administration of study drug, must be reported upon discovery or occurrence.

An SAE is defined in regulatory terminology as any untoward medical occurrence that:

- **Results in death.**
If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.
- **Is life-threatening.**
The patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
- **Requires in-patient hospitalization or prolongation of existing hospitalization for \geq 24 hours.**
- **Results in persistent or significant disability or incapacity.**
- **Is a congenital anomaly/birth defect.**
- **Is an important medical event.**

Any event that does not meet the above criteria, but that in the judgment of the investigator jeopardizes the patient, may be considered for reporting as a serious adverse event. The event may require medical or surgical intervention to prevent one of the outcomes listed in the definition of "Serious Adverse Event".

For example: allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that may not result in hospitalization; development of drug abuse or drug dependency.

7.2.4 Unanticipated Problems Involving Risks to Subject or Others

A UPIRSO is a type of SAE that includes events that meet ALL of the following criteria:

- Is *unanticipated* in terms of nature, severity, or frequency
- Places the research subject or others at a different or *greater risk of harm*
- Is deemed to be *at least possibly related* to participation in the study.

7.3 Adverse Event Reporting

7.3.1 Routine Reporting

All routine adverse events, such as those that are expected, or are unlikely or definitely not related to study participation, are to be reported on the appropriate eCRF according to the time intervals noted in the appendices. Routine AEs will be reviewed by the Data Monitoring Committee (DMC) according to the study's phase and risk level, as outlined in the DSMP.

7.3.2 Determining if Expedited Reporting is Required

This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported accordingly.

- 1) Identify the type of adverse event using the NCI CTCAE v 4.0.
- 2) Grade the adverse event using the NCI CTCAE v 4.0.
- 3) Determine whether the adverse event is related to the protocol therapy. Attribution categories are as follows:
 - Definite: AE is clearly related to the study treatment.
 - Probable: AE is likely related to the study treatment.
 - Possible: AE may be related to the study treatment.
 - Unlikely: AE not likely to be related to the study treatment.
 - Unrelated: AE is clearly NOT related to the study treatment.
- 4) Determine the prior experience of the adverse event. Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes only, when either the type of event or the severity of the event is not listed in:
 - the current protocol
 - the drug package insert
 - the current Investigator's Brochure

7.3.3 Expedited Reporting of SAEs/Other Events

7.3.3.1 Reporting to the Northwestern University QAM/DMC

All SAEs must be reported to the assigned QAM within 24 hours of becoming aware of the event. Completion of the NU CRO SAE Form is required. NU CRO SAE forms should be sent to croqualityassurance@northwestern.edu. If drug company reporting is required, Both reports can be emailed simultaneously (see section 7.3.3.4 for details on BMS reporting).

The completed form should assess whether or not the event qualifies as a UPIRSO. The report should also include:

- Protocol description and number(s)
- The patient's identification number
- A description of the event, severity, treatment, and outcome (if known)
- Supportive laboratory results and diagnostics
- The hospital discharge summary (if available/applicable)

All SAEs will be reported to, and reviewed by, the DMC at their next meeting.

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7.3.3.2 Reporting to the Northwestern University IRB

The following information pertains to the responsibilities of the lead site (Northwestern University). Additional participating sites should follow their local IRB guidelines for reporting to their local IRBs.

- Any death of an NU subject that is unanticipated in nature and at least possibly related to study participation will be promptly reported to the NU IRB within 24 hours of notification.
- Any death of an NU subject that is actively on study treatment (regardless of whether or not the event is possibly related to study treatment)
- Any death of a non-NU subject that is unanticipated and at least possibly related and any other UPIRSOs will be reported to the NU IRB within 10 working days of notification.
- All other deaths of NU subjects not previously reported, other non-NU subject deaths that were unanticipated and unrelated, and any other SAEs that were not previously reported as UPIRSOs will be reported to the NU IRB at the time of annual continuing review.

7.3.3.3 Reporting to the FDA

The FDA will be notified within 7 calendar days of any SAE that is associated with study treatment, is unexpected, and is fatal or life-threatening.

The FDA will be notified within 15 calendar days of any SAE that is associated with the study treatment, unexpected, and serious but *not fatal or life-threatening*. This includes any previous SAEs that were not initially deemed reportable, but are later determined to meet the criteria for reporting (i.e. by the DMC).

All other SAEs will be reported on an annual basis as part of the annual FDA report.

7.3.3.4 Reporting to Bristol Myers Squibb BMS (completed by study coordinator)

All SAE reports (including death by any cause), regardless of attribution and any other relevant safety information will be reported within 24 hours to BMS Global Safety (using the NU CRO SAE Form and referencing the BMS study number, CA 209-613). The assigned study coordinator will facilitate all reporting to BMS Global Safety and email QA a copy of the report upon completion. BMS Global Safety can be notified at:

Email Address: Worldwide.Safety@BMS.com

Facsimile Number: 609-818-3804

8.0 DRUG INFORMATION

8.1 Dasatinib

8.1.1 **Other Name**
Sprycel

8.1.2 Classification and Mode of Action

Dasatinib is a multi-kinase inhibitor which is known to inhibit BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EPHA2, and PDGFR-beta kinases. In vitro, dasatinib has been active in leukemic cell lines, including variants of imatinib sensitive and resistant disease. Dasatinib has been shown to inhibit the growth of chronic myeloid leukemia and acute lymphoblastic leukemia cells which over-express BCR-ABL.

8.1.3 Storage and stability

Dasatinib will be dispensed in white to off-white, biconvex, round, film-coated tablets with “BMS” debossed on one side and “524” on the other side. Dasatinib should be stored at 20° to 25°C (68° to 77°F). Excursions permitted between 15°-30°C (59°-86°F).

8.1.4 Protocol dose specifics

Dasatinib will be given at the standard dose of 140mg PO daily.

8.1.5 Preparation

No preparation is required given oral administration.

8.1.6 Route of administration for this study

Dasatinib should be given orally once daily, at approximately the same time each day, with or without food.

8.1.7 Incompatibilities

Use of concomitant strong CYP3A4 inducers may decrease dasatinib plasma concentrations and should be avoided. CYP3A4 inhibitors may increase dasatinib plasma concentrations. Selection of an alternate concomitant medication, if possible, is recommended. If dasatinib must be administered with a strong CYP3A4 inhibitor, a dose decrease should be considered.

8.1.8 Availability & Supply

Dasatinib is commercially available and will not be supplied by the study.

8.1.9 Side effects

Most Frequent Adverse Events (>10%): Myelosuppression, fluid retention events (pleural effusion, superficial localized edema, generalized edema), diarrhea, headache, musculoskeletal pain and rash.

Serious Adverse Events: pleural effusion (2%), hemorrhage (2%), congestive heart failure (1%), and pyrexia (1%).

8.1.10 Return and Retention of Study Drug

Not applicable

8.2 Nivolumab

8.2.1 Other Name

Opdivo

8.2.2 Classification and Mode of Action

Nivolumab is a human monoclonal antibody that blocks the interaction of PD-1 with its ligands, PD-L1 and PD-L2. By inhibiting the binding of PD-1 with its ligands, nivolumab blocks the inhibition of T-cell proliferation and cytokine production, therefore allowing for active T-cell immune surveillance of tumors.

8.2.3 Storage and stability

Nivolumab is available as a 100 mg/10 mL single-use vial and should be stored under refrigeration at 2°C to 8°C (36°F-46°F) in the original package until time of use in order to protect from light. Nivolumab should not be frozen or shaken. After preparation, the nivolumab infusion can be stored at room temperature for no more than 4 hours (including time for administration), or under refrigeration at

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2°C to 8°C (36°F-46°F) for no more than 24 hours from the time of infusion preparation.

8.2.4 Protocol dose specifics

The initial starting dose of nivolumab will be the standard dose of 240mg IV every 2 weeks with a dose de-escalation dose of 80mg IV every 2 weeks in the event of unacceptable toxicity.

8.2.5 Preparation

Dilute nivolumab with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP, to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL. Mix diluted solution by gentle inversion.

8.2.6 Route of administration for this study

Nivolumab will be given as an infusion over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer). The intravenous line should be flushed at the end of the infusion.

8.2.7 Incompatibilities

Other drugs should not be co administered through the same intravenous line.

8.2.8 Availability & Supply

Nivolumab is commercially available, although not FDA approved for Ph+ ALL, and therefore will be supplied by the sponsor. The drug should be shipped to each site directly.

Drug can be ordered using the Drug Request Form provided by BMS. The form is provided as a separate document and should be submitted electronically at least 7 business days before the expected delivery date. Contact and submission details can be found directly on the Drug Request Form. Deliveries will be made Tuesday through Friday.

8.2.9 Side effects

Most Frequent Adverse Events (≥20%): rash, fatigue, dyspnea, musculoskeletal pain, decreased appetite, cough, nausea, and constipation.

Less Likely (≤20%): Hyperthyroidism; Injection site reaction; Lymphocyte count decreased; Platelet count decreased; Skin hypopigmentation

Rare but Serious (<3%): Cardiac disorders - Other (cardiomyopathy); Cytokine release syndrome; Encephalopathy; Eye disorders - Other (Graves ophthalmopathy); Facial nerve disorder; Gastritis; Immune system disorders - Other (sarcoid granuloma); Musculoskeletal and connective tissue disorder - Other (polymyositis); Musculoskeletal and connective tissue disorder - Other (rhabdomyolysis); Myocarditis; Nervous system disorders - Other (demyelination myasthenic syndrome); Nervous system disorders - Other (myasthenia gravis); Peripheral sensory neuropathy; Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)

8.2.10 Return and Retention of Study Drug

At the completion of all patients' treatment, all unused drugs, partially used, or empty containers must be destroyed at the site according to the institution's

policy for drug destruction. Please maintain appropriate records of the disposal, including dates and quantities.

9.0 CORRELATIVES/SPECIAL STUDIES

The pharmacokinetic profile of dasatinib and nivolumab will be studied by measuring the serum level of dasatinib 24 hours after the start of cycle 1, and both dasatinib and nivolumab serum levels on treatment days 8, 15, and 22 prior to treatment during cycle 1. In order to address the effects of nivolumab on dasatinib's ability to induce T-cell expansion and activation, lymphocyte subpopulations, specifically T-cells, will be quantitatively measured on cycle 1 day 1, 2, 8, 15, and 22. Bone marrow aspirate samples that are required for response assessment will also be used to characterize T-cell receptor clonal expansion/diversity. Studies will be performed at Northwestern University in the core facilities. Samples will be collected and stored with PathCore. Refer to separate lab manual for additional details.

9.1 Sample Collection Guidelines

Peripheral blood will be collected to quantitatively measure T-cell subsets and serum concentrations of dasatinib and nivolumab on cycle 1, day 1, 2, 8, 15, and 22, prior to receiving treatment dose. 6 mL (approximately 1 tablespoon) of blood will be collected for each sample in heparin coated collection tubes (i.e. sodium heparin green top tubes).

Bone marrow aspirate collected prior to treatment, during response assessment and at the time of treatment failure or end of treatment will be used to characterize T-cell receptor clonal expansion/diversity by PCR and sequencing. 5 mL (approximately 1 tablespoon) of aspirate will be collected for each sample in heparin coated collection tubes (i.e. sodium heparin green top tubes).

9.2 Assay Methodology

- Peripheral blood mononuclear cells will be isolated by an adapted Ficoll density gradient separation. The cells will then be stained with fluorescence-labeled antibodies against characteristic cell markers as follows:
 - T cells: $\gamma\delta$ TCR, CD3, CD4, CD8, CD56
 - T-cell activation: CD69, CD25, HLA-DR; CD8⁺
 - T-cell subsets: CD45RA, CD28, CD197
 - CD4⁺ regulatory T cells: CD25, Foxp3
- Cells will also be assessed for PD-1 receptor occupancy by the antibody on circulating CD3⁺ T-cells by flow cytometry.
- These studies will be performed by Northwestern University Flow Cytometry and Genomics Core Facilities and analyzed in the Department of Pathology.

9.3 Specimen Banking

Unused samples will be stored for future unspecified use. Specimens will be stored indefinitely in the Northwestern University Biorepository until exhausted or a patient withdraws his or her consent for sample storage.

10.0 STATISTICAL CONSIDERATIONS

10.1 Study Design/Study Endpoints

This is a phase 1b open-label, multi-center prospective study which uses a modified 3+3 design (i.e. 3+3 followed by a 10 patient expansion cohort) to evaluate the safety and tolerability of nivolumab when given in combination with dasatinib in adults with relapsed or refractory Ph+ ALL. The primary endpoint will be dose-limiting toxicity, as defined by the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03. The secondary endpoints are the clinical response defined as complete remission rate and/or

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molecular remission after 3 cycles of nivolumab and dasatinib, the PD1 expression levels in the peripheral blood and bone marrow before and after treatment, and the T-cell levels and activation in the peripheral blood after treatment. Exploratory endpoints include the overall survival, progression free survival and duration of remission, as well as a comparison of the overall survival between patients who receive a hematopoietic stem cell transplant and those who receive no further therapy following remission, and the presence of resistance mutations at the time of disease progression.

10.2 Sample Size and Accrual

The total number of patients will depend on toxicities observed during the dose de-escalation phase, although a maximum of 12 patients is possible. The dose expansion phase will then enroll up to a total of 10 patients for an estimated total of 16-22 patients, with the justification of improving efficacy and toxicity estimates. While it is theoretically possible to expand each dose with 10 patients so that the possible maximum sample size is 32, it is expected that the dose expansion will occur only at the MTD so that the total expected sample size is 16-22 patients. Sample size is based on accrual feasibility, not on statistical power. The expected accrual rate will be 1-2 patients per month across 3-5 sites with the goal of achieving 100% accrual by 2 years. The MTD is that dose at which fewer than 4 DLTs are seen in the total number of 16 patients observed at that dose. If the true DLT rate is 13%, then there is less than a 5% chance that 4 or fewer DLTs out of 16 will be observed.

10.3 Data Analyses Plans

Toxicity profiles will be presented by rate of overall toxicity with rates of \geq grade 3 toxicities analyzed separately and combined. Adverse events will be summarized and accompanied by 95% confidence intervals using binomial distribution. Patient characteristics will be summarized using mean, median, and standard deviation for continuous variables, and tables for discrete variables. We will descriptively report observed secondary and exploratory endpoints, including rates of complete remission, duration of remission, progression free survival, overall survival, and the outcomes for patients that go on to receive hematopoietic stem cell transplant versus those who receive no further therapy after achieving remission. Rates will be estimated using exact binomial probabilities and 95% confidence intervals. Molecular remission will be estimated using an exact binomial confidence interval. Progression free survival and overall survival will be estimated using Kaplan-Meier curves. T-cell levels after treatment will be assessed using the paired t-test or the signed rank test. Levels of PD1 expression will be compared between responders versus non-responders using a Wilcoxon rank sum test. Basic pharmacokinetic parameters will be calculated and summarized using means, medians and ranges.

11.0 STUDY MANAGEMENT

11.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the

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implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

11.2 Amendments

The Principal Investigator will formally initiate all amendments to the protocol and/or informed consent. All amendments will be subject to the review and approval of the appropriate local, institutional, and governmental regulatory bodies, as well as by Janssen Scientific Affairs. Amendments will be distributed by the lead institution (Northwestern) to all affiliate sites upon approval by the Northwestern University IRB.

11.3 Registration Procedures

For potential patients, study teams are asked to inform the QAM of the date and time that the patient will need to be registered (croqualityassurance@northwestern.edu).

BEFORE a patient can be treated on study, please complete and submit the following items to confirm eligibility and receive an identification number:

- Patient's signed and dated informed consent form (upload to NOTIS and keep original hard copy in a secure location/study chart)
- Eligibility checklist (signed and dated by the treating physician – upload to NOTIS)
- Eligibility eCRF (complete in NOTIS)
- Copy of the pathology report (upload to NOTIS)

The QAM will review all source documentation required to confirm eligibility that is readily available in the patient's electronic medical record (EMR). Any information that is not available in the EMR must be de-identified and emailed to the QAM. Once the QAM confirms the patient is eligible, he or she will register the patient, assign a subject identification number, provide a cohort assignment, and send a confirmation of registration to involved personnel. Registration will then be complete and the patient may begin study treatment.

11.4 Data Submission

Once a subject is confirmed and registered to the study, eCRFs should be submitted according to the detailed data submission guidelines (provided in a separate document). Generally, all data for phase I patients during the time period patients are evaluated for Dose Limiting Toxicities (DLTs) must be submitted on a weekly basis. Generally, for all phase II patients, data are due at the end of every cycle.

This is a general template. Data Submission language can be revised as make sense for each protocol. A detailed data submission guideline must be included as a separate document for all NU IITs determined to require high or moderate level intensity monitoring. To develop your data submission guideline, contact croqualityassurance@northwestern.edu.

11.5 Data Management and Monitoring/Auditing

This study will be conducted in compliance with the Data Safety Monitoring Plan (DSMP) of the Robert H. Lurie Comprehensive Cancer Center of Northwestern University (please refer to Appendices for additional information). The level of risk attributed to this study requires High Intensity Monitoring, as outlined in the DSMP. The assigned QAM, with oversight from the Data Monitoring Committee, will monitor this study in accordance with the study phase and risk level. Please refer to the study-specific data submission instructions for timelines and requirements.

11.6 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

11.6.1 Emergency Modifications

Investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior IRB approval.

For any such emergency modification implemented, an IRB modification form must be completed within 5 business days of making the change, and the QAM must be notified within 24 hours of such change.

11.6.2 Other Protocol Deviations

All other deviations from the protocol must be reported to the assigned QAM using the appropriate form.

A protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs.
- Has no substantive effect on the risks to research participants.
- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected.
- Did not result from willful or knowing misconduct on the part of the investigator(s).

A protocol deviation may be considered an instance of Promptly Reportable Non Compliance (PRNC) if it:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

11.7 Investigator Obligations

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The PI is responsible for personally overseeing the treatment of all study patients. The PI must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected, entered onto the appropriate eCRFs, and submitted within the study-specific timeframes. Periodically, monitoring visits may be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. The study may also be subject to routine audits by the Audit Committee, as outlined in the DSMP.

11.8 Publication Policy

All potential publications and/or data for potential publications (e.g. manuscripts, abstracts, posters, clinicaltrials.gov releases) must be approved in accordance with the policies and processes set forth in the Lurie Cancer Center DSMP. The assigned QAM

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will prepare a preliminary data summary (to be approved by the DMC) no later than 3 months after the study reaches its primary completion date (the date that the final subject is examined or receives an intervention for the purposes of final data collection for the primary endpoint). If the investigator's wish to obtain DMC-approved data prior to this point (or prior to the point dictated by study design), the PI must send a written request for data to the QAM which includes justification. If the request is approved, data will be provided no later than 4 weeks after this request approval. The data will be presented to the DMC at their next available meeting, and a final, DMC-approved dataset will be released along with any DMC decisions regarding publication. The investigators are expected to use only DMC-approved data in future publications. The investigators should submit a copy of the manuscript to the biostatistician to confirm that the DMC-approved data are used appropriately. Once the biostatistician gives final approval, the manuscript may be submitted to external publishers.

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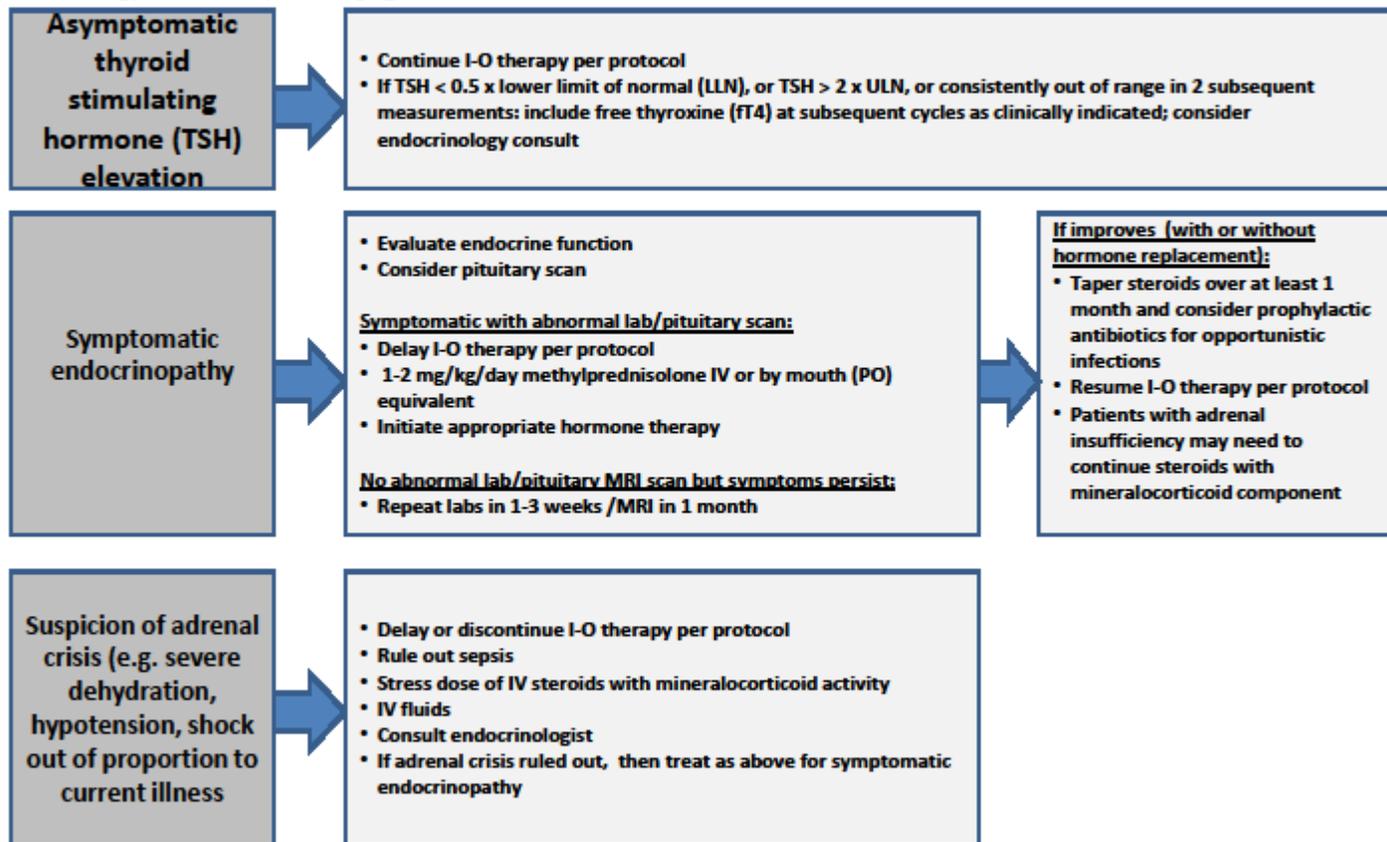
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APPENDIX 1:

Recommended management algorithms for suspected nivolumab related endocrinopathy, gastrointestinal toxicity, hepatotoxicity, neurologic toxicity, pulmonary toxicity, renal toxicity and skin toxicity.

Endocrinopathy Management Algorithm

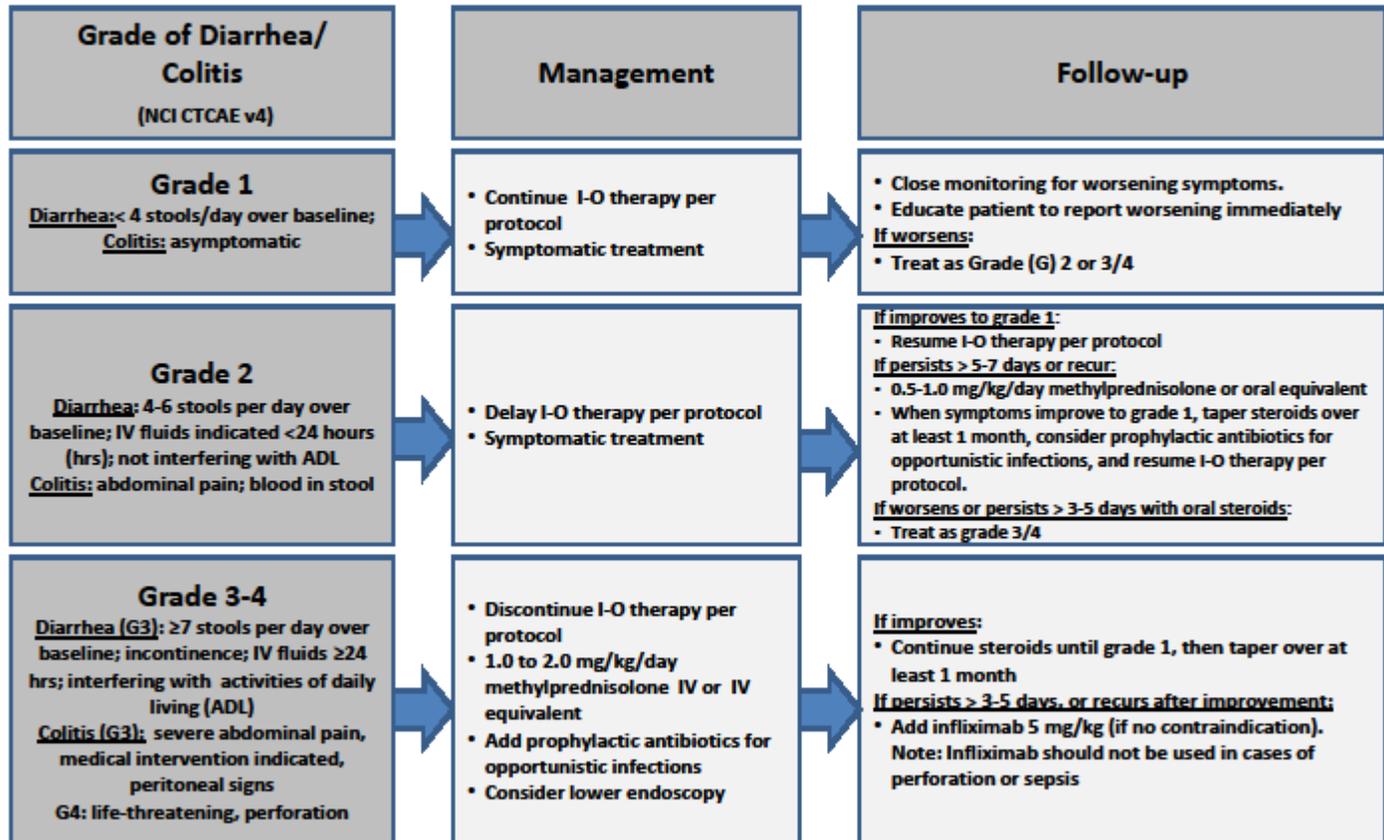
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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.

GI Adverse Event Management Algorithm

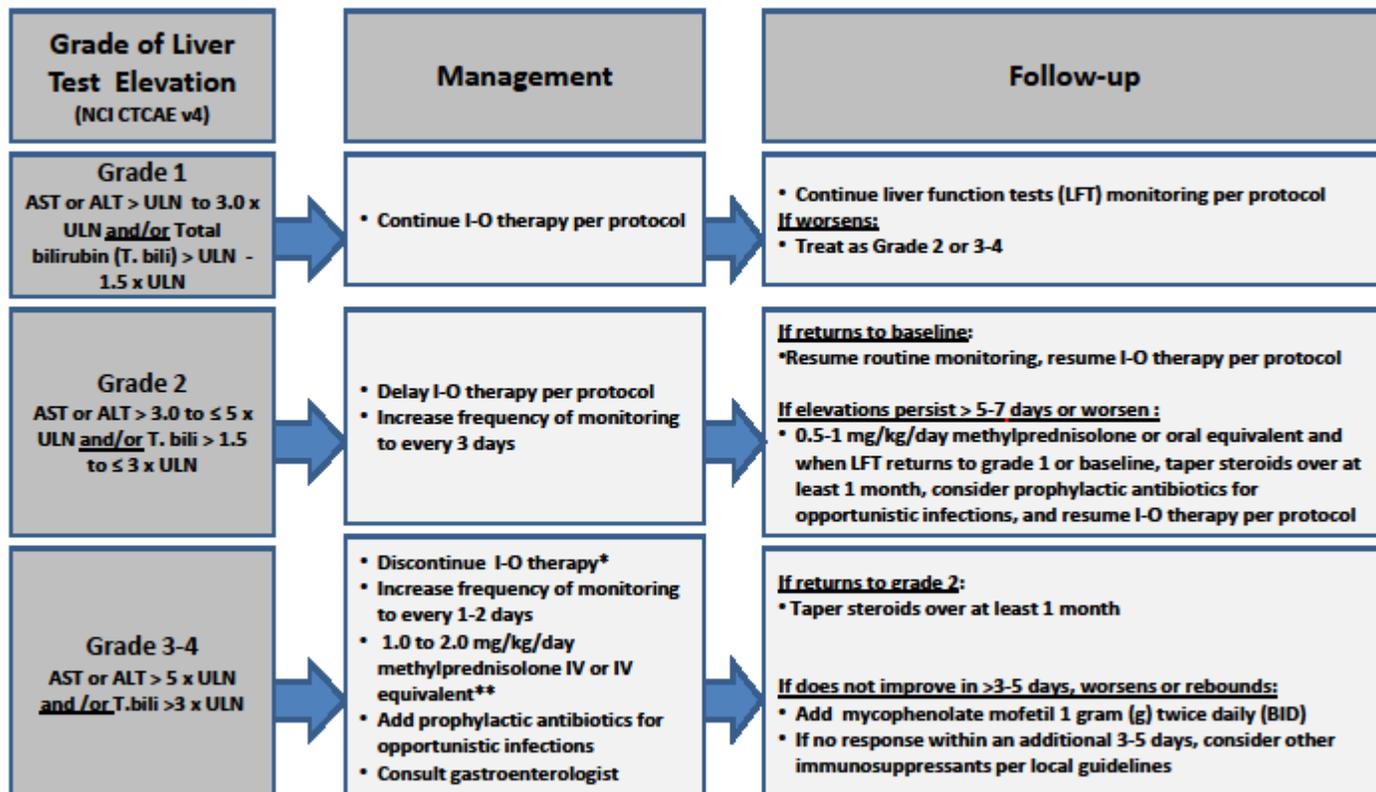
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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

Hepatic Adverse Event Management Algorithm

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



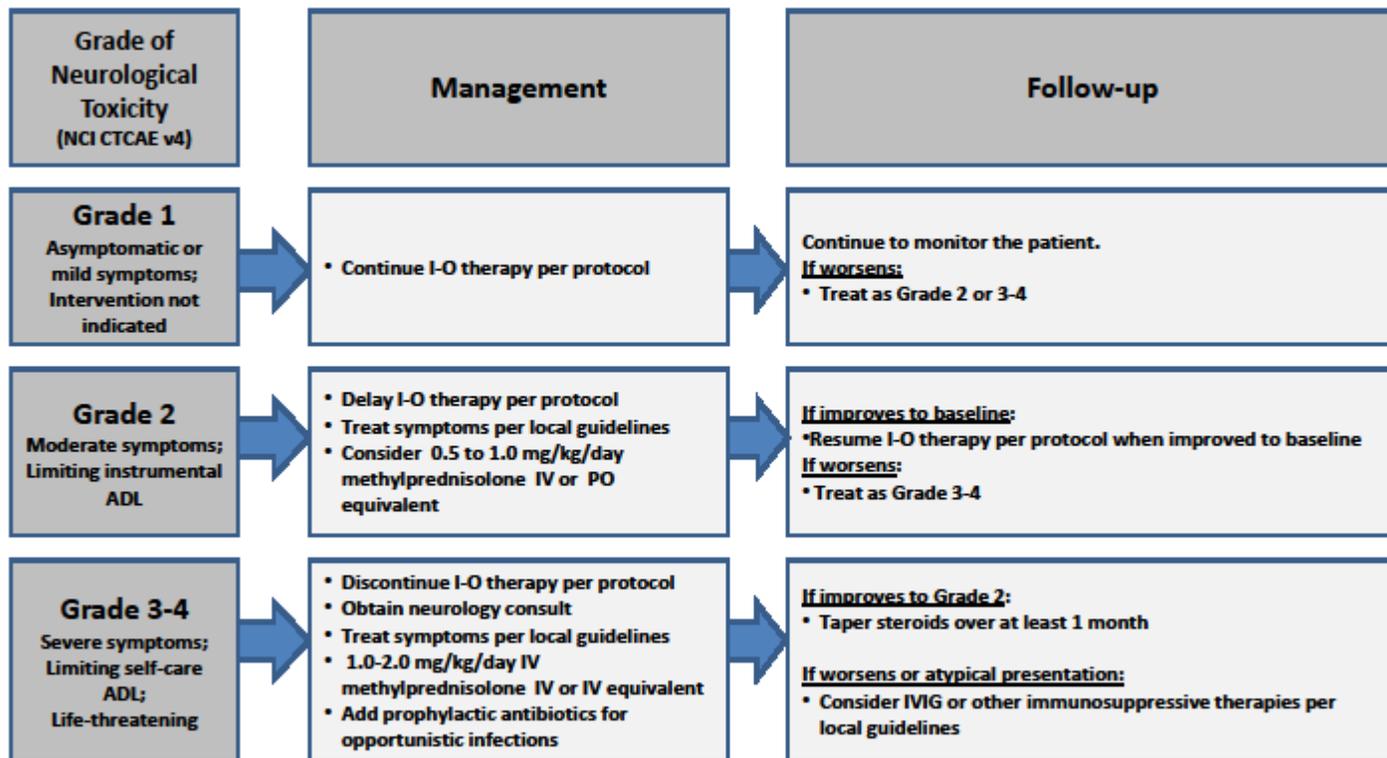
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN and T.bili ≤ 5 x ULN.

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

Neurological Adverse Event Management Algorithm

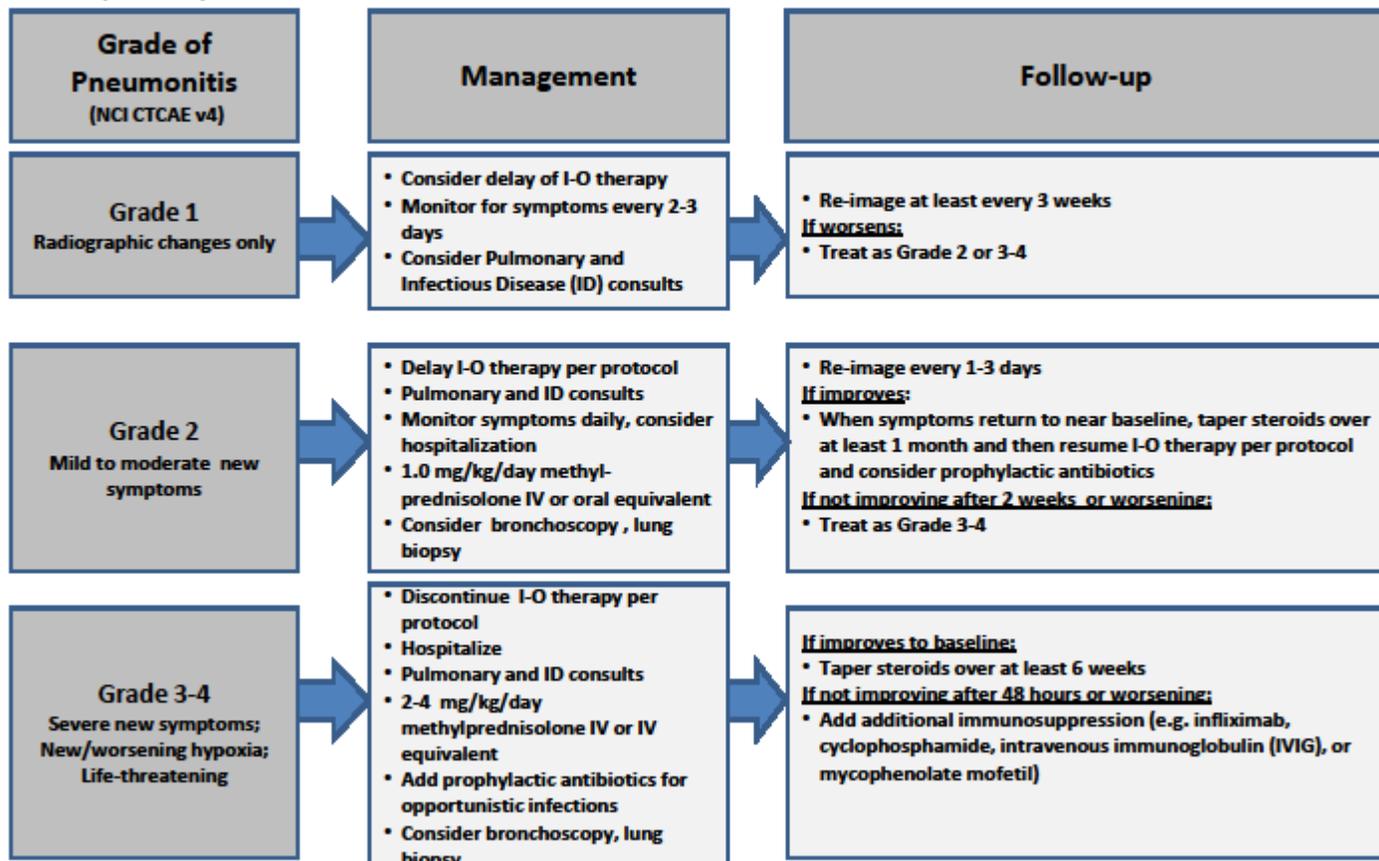
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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.

Pulmonary Adverse Event Management Algorithm

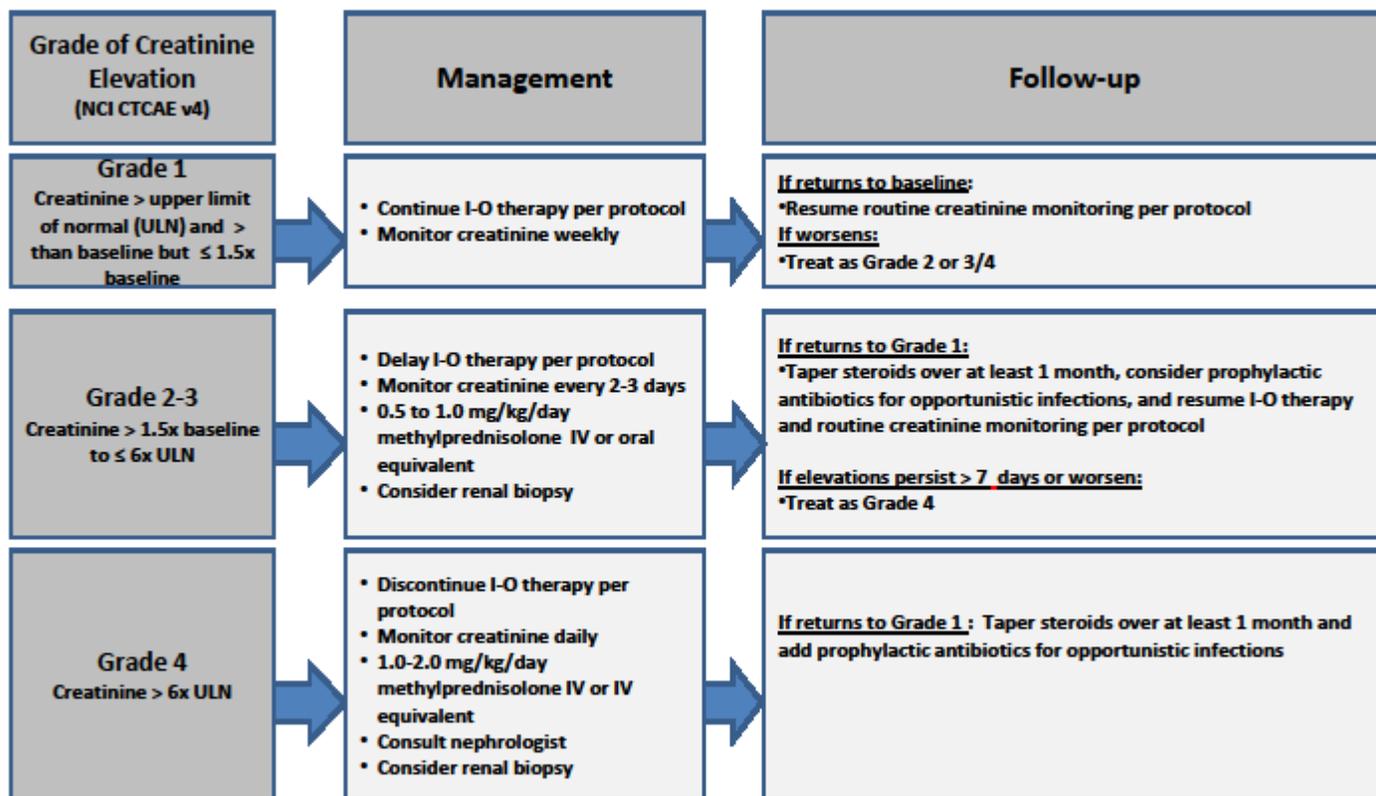
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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.

Renal Adverse Event Management Algorithm

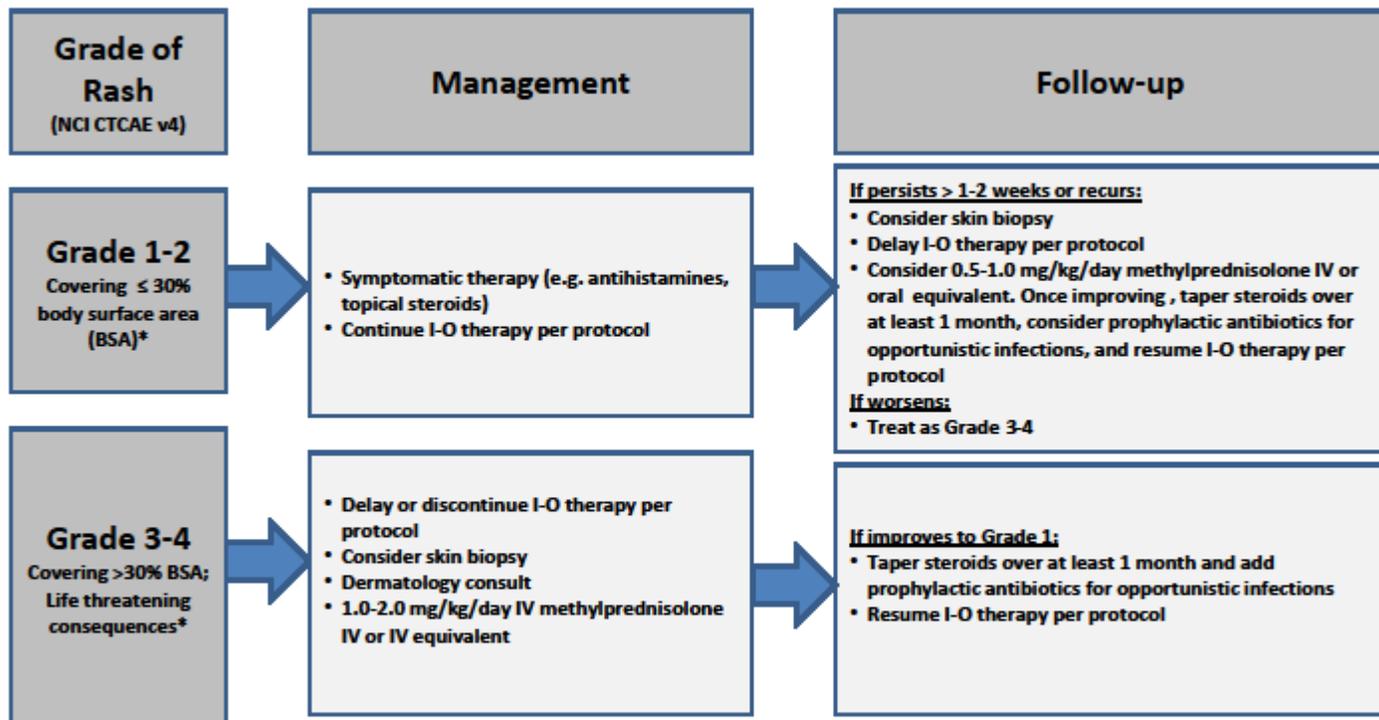
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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

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.

APPENDIX 2:

The following lists describe medications and foods which are common substrates, inducers or inhibitors of CYP3A4. This list should not be considered all inclusive. Consult individual drug labels for specific information on a compound's propensity to induce or inhibit CYP3A4.

Common CYP3A4 Substrates:

Anti-arrhythmics: quinidine

Antihistamines: astemizole, chlorpheniramine, terfenidine

Benzodiazepines: alprazolam, diazepam, dronedarone, midazolam, triazolam

Calcium Channel Blockers: amlodipine, diltiazem, felodipine, lercanidipine, nifedipine, nisoldipine, nitrendipine, verapamil

Immune Modulators: Cyclosporine, sirolimus, tacrolimus (FK506)

Macrolide Antibiotics: clarithromycin, erythromycin, telithromycin, NOT: zithromycin

HIV Antivirals: darunavir, indinavir, lopinavir, maraviroc, nelfinavir, ritonavir, saquinavir, tipranavir

HMG CoA Reductase Inhibitors: atorvastatin, cerivastatin, lovastatin, NOT: pravastatin NOT: Simvastatin

Steroid 6beta-OH: budesonide, estradiol, fluticasone, hydrocortisone, progesterone, testosterone

Others: Alfentanil, aripiprazole, aprepitant, boceprevir, buspirone, cafergot, caffeine, cilostazol, cisapride, cocaine, conivaptan, dapson, docetaxel, domperidone, codeine-Ndemethylation, darifenacin, dexamethasone, dextromethorphan, dihydroergotamine, eletriptan, eplerenone, ergotamine, everolimus, fentanyl, finasteride, gleevec, haloperidol, irinotecan, LAAM, Lidocaine, lurasidone, methadone, nateglinide, odanestron, pimozone, propranolol, quinine, quetiapine, risperidone, salmeterol, sildenafil, sorafenib, tamoxifen, taxol, tolcapten, torisel, trazodone, vardenafil, vincristine, zaleplon, ziprasidon, zolpidem

Common CYP3A4 Inducers:

HIV Antivirals: Efavirenz, nevirapine

Others: Amprenavir, Aprepitant, armodafinil, barbiturates, bosentan, carbamazepine, Echinacea, etravirine, glucocorticoids, modafinil, nafcillin, Phenobarbital, phenytoin, rifabutin, rifampin, rufinamide, St. John's wort, troglitazone

Strong CYP3A4 Inhibitors	Moderate CYP3A4 Inhibitors	Weak CYP3A4 Inhibitors
≥ 5-fold increase in AUC	≥ 2 but < 5-fold increase in AUC	≥ 1.25 but < 2-fold increase in AUC
atazanavir, boceprevir, clarithromycin, conivaptan, grapefruit juice,(a) indinavir, itraconazole, ketoconazole, mibefradil , nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycins, voriconazole	amprenavir, aprepitant, atazanavir, ciprofloxacin, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fosamprenavir, blood orange juice, pomegranate juice, grapefruit juice, ^a verapamil	Alprazolam, amiodarone, amlodipine, atorvastatin, bicalutamide, cilostazol, cimetidine, cyclosporine, fluoxetine, fluvoxamine, ginkgo ^b , goldenseal ^b , isoniazid, nilotinib, Oral contraceptives, ranitidine, ranolazine, tipranavir/ritonavir, zileuton

^a The effect of grapefruit juice varies widely among brands and is concentration-, dose-, and is preparation dependent. Studies have shown that it can be classified as a “strong CYP3A inhibitor” when a certain preparation was used (e.g., high dose, double strength) or as a “moderate CYP3A inhibitor” when another preparation was used (e.g., low dose, single strength).

^b Herbal product

APPENDIX 3: Pregnancy and Contraception Requirements

Investigators shall counsel WOCBP and male subjects who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male subjects who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of < 1% per year when used consistently and correctly.

At a minimum, subjects must agree to the use of two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed below:

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

Male condoms with spermicide

- a) Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants, and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner. Female partners of male subjects participating in the study may use hormone based contraceptives as one of the acceptable methods of contraception since they will not be receiving study drug.
- b) Nonhormonal IUDs, such as ParaGard®
- c) Tubal ligation
- d) Vasectomy.
- e) Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Subjects who choose complete abstinence are not required to use a second method of contraception, but female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

LESS EFFECTIVE METHODS OF CONTRACEPTION

- a) Diaphragm with spermicide
- b) Cervical cap with spermicide
- c) Vaginal sponge
- d) Male Condom without spermicide*
- e) Progestin only pills by WOCBP subject or male subject's WOCBP partner
- f) Female Condom*

*A male and female condom must not be used together

Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However they must still undergo pregnancy testing as described in this section.

APPENDIX 4

Amendment 1 (Version 2.0) – April 6 June 2, 2016			
Section(s) Affected	1.0 Version	2.0 Version	Rationale
8.2.9 (Nivolumab side effects)	Only listed most common side effects of nivolumab (>20%)	Includes less frequent side effects included in updated investigator's brochure, as follows: Less Likely (≤20%): Hyperthyroidism; Injection site reaction; Lymphocyte count decreased; Platelet count decreased; Skin hypopigmentation Rare but Serious (<3%): Cardiac disorders - Other (cardiomyopathy); Cytokine release syndrome; Encephalopathy; Eye disorders - Other (Graves ophthalmopathy); Facial nerve disorder; Gastritis; Immune system disorders - Other (sarcoid granuloma); Musculoskeletal and connective tissue disorder - Other (polymyositis); Musculoskeletal and connective tissue disorder - Other (rhabdomyolysis); Myocarditis; Nervous system disorders - Other (demyelination myasthenic syndrome); Nervous system disorders - Other (myasthenia gravis); Peripheral sensory neuropathy; Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)	CTEP Action Letter issued on 3/17/16 with updated safety information
Heading	Other study number was not available	BMS Study number listed as: CA209-613	
Amendment 2 (Version 3.0) – September 2, 2016 <i>SRC Approved:</i>			
Section(s) Affected	1.0 Version	2.0 Version	Rationale
<u>2.0 (Objectives & Endpoints)</u>	<u>Sections numbered inaccurately</u>	<u>Re-numbers sections appropriately</u>	<u>Typographical error</u>
<u>2.2.2 (Secondary Endpoints); 6.2 (Secondary & Exploratory Endpoints)</u>	<u>n/a</u>	<u>Adds that adverse events will be recorded from consent until 30 days after treatment (100 days for SAE's)</u>	<u>Specification</u>
<u>4.2.1 (Dasatinib)</u>	<u>"Treatment with dasatinib will begin 7 days prior to starting nivolumab. This 7-day period will be referred to as 'Cycle 0'."</u>	<u>Removes language in bold. There is no "Cycle 0" – dasatinib treatment will begin on Cycle 1 Day 8</u>	<u>Discrepancy</u>

NU Study Number: NU 15H13
BMS Study Number: CA209-613

<p><u>5.0 (Study Procedures)</u></p>	<ul style="list-style-type: none"> • <u>Nivolumab infusion was marked at C1D1 and C1D15</u> • <u>#3: The end-of-study visit was to take place within 28 days after the last dose of study drug</u> • <u>#11: "AE's will be monitored throughout the study"</u> 	<ul style="list-style-type: none"> • <u>Moves X's to C1D8 and C1D22</u> • <u>#3: Changes the end-of-study visit to 30 days (±7 days) after the last dose of study drug</u> • <u>#11: Removes "throughout the study" and adds: "from the time of consent until 30 days after completing study treatment (100 days for SAE's)"</u> 	<ul style="list-style-type: none"> • <u>To fix discrepancies in other sections of the protocol</u> • <u>Discrepancy</u> • <u>Adds more specific detail for clarity</u>
<p><u>7.2.3 (Serious Adverse Events)</u></p>	<p><u>SAE's were to be reported for 30 days after the last administration of study drug</u></p>	<p><u>Changes SAE collection to 100 days after last administration of study drug</u></p>	<p><u>To align with BMS reporting requirements</u></p>
<p><u>7.3.3.4 (Reporting to BMS)</u></p>	<p><u>n/a</u></p>	<p><u>Adds language to state that SAE reports will include death and will be reported regardless of attribution</u> <u>Also adds the BMS study number and a reminder that study coordinator is responsible for reporting</u></p>	<p><u>Clarifications</u></p>