BLOOD AND MARROW TRANSPLANTATION PROGRAM
HACKENSACK UNIVERSITY MEDICAL CENTER

Title of Protocol

Phase Ib-IIA study of combined checkpoint inhibition after autologous hematopoietic stem cell transplantation in patients at high risk for post-transplant recurrence

(CPIT Trial 001/BMS Protocol CA209-694)
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SUMMARY

Phase Ib Primary Objectives	The primary objectives of this study are: • To assess the safety of combined check point inhibition with nivolumab and ipilimumab after autologous hematopoietic stem cell transplantation in patients at high risk for post-transplant recurrence including patients with persistent and recurrent high risk diffuse large B cell lymphoma, high risk and recurrent T cell lymphoma and high risk and recurrent multiple myeloma. Primary endpoints: • Safety endpoint: The composite endpoint consisting of the occurrence of at least one treatment-related limiting toxicity (after combined checkpoint inhibitor treatment is initiated) defined as a ≥ grade 4 non-hematologic toxicity as specified by the CTCAE. Exceptions listed in section 5.9 apply to this endpoint as well. If 3 of 7 patients in a single cohort experience a treatment-related limiting toxicity, that single cohort will be terminated. • Efficacy endpoint: progression-free survival at 18 months after ASCT in patients at high risk for post-transplant recurrence including patients with persistent and recurrent high risk diffuse large B cell lymphoma, high risk and recurrent T cell lymphoma and high risk and recurrent multiple myeloma.
Phase Ib Secondary Objectives	The secondary objectives are: • To assess complete response rate at 3, 6 and 12 months after ASCT in patients at high risk for post-transplant recurrence including patients with persistent and recurrent high risk diffuse large B cell lymphoma, high risk and recurrent T cell lymphoma and high risk and recurrent multiple myeloma. • To assess progression-free survival at 12 months after ASCT in patients at high risk for post-transplant recurrence including patients with persistent and recurrent high risk diffuse large B cell lymphoma, high risk and recurrent T cell lymphoma and high risk and recurrent multiple myeloma. • To assess blood immune reconstitution, phenotype and TCR repertoire at screening (at time of informed consent), at apheresis (stem cell collection), and then serially the day 1 of week 1 of combined checkpoint inhibitors and then weeks 4, 7, 12, 18 and 26, End of Treatment, and at 9, 12, 15, and 18 months post-transplant and at time of relapse, as it occurs. • Determine the toxicities resulting from administration of the treatments. • To assess tumor site immune phenotype, T cell repertoire and PD L1/2 expression when tissue available for biopsy prior to autologous transplant conditioning and then at time of progression (within 18 months) after autologous transplant conditioning.
Phase Ib Tertiary Objectives	• To identify specific intestinal microbial strains associated with improved outcome in autologous stem cell transplantation patients treated with combined checkpoint inhibitors. The overall microbial composition in stool samples of patients will be analyzed at screening, preconditioning (to be

	collected within 48 hours prior to transplant admission), at engraftment (within 72 hours of ANC ≥ 500), and then serially, on day 1 of week 1 (to be collected within 48 hours prior to clinic visit) and then weeks 4, 7, 12, 18, and 26, End of Treatment and 9, 12, 15 and 18 months post-transplant, and at time of relapse, as it occurs.
Phase IIA Primary Objective	The primary objectives of this study are: • To assess progression-free survival at 18 months after ASCT in patients in cohorts that were deemed safe in Phase Ib (no more than 3 treatment-related toxicity) and at least 4 of 7 patients were progression free at 18 months in the Phase Ib.
Phase IIA Secondary Objectives	The secondary objectives of this study are: • To assess complete response rate at 3, 6 and 12 months after ASCT in patients at high risk for post-transplant recurrence including patients in the successor expansion cohorts following the Phase Ib trial. • To assess progression-free survival at 12 months after ASCT in patients at high risk for post-transplant recurrence including patients with in the successor expansion cohorts following the Phase Ib trial. • Determine the toxicities resulting from administration of the treatments in patients enrolled in the successor expansion cohorts following the Phase Ib trial. • To assess blood immune reconstitution, phenotype and TCR repertoire at screening (at time of informed consent), at apheresis (stem cell collection), and then serially the day 1 of week 1 of combined checkpoint inhibitors and then weeks 4, 7, 12, 18 and 26, End of Treatment, and at 9, 12, 15, and 18 months post-transplant and at time of relapse, as it occurs.
Phase IIA Tertiary Objectives	• To identify specific intestinal microbial strains associated with improved outcome in autologous stem cell transplantation patients treated with combined checkpoint inhibitors. The overall microbial composition in stool samples of patients will be analyzed at screening, preconditioning (to be collected within 48 hours prior to transplant admission), at engraftment (within 72 hours of ANC ≥ 500), and then serially, on day 1 of week 1 (to be collected within 48 hours prior to clinic visit) and then weeks 4, 7, 12, 18, and 26, End of Treatment and 9, 12, 15 and 18 months post-transplant, and at time of relapse, as it occurs.
Patient Eligibility	1. Voluntary signed and dated IRB/IEC approved written informed consent form in accordance with regulatory and local guidelines. 2. Be 18 years or older and 80 years or younger on the day of signing consent 3. Have a confirmed diagnosis of: o (GROUP A) De novo diffuse large B cell lymphoma that fails to achieve a PET negative complete response to primary rituximab and anthracycline based multi-agent chemotherapy and at least maintains stable disease after salvage chemotherapy or present double/triple hit features defined by overexpression by standard immunohistochemistry of c-MYC plus BCL2 and/or BCL6 or presence of chromosomal

	translocations as detected by break-apart FISH involving IGH/MYC plus IGH/BCL2 and/or IGH/BCL6 and who only received standard chemoimmunotherapy with rituximab, cyclophosphamide, vincristine and prednisone (R-CHOP) for induction and present at least stable disease after consolidation or salvage chemotherapy. Stable disease (SD) for lymphoma is defined in Appendix B: Lugano Classification for Response Assessment of Non-Hodgkin Lymphoma. o (GROUP B) Recurrent high-risk diffuse large B cell lymphoma defined as relapsing within one year of completion of rituximab and anthracycline based multi-agent chemotherapy or a sAAIPI (second-line age-adjusted International Prognostic Index) intermediate or high at relapse or acquisition of double/triple hit features upon relapse (as defined in group A) and at least stable disease after salvage chemotherapy. Patients with an initial diagnosis of low-grade/indolent non-Hodgkin lymphoma (i.e. follicular, marginal zone) who present relapse with histologic transformation to diffuse large B cell lymphoma (confirmed by biopsy) and meet the definition for high-risk as presented above, are also eligible. o (GROUP C) De novo high-risk T cell lymphoma with at least stable disease after primary therapy. High risk T cell lymphoma is defined as Stage III or IV disease at presentation and/or failure to achieve CR after frontline chemotherapy. Patients with ALK-positive ALCL will be excluded from the trial. Patients with ALK-negative ALCL in complete response will be excluded from the trial. o (GROUP D) Recurrent T cell lymphoma with at least stable disease after salvage therapy. Patients with ALK-positive ALCL will be excluded from the trial. o (GROUP E) Transplant-naïve high risk multiple myeloma with at least stable disease after most recent line of therapy. High risk myeloma is defined as those carrying 1q amplifications, 1p deletions, 13q deletions by conventional cytogenetics, p53 deletions, high-risk GEP 70 scores, t(4;14), t(14;16) and t(14;20), hypodiploidy. This cohort has been discontinued due to updated risks provided by the FDA. These patients will be followed for safety and correlative studies only. o (GROUP F) Recurrent myeloma within 3 years after a single or tandem autologous transplant and at least stable disease after salvage therapy. Stable disease for multiple myeloma is defined in Appendix C: International Myeloma Working Group (IMWG). This cohort has been discontinued due to updated risks provided by the FDA. These patients will be followed for safety and correlative studies only. 4. Be deemed eligible for an autologous stem cell transplantation according to the institutional guidelines of the Blood and Marrow Transplantation Program at John Theurer Cancer Center at Hackensack University Medical Center 5. Have an ECOG performance status of 2 or lower

	6. Women of childbearing potential (WOCBP) must use appropriate method(s) of contraception. WOCBP should use an adequate method to avoid pregnancy for 23 weeks (30 days plus the time required for nivolumab to undergo five half-lives) after the last dose of investigational drug. 7. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of nivolumab. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Female subjects of childbearing potential should agree to ongoing pregnancy testing, to be performed prior to each dosing of ipilimumab and nivolumab. See Note below for definition of WOCBP. 8. Women must not be breastfeeding. 9. Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving nivolumab, and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product, even if they have had a vasectomy. Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile as well as azoospermic men do not require contraception). See Note below for definition of WOCBP. 10. Females of childbearing potential must be willing to use two methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 2 years. See Note below for definition of WOCBP. 11. Allowable transplant preparative regimens are the following: o For non-Hodgkin lymphoma groups (A, B,C,D) BEAM: carmustine 300 mg/m2 day -6, etoposide 200 mg/m2 and cytarabine 200 mg/m2 days -5 to -2, melphalan 140 mg/m2 day -1 o For Myeloma groups (E and F) Melphalan 200 mg/m2 day -1 NOTE: Women of childbearing potential is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes. In addition, women under the age of 55 must have a documented serum follicle stimulating hormone (FSH) level less than 40 mIU/mL. Women of childbearing potential (WOCBP) receiving nivolumab will be instructed to adhere to contraception for a period of 23 weeks after the last dose of investigational product. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product. These durations have been calculated using the upper limit of the half-life for nivolumab (25 days) and are based on the protocol requirement that

	WOCBP use contraception for 5 half-lives plus 30 days and men who are sexually active with WOCBP use contraception for 5 half-lives plus 90 days. Exclusion Criteria The subject must be excluded from participating in the trial if the subject meets ANY of the following exclusion criteria: 1. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline), have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability. Note: Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if > 10 mg/day prednisone equivalents. 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 contact allergen) is permitted. 2. Is unable or unwilling to sign informed consent. 3. Has an active, known, or suspected autoimmune disease. Subjects are permitted to enroll if they have 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 4. Patients should be excluded if they have a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease. Note: Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if > 10 mg/day prednisone equivalents. 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 contact allergen) is permitted. 5. As there is potential for hepatic toxicity with nivolumab or nivolumab/ipilimumab combinations, drugs with a predisposition to hepatoxicity should be used with caution in patients treated with nivolumab-containing regimen.

	6. Has received an allogeneic stem cell transplant. 7. Has a history of hypersensitivity to nivolumab, ipilimumab, or any of its excipients, or severe hypersensitivity reaction to any previous monoclonal antibody. 8. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to Day 1 of checkpoint inhibitor treatment administration or who has not recovered (i.e., t administration mAb) within 4 weeks prior to dose of trial treatment. Rituximab within that period is allowed. 9. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Note: Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if > 10 mg/day prednisone equivalents. 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 contact allergen) is permitted. 10. Has known history of, or any evidence of active, non-infectious pneumonitis. 11. Has an active infection requiring intravenous systemic therapy. 12. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject's participation for the full duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator. 13. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial. 14. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 23 weeks for females and 31 weeks for males after the last dose of trial treatment. 15. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2 agent, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways. 16. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies) or known acquired immunodeficiency syndrome (AIDS). 17. Has positive test for Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected) indicating acute or chronic infection, as tested for transplant. 18. Has received a live vaccine within 30 days of planned start of study therapy. NOTE: Patients who received steroids for engraftment syndrome may initiate treatment with ipilimumab and nivolumab once steroids have been tapered off and diarrhea and/or rash are grade I or better, without the need

	for a steroid washout period. Initial dosing may be delayed up to day 28 post-transplantation to allow for completion of steroid taper.
Combined Check Point Inhibition	Start 14 to 21 days after stem cell infusion if ANC≥800 (off growth factors for at least 3 days) and Platelets≥20,000 without transfusion Delay initiation until ANC≥800 (off growth factors for at least 3 days) and Platelets≥20,000 without transfusion up to 28 days after stem cell infusion. **The first day of combined checkpoint inhibitor therapy will be considered Week 1, day 1 for the purposes of this protocol.** Post ASCT therapy may be delayed up to 28 days after stem cell infusion if deemed appropriate by the investigator.
Treatment Schema	For all Groups A, B, C, D, E, F (7 patients per group): • Ipilimumab 1 mg/kg; 6 doses Weeks 1, 4, 7, 10, 16, 22 • Nivolumab 3 mg/kg; 12 doses Weeks 1, 4, 7, 10, 12, 14, 16, 18, 20, 22, 24, 26
Statistical Consideration	This is an open label, single-arm per cohort, phase Ib-IIA study. Our goal is to determine the safety and clinical effect of combined checkpoint inhibition administered after autologous hematopoietic stem cell transplantation in each of six clinical cohorts of high risk and recurrent disease. In addition to assessing the incidence and severity of adverse events and rates of complete response and progression free survival, we intend to monitor immune reconstitution, phenotype and TCR repertoire throughout treatment and at the time of disease progression. We will also analyze the gut microbiome prior to conditioning, throughout treatment, post-transplant and at time of relapse. We intend to expand cohorts that demonstrate safety and PFS >50% at 18 months into a phase IIA successor trial. Patients will accrue to study by disease groups and followed separately by group for incidence and severity of toxicity, ability to receive intended schedule of combined checkpoint inhibitors and for complete response and progression free survival (PFS) rates. Complete response and progression free survival rates will be compared to published standards for each disease group. Expected PFS at 18 months for all post-transplant groups without checkpoint inhibitors is less than 50%. Each group with PFS at 18 months in 4 or more patients (57%) will be considered for eligibility in a successor phase IIB expansion trial.

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1.0 OBJECTIVES

This is an open label, single-arm per cohort, phase Ib-IIA study.

Our goal is to determine the safety and clinical effect of combined checkpoint inhibition administered after autologous hematopoietic stem cell transplantation in each of six clinical cohorts of high risk and recurrent disease. In addition to assessing the incidence and severity of adverse events and rates of complete response and progression free survival, we intend to monitor immune reconstitution, phenotype and TCR repertoire throughout treatment and at the time of disease progression. We will also analyze the gut microbiome prior to conditioning, throughout treatment, post-transplant and at time of relapse. We intend to expand cohorts in the lymphoma groups that demonstrate safety and PFS >50% at 18 months into a phase IIA successor trial.

Phase Ib

The primary objectives of this study are:

- To assess the safety of combined check point inhibition with nivolumab and ipilimumab after autologous hematopoietic stem cell transplantation in patients at high risk for post-transplant recurrence including patients with persistent and recurrent high risk diffuse large B cell lymphoma, high risk and recurrent T cell lymphoma and high risk and recurrent multiple myeloma.

Primary endpoints:

- Safety endpoint: The composite endpoint consisting of the occurrence of at least one treatment-related limiting toxicity (after combined checkpoint inhibitor treatment is initiated) defined as a ≥ grade 4 non-hematologic toxicity as specified by the CTCAE. Exceptions listed in section 5.9 apply to this endpoint as well. If 3 of 7 patients in a single cohort experience a treatment-related limiting toxicity, that single cohort will be terminated.
- Efficacy endpoint: progression-free survival at 18 months after ASCT in patients at high risk for post-transplant recurrence including patients with persistent and recurrent high risk diffuse large B cell lymphoma, high risk and recurrent T cell lymphoma and high risk and recurrent multiple myeloma.

The secondary objectives are:

- To assess complete response rate at 3, 6 and 12 months after ASCT in patients at high risk for post-transplant recurrence including patients with persistent and recurrent high risk diffuse large B cell lymphoma, high risk and recurrent T cell lymphoma and high risk and recurrent multiple myeloma.
- To assess progression-free survival at 12 months after ASCT in patients at high risk for post-transplant recurrence including patients with persistent and recurrent high risk diffuse large B cell lymphoma, high risk and recurrent T cell lymphoma and high risk and recurrent multiple myeloma.
- To assess blood immune reconstitution, phenotype and TCR repertoire at screening (at time of informed consent), at apheresis (stem cell collection), and then serially the day 1 of week 1 of combined checkpoint inhibitors and then weeks 4, 7, 12, 18 and 26, End of Treatment, and at 9, 12, 15, and 18 months post-transplant and at time of relapse, as it occurs. Immune phenotype and TCR will be evaluated as follows:

  T cell repertoire analysis

TCR Immunoseq for Vbeta CDR3 highest frequency specificities.

Real-Time PCR analysis:
T-bet(Th1); STAT3, RORgamma t (TH17); STAT6 (Th2); FoxP3 (Treg), granzyme A (GZMA) and perforin (PRF1)

Flow Cytometric Phenotype Analysis for:

T Cells:
CD3; CD4; CD8; CD4+CD25+PD1+; CTLA-4
Follicular Helper T: CD3+,CD4+,CXCR5+,PD1+
CD4 and CD8 T naïve (RO-; CCR7+)
Central Memory: (T^{CM};RO+,CCR7+)
Effector Memory (T^{EM}, RO+,CCR7-)
Terminally differentiated effector memory (T^{EMRA}; RO-, CCR7-)
T regulatory cells (Treg): $CD4^{+}$,$CD25^{hi}$, $CD127^{low}$, $CD39^{+}$, $CD152^{hi}$, RO^{-} (resting); $CD4^{+}$,$CD25^{hi}$, $CD127^{low}$, $CD39^{+}$, $CD152^{hi}$, RO^{+} (activated)

Dendritic Cells:
Lin-, CD11c+, CD1a+, CD80 $(B7\text{-}1)^{low}$, CD86 $(B7\text{-}2)^{low}$, MHC Class II^{low} (DC resting); CD11c+, CD1a+, CD123-, $CD80^{hi}$, $CD86^{hi}$, $HLADR^{hi}$ (DC1 activated); $HLADR^{hi}$, CD11c-, CD123+, PDL-1+ (DC2)

Macrophages:
HLADR+, CD14+, CD64+, CD25+, CCR7+ (M1); HLADR+, CD14+, CD64-, CD206+, CD25-, CCR7-, CD209+, PDL-1+ (M2)

Myeloid derived suppressor cells:
HLADR-/low, CD11b+, CD14+,CD33+hi,CD34+, CD66b-, PDL-1+ (M-MDSC); HLADR-, CD11b+, CD14-,CD33+low,CD34+, CD66b+, PDL-1+ (G-MDSC)

B Cells:
CD19+, $B7\text{-}1^{low}$, $B7\text{-}2^{low}$, MHC Class II^{low} (resting); CD19+, $B7\text{-}1^{hi}$, $B7\text{-}2^{hi}$, MHC Class II^{hi} (activated)

NK cells:
CD16+, CD3-, CD56+

NKT Cells:
CD16+, CD3+, CD56+

Plasma Cytokine levels: Multiplex 25 Cytokine - Luminex
GM-CSF, IL-1b, IL-1RA, IL-2, IL-2R, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-15, IL-17, TNF alpha; MCP-1, MIP1a, MIP1b, MIG, RANTES, IFN-alpha, IFN-gamma, IP-10, Eotaxin

- To determine the toxicities resulting from administration of the treatments.
- To assess tumor site immune phenotype, T cell repertoire and PD L1/2 expression when tissue available for biopsy prior to autologous transplant conditioning and

then at time of progression (within 18 months) after autologous transplant conditioning.

The tertiary objectives are:

- To identify specific intestinal microbial strains associated with improved outcome in autologous stem cell transplantation patients treated with combined checkpoint inhibitors. The overall microbial composition in stool samples of patients will be analyzed at screening, preconditioning (to be collected within 48 hours prior to transplant admission), at engraftment (within 72 hours of ANC $\geq$ 500), and then serially, on day 1 of week 1 (to be collected within 48 hours prior to clinic visit) and then weeks 4, 7, 12, 18, and 26, End of Treatment and 9, 12, 15 and 18 months post-transplant, and at time of relapse, as it occurs. A 16S ribosomal RNA (rRNA) miSeq Illumina platform will be used for overall microbial composition and quantitative real-time PCR analysis will validate the specific microbial strains identified by miSeq.

Phase IIA

The primary objectives of this study are:

- To assess progression-free survival at 18 months after ASCT in patients in cohorts that were deemed safe in Phase Ib (no more than 3 treatment-related toxicity) and at least 4 of 7 patients progression free at 18 months in the Phase Ib.

The secondary objectives of this study are:

- To assess complete response rate at 3, 6 and 12 months after ASCT in patients at high risk for post-transplant recurrence including patients in the successor expansion cohorts following the Phase Ib trial.
- To assess progression-free survival at 12 months after ASCT in patients at high risk for post-transplant recurrence including patients with in the successor expansion cohorts following the Phase Ib trial.
- Determine the toxicities resulting from administration of the treatments in patients enrolled in the successor expansion cohorts following the Phase Ib trial.
- To assess blood immune reconstitution, phenotype and TCR repertoire at screening (at time of informed consent), at apheresis (stem cell collection), and then serially the day 1 of week 1 of combined checkpoint inhibitors and then weeks 4, 7, 12, 18 and 26, End of Treatment, and at 9, 12, 15, and 18 months post-transplant and at time of relapse, as it occurs.

The tertiary objectives are:

- To identify specific intestinal microbial strains associated with improved outcome in autologous stem cell transplantation patients treated with combined checkpoint inhibitors. The overall microbial composition in stool samples of patients will be analyzed at screening, preconditioning (to be collected within 48 hours prior to transplant admission), at engraftment (within 72 hours of ANC $\geq$ 500), and then serially, on day 1 of week 1 (to be collected within 48 hours prior to clinic visit) and then weeks 4, 7, 12, 18, and 26, End of Treatment, and 9, 12, 15 and 18 months post-transplant, and at time of relapse, as it occurs.

2.0 BACKGROUND

2.1 Study Rationale

Autologous hematopoietic stem cell transplantation has significantly improved progression free survival and overall survival in patients with high risk and recurrent non-Hodgkin's lymphoma and multiple myeloma. Long-term disease free survival without significant persistent or late morbidity can be experienced by most patients following autologous hematopoietic stem cell transplantation. A subset of these patients, however, continues to experience low (< 50%) progression free survival at 18 months following autologous hematopoietic stem cell transplantation and remain in need of new approaches[1-3]. Included are patients with:

- De novo diffuse large B cell lymphoma that fails to achieve a PET negative complete response to primary rituximab and anthracycline based multi-agent chemotherapy and at least maintains stable disease after salvage chemotherapy or present double/triple hit features defined by overexpression by standard immunohistochemistry of c-MYC plus BCL2 and/or BCL6 or presence of chromosomal translocations as detected by break-apart FISH involving IGH/MYC plus IGH/BCL2 and/or IGH/BCL6 and who only received standard chemoimmunotherapy with rituximab, cyclophosphamide, vincristine and prednisone (R-CHOP) for induction and present at least stable disease after consolidation or salvage chemotherapy.

- Recurrent high-risk diffuse large B cell lymphoma defined as relapsing within one year of completion of rituximab and anthracycline based multi-agent chemotherapy or a sAAIPI (second-line age-adjusted International Prognostic Index) intermediate or high at relapse or acquisition of double/triple hit features upon relapse (as defined in group A) and at least stable disease after salvage chemotherapy. Patients with an initial diagnosis of low-grade/indolent non-Hodgkin lymphoma (i.e. follicular, marginal zone) who present relapse with histologic transformation to diffuse large B cell lymphoma (confirmed by biopsy) and meet the definition for high-risk as presented above, are also eligible.

- De novo high-risk T cell lymphoma with at least stable disease after primary therapy.

- Recurrent T cell lymphoma with at least stable disease after salvage therapy.

- Transplant-naïve high risk multiple myeloma with at least stable disease after most recent line of therapy. This cohort has been discontinued due to updated risks provided by the FDA. These patients will be followed for safety and correlative studies only.

- Recurrent myeloma within 3 years after a single or tandem autologous transplant and at least stable disease after salvage therapy. This cohort has been discontinued due to updated risks provided by the FDA. These patients will be followed for safety and correlative studies only.

Salvage therapy including allogeneic transplantation after progression following autologous hematopoietic stem cell transplantation for each of these disease settings results in limited (usually <25%) long term disease free survival and is often associated with significant short and long term morbidity among survivors[4,5]. Thus, it is appropriate to evaluate novel approaches to reduce progression after autologous hematopoietic stem cell transplantation among patients at an increased risk.

Emerging data suggest that a new class of immune based therapy, checkpoint inhibition, is capable of altering the natural history of disease recurrence following autologous hematopoietic stem cell transplantation among these patients at high risk of recurrence[6,7]. Monoclonal antibodies

directed against check points CTLA-4 and PD-1 have, as single agents and when combined, demonstrated significant clinical activity in a broad array of cancer types including melanoma, non-small cell lung cancer, renal cell cancer, head and neck cancer, Hodgkin's disease, non-Hodgkin's lymphoma and multiple myeloma[6-11]. In nearly all clinical settings, combined checkpoint inhibition with anti-CTLA-4 and anti-PD-1 has resulted in greater clinical efficacy but at the expense of increased incidence of immune related adverse events[12].

Anti-CTLA-4 therapy results in enhanced tumor specific neo-antigen presentation, clonal expansion and tumor infiltration of tumor specific T effector cells, down regulation of tumor specific T regulatory cells and enhanced NK cell function[11]. Anti-PD-1 therapy maintains T cell effector function despite the expression of its ligands, programmed cell death ligand (PD-L)-1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273) on malignant cells. When combined, the two checkpoint inhibitors lead to a greater number of persistent activated effectors at disease sites explaining the enhanced clinical efficacy[8].

The immediate post-autologous transplant period before recurrence provides an ideal window to introduce combined checkpoint inhibitors because disease burden is at a minimum and residual disease may be more immune responsive to checkpoint inhibition due to conditioning-induced apoptosis and inflammation. Moreover, anti-tumor immune reconstitution has been shown to be enhanced by combined checkpoint inhibition, due to the skewing of reconstituting NK cells and effector T cells towards an anti-tumor immune phenotype and away from tolerance[13].

Recent experience in non-small cell lung cancer demonstrated that a dosing schedule of anti-CTLA-4 at 1mg/kg and anti-PD1 therapy at 3mg/kg can be combined with seemingly acceptable toxicity and similar efficacy to higher and more frequent anti CTLA-4 dosing schedules[14].

Our goal is to determine the safety and clinical effect of combined checkpoint inhibition administered after autologous hematopoietic stem cell transplantation in each of six clinical cohorts of high risk and recurrent disease. In addition to assessing the incidence and severity of adverse events and rates of complete response and progression free survival, we intend to monitor immune reconstitution, phenotype and TCR repertoire throughout treatment and at the time of disease progression. We will also analyze the gut microbiome prior to conditioning, throughout treatment, post-transplant and at time of relapse. The rationale for studying the gut microbiome is based on earlier studies demonstrating that reduced diversity of intestinal microbiota leads to poor outcome post-allogeneic hematopoietic stem cell[15] and specific intestinal bacterial species have been shown to boost responses to chemotherapy[16,17] and checkpoint inhibitors[18,19] .When available, tumor site immune phenotype, TCR repertoire and PD-L1 and PD-L2 expression prior to autologous transplant conditioning and then at time of progression (within 18 months) after autologous transplant conditioning will be assessed. We intend to expand cohorts that demonstrate safety and PFS >50% at 18 months into a phase IIB successor trial.

2.2 Rationale for Checkpoint Inhibition

Programmed Cell Death-1 (PD-1)

PD-1 (CD279) is an inhibitory cell surface receptor on activated T cells that limits T cell activation and induces peripheral T cell tolerance. PD-1, a member of the CD28 family of T-cell costimulatory receptors, including CTLA-4, ICOS, and BTLA, is primarily expressed on activated T cells, B cells, natural killer cells and myeloid cells. The cytoplasmic tail of PD-1 contains two intracellular signaling motifs, a proximal immunoreceptor tyrosine inhibitory motif (ITIM) and a distal immunoreceptor tyrosine-based switch motif (ITSM). Binding to PD-L1 (B7-H1/CD274) or PD-L2

(B7-DC/CD273) triggers the phosphorylation of ITIM and ITSM which in turn recruits the phosphatase SHP-2 that subsequently dephosphorylates TCR signaling, leading to the overall inhibition of T cell activation and effector function[20,21,22].

The negative regulatory role of PD-1 was demonstrated using PD-1-deficient mice. PD-1-deficient mice develop various autoimmune phenotypes, including dilated cardiomyopathy and a lupus-like syndrome with arthritis and nephritis. The emergence of these autoimmune phenotypes is dependent upon the genetic background of the mouse strain; many of these phenotypes emerge at different times and show variable penetrance. In addition to the phenotypes of null mutations, PD-1 inhibition by antibody-mediated blockade in several murine models has been found to play a role in the development of autoimmune diseases such as encephalomyelitis, graft-versus-host disease, and type I diabetes[23]. Taken together, these results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens. Preclinical animal models of tumors have shown that blockade of PD-1 by monoclonal antibodies (mAb) can enhance the anti-tumor immune response and result in tumor rejection. This suggests that host mechanisms limit the antitumor response[24].

In humans, PD-L1 is constitutively expressed on both hematopoietic cells such as macrophages and T cells as well as non-hematopoietic cells such as lung, vascular endothelial cells, and placental syncitiotrophoblasts. Aberrant expression of PD-L1 in tumor cells has been shown to enhance apoptosis of activated tumor-specific T cells *in vitro.* Additionally, the expression of PD-L1 may protect tumor cells from T cell-induced apoptosis. Retrospective analyses of several human tumor types suggest that over-expression of PD-L1 facilitates tumor evasion of immune surveillance[24]. In renal cell carcinoma, high surface expression levels of PD-L1 are correlated with tumor aggressiveness. Subjects with high tumor and/or lymphocyte PD-L1 levels are 4.5 times more likely to die from their cancer than subjects exhibiting low levels of PD-L1 expression[25]. In multivariate analysis, high expression of PD-L1 in melanoma is an independent predictor of vertical growth of primary melanomas and of worse outcome[26].

Nivolumab is a fully human, IgG4 (kappa) isotype, mAb that binds to PD-1. Blockade of the PD-1 pathway by nivolumab resulted in a reproducible enhancement of T cell proliferation in a mixed lymphocyte reaction (MLR) assay. The effect of nivolumab on an antigen-specific recall response was investigated using a CMV-restimulation assay with human peripheral blood mononuclear cells (PBMCs), and was evaluated by ELISA. These data indicated that nivolumab, versus an isotype-matched control antibody, augmented IFN-γ secretion from CMV-specific memory T cells in a dose dependent manner[27].

The clinical activity of nivolumab was demonstrated in a variety of tumors, including melanoma (MEL), renal cell cancer (RCC), non-small cell lung cancer (NSCLC), and colorectal cancer (CRC). Clinical activity was noted across a range of doses (1 mg/kg, 3 mg/kg, 10 mg/kg) and across dosing schedules. Complete response (CR) or PR has been reported at all dose levels (1, 3, and 10 mg/kg) and in multiple tumor types (melanoma, RCC, and NSCLC). The preliminary objective response rates were 5/20 (25.0%), 7/17 (41.2%), and 4/19 (21.1%) for MEL subjects treated at 1, 3, and 10 mg/kg respectively. Response data is only available for subjects with RCC and NSCLC treated at the 10 mg/kg dose level. The preliminary objective response rates were 4/19 (21.1%) for NSCLC and 6/18 (33.3%) for RCC. The preliminary median duration of response among MEL responders at 1, 3, and 10 mg/kg were 72.3, 40.6, and 73.0 weeks respectively. The median duration of response among NSCLC and RCC subjects was 29.1 and 56.3 weeks, respectively[27-29].

Cytotoxic T lymphocyte antigen 4 (CTLA-4)

Lymphocyte homeostasis is regulated by the differential effects of cytokines and an array of cell surface signaling molecules that affect T cell proliferation. One of the primary molecules responsible for T cell expansion in response to antigenic stimulation is CD28. The interaction of CD28 on the T cell, with CD80 (B7.1) or CD86 (B7.2) on the antigen presenting cell, stimulates T cell proliferation and survival. By necessity, a mechanism for elimination of antigen stimulated T cells is required following control of the antigenic challenge to maintain the viability of the host[13]. One important regulator of T cell contraction following antigen stimulation is cytotoxic T lymphocyte antigen 4 (CTLA-4)[30]. CTLA-4 expression on T cells is increased following antigen stimulation and has a significantly higher affinity for both B7 ligands than CD28. Upon control of an antigenic challenge, CTLA-4 preferentially interacts with the antigen presenting cell to inhibit continuous proliferation of T cells and helps to contract the T cell population. The fact that CTLA-4 knockout mice have lethal systemic immune hyper-activation demonstrates the important role of CLTA-4 in down-regulating the amplitude of T-cell activation.

Ipilimumab is a fully humanized mAb that binds to CTLA-4 and inhibits its interaction with ligands on antigen presenting cells[11]. Ipilimumab has been approved for use in over 40 countries including the United States in March 2011 and the European Union in July 2011. The safety profile is detailed below. In brief, over 12,700 subjects have received ipilimumab and the most common adverse events (AEs) were inflammatory in nature, consistent with ipilimumab's mechanism of action, and were generally medically manageable with topical or systemic immunosuppressants.

Clinical trials with ipilimumab have shown activity in a broad range of tumors, including hematologic malignancies. In one phase 1 trial, two of 18 patients with B cell lymphoma had a clinical response: one complete response at > 31 months in a patient with diffuse large B cell lymphoma and one partial response lasting 19 months in a patient with follicular lymphoma[31]. In another phase 1 trial, three of 27 patients with hematologic malignancies who recurred or progressed after allogeneic hematopoietic cell transplantation had objective responses: two complete responses in patients with Hodgkin lymphoma and one partial response in a patient with mantle cell lymphoma[32].

The rationale to pursue therapy with the combination of nivolumab and ipilimumab is based on studies using mouse models. In the MC38 colon carcinoma model, tumor-bearing mice treated with either anti-PD-1 or anti-CTLA-4 mAb alone had occasional complete regression of tumor. In contrast, most mice treated with both nivolumab and ipilimumab had complete regression of tumor[33].

A clinical trial testing the concurrent combination of nivolumab and ipilimumab resulted in even greater objective response rates than those seen with either agent alone in patients with advanced melanoma[34]. A total of 53 patients received concurrent therapy resulting in an objective response rate of 40%. Evidence of clinical activity (conventional, unconfirmed, or immune related response or stable disease for > 24 weeks) was observed in 65% of patients. At the maximum doses that were associated with an acceptable level of adverse events, 53% of patients had an objective response, all with tumor reduction of 80% or more. Treatment related adverse events were observed in 93% of subjects, with the most common events being rash (55%), pruritus (47%), fatigue (38%), and diarrhea (34%). Grade 3 or grade 4 treatment related events were noted in 53% of subjects, with the most common events being elevated levels of lipase (13%), aspartate aminotransferase increased (13%) and alanine aminotransferase increased (11%). Six of 28 subjects (21%) had grade 3 or grade 4 treatment related events that were dose-limiting. Eleven subjects (21%) discontinued therapy due to treatment related adverse events. The doses

of nivolumab at 3 mg/kg and ipilimumab at 3 mg/kg exceeded the maximum tolerated dose due to the occurrence of asymptomatic grade 3 or grade 4 elevated levels of lipase that persisted for > three weeks in three of six subjects. Doses of nivolumab at 1 mg/kg and ipilimumab at 3 mg/kg (n=17 subjects), in addition to nivolumab at 3 mg/kg and ipilimumab at 1 mg/kg (n=16 subjects) were both tolerated. Additional clinical experience with over 900 subjects has shown that both combination regimens are tolerated in subjects with solid tumors[10].

2.3 Current evidence for checkpoint inhibition after autologous hematopoietic stem cell transplantation

PD-1 blockade post autologous hematopoietic stem cell transplantation (ASCT) has been previously studied in a trial which evaluated 66 patients who had undergone ASCT for relapsed DLBCL (diffuse large B-cell lymphoma) and who presented with at least stable disease (SD) following transplantation, as compared to their pre-transplant disease status[6]. Patients received three doses of pidilizumab, a mAb targeted to PD-1, starting 1 to 3 months following transplantation. Primary endpoint was improvement in PFS at 16 months following the first dose of pidilizumab. The 16-month PFS for the whole cohort was 72% and the overall survival (OS) at 16 months was 85%. Toxicities were mild, and the most frequent grade 3 and 4 adverse events (AEs) were neutropenia (19%) and thrombocytopenia (8%). Correlative studies showed that treatment with pidilizumab resulted in a significant increase in the absolute number of PD-L1 bearing activated helper T cells ($CD4^+$,$CD25^+$,PD-L1+), apparent 24 hours after first treatment and sustained until at least 16 weeks as well as PD-1 ligand monocytes ($CD14^+$, PD-L1+ and $CD14^+$, PD-L2+ cells).

To date, there have not been any clinical studies examining the effects of combined checkpoint inhibition with anti-CTLA-4 and anti-PD1 mAb in patients following autologous stem cell transplantation.

3.0 BACKGROUND DRUG INFORMATION

3.1 Nivolumab

Full background drug information and description can be found in the Nivolumab Investigator's Brochure (V14 dated 30JUN2015).

3.1.1 Description

Nivolumab is a fully humanized IgG4 mAb which binds to PD-1 (CD279) with nanomolar affinity and shows a high degree of specificity for PD-1; blocking binding of PD-1 to PD-L1 and PD-L2. Nivolumab binds selectively to human PD-1 and does not bind to other members of the CD28 family.

3.1.2 Mechanism of action

Binding of PD-L1 and PD-L2, to the PD-1 on T cells, inhibits T-cell proliferation and cytokine production. Upregulation of PD-1 ligands occur in some tumors and signaling through this pathway contributes to tumor evasion of active T-cell immune surveillance. Nivolumab is a human immunoglobulin G4 (IgG4) mAb that binds to the PD-1 receptor and blocks its interaction with PD-L1 and PD-L2, releasing PD-1 pathway-mediated inhibition of the immune response, including

theanti-tumorimmuneresponse[27].

Blockade of the PD-1 pathway by nivolumab was studied using the mixed lymphocyte reaction (MLR). PD-1 blockade resulted in a reproducible enhancement of both proliferation and IFN-γ release in the MLR. The effect of nivolumab on antigen-specific recall response was investigated using a CMV-restimulation assay with human peripheral blood mononuclear cells (PBMCs), and was evaluated by ELISA. These data indicated that nivolumab, versus an isotype-matched control antibody, augmented IFN-γ secretion from CMV-specific memory T cells in a dose-dependent manner.

In syngeneic mouse tumor models, blocking PD-1 activity resulted in decreased tumor growth. Combined nivolumab (anti-PD-1) and ipilimumab (anti-CTLA-4) mediated inhibition results in enhanced T-cell function that is greater than the effects of either antibody alone, and results in improved anti-tumor responses in metastatic melanoma.

3.1.3 Pharmacokinetics

Nivolumab pharmacokinetics (PK) was assessed using a population PK approach for both single-agent and in combination with ipilimumab. Nivolumab as a single agent: The PK of single-agent nivolumab was studied in patients over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. The geometric mean (% coefficient of variation [CV%]) clearance (CL) is 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (Vss) is 8.0 L (30.4%), and geometric mean elimination half-life (t1/2) is 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg every 2 weeks, and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. Nivolumab in combination with ipilimumab: The geometric mean (CV%) CL, Vss, and terminal half-life of nivolumab were 10.0 mL/h (50.3%), 7.92 L (30.1%), and 24.8 days (94.3%), respectively. When administered in combination, the CL of nivolumab was increased by 24%, whereas there was no effect on the clearance of ipilimumab. When administered in combination, the clearance of nivolumab increased by 42% in the presence of anti-nivolumab antibodies. There was no effect of anti-ipilimumab antibodies on the clearance of ipilimumab.

Specific Populations: Based on a population PK analysis, the clearance of nivolumab increased with increasing body weight supporting a weight-based dose. The population PK analysis suggested that the following factors had no clinically important effect on the clearance of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1 expression, tumor type, tumor size, renal impairment, and mild hepatic impairment.

Renal Impairment: The effect of renal impairment on the clearance of nivolumab was evaluated by a population PK analysis in patients with mild (eGFR 60 to 89 mL/min/1.73 m^2 ; n=313), moderate (eGFR 30 to 59 mL/min/1.73 m^2 ; n=140), or severe (eGFR 15 to 29 mL/min/1.73 m^2; n=3) renal impairment. No clinically important differences in the clearance of nivolumab were found between patients with renal impairment and patients with normal renal function.

Hepatic Impairment: The effect of hepatic impairment on the clearance of nivolumab was evaluated by population PK analyses in patients with mild hepatic impairment (total bilirubin [TB] less than or equal to the upper limit of normal [ULN] and AST greater than ULN or TB less than 1 to 1.5 times ULN and any AST; n=92). No clinically important differences in the clearance of nivolumab were found between patients with mild hepatic impairment and patients with normal hepatic function. Nivolumab has not been studied in patients with moderate (TB greater than 1.5

to 3 times ULN and any AST) or severe hepatic impairment (TB greater than 3 times ULN and any AST).

3.1.4 Non-clinical toxicology

No studies have been performed to assess the potential of nivolumab for carcinogenicity or genotoxicity. Fertility studies have not been performed with nivolumab. In 1-month and 3-month repeat-dose toxicology studies in monkeys, there were no notable effects in the male and female reproductive organs; however, most animals in these studies were not sexually mature.

In animal models, inhibition of PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. Inhibition of PD-1 signaling increased the severity of some infections and enhanced inflammatory responses. PD-1 knockout mice have also shown decreased survival following infection with lymphocytic choriomeningitis virus.

3.1.5 Adverse Events

The overall safety experience with nivolumab, as monotherapy or in combination with other therapeutics, is based on experience in approximately 1,500 subjects treated to date. For monotherapy, the safety profile is similar across tumor types. The one exception is pulmonary inflammation AEs (adverse events) which may be numerically greater in subjects with non-small cell lung cancer because in some cases it can be difficult to distinguish between nivolumab related and unrelated causes of pulmonary symptoms and radiographic changes. There was no pattern in the incidence, severity, or causality of AEs to nivolumab dose level.

In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics and targeted therapies is being explored. Most studies are ongoing and as such, the safety profile of nivolumab combinations continues to evolve. The most advanced combination under development is nivolumab and ipilimumab in subjects with melanoma. Thus far, the combination of both agents results in a safety profile with similar types of AEs as either agent alone, but in some cases with greater frequency.

Overall, the safety profile of nivolumab monotherapy as well as combination therapy is manageable and generally consistent across completed and ongoing clinical trials with no MTD reached at any dose tested, up to 10 mg/kg. There was no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. Most AEs were low grade (grade 1 to grade 2) with relatively few related high grade (grade 3 to grade 4) AEs. Most high grade events were manageable with the use of corticosteroids or hormone replacement therapy for endocrinopathies.

Nivolumab should not be used in subjects with active autoimmune disease given the mechanism of action of the antibody.

The adverse events for nivolumab are mostly immune-mediated.

Immune-Mediated Pneumonitis: Immune-mediated pneumonitis or interstitial lung disease, defined as requiring use of corticosteroids and no clear alternate etiology, including fatal cases, occurred with nivolumab treatment. Across clinical trial experience with solid tumors receiving nivolumab as a single agent, fatal immune-mediated pneumonitis occurred in 0.3% (5/1590) of patients. All five fatal cases occurred in a dose-finding study with nivolumab doses of 1 mg/kg

(two patients), 3 mg/kg (two patients), and 10 mg/kg (one patient). Across the clinical trial experience in 188 patients with melanoma who received nivolumab in combination with ipilimumab, fatal immune-mediated pneumonitis occurred in 0.5% (1/188) of patients.

Immune-Mediated Colitis: Immune-mediated colitis, defined as requiring use of corticosteroids with no clear alternate etiology, can occur with nivolumab treatment. Across trials of nivolumab as single agent, the incidence of immune-mediated colitis was 25-28% in trials where nivolumab was used in combination with ipilimumab, the incidence of immune-mediated colitis was 33%.

Immune-Mediated Hepatitis: Immune-mediated hepatitis, defined as requiring use of corticosteroids and no clear alternate etiology, can occur with nivolumab treatment. In trials of nivolumab as single agent, the incidence of auto-immune hepatitis was 0.9-1.1%.

Immune-mediated endocrinopathies: Immune-mediated endocrinopathies, such as hypophysitis, adrenal insufficiency, hypothyroidism, hyperthyroidism and diabetes mellitus type 1 can occur with nivolumab treatment. In trials using nivolumab as single agent, immune-mediated endocrinopathies occurred in up to 8% of subjects, whereas in combination with ipilimumab it occurred in up to 19% of subjects.

Immune-Mediated Nephritis: Immune-mediated nephritis, defined as renal dysfunction occurred in up to 19% of subjects. In trials where nivolumab was used as single agent, the incidence of immune-mediated nephritis was as high as 0.7%. When used in combination with ipilimumab, the incidence was up to 2.1%.

Immune-Mediated Rash: In clinical trials using nivolumab as single agent, immune-mediated rash was seen in up to 28% of patients. In trials using nivolumab in combination with ipilimumab, the incidence was up to 37%.

Immune-mediated encephalitis: Across clinical studies of 8490 patients receiving nivolumab as a single agent or in combination with ipilimumab, less than 1.0% of patients were identified as having encephalitis.

Other immune-mediated adverse reactions: The following clinically significant, immune-mediated adverse reactions occurred in less than 1.0% of patients receiving nivolumab as a single agent or in combination with ipilimumab: uveitis, pancreatitis, facial and abducens nerve paresis, demyelination, polymyalgia rheumatica, autoimmune neuropathy, Guillain-Barre syndrome, hypopituitarism, and systemic inflammatory response syndrome.

3.2 Ipilimumab

Full background drug information and description please reference Ipilimumab Investigator's Brochure (V18 dated 10MAR2015).

3.2.1 Description

Ipilimumab is a recombinant, human mAb that binds to the cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4). Ipilimumab is an IgG1 kappa immunoglobulin with an approximate molecular weight of 148 kDa. Ipilimumab is produced in mammalian (Chinese hamster ovary) cell culture.

3.2.2 Mechanism of action

CTLA-4 is a negative regulator of T-cell activity. Ipilimumab is a mAb that binds to CTLA-4 and blocks the interaction of CTLA-4 with its ligands, CD80/CD86. Blockade of CTLA-4 has been shown to augment T-cell activation and proliferation, including the activation and proliferation of tumor infiltrating T-effector cells. Inhibition of CTLA-4 signaling can also reduce T-regulatory cell function, which may contribute to a general increase in T cell responsiveness, including the anti-tumor immune response[9].

3.2.3 Pharmacokinetics

The pharmacokinetics (PK) of ipilimumab was studied in 785 patients with unresectable or metastatic melanoma who received doses of 0.3, 3, or 10 mg/kg once every 3 weeks for 4 doses. The PK of ipilimumab is linear in the dose range of 0.3 to 10 mg/kg. Following administration of ipilimumab every 3 weeks, the systemic accumulation was 1.5-fold or less. Steady-state concentrations of ipilimumab were reached by the third dose; the mean Cmin at steady state was 19.4 mcg/mL at 3 mg/kg and 58.1 mcg/mL at 10 mg/kg every 3 weeks. The mean value (percent coefficient of variation) based on population PK analysis for the terminal half-life (t1/2) was 15.4 days (34%) and for clearance (CL) was 16.8 mL/h (38%).

The effects of various covariates on the PK of ipilimumab were assessed in population PK analyses. The CL of ipilimumab increased with increasing body weight supporting the recommended body weight (mg/kg) based dosing. The following factors had no clinically important effect on the CL of ipilimumab: age (range: 23 to 88 years), sex, performance status, renal impairment, mild hepatic impairment, previous cancer therapy, and baseline lactate dehydrogenase (LDH) levels. The effect of race was not examined due to limited data available in non-Caucasian ethnic groups.

3.2.4 Non-clinical toxicology

The carcinogenic potential of ipilimumab has not been evaluated in long-term animal studies, and the genotoxic potential of ipilimumab has not been evaluated. Fertility studies have not been performed with ipilimumab.

3.2.5 Adverse events

More than 12,700 subjects with several cancer types have received ipilimumab in completed and ongoing studies, as well as a compassionate use program. The focus of the clinical program is in melanoma, prostate cancer, and lung cancer, with advanced melanoma being the most comprehensively studied indication. Ipilimumab is being investigated both as monotherapy and in combination with other modalities such as chemotherapy, radiation therapy, and other immunotherapies. Phase 3 programs are ongoing in melanoma, prostate cancer, and lung cancer.

The unique immune based mechanism of action is also reflected in the safety profile. The most common treatment related adverse events (AEs) are inflammatory in nature, consistent with the mechanism of action of ipilimumab, and generally medically manageable with topical or systemic immunosuppressants. Such immunological safety events are described as immune-related AEs (irAEs). The irAEs are described as AEs of unknown etiology that were consistent with an immune phenomenon, and were considered causally related to drug exposure by investigators. The irAEs primarily involve the gastrointestinal tract and the skin. Immune-related AEs in the liver were also observed, particularly in subjects receiving 10 mg/kg. Endocrinopathy and neuropathy were important irAEs observed less frequently.

4.0 PATIENT ELIGIBILITY

4.1 Inclusion Criteria

In order to be eligible for participation in this trial, the subject must meet the following inclusion criteria:

1. Voluntary signed and dated IRB/IEC approved written informed consent form in accordance with regulatory and local guidelines.
2. Be 18 years or older and 80 years or younger on the day of signing consent
3. Have a confirmed diagnosis of:

    - (GROUP A) De novo diffuse large B cell lymphoma that fails to achieve a PET negative complete response to primary rituximab and anthracycline based multi-agent chemotherapy and at least maintains stable disease after salvage chemotherapy or present double/triple hit features defined by overexpression by standard immunohistochemistry of c-MYC plus BCL2 and/or BCL6 or presence of chromosomal translocations as detected by break-apart FISH involving IGH/MYC plus IGH/BCL2 and/or IGH/BCL6 and who only received standard chemoimmunotherapy with rituximab, cyclophosphamide, vincristine and prednisone (R-CHOP) for induction and present at least stable disease after consolidation or salvage chemotherapy. Stable disease (SD) for lymphoma is defined in Appendix B: Lugano Classification for Response Assessment of Non-Hodgkin Lymphoma.

    - (GROUP B) Recurrent high-risk diffuse large B cell lymphoma defined as relapsing within one year of completion of rituximab and anthracycline based multi-agent chemotherapy or a sAAIPI (second-line age-adjusted International Prognostic Index) intermediate or high at relapse or acquisition of double/triple hit features upon relapse (as defined in group A) and at least stable disease after salvage chemotherapy. Patients with an initial diagnosis of low-grade/indolent non-Hodgkin lymphoma (i.e. follicular, marginal zone) who present relapse with histologic transformation to diffuse large B cell lymphoma (confirmed by biopsy) and meet the definition for high-risk as presented above, are also eligible.

    - (GROUP C) De novo high-risk T cell lymphoma with at least stable disease after primary therapy. High risk T cell lymphoma is defined as Stage III or IV disease at presentation and/or failure to achieve CR after frontline chemotherapy. Patients with ALK-positive ALCL will be excluded from the trial. Patients with ALK-negative ALCL in complete response will be excluded from the trial.

    - (GROUP D) Recurrent T cell lymphoma with at least stable disease after salvage therapy. Patients with ALK-positive ALCL will be excluded from the trial.

4. Be deemed eligible for an autologous stem cell transplantation according to the institutional guidelines of the Blood and Marrow Transplantation Program at John Theurer Cancer Center at Hackensack University Medical Center
5. Have an ECOG performance status of 2 or lower
6. Women of childbearing potential (WOCBP) must use appropriate method(s) of contraception. WOCBP should use an adequate method to avoid pregnancy for 23 weeks

(30 days plus the time required for nivolumab to undergo five half-lives) after the last dose of investigational drug.

7. Women of childbearing potential (WOCBP) must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of nivolumab. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required. Female subjects of childbearing potential should agree to ongoing pregnancy testing, to be performed prior to each dosing of ipilimumab and nivolumab. See Note below for definition of WOCBP.
8. Women must not be breastfeeding.
9. Men who are sexually active with WOCBP must use any contraceptive method with a failure rate of less than 1% per year. Men receiving nivolumab, and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product, even if they have had a vasectomy. Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile as well as azoospermic men do not require contraception). See Note below for definition of WOCBP.
10. Females of childbearing potential must be willing to use two methods of birth control or be surgically sterile, or abstain from heterosexual activity for the course of the study through 120 days after the last dose of study medication. Subjects of childbearing potential are those who have not been surgically sterilized or have not been free from menses for > 2 years. See Note below for definition of WOCBP.
11. Allowable transplant preparative regimens are the following:
    - For non-Hodgkin lymphoma groups (A, B,C,D) BEAM: carmustine 300 mg/m2 day -6, etoposide 200 mg/m2 and cytarabine 200 mg/m2 days -5 to -2, melphalan 140 mg/m2 day -1
    - For Myeloma groups (E and F) Melphalan 200 mg/m2 day -1

NOTE: Women of childbearing potential is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes. In addition, women under the age of 55 must have a documented serum follicle stimulating hormone (FSH) level less than 40 mIU/mL.

Women of childbearing potential (WOCBP) receiving nivolumab will be instructed to adhere to contraception for a period of 23 weeks after the last dose of investigational product. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 31 weeks after the last dose of investigational product. These durations have been calculated using the upper limit of the half-life for nivolumab (25 days) and are based on the protocol requirement that WOCBP use contraception for 5 half-lives plus 30 days and men who are sexually active with WOCBP use contraception for 5 half-lives plus 90 days.

4.2 Exclusion Criteria

The subject must be excluded from participating in the trial if the subject meets ANY of the following exclusion criteria:

1. Has known active central nervous system (CNS) metastases and/or carcinomatous meningitis. Subjects with previously treated brain metastases may participate provided they are stable (without evidence of progression by imaging for at least four weeks prior to the first dose of trial treatment and any neurologic symptoms have returned to baseline),

have no evidence of new or enlarging brain metastases, and are not using steroids for at least 7 days prior to trial treatment. There must also be no requirement for immunosuppressive doses of systemic corticosteroids (> 10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration. This exception does not include carcinomatous meningitis, which is excluded regardless of clinical stability. Note: Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if > 10 mg/day prednisone equivalents. 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 contact allergen) is permitted.

2. Is unable or unwilling to sign informed consent.
3. Has an active, known, or suspected autoimmune disease. Subjects are permitted to enroll if they have 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
4. Patients should be excluded if they have a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease. Note: Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if > 10 mg/day prednisone equivalents. 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 contact allergen) is permitted.
5. As there is potential for hepatic toxicity with nivolumab or nivolumab/ipilimumab combinations, drugs with a predisposition to hepatoxicity should be used with caution in patients treated with nivolumab-containing regimen.
6. Has received an allogeneic stem cell transplant.
7. Has a history of hypersensitivity to nivolumab, ipilimumab, or any of its excipients, or severe hypersensitivity reaction to any previous monoclonal antibody.
8. Has had a prior anti-cancer monoclonal antibody (mAb) within 4 weeks prior to Day 1 of checkpoint inhibitor treatment administration or who has not recovered (i.e., t administration mAb) within 4 weeks prior to t dose of trial treatment. Rituximab within that period is allowed.
9. Has active autoimmune disease that has required systemic treatment in the past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg. thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Note: Subjects are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if > 10 mg/day prednisone equivalents. 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 contact allergen) is permitted.
10. Has known history of, or any evidence of active, non-infectious pneumonitis.
11. Has an active infection requiring intravenous systemic therapy.
12. Has a history or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the trial, interfere with the subject’s participation for the full

duration of the trial, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

13. Has known psychiatric or substance abuse disorders that would interfere with cooperation with the requirements of the trial.
14. Is pregnant or breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the pre-screening or screening visit through 23 weeks for females and 31 weeks for males after the last dose of trial treatment.
15. Has received prior therapy with an anti-PD-1, anti-PD-L1, anti-PD-L2 agent, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways.
16. Has a known history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies) or known acquired immunodeficiency syndrome (AIDS).
17. Has positive test for Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected) indicating acute or chronic infection, as tested for transplant.
18. Has received a live vaccine within 30 days of planned start of study therapy.

NOTE: Patients who received steroids for engraftment syndrome may initiate treatment with ipilimumab and nivolumab once steroids have been tapered off and diarrhea and/or rash are grade I or better, without the need for a steroid washout period. Initial dosing may be delayed up to day 28 post-transplantation to allow for completion of steroid taper.

5.0 TREATMENT PLAN

5.1 Product Information

5.1.1 Drug Ordering and Accountability

Bristol-Meyers Squibb is supplying study drug. Please see Appendix H for information on provisions for ordering study drug from BMS. It is possible that sites may have more than one clinical study on the same drug ongoing at the same time. It is imperative that only drug product designated for this protocol be used for this study. The investigator is responsible for ensuring that the investigational product is stored under the appropriate environmental conditions (temperature, light, and humidity). If concerns regarding the quality or appearance of the investigational product arise, do not dispense the investigational product, and contact BMS immediately.

It is the investigator's responsibility to ensure that arrangements have been made for drug destruction, including the disposal, and that procedure for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures.

5.1.2 Product Description and Dosage Form

Please provide information on the product as shown in the sample table below:

Product Description & Dosage Form	**Potency**	**Primary Packaging (Volume)/ Label Type**	**Secondary Packaging (Qty)/ Label Type**	**Appearance**	**Storage Conditions (per label)**
Nivolumab BMS-936558-01 Solution for Injection[a]	100 mg (10 mg/mL)	10 mL vial	5 or 10 vials per carton/ Open-label	Clear to opalescent colorless to pale yellow	2 to 8°C. Protect from light and freezing

				liquid. May contain particles	
Ipilimumab Solution for Injection	200 mg (5 mg/mL)	40 mL vial	4 vials per carton/Open-label	Clear, colorless to pale yellow liquid. May contain particles	2 to 8°C. Protect from light and freezing.

[a]Nivolumab may be labeled as BMS-936558-01 or Nivolumab Solution for Injection

If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab and ipilimumab include laboratory coats and gloves. For additional details on prepared drug storage and use time of nivolumab or ipilimumab under room temperature/light and refrigeration, please refer to the BMS-936558 (nivolumab) and Ipilimuab Investigator Brochure section for "Recommended Storage and Use Conditions."

5.2 Treatment Schema

- Patients must sign informed consent and be registered.
- Informed consent should be signed within 60 days prior to beginning of ASCT conditioning. Subject recruitment and informed consent will take place in the BMT Service at HackensackUMC and in the BMT service at Georgetown University. Patients who already had stem cell mobilization and collection will also be allowed to sign informed consent and be enrolled in the trial.
- The first administration of study therapy will be administered in the BMT Service.
- 14 to 21 days after stem cell infusion, if ANC>800 (off growth factors for at least 3 days) and Platelets>20,000 without transfusion, ipilimumab and nivolumab should be started.
- Delay initiation of post ASCT therapy until ANC>800 (off growth factors for at least 3 days) and Platelets>20,000 without transfusion up to 28 days after stem cell infusion.
- Post ASCT therapy may be delayed up to 28 days after stem cell infusion if deemed appropriate by the investigator.
- The first day of ipilimumab/nivolumab infusion will be considered Day 1 of Week 1. Prior to patient's drug administration on Day 1 of Week 1, all patients must be re-assessed to confirm eligibility.
- Laboratory assessments must be evaluated within 72 hours prior to re-dosing
- All visits will be given a +/- 2-day window.
- At screening visit and each subsequent visit, the patient should be given a stool collection kit.

Group A	De novo diffuse large B cell lymphoma that fails to achieve a PET negative complete response to primary rituximab and anthracycline based multi-agent chemotherapy and at least maintains stable disease after salvage chemotherapy or present double/triple hit features defined by overexpression by standard immunohistochemistry of c-MYC plus BCL2 and/or BCL6 or presence of chromosomal translocations as detected by break-apart FISH involving IGH/MYC plus IGH/BCL2 and/or IGH/BCL6 and who only received standard chemoimmunotherapy with rituximab, cyclophosphamide, vincristine and prednisone (R-CHOP) for induction and present at least stable disease after consolidation or salvage chemotherapy.

Group B	Recurrent high-risk diffuse large B cell lymphoma defined as relapsing within one year of completion of rituximab and anthracycline based multi-agent chemotherapy or a sAAIPI (second-line age-adjusted International Prognostic Index) intermediate or high at relapse or acquisition of double/triple hit features upon relapse (as defined in group A) and at least stable disease after salvage chemotherapy. Patients with an initial diagnosis of low-grade/indolent non-Hodgkin lymphoma (i.e. follicular, marginal zone) who present relapse with histologic transformation to diffuse large B cell lymphoma (confirmed by biopsy) and meet the definition for high-risk as presented above, are also eligible.
Group C	De novo high-risk T cell lymphoma with at least stable disease after primary therapy. Patients with ALK-positive ALCL will be excluded from the trial. Patients with ALK-negative ALCL in complete response will be excluded from the trial.
Group D	Recurrent T cell lymphoma with at least stable disease after salvage therapy. Patients with ALK-positive ALCL will be excluded from the trial.

5.3 Administration

Nivolumab 3 mg/kg for 12 doses, on day 1 of weeks 1, 4, 7, 10, 12, 14, 16, 18, 20, 22, 24, 26
Ipilimumab 1 mg/kg for 6 doses, on day 1 of weeks 1, 4, 7, 10, 16, 22

Nivolumab is to be administered as a 60-minute IV infusion, using a volumetric pump with a 0.2/1.2 micron pore size, low-protein binding polyethersulfone membrane in-line filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline for delivery but the total drug concentration of the solution cannot be below 1 mg/mL. It is not to be administered as an IV push or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

Ipilimumab is to be administered as a 90-minute IV infusion, using a volumetric pump with a 0.2/1.2 micron low-protein binding in-line filter. Ipilimumab is given undiluted or further diluted in 0.9% NaCl Injection, USP or 5% Dextrose Injection, USP in concentrations between 1 mg/mL and 4 mg/mL.

The dosing calculations should be based on the actual screening body weight. If the subject's weight on the day of dosing differs by > 10% from the weight used to calculate the dose, the dose must be recalculated. All doses should be rounded up or to the nearest milligram per institutional standard. There will be no dose modifications allowed.

When infusions of ipilimumab and nivolumab are given on the same day, the preferred treatment is to give nivolumab followed by ipilimumab. Separate infusion bags and filters must be used for each infusion. The nivolumab infusion must be promptly followed by a saline flush to clear the line of nivolumab before starting the ipilimumab infusion. The second infusion will always be ipilimumab, and will start approximately 30 minutes after completion of the nivolumab infusion.

Patients may be dosed 2 days prior or up to 2 days after the scheduled date, if necessary. The original scheduled date should be adhered to throughout the protocol.

Toxicity management for the combined agents follows the same template guidelines and algorithms for single agent nivolumab.

5.4 Dose Modifications

There will be no dose modifications permitted for study drug, with the exception of changes due to fluctuation in weight. Dose reductions or dose escalations are not permitted.

5.5 Premedication

Only needs to be given for transfusion reactions (See Appendix G for Transfusion Reactions)

5.6 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with adverse events that can differ in severity and duration than adverse events caused by other therapeutic classes. Nivolumab and ipilimumab are considered immuno-oncology agents in this protocol. Management algorithms have been developed to assist investigators in assessing and managing the following groups of adverse events: Gastrointestinal, Renal, Pulmonary, Hepatic, Endocrinopathies, Skin, and Neurological.

Early recognition and intervention are recommended according to the management algorithms; and in addition include ophthalmologic evaluations for any visual symptoms in order to evaluate for nivolumab or ipilimumab related uveitis.

The recommendations are to follow the algorithms in the nivolumab investigator brochure for immune related events; while the ipilimumab investigator brochure contains similar algorithms, the algorithms in the nivolumab brochure have been aligned to accommodate combinations as well as nivolumab monotherapy. Therefore, the algorithms recommended for utilization are in Appendix G for reference.

For subjects expected who require more than 4 weeks of corticosteroids or other immunosuppressants to manage an adverse event, consider the following recommendations

- Antimicrobial/antifungal prophylaxis per institutional guidelines to prevent opportunistic infections such as Pneumocystis jiroveci and fungal infections.
- Early consultation with an infectious disease specialist should be considered. Depending on the presentation, consultation with a pulmonologist for bronchoscopy or a gastroenterologist for endoscopy may also be appropriate.
- In patients who develop recurrent adverse events in the setting of ongoing or prior immunosuppressant use, an opportunistic infection should be considered in the differential diagnosis.

Additional details on the safety of nivolumab and ipilimumab, including results from clinical studies, are available in the IB.

5.7 Dose Delay Criteria

Dose delay criteria apply for all drug-related adverse events (regardless of whether or not the event is attributed to nivolumab, ipilimumab or both). All study drugs must be delayed until treatment can resume. In the case that a treatment cannot be administered at a scheduled visit (with +/-2 day window), proceed to the next scheduled dose.

Nivolumab and ipilimumab administration should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, with the following exceptions:

    - Grade 2 drug-related fatigue or laboratory abnormalities do not require a treatment delay
- Any Grade 3 skin, drug-related adverse event
- Any Grade 3 drug-related laboratory abnormality, with the following exceptions for asymptomatic amylase or lipase, AST, ALT, or total bilirubin:
    - Grade 3 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis do not require a dose delay. It is recommended to consult with the principle investigator for Grade 3 amylase or lipase abnormalities.
    - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade ≥ 2 toxicity
    - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

5.8 Criteria to Resume Treatment

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

- Subjects may resume treatment in the presence of Grade 2 fatigue
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity
- Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT OR total bilirubin
- Subjects with combined Grade 2 AST/ALT AND total bilirubin values meeting discontinuation parameters (Section 5.9) should have treatment permanently discontinued
- Drug-related pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment

If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled timepoint per protocol. <u>However, if the treatment is delayed past the next scheduled timepoint per protocol, the next scheduled timepoint will be delayed until dosing resumes.</u>

If treatment is delayed > 6 weeks, the subject must be permanently discontinued from study therapy, except as specified in discontinuation Section 5.9.

Peripheral blood and stool sample collection will continue to take place for subjects discontinued from the study up to 18 months post ASCT and/or relapse, if it occurs.

5.9 Discontinuation Criteria

Treatment should be permanently discontinued for the following:

- Any Grade 2 drug-related uveitis or 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 drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic adverse event, hypersensitivity reactions, and infusion reactions
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic adverse event, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except those noted below
        - 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 > 8 x ULN
            - Total bilirubin > 5 x ULN
            - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any Grade 4 drug-related adverse event or non-hematological laboratory abnormality, except for the following events which do not require discontinuation:
    - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset.
    - 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
- Any dosing interruption lasting > 6 weeks 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 interruption lasting > 6 weeks, the Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted
    - Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the Investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Investigator must be consulted. Tumor assessments should continue as per protocol even if dosing is interrupted
- 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 or ipilimumab dosing
- Any patient that meets disease-specific criteria for relapse or progressive disease should be discontinued from study therapy.

Peripheral blood and stool sample collection will continue to take place for subjects discontinued from the study up to 18 months post ASCT and/or at relapse, if it occurs.

6.0 SUBJECT SCREENING EVALUATION

6.1 Evaluation of the patient after informed consent is signed. Any of the evaluations listed below will be accepted if performed prior to signing consent if done within the described timeframe, without need for repeating procedures.

- History and physical examination within 30 days prior to start of ASCT conditioning regimen.

- CBC, differential, haptoglobin, LFTs, total CK, complete metabolic panel within 30 days prior to start of ASCT conditioning regimen.
- Evaluation for CMV, HIV, HTLV, and hepatitis B & C within 30 days prior to start of ASCT conditioning regimen.
- Baseline electrocardiogram (EKG) and MUGA scan or echocardiogram with measurement of LVEF within 90 days prior to start of ASCT conditioning regimen.
- Chest radiography within 90 days prior to start of ASCT conditioning regimen.
- Pulmonary function test (PFT) within 90 days prior to start of ASCT conditioning regimen.
- Cut-off values for the above-mentioned studies will be consistent with institutional standard operating procedures (SOPs) for eligibility screening prior to ASCT.
- For groups A,B,C,D: PET-CT scan **and** CT scan with intravenous/oral contrast of neck, chest, abdomen and pelvis within 30 days prior to initiation of ASCT conditioning
- For groups E and F: Within 30 days prior to initiation of ASCT conditioning: Serum protein electrophoresis with immunofixation, quantitative serum IgG, IgM, IgA (IgE in cases where this is the involved immunoglobulin), serum free light chains, 24-hour urine for protein electrophoresis with immunofixation and protein quantification.
- For groups E and F: Within 30 days prior to initiation of ASCT conditioning: Skeletal Survey.
- For all groups, within 30 days prior to ASCT conditioning (at the time of informed consent): Peripheral blood collection for blood immune phenotype and metabolomics analysis.
- For all groups post consent, prior to ASCT conditioning: Stool samples will be collected for baseline gut microbiome analysis.
- For all groups: Acquisition of tumor tissue biopsy (either new or archival tissue, if available) or bone marrow biopsy (if known involvement) for evaluation of PD1/PDL1 expression and baseline tumor immune profile. Tumor Biopsies and/or Bone Marrow Biopsies for Lymphoma subjects (Groups A through D) and Bone Marrow Biopsies for Multiple Myeloma subjects (Groups E & F) will be collected at screening, end of treatment, complete response, and at relapse, if clinically indicated. For Bone Marrow Biopsies, the research sample will be collected (aspirate, send the first pull, yellow top tube) to Dr. Korngold's lab. Additional samples for all disease groups will be sent to pathology for immunostaining of fixed tissue for PDL1 expression on tumor cells and for the in situ presence of CD4 and CD8 T cells with PD1 expression. If viable biopsy material is unavailable for research purposes, Dr. Korngold's lab will access fixed archival tumor materials for preparing tumor lysates and possibly for retrieving T cell DNA for repertoire analysis. Samples for Georgetown University subjects are to be shipped via Fed Ex on the day of collection – tubes banded in sealed plastic bag and wrapped in bubble wrap at room temperature to Dr. Korngold's lab.

6.2 Evaluation and Response

6.2.1 For Groups A, B, C, and D:

- PET-CT scan and/or CT scan with intravenous/oral contrast of neck, chest, abdomen and pelvis will be performed for response evaluation 90-100 days post ASCT, 180-200days post ASCT, 360-380 days post ASCT and 540-560 days post ASCT. Response criteria will follow the Lugano Classification (see Appendix B). **Both** PET/CT **and** CT scan should be done within 30 days prior to initiation of ASCT conditioning for baseline response evaluation purposes. **Either** PET/CT **or** CT scan are acceptable for response evaluation **after** ASCT, and should be compared to the pre-ASCT baseline scan.
- Physical exam, laboratory work-up and correlative studies will be performed as delineated in the Clinical Trial Flowchart (Appendix D)

6.2.2 For Groups E and F:

- Serum protein electrophoresis with immunofixation, quantitative serum IgG, IgM, IgA (IgE or IgD in cases where this is the involved immunoglobulin), serum free light chains, 24-hour urine for protein electrophoresis with immunofixation and protein quantification will be collected for response evaluation 30-40 days post ASCT, 60-70 days post ASCT, 90-100 days post ASCT, 180-200 days post ASCT, 270-290 days post ASCT, 360-380 days post ASCT, 450-470 days post ASCT and 540-560 days post ASCT. Response criteria will follow the International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma (see Appendix C). For patients who achieve CR by IMWG Criteria, a bone marrow biopsy will be required for confirmation and tumor immunophenotype analysis
- Physical exam, laboratory work-up, and correlative studies will be performed as delineated in the Clinical Trial Flowchart (Appendix D)

6.2.3 For All Groups:

- If a patient signs consent but does not receive treatment, the patient will not be evaluable and no further safety information will be collected. The slot will be released and may be re-assigned to another patient.
- If there is progressive disease or relapse documented by any of the criteria, a confirmatory lymph node and/or bone marrow biopsy will be performed for confirmation of disease relapse and tumor immunophenotype studies.

7.0 DATA SAFETY MONITORING

The Georgetown Lombardi Comprehensive Cancer Center will be responsible for the data and safety monitoring of this multi-site trial. As this study is an investigator initiated Phase Ib/IIa study utilizing a non-FDA approved drug for this indication which the FDA has deemed IND-exempt, it is considered a high-risk study, which requires real-time monitoring, by the PI and study team and reviewed every 4 months by the LCCC Data and Safety Monitoring Committee (DSMC).

The Principal Investigator and the Co-Investigators will review the data including safety monitoring at their weekly institution based disease group meetings and on monthly disease group teleconferences.

All Severe Adverse Events (SAEs) are required to be reported to the IRB. Based on SAEs, the IRB retains the authority to suspend further accrual pending more detailed reporting and/or modifications to further reduce risk and maximize the safety of participating patients.

Progress on the trial and the toxicities experienced will be reviewed by the LCCC Data and Safety Monitoring Committee every 4 months from the time the first patient is enrolled on the study. Results of the DSMC meetings will be forwarded to the IRB with recommendations regarding need for study closure.

DSMC recommendations should be based not only on results for the trial being monitored as well as on data available to the DSMC from other studies. It is the responsibility of the PI to ensure that the DSMC is kept apprised of non-confidential results from related studies that become available. It is the responsibility of the DSMC to determine the extent to which this information is relevant to its decisions related to the specific trial being monitored.

A written copy of the DSMC recommendations will be given to the trial PI and the IRB. If the DSMC recommends a study change for patient safety or efficacy reasons the trial PI must act to implement the change as expeditiously as possible. In the unlikely event that the trial PI does not concur with the DSMC recommendations, then the LCCC Associate Director of Clinical Research must be informed of the reason for the disagreement. The trial PI, DSMC Chair, and the LCCC AD for Clinical Research will be responsible for reaching a mutually acceptable decision about the study and providing details of that decision to the IRB. Confidentiality must be preserved during these discussions. However, in some cases, relevant data may be shared with other selected trial investigators and staff to seek advice to assist in reaching a mutually acceptable decision.

If a recommendation is made to change a trial for reasons other than patient safety or efficacy the DSMC will provide an adequate rationale for its decision. If the DSMC recommends that the trial be closed for any reason, the recommendation will be reviewed by the Associate Director for Clinical Research at G-LCCC. Authority to close a trial for safety reasons lies with the IRB, with the above described input from DSMC and the AD for Clinical Research.

8.0 STATISTICAL CONSIDERATION

This is an open label, single-arm per cohort, phase Ib-IIA study.

Our goal is to determine the safety and clinical effect of combined checkpoint inhibition administered after autologous hematopoietic stem cell transplantation in each of six clinical cohorts of high risk and recurrent disease. In addition to assessing the incidence and severity of adverse events and rates of complete response and progression free survival, we intend to monitor immune reconstitution, phenotype and TCR repertoire throughout treatment and at the time of disease progression. We will also analyze the gut microbiome prior to conditioning, throughout treatment, post-transplant and at time of relapse. We intend to expand cohorts that demonstrate safety and PFS >50% at 18 months into a phase IIA successor trial.
This is an open label, single-arm per cohort, phase Ib-IIA study.

Phase Ib

The primary objectives of this study are:

- To assess the safety of combined check point inhibition with nivolumab and ipilimumab after autologous hematopoietic stem cell transplantation in patients at high risk for post-transplant recurrence including patients with persistent and recurrent high risk diffuse large B cell lymphoma, high risk and recurrent T cell lymphoma and high risk and recurrent multiple myeloma.

Primary endpoints:

- Safety endpoint: The composite endpoint consisting of the occurrence of at least one treatment-related limiting toxicity (after combined checkpoint inhibitor treatment is initiated) defined as a ≥ grade 4 non-hematologic toxicity as specified by the CTCAE. Exceptions listed in section 5.9 apply to this endpoint as well. If 3 of 7 patients in a single cohort experience a treatment-related limiting toxicity, that single cohort will be terminated.
- Efficacy endpoint: progression-free survival at 18 months after ASCT in patients at high risk for post-transplant recurrence including patients with persistent and recurrent high risk diffuse large B cell lymphoma, high risk and recurrent T cell lymphoma and high risk and recurrent multiple myeloma.

The secondary objectives are:

- To assess complete response rate at 3, 6 and 12 months after ASCT in patients at high risk for post-transplant recurrence including patients with persistent and recurrent high risk diffuse large B cell lymphoma, high risk and recurrent T cell lymphoma and high risk and recurrent multiple myeloma.
- To assess progression-free survival at 12 months after ASCT in patients at high risk for post-transplant recurrence including patients with persistent and recurrent high risk diffuse large B cell lymphoma, high risk and recurrent T cell lymphoma and high risk and recurrent multiple myeloma.
- To assess blood immune reconstitution, phenotype and TCR repertoire at screening (at time of informed consent), at apheresis (stem cell collection), and then serially the day 1 of week 1 of combined checkpoint inhibitors and then weeks 4, 7, 12, 18 and 26, and at 9, 12, 15, and 18 months post-transplant and at time of relapse, as it occurs. Immune phenotype and TCR will be evaluated as follows:

  T cell repertoire analysis
  TCR Immunoseq for Vbeta CDR3 highest frequency specificities.

  Real-Time PCR analysis:
  T-bet(Th1); STAT3, RORgamma t (TH17); STAT6 (Th2); FoxP3 (Treg), granzyme A (GZMA) and perforin (PRF1)

  Flow Cytometric Phenotype Analysis for:

  T Cells:
  CD3; CD4; CD8; CD4+CD25+PD1+; CTLA-4
  Follicular Helper T: CD3+,CD4+,CXCR5+,PD1+
  CD4 and CD8 T naïve (RO-; CCR7+)
  Central Memory: (TCM;RO+,CCR7+)
  Effector Memory (TEM, RO+,CCR7-)
  Terminally differentiated effector memory (TEMRA; RO-, CCR7-)
  T regulatory cells (Treg): CD4+,CD25hi, CD127low, CD39+, CD152hi, RO- (resting); CD4+,CD25hi, CD127low, CD39+, CD152hi, RO+ (activated)

  Dendritic Cells:
  Lin-, CD11c+, CD1a+, CD80 (B7-1)low, CD86 (B7-2)low, MHC Class IIlow (DC resting); CD11c+, CD1a+, CD123-, CD80hi, CD86hi, HLADRhi (DC1 activated); HLADRhi, CD11c-, CD123+, PDL-1+ (DC2)

  Macrophages:
  HLADR+, CD14+, CD64+, CD25+, CCR7+ (M1); HLADR+, CD14+, CD64-, CD206+, CD25-, CCR7-, CD209+, PDL-1+ (M2)

  Myeloid derived suppressor cells:
  HLADR-/low, CD11b+, CD14+,CD33+hi,CD34+, CD66b-, PDL-1+ (M-MDSC); HLADR-, CD11b+, CD14-,CD33+low,CD34+, CD66b+, PDL-1+ (G-MDSC)

  B Cells:
  CD19+, B7-1low, B7-2low, MHC Class IIlow (resting); CD19+, B7-1hi, B7-2hi, MHC Class IIhi (activated)

NK cells:
CD16+, CD3-, CD56+

NKT Cells:
CD16+, CD3+, CD56+

Plasma Cytokine levels: Multiplex 25 Cytokine - Luminex
GM-CSF, IL-1b, IL-1RA, IL-2, IL-2R, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-15, IL-17, TNF alpha; MCP-1, MIP1a, MIP1b, MIG, RANTES, IFN-alpha, IFN-gamma, IP-10, Eotaxin

- To determine the toxicities resulting from administration of the treatments.
- To assess tumor site immune phenotype, T cell repertoire and PD L1/2 expression when tissue available for biopsy prior to autologous transplant conditioning and then at time of progression (within 18 months) after autologous transplant conditioning.

The tertiary objectives are:

- To identify specific intestinal microbial strains associated with improved outcome in autologous stem cell transplantation patients treated with combined checkpoint inhibitors. The overall microbial composition in stool samples of patients will be analyzed at screening, preconditioning (to be collected within 48 hours prior to transplant admission), at engraftment (within 72 hours of ANC $\geq$ 500), and then serially, on day 1 of week 1 (to be collected within 48 hours prior to clinic visit) and then weeks 4, 7, 12, 18, and 26, End of Treatment, and 9, 12, 15 and 18 months post-transplant, and at time of relapse, as it occurs. A 16S ribosomal RNA (rRNA) miSeq Illumina platform will be used for overall microbial composition and quantitative real-time PCR analysis will validate the specific microbial strains identified by miSeq.

Phase IIA

Primary Objective

- To assess progression-free survival at 18 months after ASCT in patients in cohorts that were deemed safe in Phase Ib (no more than 3 treatment-related toxicity) and at least 4 of 7 patients progression free at 18 months in the Phase Ib.

Secondary Objectives

- To assess complete response rate at 3, 6 and 12 months after ASCT in patients at high risk for post-transplant recurrence including patients in the successor expansion cohorts following the Phase Ib trial.
- To assess progression-free survival at 12 months after ASCT in patients at high risk for post-transplant recurrence including patients with in the successor expansion cohorts following the Phase Ib trial.
- Determine the toxicities resulting from administration of the treatments in patients enrolled in the successor expansion cohorts following the Phase Ib trial.
- To assess blood immune reconstitution, phenotype and TCR repertoire at screening (at time of informed consent), at apheresis (stem cell collection), and then serially the day 1 of week 1 of combined checkpoint inhibitors and then weeks 4, 7, 12, 18 and 26, and at 9, 12, 15, and 18 months post-transplant and at time of relapse, as it occurs.

Tertiary Objectives

- To identify specific intestinal microbial strains associated with improved outcome in autologous stem cell transplantation patients treated with combined checkpoint inhibitors.

The overall microbial composition in stool samples of patients will be analyzed at screening, preconditioning (to be collected within 48 hours prior to transplant admission), at engraftment (within 72 hours of ANC $\geq$ 500), and then serially, on day 1 of week 1 (to be collected within 48 hours prior to clinic visit) and then weeks 4, 7, 12, 18, and 26, End of Treatment, and 9, 12, 15 and 18 months post-transplant, and at time of relapse, as it occurs.

8.1 Determination of Sample Size

- The Phase Ib feasibility trial will require 42 patients divided in 6 cohorts, with 7 patients each.Enrolled patients will have hematologic malignancies with a high risk for post-autologous stem cell transplant recurrence including patients with persistent and recurrent high risk diffuse large B cell lymphoma, high risk and recurrent T cell lymphoma and high risk and recurrent multiple myeloma.
- The Phase IIA will require up to 148 patients, assuming all cohorts followed in Phase Ib meet the criteria for expansion.

Accrual goal is 7 patients per cohort. Accrual period goal is 36 months. Patients will accrue to study by disease groups (cohorts) and followed separately by group for incidence and severity of toxicity, ability to receive intended schedule of combined checkpoint inhibitors and for complete response and progression free survival (PFS) rates. Complete response and progression free survival rates will be compared to published standards for each disease group. Expected PFS at 18 months (PFS18) for all post-transplant groups without checkpoint inhibitors is 40-50%[1-3]. Groups A, B, C, and D with PFS at 18 months in 4 or more patients (57%) will be considered for eligibility in a successor phase IIa expansion trial. The primary efficacy endpoint of the phase Ib portionis to achieve PFS of 18 months in ≥4 patients per cohort (≥57%).

Phase Ib
The initial part of the trial titled is designed as a feasibility Phase Ib study. This will determine which of 6 cohorts of patients would be studied in an expansion Phase IIa trial. In this pilot feasibility study, designed to assess the safety of the combined checkpoint inhibitor, sample size was not performed to estimate power, as it was designed to obtain initial estimates of toxicity to inform the successor trial Phase IIA. Therefore, this pilot feasibility study is not powered to detect significant differences in PFS. We have preemptively established a cut-off of ≥57% PFS at 18 months as the minimum benefit needed to proceed to Phase IIa for each individual cohort, if a maximum of 3 patients in each cohort experience severe adverse events which would lead to trial discontinuation (for that particular cohort). Historical data for such patient populations predicts PFS 40-50% at 18 months.

Phase IIa
For the expansion cohort, the efficacy endpoint is PFS at 18 months. Then, to determine the sample size for testing if PFS at 18 months is at least 57%, we need to define a clinically uninteresting rate of surviving progression against which the 57% will be compared. Exploring PFS18 ranging from 40%, to 45%, we obtained the following sample size for detecting the check point inhibition effect with 80% power, using significance level of 0.05 and 0.10 for a one-sided test. For this Phase II study, we can use alpha=0.10.

Historical PFS18 months	Required sample Size	Approximate upper Critical Cut-off		
	Alpha=0.05	Alpha=0.10	Alpha=0.05	Alpha=0.10
0.40	**49**	**37**	**0.53**	**0.52**

0.41	55	42	0.53	0.52
0.42	63	48	0.54	0.52
0.43	73	55	0.54	0.52
0.44	85	64	0.54	0.53
0.45	100	75	0.54	0.53

Samples sizes were calculated using one arm survival module in Stats tools from Cancer Research and Biostatistics (CRAB) (https://stattools.crab.org/), assuming 36 months accrual and 18 month of follow-up for progression event.

When utilizing a PFS18 of 40% as the uninteresting rate in the check point inhibitor naïve population, then according to the calculations in the table provided, each expansion cohort would require a sample size of 37 to examine if PFS18 ≥ 57%. Approximately, if PFS18 is at least 52% then study will have demonstrated the early efficacy that was being sought.

Num of cohorts	Total required sample Size	
	Alpha=0.05	Alpha=0.10
1	49	37
2	98	74
3	147	111
4	196	148

Thus, if all the cohorts had met the criteria for expansion after Phase I, the total study will be 148 (37x4); if only 3 groups met the criteria, study size will be 111; if only 2 groups met the criteria, study size will be 74; and if only 1 group met the criteria, study size will be 37.

8.2 Populations for Analysis

- The All-Subjects-as-Treated (ASaT) population will be employed for safety analyses. Descriptive tables that summarize the number and percentage of subjects that experience adverse events as categorized in the NCI CTCAE Version 4.03 will be generated by cohort/group.
- The intent-to-treat (ITT) population will be employed for response and PFS analyses. Descriptive tables that summarize the number and percentage of subjects with responses and PFS will be generated by cohort/group.

8.3 Statistical Methods

8.3.1 Safety Analysis

The safety of combined checkpoint inhibition with nivolumab and ipilimumab, after autologous hematopoietic stem cell transplantation in patients at high risk for post-transplant recurrence, will be evaluated for composite endpoint (at least one treatment-related toxicity and all adverse events observed in each cohort and presented as counts (percentages) and corresponding exact binomial 95% confidence intervals for proportion. Adverse events will include Immune-mediated colitis, hepatitis, endocrinopathies, nephritis, rash, encephalitis and immune-related AEs (irAEs).

8.3.2 Complete Response Rate

Complete response rate will be evaluated at 3, 6 and 12 months after ASCT in each of the 6 cohorts. The estimates of the CR will be presented as count (proportion) and corresponding exact binomial 95% confidence intervals for proportion at each time point.

8.3.3 Progression Free Survival at 12, 18 months

Progression-free survival (PFS) is defined as time interval from date of transplantation to pathologic disease progression or death from any cause. PFS of patients at high risk for post-autologous stem cell transplant recurrence in each cohort will be estimated using Kaplan-Meier method and probabilities will be calculated for months 12 months and 18 months, along with 95%. In Phase II, if PFS18 is at least 52% then study will have demonstrated the early efficacy that was sought in that particular cohort, i.e. PFS18 ≥ 57%.

8.3.4 Longitudinal analysis of TCR repertoire and blood immune phenotype

Longitudinal analysis of TCR repertoire analysis results reported as diversity scores will be conducted on samples as determined by DNA sequencing and analyzed by ImmunoSeq software (Adaptive Biotechnologies). TCR repertoire diversity scores in evaluable patient samples will be over time using mixed model repeated measures (MMRM) by utilizing PROC MIXED SAS 9.4. In this models, the status of infection as a time-dependent will be included to examine the effect of both time and infection on cell cytokine levels.

Longitudinal analysis will be performed on blood samples collected at 14 time points:

1) Screening Visit (at time of informed consent)
2) Apheresis Sample (except for group F, due to stem cell collection having occurred previously). For those patients who sign informed consent after apheresis has already occurred, the Apheresis Sample will be performed on the previously collected, frozen product.
3) Day 1 of Week 1 of combined checkpoint therapy,
4) Day 1 of Week 4 of combined checkpoint therapy,
5) Day 1 of Week 7 of combined checkpoint therapy,
6) Day 1 of Week 12 of combined checkpoint therapy,
7) Day 1 of Week 18 of combined checkpoint therapy, and
8) Day 1 of Week 26 of combined checkpoint therapy.
9) End of Treatment Visit
10) Post-transplant, 9 months,
11) Post-transplant, 12 months,
12) Post-transplant, 15 months,
13) Post-transplant, 18 months and / or
14) Relapse, as it occurs.

Cell counts in all subsets will be analyzed as repeated measurements obtained at the 14 timepoints to examine the changes over time or less when time of relapse as the last timepoint. This longitudinal analysis will be performed by fitting an overall model across subsets of cells and a separate longitudinal analysis within each subpopulation.

1. Overall model

   Using all subsets, T cells, (T cells (CD4 versus CD8, Tregs, memory (central versus effector versus terminally differentiated effector memory), dendritic cells, macrophages, myeloid suppression cells, B cells, NK cells, NKT cells, analysis of cell counts will be performed to examine changes in counts over time (14 time points) and difference in counts between levels

of their state, naïve versus activated, as appropriate. The covariates in this model will be timepoints (14 timepoints listed above) and subset of cell population.
2. Within each subset, the following separate longitudinal analysis of cell counts over time will conducted:

i. Count of dendritic cells as a function of time (14 timepoints) and status (DC1 versus DC2),
ii. Count of DC2 as a function of time (14 timepoints) and PDL-1+/- status,
iii. Count of macrophages as a function of time (14 timepoints) and status (M1 versus M2)
iv. Count of M2 cell as a function of time (14 timepoints) and PDL-1+/- status,
v. Count of CD4 T cells as a function of time (14 timepoints) and follicular helper function status,
vi. Count of T cells as a function of time (14 timepoints) and activated status (activated versus naïve),
vii. Count of activated T cells as a function of time (14 timepoints) and PD1+/- status,
viii. Count of Tregs as a function of time (14 timepoints) and activated status (activated versus resting),
ix. Count of memory T cells as a function of time (over 14 timepoints) and type of memory cells (effector versus central memory versus terminally differentiated effector memory,
x. Count of B cells as a function of time (14 timepoints) and activated status (activated versus resting),
xi. Count of myeloid suppressor cells as a function of time (14 timepoints) and PDL-1+/- status,

For these count variables, Poisson Regression Analysis based on generalized estimating equations (GEE) method will be performed by utilizing the procedure PROC GENMOD SAS 9.4 with Poisson distribution, log link function and independent covariance structure.

Continuous variables such as cytokine levels (GM-CSF, IL-1b, IL-1RA, IL-2, IL-2R, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12, IL-13, IL-15, IL-17, TNF alpha; MCP-1, MIP1a, MIP1b, MIG, RANTES, IFN-alpha, IFN-gamma, IP-10, Eotaxin) will be examined over time (14 timepoints) using mixed model repeated measures (MMRM) by utilizing PROC MIXED SAS 9.4. In both of the models to be fit to these immune markers, the status of infection as a time-dependent covariate will be included to examine the effect of both time and infection on cell cytokine levels.

8.3.5 Longitudinal analysis of the gut microbiome.

The time points of stool sample collection are:
1) Screening Visit (up to 7 days post consent). If patient signs consent within 7 days of transplant admission, stool sample collection will start from item “2” (Preconditioning)
2) Preconditioning (to be collected within 48 hours prior to transplant admission)
3) Engraftment, (within 72 hours of ANC $\geq$ 500)
4) Day 1 of Week 1 of combined checkpoint therapy,
5) Day 1 of Week 4 of combined checkpoint therapy,
6) Day 1 of Week 7 of combined checkpoint therapy,
7) Day 1 of Week 12 of combined checkpoint therapy,
8) Day 1 of Week 18 of combined checkpoint therapy, and
9) Day 1 of Week 26 of combined checkpoint therapy.
10) End of Treatment Visit
11) Post-transplant, 9 months,
12) Post-transplant, 12 months,

13) Post-transplant, 15 months,
14) Post-transplant, 18 months and / or
15) Relapse, as it occurs.

Counts of specific intestinal microbial strains will be examined overtime (15 time points) using Poisson regression analysis utilizing PROC GENMOD as described in analysis of blood immune markers. In each of the models for each microbial strain, status of infection as a time-dependent covariate will be included as microbial along timepoint variable.
The overall microbial composition will be determined by 16S rRNA miSeq Illumina platform and analyzed by Second Genome Solutions proprietary 16S bioinformatic data analysis software package.

8.4 Additional Endpoint Analyses

8.4.1 Toxicities of the treatments

The toxicity of combined checkpoint inhibition with nivolumab and ipilimumab after autologous hematopoietic stem cell transplantation in patients at high risk for post-transplant recurrence will be evaluated for all adverse events with grade 3 or grade 4 observed in each cohort and presented as counts (proportion) and corresponding exact binomial 95% confidence intervals for proportion.

8.4.2 Evaluation of tumor site phenotype

Absolute number of PD-L1/L2-bearing activated helper T cell subpopulations from biopsy at tumor site will be examined for two time points prior to conditioning and time of progression (within 18 months post-transplant) using Poisson regression analysis with GEE described in analysis of blood phenotype above.

8.4.3 General Data Analysis

The summary of the demographic characteristics will be presented. Continuous variables will be summarized using mean (SD) or median (interquartile range) depending on whether or not the data follow the normal distribution. Categorical variables will be summarized by frequency (percentage). All adverse events will be presented as listings. All analysis will be performed using SAS version 9.4 (SAS Institute Inc. Cary, NC, USA).

8.5 Withdrawal of Patients

Patients may withdraw from the study treatment and assessments at any time. Specific reasons for withdrawal include:

A. Voluntary withdrawal of consent by the patient or guardian
B. Safety reasons requiring discontinuation as determined by the physician(s) caring for the patient
C. Non-compliance to protocol
D. Loss to follow-up
E. Completion of all study procedures and follow-up

8.6 Stopping Rules

Phase Ib Stopping Rules

If 3 of 7 patients in a single cohort experience a treatment-related limiting toxicity (after combined checkpoint inhibitor treatment is initiated) defined as a ≥ grade 4 non-hematologic toxicity as specified by the Common Terminology Criteria for Adverse Events v4.03 (CTCAE), that single cohort will be terminated. Exceptions listed in section 5.9 apply to this endpoint as well. (http://ctep.cancer.gov/reporting/ctc.html)

Phase IIA Stopping Rules

Toxicity monitoring rule for each cohort of 37 patients treated with ipilimumab/nivolumab in Phase IIA was derived using toxicity based on repeated significance testing method obtained from R-Package "Clinfun" in R version 3.4.3, the R Foundation for Statistical Computing, Vienna, Austria. Based on toxicity rate observed in Phase 1b, we considered toxicity rate of 0.25 to be the acceptable rate and occurrence rate of 0.30 to the unacceptable rate of toxicity. Thus, using CLINFUN function 'toxbdry' with arguments pLo=0.25, pHi=0.30, sequence of looks 2:37, significance level (probability of declaring treatment as unacceptable when toxicity rate is 0.30=0.10, 90% power of declaring Ipinivo treatment with toxicity 0.30 as unacceptable, boundary shape parameter delta=0.15 and taking the alternative priority error threshold, the monitoring rule given in Table 7 was obtained.

Table-A Stopping Boundaries for combined checkpoint inhibition with nivolumab and ipilimumab after autologous hematopoietic stem cell transplantation

Monitoring Look	Number of Patients at Monitoring Look	Stop if Number of Toxicities is at least
1	2	1
2	5	2
3	9	3
4	13	4
5	17	5
6	21	6
7	25	7
8	29	8
9	33	9
10	37	10

In each expansion cohort of size 37 the trial will be terminated based on the above table-A using the rules:

Out of the first 2 patients, stop if 1 or more report toxicities. Out of the first 5 patients, stop if 2 or more report toxicities. Out of the first 5 patients, stop if 2 or more report toxicities. Out of the first 9 patients, stop if 3 or more report toxicities. Out of the first 13 patients, stop if 4 or more report toxicities. Out of the first 17 patients, stop if 5 or more report toxicities. Out of the first 21 patients, stop if 6 or more report toxicities. Out of the first 25 patients, stop if 7 or more report toxicities. Out of the first 29 patients, stop if 8 or more report toxicities. Out of the first 33 patients, stop if 9 or more report toxicities. Out of the first 37 patients, stop if 10 or more report toxicities.

Table-B Operating Characteristics of Toxicity Monitoring for Pa=0.25 vs Pu=0.30 (n=37)

Toxicity rate number	Toxicity Rate	Prob. of crossing low boundary	Prob. of stopping low boundary	Expected sample size for low boundary	Prob. of crossing high boundary	Prob. of stopping high boundary	Expected sample size for high boundary

1	0.25	0.781	0.776	13.3	0.772	0.766	13.9
2	0.26	0.810	0.805	12.5	0.802	0.796	13.0
3	0.27	0.837	0.831	11.7	0.830	0.824	12.2
4	0.28	0.861	0.856	10.9	0.855	0.849	11.4
5	0.29	0.883	0.877	10.2	0.877	0.872	10.6
6	0.30	0.902	0.897	9.5	0.897	0.892	9.9
P_a, toxicity rate that is acceptable; P_u, toxicity rate that is unacceptable; Prob, probability							

From the operating characteristics in Table B, it observed that the stopping guideline will have 90% power (prob. crossing high boundary=0.897) to terminate the trial in any cohort of size 37 when the true toxicity rate is 0.30, and expected sample size for early termination at this rate will be 10 patients(expected sample size for high boundary=9.9).
The definition of unacceptable toxicity will be as follows:

- Any Grade 2 drug-related uveitis or 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 drug-related laboratory abnormalities, uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic adverse event, hypersensitivity reactions, and infusion reactions
    - Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic adverse event, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation
    - Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except those noted below
        - 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 > 8 x ULN
            - Total bilirubin > 5 x ULN
            - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any Grade 4 drug-related adverse event or non-hematological laboratory abnormality, except for the following events which do not require discontinuation:
    - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset.
    - 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
- Any Grade 5 drug-related death

8.7 Data Management and Analysis

Case report forms will be created for management of data collected during this study, and will be available in electronic format. A database in Access will be created based on the case report forms. All study data will be imported into SAS and data management will be utilized to flag, and generate queries on out of range data issues until they are resolved. All analysis will be performed using SAS software version 9.4 (SAS Institute Inc. Cary, NC).

9.0 SAFETY REPORTING

9.1 Definitions

9.1.1 Adverse Event Definition

An adverse event (AE) is any new untoward medical occurrence or worsening of a preexisting medical condition in a patient administered a pharmaceutical product, which does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (e.g., including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the drug, whether or not it is considered to be drug related. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of drug. The following information should be considered when determining whether or not to record a test result, medical condition, or other incident when collecting and reporting Adverse Events:

- From the time of informed consent through the day prior to Day 1 Week 1 of combined checkpoint therapy, only study protocol-related AEs should be recorded. A protocol-related AE is defined as an untoward medical occurrence as a result of a protocol mandated procedure that is not standard of care.
- All medical conditions present or ongoing pre-dose on Day 1 Week 1 of combined checkpoint therapy should be recorded.
- All AEs or complications associated with any procedures (study related or not) should be recorded from Day 1 Week 1 of combined checkpoint therapy through the end of the safety-reporting period of 100 days after the last dose of study therapy or until the start of a subsequent systemic anti-cancer therapy, if earlier.
- Changes in medical conditions and AEs, including changes in severity, frequency, or character, during the safety-reporting period should be recorded.
- Generally, abnormal laboratory values should not be recorded as an AE unless it is associated with clinical signs or symptoms requires an intervention, or results in a serious adverse event, or results in study termination, or interruption/discontinuation of study treatment. When recording an AE resulting from a laboratory abnormality, the resulting medical condition rather than the abnormality itself should be recorded.

9.1.2 Serious Adverse Event Definition

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

- results in death
- is life-threatening (defined as an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization. The following hospitalizations are not considered SAEs:
    - a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)

- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (e.g., routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (e.g., lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).

- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect
- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [e.g., medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization, or the development of drug dependency or drug abuse.)
- Potential drug induced liver injury (DILI) is also considered an important medical event.
- Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.
- Although pregnancy, overdose, and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

9.2 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study subject is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 6 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (e.g., dose tapering if necessary for subject safety).

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

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

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form.

9.3 Overdose

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

9.4 Other Safety Considerations

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

9.5 Procedures for AE and SAE Reporting

All Adverse Events and Serious Adverse Events (SAEs) that occur following the subject's first dose of therapy on Day 1 of Week 1 of combined checkpoint therapy in the study through 100 days of discontinuation of dosing or until the start of a subsequent systemic anti-cancer therapy, if earlier, must be reported to BMS Worldwide Safety, and according to local regulations. All serious adverse events (SAE) regardless of causality must be reported to the PI, (within 24 hours) and the research coordinator for notification of Hackensack University Medical Center's IRB.

The local IRB must be informed of any serious, unexpected, or alarming adverse events that occur during the approval period involving a subject within seven days of occurrence, or sooner if local guidelines apply. Any deaths of subjects require immediate (within 24 hours) reporting.

Sponsor generated reports of adverse events occurring at other investigative sites within fourteen days of receipt if the event is definitely related or possibly related to the research protocol as deemed by the sponsor lead investigator, and/or the DSMB.

Intensity for each adverse event, including any lab abnormality, will be determined by using the NCI CTCAE, version 4.03, as a guideline, wherever possible. The criteria are available online at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf.

9.6 Assessment of Toxicity

Common Terminology Criteria for Adverse Events (CTCAE) will be used for the assessment and grading of all toxicities experienced by patients enrolled into this study (http://ctep.cancer.gov/forms/CTCAE_Index.pdf)

If the nature of the adverse experience is listed in the CTCAE, **the maximum grade will be reported.**

If the adverse experience is not listed in the NCI CTCAE Common Terminology Criteria Adverse Events, report the toxicity grade using the following criteria:

- Grade 1 = Mild: an adverse experience which is easily tolerated by the patient, causing minimal discomfort and not interfering with everyday activities.
- Grade 2 = Moderate: an adverse experience which is sufficiently discomforting to interfere with normal everyday activities.
- Grade 3 = Severe: an adverse experience which is incapacitating and prevents normal everyday activities.

- Grade 4 = Life Threatening: an adverse experience which places the patient at immediate risk of death.
- Grade 5 = Death

9.7 Assessment of Causality

The local Investigator will explain each adverse experience and assess its relationship, if any, to study drug treatment. Causality will be determined by the local Investigator using the following categories: Not Related, Unlikely, Suspected (Reasonable Possibility), Probable.

- Not related: The adverse experience is definitely not related to the test drug.
- Unlikely: There are other, more likely causes and the drug is not suspected as a cause.
- Suspected (reasonable possibility): A direct cause and effect relationship between the drug and the adverse experience has not been demonstrated but there is a reasonable possibility that the experience was caused by the drug.
- Probable: There probably is a direct cause and effect relationship between the adverse experience and the study drug.

The degree of certainty with which an adverse experience is attributed to drug treatment (or alternative causes, e.g. natural history of the underlying diseases, concomitant therapy, etc.) will be determined by how well the experience can be understood in terms of one or more of the following:

Known pharmacology of the drug. Reaction of similar nature being previously observed with this drug or class of drug. The experience having often been reported in literature for similar drugs as drug related e.g. skin rashes, blood dyscrasia. The experience being related by time to drug ingestion terminating with drug withdrawal (dechallenge) or reproduced on rechallenge.

9.8 Follow-up of Adverse Experiences

Patients with adverse experiences or serious adverse events will be actively followed until the event has subsided (disappeared) or until the condition has stabilized.

10.0 ADMINISTRATIVE REQUIREMENTS

10.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

10.2 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

A conference will be held with the patient and family to discuss this study and alternative treatments available for treatment of the underlying disease. All potential risks associated with the use of Nivolumab and ipilimumab will will be discussed as objectively as possible. The patient has the right to review and correct the results of the pre-transplant evaluation.

10.3 Protocol Registration

All patients will be assigned a unique patient number (UPN) in accordance with HUMC Standard Practice.

10.4 Patient Confidentiality

In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) or its designees and regulatory authority(ies) access to the patient accountability records, study reports and communications. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

10.6 Record Retention

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s). The licensed medical records department, affiliated with the institution where the patient receives medical care, maintains all original inpatient and outpatient chart documents.

11.0 ECOG PERFORMANCE STATUS SCALE

Grade	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
* As published in Am. J. Clin. Oncol.: *Oken, M.M., Creech, R.H., Tormey, D.C., Horton, J., Davis, T.E., McFadden, E.T., Carbone, P.P.: Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group. Am J Clin Oncol 5:649-655, 1982.* The Eastern Cooperative Oncology Group, Robert Comis M.D., Group Chair.	

12.0 BODY SURFACE AREA

Body surface area (BSA) should be calculated using a standard nomogram that yields the following results in meters squared (m^2):

$$\text{BSA} = \sqrt{\frac{Ht(inches) \times Wt(lbs)}{3131}}$$

or

$$\text{BSA} = \sqrt{\frac{Ht(cm) \times Wt(kg)}{3600}}$$

13.0 ETHICAL CONSIDERATIONS

This study is to be conducted according to US and international standards of Good Clinical Practice (GCP), FDA Title 21 part 312 and International Conference on Harmonization guidelines, applicable government regulations and Institutional research policies and procedures. This study is to be performed by personnel who are qualified by education, training, and experience to perform their respective tasks and that the study will not use the services of study personnel for whom sanctions have been invoked or where there has been scientific misconduct or fraud.

This protocol, informed consent form, and any accompanying materials provided to the subject, will be submitted to a properly constituted independent Ethics Committee (EC) or Institutional Review Board (IRB), in agreement with local legal regulations, for formal approval of the study conduct. The decision of the EC/IRB concerning the conduct of the study will be made in writing to the investigator and a copy of this decision will be provided to the sponsor before commencement of this study. Any modifications made to the protocol after receipt of the EC/IRB approval must be submitted by the investigator to the committee as an amendment, in accordance with local procedures and regulatory requirements. This study is to be conducted according to the IRB/EC approved protocol.

13.1 Informed Consent

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. The information includes, but is not limited to: the purpose, potential risks and benefits, alternatives to participation, confidentiality statement, and other critical issues regarding the clinical study in which they volunteer to participate. This consent form will be submitted with the protocol for review and approval by the EC/IRB for the study. The formal consent of a subject, using the EC/IRB-approved consent form, must be obtained before that subject undergoes any study procedure. The consent form must be signed and dated by the subject or legally acceptable representative, and the investigator designated research professional obtaining the consent.

14.0 CTCAE

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE4.032010-06-14QuickReference8.5x11.pdf

15.0 REFERENCES

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APPENDIX A: Second-Line Age Adjusted International Prognostic Index (sAAIPI)

Factors:

- **Stage III or IV**
- **LDH> Upper limit of normality**
- **ECOG Performance Status ≥ 2**

Low-risk: 0 factors
Low-Intermediate: 1 factor
High-intermediate: 2 factors
High: 3 factors

APPENDIX B: The Lugano Classification for Response Assessment of Non-Hodgkin Lymphoma

Response and Site	PET-CT–Based Response	CT-Based Response
Complete	Complete metabolic response	Complete radiologic response (all of the following)
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS†	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi
	It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial	Partial metabolic response	Partial remission (all of the following)
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites
	At interim, these findings suggest responding disease	When a lesion is too small to measure on CT, assign 5 mm × 5 mm as the default value
	At end of treatment, these findings indicate residual disease	When no longer visible, 0 × 0 mm
		For a node > 5 mm × 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not applicable
No response or stable disease	No metabolic response	Stable disease
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not applicable
Progressive disease	Progressive metabolic disease	Progressive disease requires at least 1 of the following
Individual target nodes/nodal masses	Score 4 or 5 with an increase in intensity of uptake from baseline and/or	PPD progression:
Extranodal lesions	New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤ 2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Nonmeasured lesions	None	New or clear progression of preexisting nonmeasured lesions

Response and Site	PET-CT–Based Response	CT-Based Response
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement

Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions.

*A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).

†PET 5PS: 1, no uptake above background; 2, uptake ≤ mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

As published by Cheson et al, *JCO August 11, 2014*

APPENDIX C: INTERNATIONAL MYELOMA WORKING GROUP

International Myeloma Working Group uniform response criteria for multiple myeloma

Durie et al. International uniform response criteria for multiple myeloma. Leukemia. 2006; 20:1467-1473.
Criteria for multiple myeloma disease assessment:

Table 5 International Myeloma Working Group uniform response criteria: CR and other response categories

Response subcategory	*Response criteria*[a]
sCR	CR as defined below plus Normal FLC ratio and Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c]
CR	Negative immunofixation on the serum and urine and Disappearance of any soft tissue plasmacytomas and ≤5% plasma cells in bone marrow[b]
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
PR	≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to <200 mg per 24 h If the serum and urine M-protein are unmeasurable,[d] a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria If serum and urine M-protein are unmeasurable, and serum free light assay is also unmeasurable, ≥50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥30% In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
SD (not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates)	Not meeting criteria for CR, VGPR, PR or progressive disease

Abbreviations: CR, complete response; FLC, free light chain; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response.
[a]All response categories require two consecutive assessments made at anytime before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.
[b]Confirmation with repeat bone marrow biopsy not needed.
[c]Presence/absence of clonal cells is based upon the k/λ ratio. An abnormal k/λ ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/λ of >4:1 or <1:2.
[d]Refer to Table 4 for definitions of measurable disease.

Table 6 International Myeloma Working Group uniform response criteria: disease progression and relapse

Relapse subcategory	*Relapse criteria*
Progressive disease[a] To be used for calculation of time to progression and progression-free survival end points for all patients including those in CR (includes primary progressive disease and disease progression on or off therapy)	Progressive Disease: requires any one or more of the following: Increase of ⩾25% from baseline in Serum M-component and/or (the absolute increase must be ⩾0.5 g/dl)[b] Urine M-component and/or (the absolute increase must be ⩾200 mg/24 h Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be >10 mg/dl. Bone marrow plasma cell percentage: the absolute % must be ⩾10%[c] Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia (corrected serum calcium >11.5 mg/dl or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder
Clinical relapse[a]	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features)[b] It is not used in calculation of time to progression or progression-free survival but is listed here as as something that can be reported optionally or for use in clinical practice 1 Development of new soft tissue plasmacytomas or bone lesions 2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion 3. Hypercalcemia (>11.5 mg/dl) [2.65 mmol/l] 4. Decrease in hemoglobin of ⩾2 g/dl [1.25 mmol/l] (see Table 3 for further details) 5. Rise in serum creatinine by 2 mg/dl or more [177 μmol/l or more]
Relapse from CR[a](To be used only if the end point studied is DFS)[d]	Any one or more of the following: Reappearance of serum or urine M-protein by immunofixation or electrophoresis Development of ⩾5% plasma cells in the bone marrow[c] Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia see below)

Abbreviations: CR, complete response; DFS, disease-free survival.
[a]All relapse categories require two consecutive assessments made at anytime before classification as relapse or disease progression and/or the institution of any new therapy.
[b]For progressive disease, serum M-component increases of ⩾1 gm/dl are sufficient to define relapse if starting M-component is ⩾5 g/dl.
[c]Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.
[d]For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.

APPENDIX D: STUDY FLOWCHART

	Screening Phase	Treatment cycles	Safety Visits	End of treatment	Post treatment		
	Screening (Visit 1)	Day 1 (+/- 2 days) of weeks 1, 4, 7, 10, 12, 14, 16, 18, 20, 22, 24, 26 Week 1 is defined as initiation of checkpoint inhibitors, **not** weeks post ASCT.	Day 1 (+/- 2 days) of weeks 2, 3, 5, 6, 8, and 9 Week 1 is defined as initiation of checkpoint inhibitors, **not** weeks post ASCT.	For study completion or discontinuation of therapy (discon) (To be completed within 2 weeks of last dose) (+/- 14 days)	Safety visit 30 days post End of Treatment Visit (+/- 14 days)	Follow up visits every 12 weeks post End of Treatment Visit (+/- 14 days)	Survival visits every 12 weeks post End of Treatment (+/- 14 days)
Administrative Procedures							
Informed Consent	X[a]						
Informed Consent for Future Biomedical Research - Optional	X[n]						
Inclusion/Exclusion Criteria	X						
Demographics/Medical History	X[a]						
Prior and Concomitant Medication Review	X	X	X	X	X	X[g]	
Trial Treatment Administration (See Section 5.0)		X					
Post-study disease status				X	X	X	
Survival Status							X[h]
Clinical Procedures/Assessments							
Review Adverse Events	X	X	X	X	X	X[g]	
Physical Examination	X[d]	X	X	X	X	X	
Vital Signs and Weight	X[d]	X	X	X	X	X	
12-Lead Electrocardiogram	X[b]						
MUGA or ECHO with LVEF	X[b]						
Imaging Assessment[e]	X[b, e]						
Pulmonary Function Test	X[b]						
ECOG PS	X[d]	X		X	X	X	
Laboratory Assessments							
CMV, HIV, HTLV, Hepatitis B, Hepatitis C evaluations	X[d]						
Pregnancy Test[c]	X[d]	X		X	X		
CBC with differential	X[d]	X	X	X	X	X	

Complete Metabolic Panel (Na, K, BUN, Creatinine, Cl, CO2, Anion Gap, Ca, P, Mg, Uric Acid, Alk Phos, AST, ALT, bilirubin, albumin, LDH, Glucose, GGTP).	X[d]	X	X	X	X	X	
Total CK	X [d]	X			X		
LFTs (PT/INR, aPTT, albumin, total bilirubin)	X[d]						
Baseline disease assessments	X [d, f]						
Urinalysis	X [d]	On weeks 1,7,14,22 and 26 only		X			
Haptoglobin	X [d]	On weeks 1, 7, 12, 16, 20, and 24 only			X		
TSH, T3 and free T4; lipase and amylase, cortisol	X [d]	On weeks 1,7,14,22 and 26 only		X			
Bone Marrow Biopsy / Tumor Biopsy	X[k]			X[k]			
Peripheral blood collection for blood immune phenotype and metabolomics analysis	X[L]	X On weeks 1, 4, 7, 12, 18 and 26 only				Post transplant months 9, 12,15 and 18 and at time of relapse	
Stool sample for microbiome analysis	X[m]	X On weeks 1,4, 7, 12, 18 and 26 only				Post transplant months 9, 12,15 and 18 and at time of relapse	
	Response Assessment						
For groups A,B,C,D		PET-CT scan and/or CT scan with intravenous/oral contrast of neck, chest, abdomen, and pelvis will be performed for response evaluation 90-100 days post ASCT, 180-200 days post ASCT, 360-380 days post ASCT and 540-560 days post ASCT. Response criteria will follow the Lugano Classification (see Appendix B).					
For groups E and F		Serum protein electrophoresis with immunofixation, quantitative serum IgG, IgM, IgA (IgE or IgD in cases where this is the involved immunoglobulin), serum free light chains, 24-hour urine for protein electrophoresis with immunofixation and protein quantification will be collected for response evaluation 30-40 days post ASCT, 60-70 days post ASCT, 90-100 days post ASCT, 180-200 days post ASCT, 270-290 days post ASCT, 360-380 days post ASCT, 450-470 days post ASCT and 540-560 days post ASCT.					

		Response criteria will follow the International Myeloma Working Group (IMWG) Uniform Response Criteria for Multiple Myeloma (see Appendix C).

[a] To be completed within 60 days prior to start of ASCT conditioning regimen

[b] To be completed within 90 days prior to start of ASCT conditioning regimen

[c] Pregnancy test can be urine or serum Beta-HCG (for women of child-bearing potential)

[d] To be completed within 30 days prior to start of ASCT conditioning regimen

[e] Chest radiography to be completed within 90 days prior to start of ASCT conditioning regimen.

[f] **For groups A, B, C, D**: PET-CT scan and/or CT scan with intravenous/oral contrast of neck, chest, abdomen, and pelvis within 30 days prior to initiation of ASCT conditioning must be completed

For groups E&F: Skeletal Survey must be completed within 30 days prior to initiation of ASCT conditioning. Serum protein electrophoresis with immunofixation, quantitative serum IgG, IgM, IgA (IgE or IgD in cases where this is the involved immunoglobulin), serum free light chains, 24-hour urine for protein electrophoresis with immunofixation and protein quantification will be collected for response evaluation.

[g] Subjects will be followed through 100 days of discontinuation of dosing or until the start of a subsequent systemic anti-cancer therapy, if earlier, for Adverse Events and Concomitant Medications

[h] Survival Status may be conducted by telephone

[k] Tumor Biopsies and/or Bone Marrow Biopsies for Lymphoma subjects (Groups A through D) and Bone Marrow Biopsies for Multiple Myeloma subjects (Groups E & F) will be collected at screening, end of treatment, complete response, and at relapse, if clinically indicated . Tumor Biopsies and/or Bone Marrow Biopsies will be performed to confirm complete response at the discretion of the investigator. For Bone Marrow Biopsies, the research sample will be collected (aspirate, send the first pull, yellow top tube) to Dr. Korngold's lab. Additional samples for all disease groups will be sent to pathology for immunostaining of fixed tissue for PDL1 expression on tumor cells and for the in situ presence of CD4 and CD8 T cells with PD1 expression. If viable biopsy material is unavailable for research purposes, Dr. Korngold's lab will access fixed archival tumor materials for preparing tumor lysates and possibly for retrieving T cell DNA for repertoire analysis. Samples for Georgetown University subjects are to be shipped via Fed Ex on the day of collection – tubes banded in sealed plastic bag and wrapped in bubble wrap at room temperature to Dr. Korngold's lab.

[L] Two time points are to be collected for peripheral blood samples prior to combined checkpoint therapy initiation: 1. During the screening visit; and 2. An apheresis sample from the Apheresis product (1x yellow top tube – ½ full (4mL)). For patients in groups A-E who already had Apheresis product collected, the apheresis sample may be performed on the frozen product. For group F ONLY, apheresis sample will not be collected.

[m] Three time points are to be collected for stool samples prior to combined checkpoint therapy initiation: 1. Screening Visit (up to 7 days post consent); 2. Preconditioning (to be collected within 48 hours prior to transplant admission); and 3. At engraftment (within 72 hours of ANC $\geq$ 500). For patients who sign consent within 7 days of transplant admission, the Screening Visit sample will not be collected, and collection will start with the Preconditioning sample.

[n] An optional informed consent for the Hackensack University Medical Center sampling protocol, TMBK 06.05.039, will be presented at time of screening if the subject is not currently participating.

APPENDIX E: Events of Clinical Interest Reference Table

Pneumonitis (reported as ECI if ≥ Grade 2)		
Acute interstitial pneumonitis	Interstitial lung disease	Pneumonitis
Colitis (reported as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Intestinal Obstruction	Colitis	Colitis microscopic
Enterocolitis	Enterocolitis hemorrhagic	Gastrointestinal perforation
Necrotizing colitis	Diarrhea	
Endocrine (reported as ECI if ≥ Grade 3 or ≥ Grade 2 and resulting in dose modification or use of systemic steroids to treat the AE)		
Adrenal Insufficiency	Hyperthyroidism	Hypophysitis
Hypopituitarism	Hypothyroidism	Thyroid disorder
Thyroiditis	Hyperglycemia, if ≥Grade 3 and associated with ketosis or metabolic acidosis (DKA)	
Endocrine (reported as ECI)		
Type 1 diabetes mellitus (if new onset)		
Hematologic (reported as ECI if ≥ Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Autoimmune hemolytic anemia	Aplastic anemia	Thrombotic Thrombocytopenic Purpura (TTP)
Idiopathic (or immune) Thrombocytopenia Purpura (ITP)	Disseminated Intravascular Coagulation (DIC)	Haemolytic Uraemic Syndrome (HUS)
Any Grade 4 anemia regardless of underlying mechanism		
Hepatic (reported as ECI if ≥ Grade 2, or any grade resulting in dose modification or use of systemic steroids to treat the AE**)**		
Hepatitis	Autoimmune hepatitis	Transaminase elevations (ALT and/or AST)
Infusion Reactions (reported as ECI for any grade)		
Allergic reaction	Anaphylaxis	Cytokine release syndrome
Serum sickness	Infusion reactions	Infusion-like reactions
Neurologic (reported as ECI for any grade)		
Autoimmune neuropathy	Guillain-Barre syndrome	Demyelinating polyneuropathy
Myasthenic syndrome		
Ocular (report as ECI if ≥ Grade 2 or any grade resulting in dose modification or use of systemic steroids to treat the AE)		
Uveitis	Iritis	
Renal (reported as ECI if ≥ Grade 2)		
Nephritis	Nephritis autoimmune	Renal Failure
Renal failure acute	Creatinine elevations (report as ECI if ≥Grade 3 or any grade resulting in dose modification or use of systemic steroids to treat the AE)	
Skin (reported as ECI for any grade)		
Dermatitis exfoliative	Erythema multiforme	Stevens-Johnson syndrome
Toxic epidermal necrolysis		
Skin (reported as ECI if ≥ Grade 3)		
Pruritus	Rash	Rash generalized
Rash maculo-papular		
Any rash considered clinically significant in the physician's judgment		
Other (reported as ECI for any grade)		
Myocarditis	Pancreatitis	Pericarditis
Any other Grade 3 event which is considered immune-related by the physician		

APPENDIX F: ECI Management Algorithm

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

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

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

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

Where I-O therapy is referred, it means Ipilimumab and Nivolumab combination therapy.

In general terms, each immune-related adverse event (irAE) should be managed as follows:

- Grade I: Continue treatment as scheduled, manage with symptomatic treatment
- Grade II: Withhold therapy with I-O until improvement to grade I or better. If patient misses a dose of treatment drug due to an irAE, the following dose will be given as per the original schedule, and there will not be “catch-up” doses (i.e. treatment with I-O should not exceed original 26 weeks from initiation)
- If there has been no improvement within 7 days, then steroid therapy should be initiated. Dosage should be 1-2mg/kg/day of methylprednisolone IV (or equivalent) divided in 2 daily doses. The initial dosage should be continued until irAE have improved to Grade I or better. At that time, steroid should be tapered over the course of 2 weeks to the equivalent of 20 mg/day of methylprednisolone. If there has been no exacerbation of irAE with steroid taper, once the steroid dosage is 20 mg/day, as above, I-O can be resumed. Steroids should continue to be tapered off completely over a course of 2 additional weeks.
- Grades III-IV: Interrupt therapy and start steroids as per protocol above (Grade II). I-O should be resumed as described above.

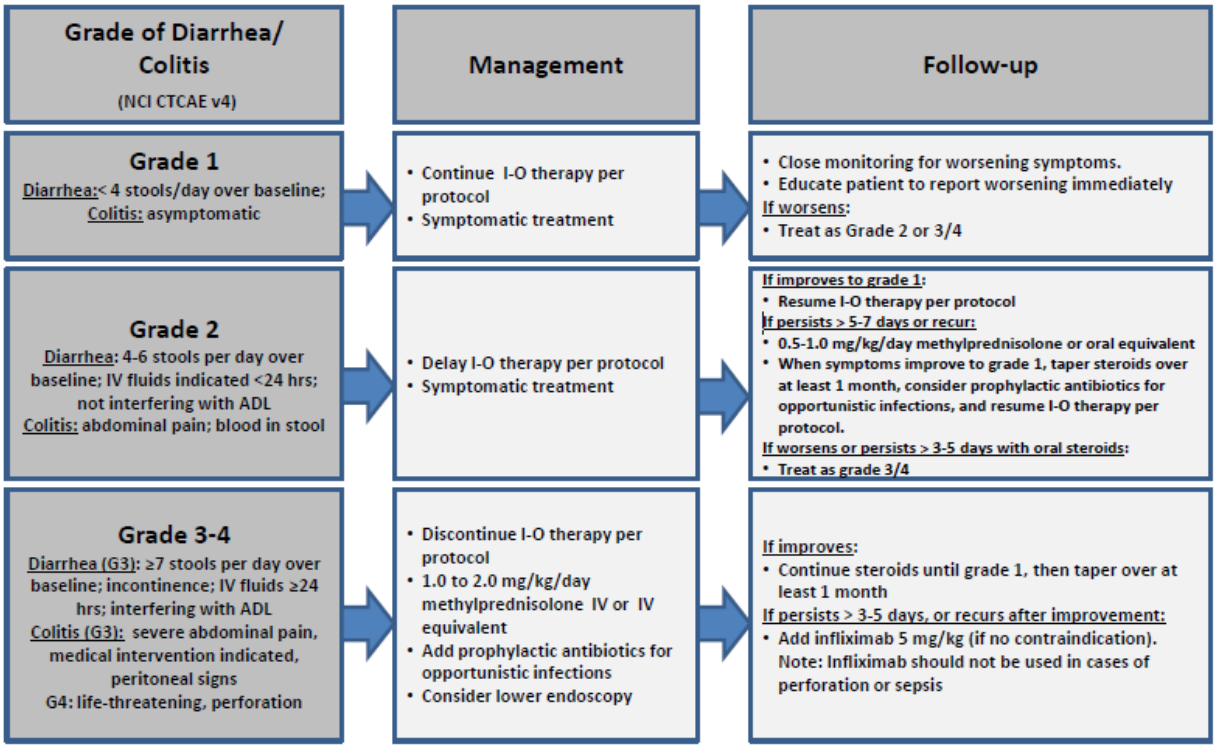
If irAE persists after 3-5 days of high-dose steroids, or if it recurs after initial improvement, consideration should be given to infliximab 5 mg/kg or mycophenolate mofetil 500-750mg three times a day.

If there is recurrence of Grade III or IV irAE, subject should be removed from study.

Please follow algorithms below for specific irAE management.

GI Adverse Event Management Algorithm

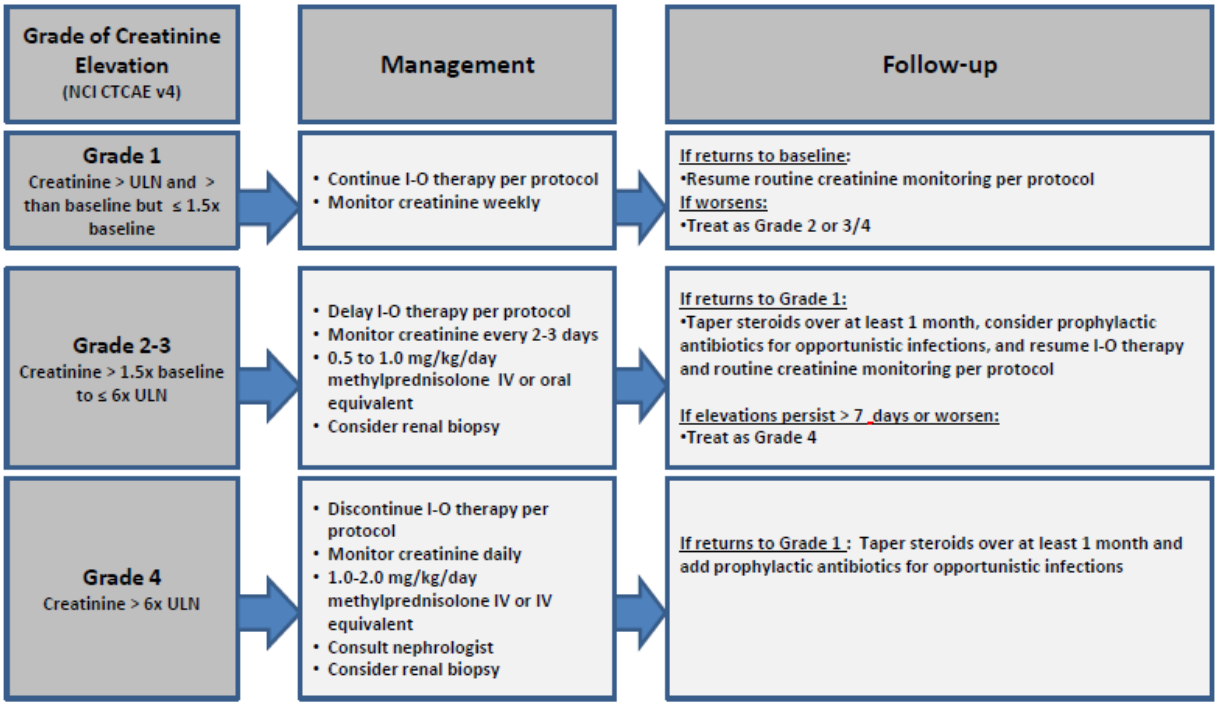
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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.

Renal Adverse Event Management Algorithm

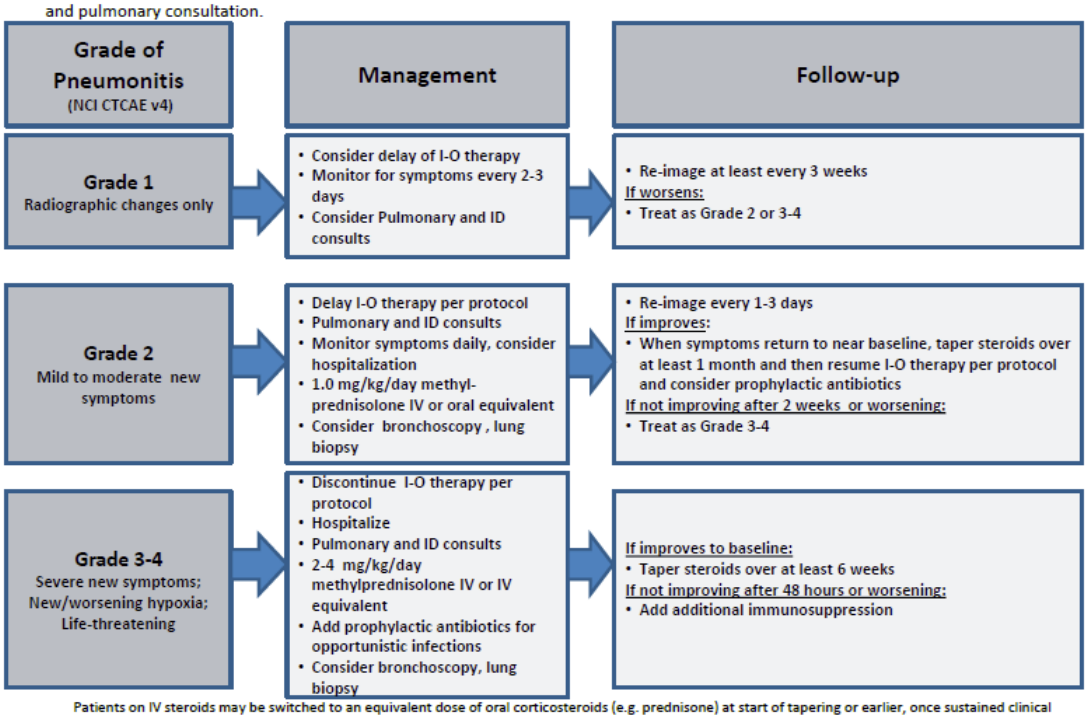
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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

Pulmonary Adverse Event Management Algorithm

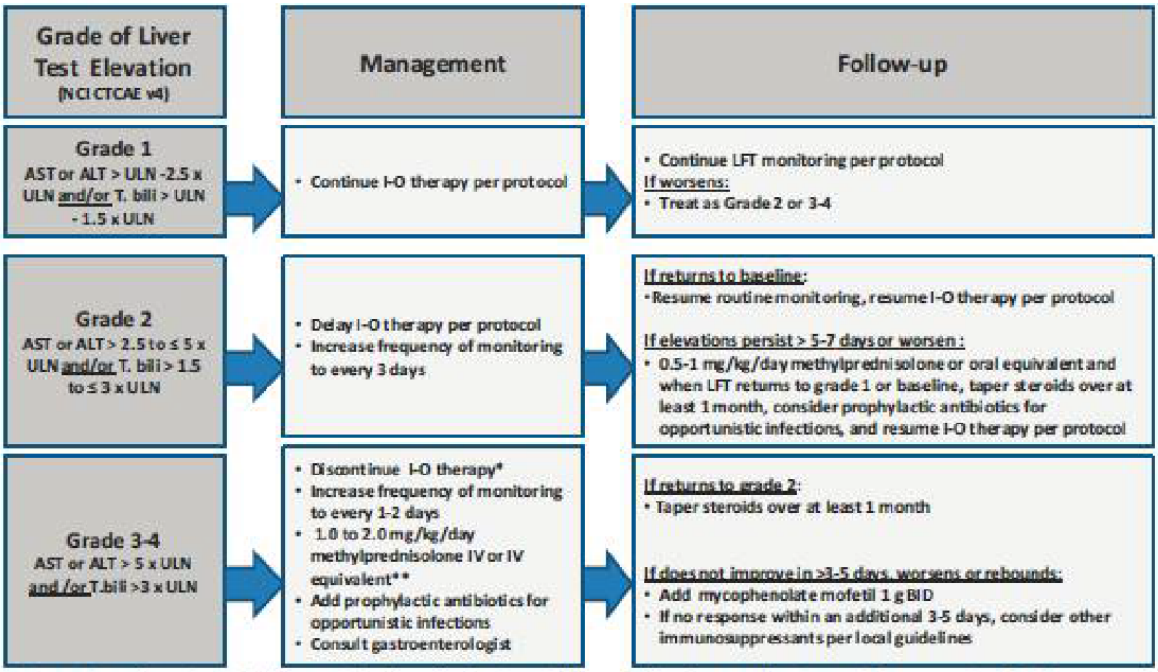
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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

Hepatic Adverse Event Management Algorithm

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



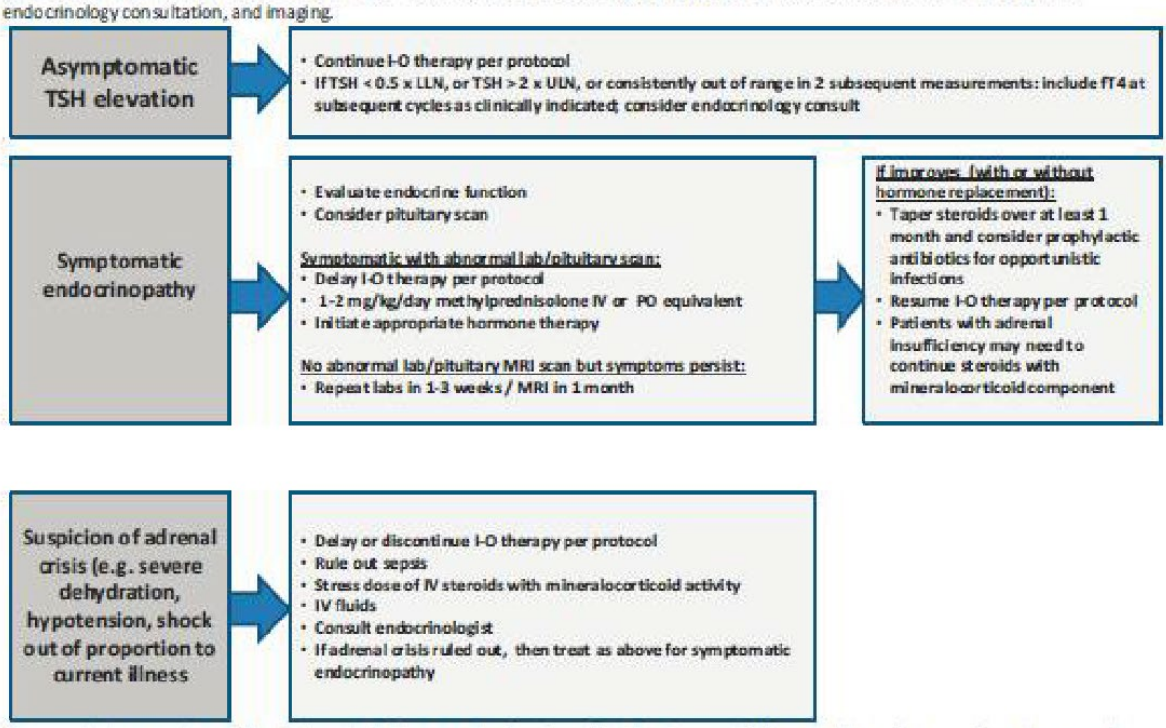
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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

Endocrinopathy Management Algorithm

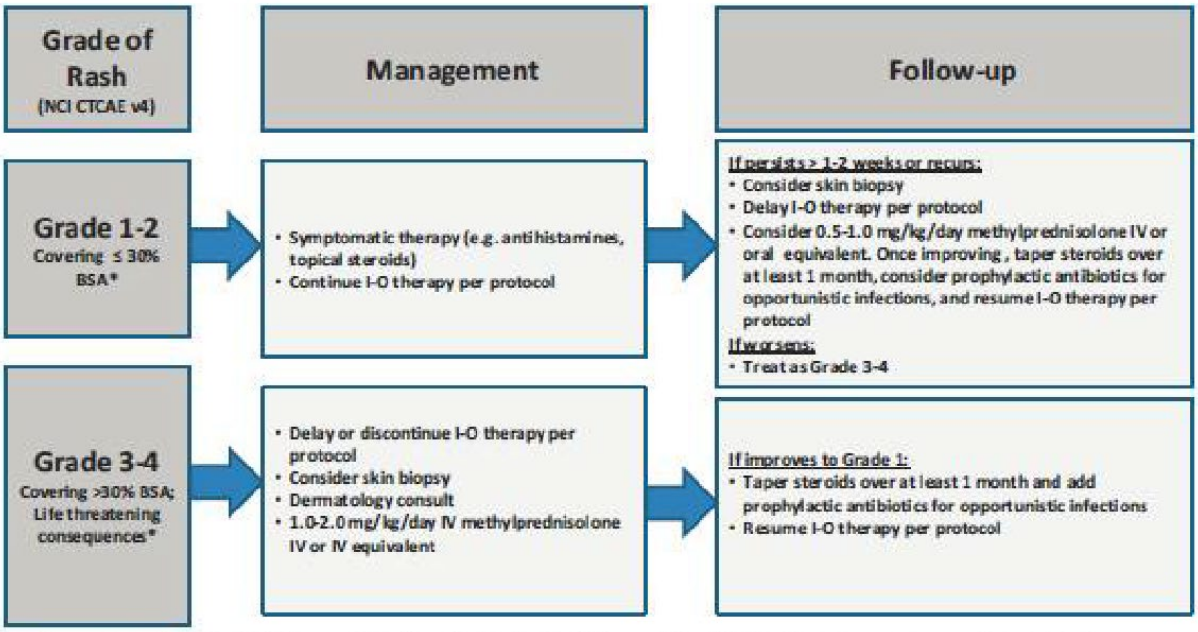
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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.

Skin Adverse Event Management Algorithm

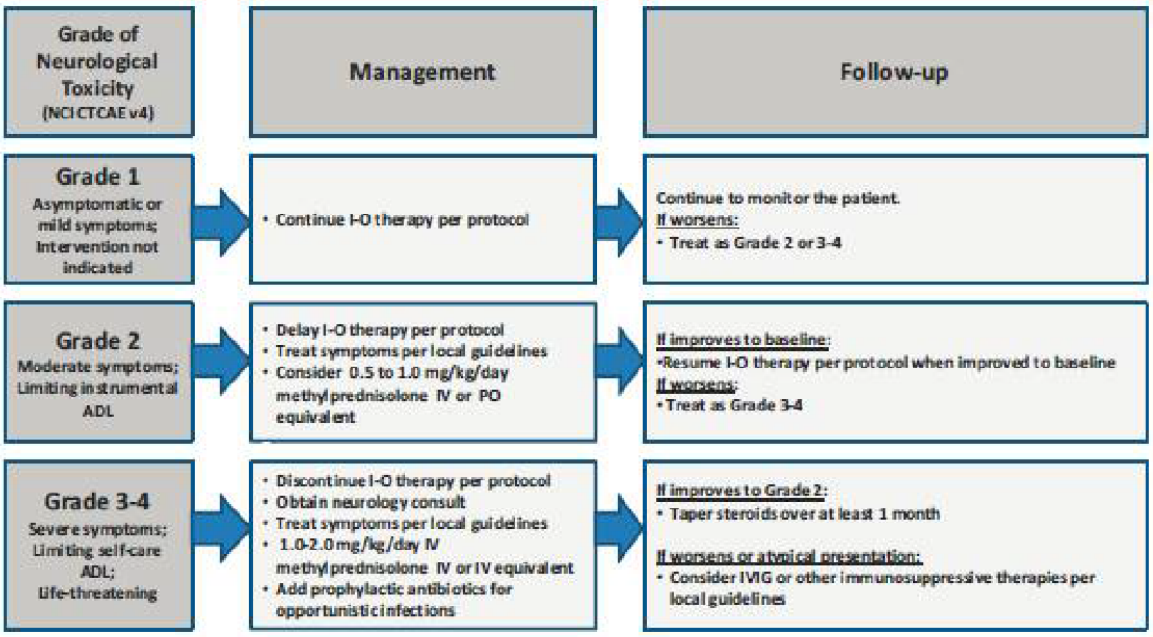
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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.

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.

APPENDIX G: Treatment of Nivolumab or Ipilimumab Related Infusion Reactions

Treatment of Nivolumab or Ipilimumab Related Infusion Reactions
Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

Since Nivolumab and ipilimumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms.

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE (version 4.03)) guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

- **For Grade 1 symptoms:** (Mild reaction; infusion interruption not indicated; intervention not indicated)
  Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premeditations are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab or ipilimumab administrations.

- **For Grade 2 symptoms:** (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for 24 hours).
  Stop the nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur then no further nivolumab or ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premeditations are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab or ipilimumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

- **For Grade 3 or Grade 4 symptoms:** (Severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]). Grade 4: (life-threatening; pressor or ventilator support indicated).

Immediately discontinue infusion of nivolumab or ipilimumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

APPENDIX H: Sample of Drug Ordering and Pharmacy Reference Material

Initial Orders

- Following submission and approval of the required regulatory documents, a supply of nivolumab and ipilimumab may be ordered from by completing a Drug Request Form provided by BMS for this specific trial.
- The initial order should be limited to the amount needed for two doses. Allow 5 business days for shipment of drug from BMS receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. All drug products will be shipped by courier in a temperature-controlled container. It is possible that sites may have more than one nivolumab clinical study ongoing at the same time. It is imperative that only drug product designated for this protocol number be used for this study.
- Pharmacy supplies not provided by BMS: Empty IV bags/containers, approved diluents, In-line filters and infusion tubing

Re-Supply

- Drug re-supply request form should be submitted electronically at least 7 business days before the expected delivery date. Deliveries will be made Tuesday through Friday.
- When assessing need for resupply, institutions should keep in mind the number of vials used per treatment dose, and that shipments may take 14 business days from receipt of request. Drug is not patient-specific. Be sure to check with your pharmacy regarding existing investigational stock to assure optimal use of drug on hand.

Drug Excursions

- Drug excursions should be reported immediately to BMS on the form provided with the study-specific drug order form

Please refer to the most recent version of the nivolumab and ipilimumab Investigator Brochure for additional information to be included as per institutional or regulatory standards.

Nivolumab (BMS-936558) Pharmacy Reference Material

As this is provided for guidance only, please see investigator brochure for additional information regarding preparation and administration.

Nivolumab has a concentration of 10mg/mL and is provided in a 10mL vial. Ten or five vials are provided in a carton.

Storage Conditions & Handling:

- Store at 2-8°C (36-46°F), protect from light, freezing, and shaking.
- If any temperature excursions are encountered during storage, please report these to BMS for assessment via the Temperature Excursion Response Form.
- As with all injectable drugs, care should be taken when handling and preparing nivolumab. Whenever possible, nivolumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents applying aseptic technique.
- Partially used vials should be disposed at the site following procedures for the disposal of anticancer drugs.

After final drug reconciliation, unused nivolumab vials should be disposed at the site following procedures for the disposal of anticancer drugs. For further information, please either discuss with your BMS CSR&O protocol manager or refer to your site IP Destruction policies and procedures

Use Time/Stability: Please refer to the appropriate section of the current Investigator Brochure/Addendum. Due to parameters surrounding the use time of nivolumab and ipilimumab, the time of preparation should be noted in the Pharmacy Source documents [accountability logs] or in study files as required for investigator sponsored research [FDA and GCP]

The administration of BMS-936558-01 injection prepared for dosing nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 20 hours in a refrigerator at under refrigeration conditions (2°-°-8°C (, 36°-46°F) and used within 24 hours, and a maximum of 4 hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and under room light. The maximum 4-hour period under room temperature and room light conditions for undiluted and diluted solutions of BMS-936558-01 injection in the IV bag includes the product administration period.

Preparation and Administration:

1. Visually inspect the drug product solution for particulate matter and discoloration prior to administration. Discard if solution is cloudy, if there is pronounced discoloration (solution may have a pale-yellow color), or if there is foreign particulate matter other than a few translucent-to-white, amorphous particles.Note: Mix by gently inverting several times. Do not shake.
2. Aseptically withdraw the required volume of nivolumab solution into a syringe, and dispense into an IV. bag. If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall. Do not enter into each vial more than once. Do not administer study drug as an IV push or bolus injection
3. Add the appropriate volume of 0.9% Sodium Chloride Injection solution or 5% Dextrose Injection solution. It is acceptable to add nivolumab solution from the vials into an appropriate pre-filled bag of diluent.
4. Note: Nivolumab infusion concentration must be at or above the minimum allowable concentration of 0.35 mg/mL [IBV13 Addendum Section 3.2.2]
5. Note: It is not recommended that so-called “channel” or tube systems are used to transport prepared infusions of nivolumab.
6. Attach the IV bag containing the nivolumab solution to the infusion set and filter.
7. At the end of the infusion period, flush the line with a sufficient quantity of approved diluents.

Ipilimumab Pharmacy Reference Material

Ipilimumab vials (40 mL) are shipped in quantities of four..
Ipilimumab (BMS-734016) Injection (5 mg/ml) must be stored refrigerated (2-8°C, 36-46°F) with protection from light and from freezing. Ipilimumab may be stored in IV infusion bags (PVC, non-PVC/non-DEHP) or glass infusion containers for up to 24 hours at room temperature (20-25°C, 68-77°F) or refrigerated (2-8°C, 36-46°F). This would include any time in transit and the total time for infusion. Drug must be completely delivered within 24 hours of preparation.

Storage Conditions & Handling:

Ipilimumab injection may be stored undiluted, 200 mg/vial (5 mg/mL), or following dilution to concentrations between 1 mg/mL and 4 mg/mL in 0.9% Sodium Chloride Injection (USP), or 5% Dextrose Injection (USP) in PVC, non-PVC/ or glass containers for up to 24 hours in the refrigerator (2°C to 8°C) or at room temperature/room light. For longer storage, ipilimumab should be kept refrigerated (2°C to 8°C) with protection from light.
Ipilimumab injection must not be frozen.

Partially used vials or empty vials of Ipilimumab Injection should be discarded at the site according to appropriate drug disposal procedures.

Preparation and Administration

As this is provided for guidance only, please see investigator brochure for additional information regarding preparation and administration.

1. As ipilimumab is stored long term at refrigerated temperatures (2-8ºC) and protected from light, allow the appropriate number of vials of ipilimumab to stand at room temperature for approximately five minutes.
2. Ensure that the ipilimumab solution is clear colorless, essentially free from particulate matter on visual inspection. If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring, repeated friction of plunger against syringe barrel wall, etc.
3. Aseptically transfer the required volume of ipilimumab solution into a syringe. [Note: A sufficient excess of ipilimumab is incorporated into each vial to account for withdrawal losses].
4. Do not draw into each vial more than once. Discard partially used vials or empty vials.
5. Ipilimumab solution should be added to an appropriate size infusion container to accommodate the calculated final volume.
   Total dose should be calculated using the most recent subject weight; if weight on dosing day differs by 10% from prior weight used to calculate dosing, the dose should be recalculated and study drug adjusted accordingly.
   Mix by GENTLY inverting several times. DO NOT shake.
   Ipilimumab injection may be diluted in 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP.
6. Visually inspect the final solution. If the initial diluted solution or final solution for infusion is not clear or contents appear to contain precipitate, the solution should be discarded.
7. Immediately after the infusion is complete, flush with an adequate amount of 0.9% Sodium Chloride injection (USP) or 5% Dextrose injection (USP) to completely flush the residual fluid (dead space) in your administration set (approximately 30-50mL); this will ensure that all active drug is delivered to the study participant
8. Safely discard any unused portion of the infusion solution. Do not store for reuse.

Ipilimumab should be administered under the supervision of a physician experienced in the use of intravenous (IV) agents. Ipilimumab is administered as an IV infusion only

It is possible that sites may have more than one ipilimumab clinical study ongoing at the same time. It is imperative that only product designated for this protocol be used for this study.

APPENDIX I: Adverse Event Reporting

- All Adverse Events and Serious Adverse Events (SAEs) that occur following the subject's first dose of therapy on Day 1 of Week 1 of combined checkpoint therapy in the study through 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety, and according to local regulations.
- If the BMS safety address is not included in the protocol document (e.g. multicenter studies where events are reported centrally), the procedure for safety reporting must be reviewed/approved by the BMS Protocol Manager. Procedures for such reporting must be reviewed and approved by BMS prior to study activation.
- The BMS SAE form should be used to report SAEs. If the BMS form cannot be used, another acceptable form (i.e CIOMS or Medwatch) must be reviewed and approved by BMS. The BMS protocol ID number must be included on whatever form is submitted by the Sponsor/Investigator.
- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure.
- In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (i.e., not previously described in the IB). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of an expedited safety report (ESR).
    - Other important findings which may be reported by the as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, important safety recommendations from a study data monitoring committee, or sponsor decision to end or temporarily halt a clinical study for safety reasons.
    - Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.
    - In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

Serious Adverse Event Collection and Reporting

Following the subject's first dose of therapy on Day 1 of Week 1 of combined checkpoint therapy to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. All SAEs must be collected that occur within 100 days of discontinuation of dosing.

All SAEs must be collected that occur during the screening period. If applicable, SAEs must be collected that relate to any protocol-specified procedure (eg, a follow-up skin biopsy). The

investigator should report any SAE that occurs after these time periods that is believed to be related to study drug or protocol-specified procedure.

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on BMS or an approved form; pregnancies on a Pregnancy Surveillance Form.

All SAEs should simultaneously be faxed or e-mailed to BMS at:
Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.Safety@bms.com

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

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

All SAEs should be followed to resolution or stabilization. If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.
If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to BMS using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization. All SAEs should be followed to resolution or stabilization.

The Sponsor/Investigator will ensure that all SAEs in the clinical database are reported to BMS and any applicable health authority during the conduct of the study. This reconciliation will occur at least quarterly and be initiated by the sponsor/investigator. Sponsor/investigator will request a reconciliation report from: aepbusinessprocess@bms.com. During reconciliation, any events found to not be reported previously to BMS must be sent to Worldwide.Safety@BMS.com.

APPENDIX J: Research Biospecimen Sample Collection

CPIT Trial 001	**Date of Transplant:**
Patient ID	**Disease:**
Code for Correlative Studies	**CPIT 001-(PtID) (Timepoint) (Date)**
Peripheral Blood Samples (8x Yellow top tubes (BD Vacutainer ACD Solution A Blood Collection tubes – 8.5ml) – 68 ml ***to be collected prior drug administration****	**Timepoint ID**
Screening Visit	S
Apheresis product (1x Yellow top tube – 1/2 full – 4mL)	Aph
Day 1 (+/-2 days), Week 1*	1
Day 1 (+/-2 days), Week 4*	4
Day 1 (+/-2 days), Week 7*	7
Day 1 (+/-2 days), Week 12*	12
Day 1 (+/-2 days), Week 18*	18
Day 1 (+/-2 days), Week 26*	26
End of Treatment Visit	ET
Post BMT, 9 mo	9M
Post BMT, 12 mo	12M
Post BMT, 15 mo	15M
Post BMT, 18 mo	18M
Relapse	R

All Peripheral blood samples are to be kept at room temperature – no immediate processing needed.

Samples for HackensackUMC subjects are to be delivered via courier to lab in Room 352, Jurist Research Building ASAP. If sample is collected in the late afternoon, please store at room temperature on a shaker (slow speed) until delivered to Dr. Korngold's Laboratory the next day.

Samples for Georgetown University subjects are to be shipped via Fed Ex on the day of collection. The tubes are to be banded in sealed plastic bag and wrapped in bubble wrap. If sample is collected in the late afternoon, please store at room temperature on a shaker (slow speed) until next shipment day.

Please ship to:
Robert Korngold, PhD
Hackensack University Medical Center
Jurist Research Building
40 Prospect Ave
Room 352
Hackensack, NJ 07601

A subset of the Peripheral blood samples delivered to Dr. Korngold's Laboratory will be shipped to Georgetown Lombardi Comprehensive Cancer Center for Metabolomics Analysis.

Stool Samples **To be collected up to 48 hours prior to clinic visit and * prior to drug administration**	**Timepoint ID**
Screening Visit	S
Preconditioning (to be collected within 48 hours prior to transplant admission)	P
Engraftment (within 72 hours of ANC ≥ 500)	E
Day 1, Week 1*	1
Day 1, Week 4*	4
Day 1, Week 7*	7
Day 1, Week 12*	12
Day 1, Week 18*	18
Day 1, Week 26*	26
End of Treatment Visit	ET
Post BMT, 9 mo	9M
Post BMT, 12 mo	12M
Post BMT, 15 mo	15M
Post BMT, 18 mo	18M
Relapse	R

All stool samples at HackensackUMC are to be kept at -80°C - no immediate processing needed.

Samples for HackensackUMC Subjects are to be delivered via courier to lab in an insulated container or pouch with an ice pack or ice to Room 352, Jurist Research Building ASAP.

Samples for Georgetown University subjects are to be shipped via Fed Ex on the day of collection. The tubes are to be placed in sealed plastic bag and shipped on dry ice. If sample is collected in the late afternoon, please store immediately at -20°C and ship on dry ice the following day.

Please ship to:

Robert Korngold, PhD
Hackensack University Medical Center
Jurist Research Building
40 Prospect Ave
Room 352
Hackensack, NJ 07601

Note: For those patients who sign informed consent after apheresis has already occurred, the Apheresis Blood Sample will be performed on the previously collected, frozen product.

Note: If patient signs consent within 7 days of transplant admission, stool sample collection will start from item “2” (Preconditioning).