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Protocol Page

Phase I/II Study of Idarubicin, Cytarabine, and Nivolumab in patients with high-risk MDS and AML
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Core Protocol Information

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Phase I-II study of Idarubicin, Cytarabine, and Nivolumab in patients with high-risk MDS and AML

Core Protocol Information

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1.0 Table of Contents

2.0 Background

2.1 The Diseases

a. Myelodysplastic syndrome (MDS) is a marrow disorder characterized by paradoxical peripheral cytopenias and a hyperplastic marrow, usually in elderly patients (median age 65 years).[1] Exposure to carcinogens and a high frequency of cytogenetic abnormalities are generally observed.[2,3] The pathophysiology of the disease appears to be an initial increase in apoptosis of the primitive stem cells with compensatory marrow proliferation, and later escape of clonal disease with malignant potential for transformation to acute leukemia.[1,4,5] Overall, 50% of patients transform to AML, while the others die of complications of cytopenias (infections, bleeding) while in MDS phase.[1] MDS is divided into low-risk and high-risk. Low-risk MDS includes refractory anemia (RA) and RA-sideroblastic (RA-S) by the French-American-British (FAB) classification and low or intermediate -1 risk by the International Prognostic Scoring System (IPSS). High-risk MDS (usually marrow blasts $\geq$ 10%) includes RA with excess blasts (RAEB) and RAEB in transformation (RAEB-T) by FAB and intermediate –2 or high risk by IPSS.[6] Median survival in low-risk MDS is 3-4 years, and in high-risk MDS 12 months or less.[7,8]

There is no current uniformly accepted standard treatment for MDS. Low-risk MDS is usually observed and later treated according to complications with red cell or platelet transfusions, antibiotics, and growth factors (EPO, G-CSF). Investigational studies include amifostine, thalidomide, TNF-α inhibitors (e.g. Enbrel), Mylotarg, arsenic trioxide and hypomethylating agents.[9,10] High-risk MDS is usually treated with investigational therapies including AML regimens, topotecan + ara-C, above investigational strategies, and allogeneic stem cell transplant.[10-12] Recently, 5-azacytidine and decitabine have been FDA approved for use in appropriately selected patients. Results have included improved responses (both clinical and cytogenetic), better quality of life, but no statistically significant survival advantage. Additionally, lenalidomide has also been FDA approved for use in patients with the 5q- syndrome, with an improvement in red blood cell transfusion dependence as well as cytogenetic response. MDS affects 12,000 to 20,000 individuals in the USA yearly. RAS mutations occur in 30% to 65% of MDS cases.[13,14]

b. AML: Prognosis in AML in adults has improved modestly. With modern regimens, including anthracyclines plus cytarabine, the CR rates are 60% to 70% and the cure rates are 15% to 25%. Prognosis is related to 1) leukemia karyotype, 2) patient age, and 3) performance and organ functions. Patients with t(8;21), inversion 16 or t(15;17) have CR rates of

90% and cure rates of 50% to 80%. Younger patients (age ≤ 50 years) with diploid karyotypes have CR rates of 70% to 80% and cure rates of 20% to 25%. Older patients and those with adverse karyotypes have CR rates of 35% to 50% and cure rates of 10% or less. Elderly patients with AML have a poor prognosis. This is due in part to the poor tolerance to therapy, and also the higher frequency of poor prognostic features, such as high-risk cytogenetic abnormalities and MDR expression. The experience at M.D. Anderson from 1996 to 2000 for patients age 65 years or older is a clear example of this poor prognosis. We treated 245 patients in this age group during this period. CR was achieved in 118 (48%) while induction mortality (i.e., death within 7 weeks from the start of chemotherapy) occurred in 54 (22%). 38 patients (18%) were alive in CR after 1 year, and 16 (8%) at 2 years.[15,16]

2.2 Maintenance therapy in MDS and AML

The role of post-remission therapy has been fully established in treating adult patients with AML. Several older studies have suggested that there is no role for maintenance therapy in AML. An ECOG study randomized patients after receiving standard induction therapy into 2 arms; one receiving 2 further courses of attenuated induction followed by maintenance, versus maintenance therapy only for 2 years. This study demonstrated that a more intensive post-remission therapy is necessary and questioned the role of maintenance. A randomized CALGB study demonstrated that protracted maintenance for 36 months was not superior to 8 months of maintenance and led to further questioning of role of maintenance. Other studies have also questioned the benefit of maintenance therapy.

On the other hand, several studies have convincingly demonstrated the benefit of maintenance therapy in older adults. A study by the German AML cooperative group patients achieving CR after receiving a standard induction regimen were randomized to receive either a protracted maintenance therapy or 'observation only'. Disease free survival at 3 years was 30% versus 17% (p=0.003) in favor of the maintenance arm. As a result of this study, maintenance therapy has been established as an integral part of front-line therapy in AML patients by the German group. Other studies, including studies by SWOG and Japanese adult leukemia study group (JALSG) have confirmed the benefit of maintenance. Therefore, although maintenance therapy is clearly effective its precise role has not been well defined. Maintenance therapy is likely to be beneficial in older adults with high-risk disease and is less likely to be effective in younger adults who are able to tolerate more intensive forms of post-remission therapy. An important factor in considering post-remission therapy in older adults with AML is the availability of an effective

and non-toxic regimen. Studies of interleukin- 2 (IL-2) in the maintenance setting of AML were largely unsuccessful particularly due to the difficulty in delivering the drug due to its significant toxicity.

PD-1 is a negative co-stimulatory receptor on activated T lymphocytes, which counters the activation signal provided by TCR ligation.[17a] PD-1 can also be induced in natural killer cells, B cells and monocytes. The two ligands of PD-1 are PD-L1 and PD-L2. They have distinct cellular expression patterns. Expression of PD-L2 is largely restricted to antigen presenting cells while PD-L1 is broadly expressed in tissues and can be further induced by exposure to interferon IFN-γ.[17a] PD-L1 is the major ligand for PD-1-mediated immune-suppression. Increased evidence suggests that PD-L1 expression on solid tumor cells is capable of dampening antitumor immune responses, and blockade of PD-L1 inhibits tumor growth and delays progression in murine models.[17a] Yang and colleagues have demonstrated that PD-1 and its two ligands, PD-L1 and PD-L2, as well as CTLA4, are aberrantly upregulated in 8–34% of bone marrow CD34+ cells from patients with myeloid leukemias.[18a] Tumor cells may suppress the function of tumor infiltration T cells by modulating PD-1. PD-1 has been reported to be upregulated on tumor infiltration T cells in melanoma and lung cancer.[17] In AML and MDS bone marrow biopsies, it has been reported that blasts are positive for PD-L1 whereas stroma/non-blast cellular compartment are positive for PD-1. Therefore, PD-1 ligands expressed on tumor cells may act through PD-1-positive stroma within the tumor microenvironment of AML and MDS patients.[18a]

In another study, Zhang, et al using the murine leukemia cell line, C1498 showed that when transferred intravenously into immunocompetent mice, C1498 cells grew progressively and apparently evaded immune destruction.(19a) Low levels of PD-L1 expression were found on C1498 cells grown in vitro. However, PD-L1 expression was up-regulated on C1498 cells when grown in vivo. PD-1(-/-) mice challenged with C1498 cells generated augmented antitumor T-cell responses, showed decreased AML burden in the blood and other organs, and survived significantly longer than did wild-type mice. Similar results were obtained with a PD-L1 blocking antibody.(19a) These data suggest the importance of the PD-1/PD-L1 pathway in immune evasion in AML, providing a rationale for clinical trials targeting this pathway in leukemia patients.

We propose to investigate nivolumab in patients with high-risk MDS and AML as maintenance following achievement of complete remission after induction with idarubicin and cytarabine, In the phase I portion of the trial, the aim is to define the tolerability of the administration of Nivolumab after achieving CR. In the phase II portion of the trial, the event free survival in newly diagnosed patients

with AML and high-risk MDS (≥ 10% blasts) will be determined and compared to historical controls.

2.3 The Treatment

PD-1 (or CD279),a 55-kd type 1 transmembrane protein, is a member of the CD28 family of T-cell costimulatory receptors that include immunoglobulin super family members CD28, CTLA-4, inducible co-stimulator (ICOS), and B and T-lymphocyte attenuator (BTLA). PD-1 is highly expressed on activated T cells and B cells. PD-1 expression can also be detected on memory T-cell subsets with variable levels of expression. Two ligands specific for PD-1 have been identified: PD-L1 (also known as B7-H1 or CD274) and PD-L2 (also known as B7-DC or CD273). PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems.[15,16,17] The interaction of PD-1 with its ligands, PD-L1and PD-L2, that are expressed on antigen-presenting cells (APC) and dendritic cells (DC), transmits negative regulatory stimuli to down-modulate the activated T-cell immune response. The absence or inhibition of PD-1 in murine models has resulted in the development of various autoimmune phenotypes and autoimmune diseases.[1] Taken together, these results suggests that inhibition of PD-1 binding to its ligands has the potential to activate T-cell responses. Since these responses are variable and dependent upon various host genetic factors, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self antigens.

Tumors can express tumor-specific antigens as a result of mutational burden and ongoing immune surveillance is believed to control the development of many tumors. Tumor progression may depend upon acquisition of mechanisms which permit them to evade an effective immune response. One such mechanism of evasion may be the expression of ligands which engage inhibitory receptor(s) on anti-tumor T-cells of many tumors. PD-L1 expression has been found on a number of tumors, and may be a mechanism by which tumors can directly engage PD-1 to evade an effective anti-tumor immune response.[18,19,20]

Expression of INF-γ by T-cells is known to induce PD-L1 expression in tumors.[21] PD-L1 expression has been associated with poor prognoses in renal,[22,23,24] esophageal,[25] gastric,[26] ovarian,[20] pancreatic,[27] and lung cancer.[28] PD-1 engagement on T-cells by PD-L1+ APC or PD-L1+ tumor cells in the tumor microenvironment may limit effective immune responses. In contrast to the findings above,

PD-L1 expression may result from CD3+ T-cell infiltration into tumors, which was observed to be a positive prognostic factor. Co-localization of lymphoid cell infiltrates and PD-L1 staining has been observed in human melanoma lesions.[29] More recent data have implicated the role of PD-1 in human infections, particularly in HCV[30] and human immunodeficiency virus (HIV).[31] In these cases, high expression levels of PD-1 have been found in viral-specific CD8+ T-cells that also display a non-responsive or exhausted phenotype. The observation that PD-1 expression is reduced in antigen loss variants of the target

epitope of PD-1 high antigen-specific T-cells is consistent with the chronic stimulation hypothesis.[8] Non-responsive PD-1 high T-cells have been observed in simian immunodeficiency virus (SIV) infection in rhesus macaques. More important, treatment of SIV-infected macaques with an anti-PD-1 mAb (3 mg/kg x4) resulted in decreased viral loads and increased survival along with expanded T-cells with increased T-cell functionality.[4] These studies have led to anti-PD-1 testing in tumor models.

Studies in multiple tumor models using a chimeric murine anti-mouse PD-1 antibody showed that PD-1 blockade has anti-tumor activity (Section 4.1.3).[32] Blocking PD-1 in PD-L1+ tumors may reverse the inactivation of tumor-specific effector T-cells at the tumor site as well activate anti-tumor responses that are limited by PD-L1 expression on "host" DC or APC. The anti-tumor effects of anti-PD-1 observed in several murine models suggest that both PD-L1+ and PD-L1- tumors may be targeted using this approach. In addition, in several tumor models in which anti-PD-1 has proved ineffective, PD-1 blockade can be combined with vaccines or other immunomodulatory antibodies for improved therapeutic efficacy.[33,34,35] PD-1 blockade by nivolumab is a promising avenue to pursue as an anti-tumor therapy for recurrent or treatment-refractory malignancies or as an anti-viral therapy for chronic viral infections.

3.0 Objectives

3.1 **For phase I portion of study***:* To determine the tolerability of the combination of idarubicin, cytarabine (ara-C), and nivolumab (IAN) in patients with high-risk MDS and AML.

3.2 **For phase II portion of study:** To determine event-free survival (EFS) where the events is defined as death or relapse using the combination of idarubicin, cytarabine, and nivolumab in patients with high-risk Myelodysplastic syndrome (MDS) and Acute Myeloid Leukemia (AML).

4.0 Patient Eligibility

Inclusion Criteria:

4.1 Diagnosis of 1) AML (WHO classification definition of ≥ 20% blasts), or 2) high risk MDS (defined as the presence of 10% blasts).

4.2 Patients aged 18 to 60 years are eligible. Patients older than 60 who are deemed fit to receive intensive chemotherapy by the treating physician are eligible after discussion with the PI.

4.3 In the Phase I portion, patients with relapsed or refractory AML/MDS are also eligible, as per the treating physician's discretion.

4.4 For the Phase II portion of the study, patients must be chemo-naïve, i.e. not have received any prior chemotherapy (except hydrea or one dose of ara-C ≤ 2g) for AML or MDS. They could have received hypomethylator agents, transfusions, hematolopoietic growth factors or vitamins. Temporary prior measures such as apheresis or hydrea or one dose of ara-C ≤ 2g are allowed in order to safely control hyperleucocytosis prior to enrollment.

4.5 Serum biochemical values with the following limits unless considered due to leukemia:
- creatinine ≤ 1.5 mg/dl
- total bilirubin ≤ 1.5 mg/dL, unless increase is due to hemolysis or congenital disorder
- transaminases (SG PT) ≤2.5x ULN

4.6 Ability to take oral medication.

4.7 Ability to understand and provide signed informed consent.

4.8 Baseline test of ejection fraction must be ≥50%.

4.9 Performance status <3, unless directly related to disease process as determined by the Principal Investigator

Exclusion Criteria:

4.10 Subjects with APL.

4.11 Any coexisting medical condition that in the judgment of the treating physician is likely to interfere with study procedures or results.

4.12 Nursing women, women of childbearing potential with positive urine pregnancy test, or women of childbearing potential who are not willing to maintain adequate contraception (such as birth control pills, IUD, diaphragm, abstinence, or condoms by their partner) over the entire course of the study.

- 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*
- Women of childbearing potential 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
- Women must not be breastfeeding

- 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 Women who are not of childbearing potential (ie, who are postmenopausal or surgically sterile as well as azoospermic men do not require contraception*

4.13 Cardiac disease: Congestive heart failure > class II NYHA. Patients must not have unstable angina (anginal symptoms at rest) or new onset angina (began within the last 3 months) or myocardial infarction within the past 6 months.

4.14 History of cardiac ventricular arrhythmias requiring anti-arrhythmic therapy within past 3 months.

4.15 Thrombotic or embolic events such as a cerebrovascular accident including transient ischemic attacks within the past 6 months.

4.16 Pulmonary hemorrhage/bleeding event ≥ CTCAE Grade 2 within 4 weeks of first dose of study drug.

4.17 Major surgery, open biopsy or significant traumatic injury within 4 weeks of first study drug.

4.18 Active clinically serious and uncontrolled infection > CTCAE Grade 2 uncontrolled with antibiotics

4.19 Patients should be excluded if they have 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

4.20 Patients should be excluded if they are known to be positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection

4.21 Patients should be excluded if they have known history of testing positive for human immunodeficiency virus (HIV) or known acquired immunodeficiency syndrome (AIDS)

4.22 History of allergy to study drug components

4.23 Prior immune checkpoint targeting drugs (e.g., anti PD1, anti PDL1, anti-kir, anti CD137…etc)

5.0 Treatment Plan

5.1 **General**: All patients should be registered with PDMS. Information pertaining to important prognostic factors such as age, performance status and prior therapy will be recorded.

5.2 **Treatment Schedule**: (Each cycle is approximately 28-35 days)

a. Phase I

Nivolumab dosed as indicated below starting approximately on day 24 ± 2 days
Idarubicin 12 mg/m^2 IV over 15 to 30 minutes daily x 3 (days 1-3)
ara-C 1.5 g/m^2 IV over 24 hours daily (days 1-4)
Solumedrol 50 mg or dexamethasone 10 mg IV daily for 3-4 days with ara-C (days 1-4)
All patients may receive a second induction course at the discretion of treating physician.

The dose of investigational agent, that is, Nivolumab, will be escalated in successive cohorts of patients. Patients will be entered sequentially to each dose level. If none of the first 3 patients at a dose level experience first cycle dose-limiting toxicity (DLT), new patients may be entered at the next higher dose level. If 1 of 3 patients experience first cycle DLT, up to 3 more patients are started at that same dose level. If 1of 6 experience DLT, then new patients may be entered at the next higher dose level. If 2 or more experience first cycle DLT, no further patients are started at that dose. The MTD is the highest dose level in which <2 patients of 6 develop first cycle DLT. The following table lists out the 3 dosage levels that will be used in the study, and the starting dose is 1mg/kg IV of Nivolumab. There will be no intra-patient dose escalation for Nivolumab.

The enrollment of participants will be staggered; all the participants in each cohort will be observed for approximately 3 weeks from the first dose of Nivolumab before proceeding to the next cohort.

Dose of nivolumab will be as follows:

Dose level	Nivolumab (mg/kg IV)	No of patients
-1	0.3	3
0	1	3
1	3	3

b. Phase II (Each cycle is approximately 28-35 days)
Patients will receive 1 or 2 induction cycles of therapy according to the following starting schedule:

Nivolumab starting approximately on day 24 ± 2 days at a dose defined by Phase I portion of the study but it is expected that the dose 3 mg/kg will be selected based on prior studies.
Idarubicin 12 mg/m^2 IV over 15 to 30 minutes daily x 3 (days 1-3)
ara-C 1.5 g/m^2 IV over 24 hours daily (days 1-4) (days 1-3 for patients older than 60)
Solumedrol 50 mg or dexamethasone 10 mg IV daily for 3-4 days with ara-C (days 1-4) (days 1-3 for patients older than 60).

Nivolumab will be administered at approximately 2 week intervals for up to 1 year.

5.3 **Dose modifications during phase II:**

Patients who experience nivolumab-specific (defined as determined by the principal investigator) grade 3-4 extramedullary toxicities during induction cycle #1, and who are not in CR after cycle #1, may receive a second induction course at a similar or lower dose level with respect to idarubicin and cytarabine. Other dose modification schedules felt to be in the best interest of the patient may be permitted, after discussion with the principal investigator. There will be no dose modifications of idarubicin or cytarabine for either induction cycle #1, or second induction course, secondary to myelosuppression. There will be no dose reduction with respect to Nivolumab but dose delays or interruptions are permitted after discussion with the PI.

5.4 **Administration guidelines for nivolumab:** Nivolumab will be administered by IV infusion over approximately 60 minutes ± 10 minutes. The recommended infusion duration for the product is 60 minutes and every effort should be made to adhere to this time as closely as possible.

5.5 No dose reduction is allowed for Nivolumab. Dose delays and interruptions should follow the guidance in section 6.10.3.

5.6 **Myelosuppression**

Patients with acute leukemia usually present with abnormal peripheral blood counts at the time therapy is started, and myelosuppression is an expected event during the course of therapy for acute leukemias and myelodysplastic syndromes. Thus, no dose adjustments or treatment interruptions for myelosuppression will be planned for the first 6 weeks of therapy. After this time, treatment interruptions and dose adjustments may be considered according to the following guidelines:

Patients with neutropenia or thrombocytopenia as a consequence of the disease prior to the start of therapy do not require treatment interruptions for myelosuppression. Dose reductions of the chemotherapy agents in these patients should be considered on an individual case basis and discussed with the PI.

Nivolumab is not associated with myelosuppression – it can be held if necessary but no dose reductions are needed after resumption

5.7 **Dose adjustments for only one of the drugs** can be made if, in the opinion of the treating physician, the toxicity is attributable to one of the drugs.

5.8 Patients who show no significant anti-tumor effect (i.e. no CR or CRp) after 2 courses will be taken off the study.

5.9 **Remission Consolidation/Maintenance:** Patients achieving a CR or CRp may receive consolidation maintenance therapy as follows:

a. Consolidation – Up to 5 additional courses as follows:

- Idarubicin 8 mg/m^2 IV over 15 to 30 minutes daily x 2 days (or the final induction dose, whichever is lower).(days 1-2)
- Ara-C 0.75 g/m^2 IV over 24 hours daily x 3 days (or the final induction dose, whichever is lower) (days 1-3)
- Nivolumab dose as per induction IV every 2 weeks as a continuation of the induction treatment.
- Solumedrol 50-100 mg or dexamethosone 10 mg IV daily x 3 days with ara-C (days 1-3)

→ courses given every 4-6 weeks upon recovery of counts and toxicities

b. Maintenance – Nivolumab will be administered every 2 weeks for up to 1 year with no breaks except for toxicity. Maintenance will only be administered in patients in CR or CRp.

c. Consideration of allogeneic transplant in CR. Patients eligible for allogeneic.

SCT will be evaluated for the procedure, if felt to be in their best interest. Therapy with nivolumab will be discontinued at least approximately one week prior to admission for the transplant procedure.

5.9.1 If judged more beneficial for patient care and disease control, patients may have dose reductions to allow for continuation of therapy with acceptable myelosuppression.

5.9.2 The dose of chemotherapy treatment (ie idarubicin/cytarbine) in subsequent courses will be reduced by 25% for grade 3-4 extramedullary toxicities, or for severe life-threatening infections.

5.9.3 In responding patients, courses will be given at 4 to 6 week intervals provided the granulocyte count has recovered to > $1.0x10^9$/L and the platelet count to >$50x10^9$/L. In patients with persistent disease, therapy could be restarted once counts recover to the pretreatment values.

5.9.4 Dose adjustments for only one of the drugs can be made if, in the opinion of the treating physician, the toxicity is attributable to one of the drugs.

5.10 **Administration guidelines for consolidation/maintenance nivolumab**: Nivolumab will be administered IV approximately every 2 weeks starting from day 24 ± 2 days of first induction course. If a dose is missed, the next dose will not be increased to account for missing a dose. The patient will take the next regular dose at the regularly scheduled time.

5.10.1 Patient Monitoring During Infusion

Initial dose vital signs should be monitored prior to dosing, approximately every 30 minutes after initiation of infusion, and up to approximately 60 minutes after the completion of the infusion, or longer if indicated, until the vital signs normalize or return to baseline. For subsequent infusions, vital signs should be collected prior to dosing, and at the completion of the infusion. If the patient experiences an infusion reaction, the patient will be monitored for up to 60 minutes after the completion of the infusion, or longer if indicated, until the vital signs normalize or return to baseline. A +/- 30 minute window applies to all vital signs time points.

5.10.2 Treatment of nivolumab Related Infusion Reactions

Since nivolumab 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, pruritis, arthralgia's, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the BMS Medical Monitor and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE (version 4.03) guidelines.

Treatment recommendations for nivolumab related infusion reactions are provided below and may be modified based on MD Anderson 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 premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.

For Grade 2 symptoms (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [e.g. antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours):

Stop the nivolumab infusion, begin an IV infusion of normal saline, (at approximately 40cc/hour but adjusted according to the clinical situation to ensure stabilization of blood pressure) and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen 325 to 1000 mg; 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 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 case report form (CRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg should be administered at least 30 minutes before additional nivolumab 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 ventilatory support indicated]:

Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, (at approximately 40cc/hour but adjusted according to the clinical situation to ensure stabilization of blood pressure) 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 will be permanently discontinued. Institutional guidelines will be followed for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (e.g. appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g. oral antihistamine or corticosteroids).

For further details regarding dose-calculation of nivolumab, preparation and dispensing of nivolumab, administration of nivolumab please see the dosing procedure manual.

5.10.3 Nivolumab dose delay for immune-oncology drug-related adverse events, clinically significant in the opinion of the investigator

Nivolumab administration should be delayed for the following drug-related AEs:

- Any Grade >2 non -skin AE, except that
  - Grade 2 fatigue or laboratory abnormalities do not require delay, however
    - For a subject with baseline AST, ALT, or total bilirubin within normal limits, delay dosing for drug-related Grade >2 values
- Any Grade 3 skin AE, or Grade 3 laboratory abnormality, with the following exceptions:
  - Grade 3 lymphopenia or leukopenia does not require dose delay.
  - If a subject has Grade 1 baseline AST, ALT, or total bilirubin, delay dosing for drug-related Grade 3 toxicity
- Any AE, laboratory abnormality, or intercurrent illness, which in the judgment of the investigator, warrants delaying the dose of study medication.
- Nivolumab dose reductions are not permitted in this study (only dose delays when indicated).

Detailed management algorithms for immune-oncology drug-related adverse events (including gastrointestinal, renal, pulmonary, hepatic, endocrine, skin and neurological) are provided in Appendix E. These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor. If the criterion to resume treatment is met, the subject should restart treatment at the next scheduled time-point per protocol.

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 (Discontinuation Section below) 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. However, if the treatment is delayed past the next scheduled timepoint per protocol, the next scheduled timepoint will be delayed until dosing resumes.

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

Nivolumab 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 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 dosing

5.11 **Definition of Dose Limiting Toxicity (DLT)**

Dose-Limiting Toxicity will be graded according to the NCI Common Toxicity Criteria version4.03. See NCI Common Toxicity Criteria for definitions of DLT by organ system.

a) All ≥ grade 3 drug-related, clinically significant non-hematologic toxicities will be considered DLTs. A study drug-related occurrence of an elevation in AST/ALT > 3 x ULN and concomitant Bilirubin of > 2 x ULN is a Dose Limiting Toxicity and patients meeting this criteria should be permanently discontinued from study treatment (nivolumab).
As the following are common events in patients with leukemia (> 50%), they will not be used for the definition of MTD and DLT, nor will they be reported as ADRs: low blood pressure due to dehydration requiring fluid replacement, abnormalities of LDH (lactate dehydrogenase) and alkaline phosphatase, disturbances in electrolytes (magnesium, phosphorus,

calcium), alopecia, nausea and vomiting (if manageable with supportive care measures).

b) Grade 3 hematologic toxicity (criteria for leukemia on the CTC version 3.0) lasting for 6 weeks or more after interruption of therapy with a hypocellular bone marrow and no marrow blasts. Anemia will not be considered a hematologic DLT. As the following are common events in patients with leukemia (> 50%), they will not be used for the definition of MTD and DLT, nor will they be reported as ADRs: prolonged myelosuppression (grade 3 - 4), neutropenic fever without infection (grade 3), non-neutropenic fever (grade 3), infections with grade 3 and 4 neutropenia, infections without neutropenia (grade 3), readmission associated with NCI grade 3 toxicity cytopenias not resulting in death, transfusions of platelets and packed RBCs (grade 3).

5.12 **Concomitant medications**: In the event of severe anemia, thrombocytopenia or neutropenia, patients may receive appropriate supportive care (e.g., transfusions, prophylactic antibiotics, antifungals and/or antivirals, hematopoietic growth factors). In the event of high white blood cell (WBC) counts, patients may receive hydroxyurea (at any dose) or 1 dose of cytarabine (up to ≤ 2g) prior to start of study treatment in order to keep their WBC at an acceptable level while being evaluated for the study. During the trial they may undergo leukopheresis for the same purpose.

Concomitant administration of any other therapy specific for MDS or AML, including any use of systemic retinoids, is prohibited. Concomitant administration of any other anticancer therapy is prohibited. Intrathecal chemotherapy is allowed, when indicated.

Subjects may receive anti-infective prophylaxis according to institutional practices. Use of recombinant myeloid colony stimulating factors (CSF) is allowed, if patients have febrile neutropenia or documented infections.

Concomitant medications will be recorded in the medical records only.

6.0 Protocol Summary/Schema

6.1 **Proposed Study**

We propose to investigate the combination of idarubicin, cytarabine and nivolumab in patients with high-risk MDS and AML. In the phase I portion of the trial, the aim is to determine the tolerability of the combination. In the phase II

portion of the trial, the event free survival in newly diagnosed patients with AML and high-risk MDS (≥ 10% blasts) will be determined.

Schedule of Evaluations/ Study Calendar (refer to section 7.0 - 8.0 of protocol body)							
Parameter	**Prestudy**	**Weeklyx4 During first course**	**Induction phase every 4-7 days**	**Induction phase every 1-2 weeks**	**Consolidation Maintenance phase every 1-4 wks**	**Consolidation Maintenance phase every 4-8 wks**	**End of Study**
H&P	**x**	**x**					**x**
Weight/BP	**x**						
CBC, diff+platelet	**x**	**x**	**x**		**x**		
Chemistry+Coag:							
total bili	**x**	**x**		**x**		**x**	
creatinine	**x**	**x**		**x**		**x**	
SGPT	**x**	**x**		**x**		**x**	
PT/PTT/INR	**x**			**x**		**x**	
TSH	**x**						
pregnancy test* **	**x**						
BMA**	**x**						
Echo/Muga	**x**						
MRD**	**x**						
Correlative studies: see section 16							

*** Blood or Urine pregnancy test on women of childbearing potential

****Bone Marrow Aspirate Pre-Treatment - within one month with cytogenetics and molecular studies if not done before. On-Study: BMA + cytogenetics and molecular studies (if abnormal at start) on day 21-28, then every 1-2 wks as required until CR. Then every 3-6 months. X 1 year. May be omitted in patients with clear evidence of active disease (see section 8.2).
Minimal residual disease (MRD) studies by flow cytometry to be performed on pre-treatment bone marrow and all subsequent bone marrow exams

7.0 Pretreatment Evaluation

7.1 History and physical examination, weight, BP.

7.2 CBC, platelet count, differential, creatinine, total bilirubin, SGPT, PT, PTT, INR, TSH.
Serum or urine pregnancy test for women of childbearing potential.

7.3 Bone marrow aspirate for morphology (within one month) and cytogenetics and molecular studies (if not done before).

7.4 Blood samples (10cc)/bone marrow, optional, for correlative studies.

7.5 Echocardiogram or MUGA scan.

8.0 Evaluation During Study

8.1 CBC, platelet, differential (if WBC > 10^9/L) every 4-7 days during remission induction and every 1 to 4 weeks during maintenance therapy.

8.2 Bone marrow aspirate and cytogenetics and molecular studies (if abnormal at start) on day 21-28; then aspirate every 1-2 weeks as required until CR; then every 3-6 months in year 1 if deemed necessary by the treating physician. Bone marrow aspiration may be omitted in patients where there is clear evidence of active disease (e.g., persistent blasts in peripheral blood).

8.3 Creatinine, total bilirubin and SGPT, PT, PTT, and INR every 1-2 weeks during induction then every 4-8 weeks on study.

8.4 Blood samples (10cc)/bone marrow (optional studies, see Section 14)

8.5 End of Study: History and physical exam
End of study evaluation will be performed after the completion of the maintenance therapy, or any time before that if the patient withdraws from the study or the treatment is discontinued for toxicity or disease relapse/progression.

9.0 Criteria for Response and Toxicity

9.1 Responders are patients who obtain a CR or PR, with or without cytogenetic response, or CRp (i.e., CR except for platelet counts <100 x10^9/L but not requiring platelet transfusions).

9.2 **Definitions**

a. Complete Response (CR): Normalization of marrow (≤ 5% blasts and of peripheral blood counts (neutrophil count ≥ 10^9/L, platelet count > 100 x 10^9/L).

b. Partial response (PR): as for CR but with reduction of marrow blasts by >50% and to <10%.

c. CRp = CR, but platelets <100 x 10^9/L.

d. Progressive disease: increase of blasts to ≥ 10% after an initial response.

10.0 Reporting of Adverse Events

These guidelines serve to bring the Department of Leukemia in compliance with the institutional policy on Reporting of Serious Adverse Events.

Adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment. Adverse drug reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.

Assessing causal connections between agents and disease is fundamental to the understanding of adverse drug reactions. In general, a drug may be considered a contributory cause of an adverse event if, had the drug not been administered, 1) the event would not have happened at all, 2) the event would have occurred later than it actually did, or 3) the event would have been less severe.

Only unexpected AEs related to leukemia and events resulting in dose modification/delay will be recorded in the Case Report Form (CRF).

Expected events during leukemia therapy are:

- Myelosuppression related events (due to disease or leukemia therapy)
- Febrile or infection episodes not requiring management in the intensive care unit
- Epistaxis or bleeding except for catastrophic CNS or pulmonary hemorrhage
- Anemia, neutropenia, lymphopenia, thrombocytopenia, leukopenia
- Disease related events
- Symptoms associated with anemia (fatigue, weakness, shortness of breath)
- Electrolyte abnormalities (sodium, potassium, bicarbonate, CO2, magnesium)
- Chemistry abnormalities (LDH, phosphorus, calcium, BUN, protein, albumin, uric acid, alkaline phosphatase, glucose)
- Coagulation abnormalities
- Disease specific therapy (induction, maintenance, salvage, or stem cell therapy)

- Alopecia
- Bone, joint, or muscle pain
- Disease progression
- Abnormal hematologic values
- General therapy related events
- Catheter related events
- Renal failure related to tumor lysis syndrome or antibiotic/ antifungal therapy
- Rash related to antibiotic use
- Hospitalization for the management of any of the above expected events
- Abnormal hematologic values will not be recorded on the case report form. For abnormal chemical values, the apogee or nadir (whichever is appropriate) will be reported per course on the case report form.

All events that are not listed as expected in section 10.0 will be collected for the purpose of grading, and determining attribution to study drug by the PI.

All grade 3 and greater non-hematological events that are felt to be related to protocol treatment drugs will be documented on the toxicity log and entered into the case report form. The toxicity log and case report form data must reflect relationship to the drug the event is felt to be related to.

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- **Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an**

SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events,** that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- **Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.**
- **Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.**

- **Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.**

Reporting to the FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

The investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

Adverse events and protocol specific data will be entered into PDMS/CORe and PDMS/CORe will be used as the electronic case report form for this protocol.

10.1 Adverse Events Requiring Expedited Reporting:

Briston Meyers-Squibb Adverse Event Reporting:
Serious adverse events (SAEs) considered associated with therapy should be reported to the Principal Investigator within 48 hours of observing or learning of the event. All AEs should be reported to the research nurse. The principal investigator, in turn, will be responsible for reporting the event to the IRB.

All Serious Adverse Events must be reported to BMS Worldwide Safety

- All SAEs, whether related or unrelated to Nivolumab and all pregnancies must be reported to BMS (by the investigator or designee) within 24 hours.
- All SAEs should be reported via confirmed facsimile (fax) transmission, or scanned and reported via electronic mail to:
  SAE Email Address: Worldwide.Safety@BMS.com
  SAE Fax Number: 609-818-3804

Serious Adverse Event (SAE): any untoward medical occurrence at any dose (including overdose) that:

a. Results in death (caused or led to death); or
b. Is life-threatening (placed the subject at immediate risk or death; and/or
c. Requires or prolongs inpatient hospitalization (elective medical/surgical procedures, scheduled therapies, or routine check-ups excluded); and/or
d. Is disabling (substantial disruption of the subject's ability to carry out normal life functions); and/or
e. Is a congenital anomaly/birth defect (adverse outcome in a child or fetus of a subject exposed to a medicinal product prior to conception or during pregnancy; or
f. Does not meet any of the above serious criteria but may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above.

Associated Adverse Event:

a. If there is a clinically plausible time sequence between the onset of the AE and administration of therapy; and/or
b. If there is a biologically plausible mechanism for therapy causing or contributing to the AE; and the AE may or may not be attributed to concurrent/underlying illnesses, other drugs, or procedures.

10.3 **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 will be utilized for AE reporting. All

appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

'Expectedness': AEs can be 'Unexpected' or 'Expected' for expedited reporting purposes only. 'Expected' AEs (the ASAEL) are ***bold and italicized*** in the CAEPR.

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

10.4 All safety reports, including SADRs, shall be sent electronically to wh-adverse.events@bayer.com or by fax to (203) 812-6053 to the attention of one of the Bayer Drug Safety Assurance contacts listed below:
The Principal Investigator commits to respond promptly to any query from Bayer regarding SADR reports.

11.0 Criteria for Removal from the Study

11.1 Progressive disease or failure to respond after 2 courses of therapy.

11.2 Unacceptable (Grade 3 or 4) toxicity in the absence of significant antileukemic effect.

11.3 Patient request; non-compliance.

12.0 Statistical Considerations

12.1 *General Description*
The overall trial objective is to provide a very early assessment of efficacy (phase II A) of Nivolumab when used in combination with the standard combination of idarubicin and cytarabine. Initially, a small dose escalation trial will determine the dose at which the regimen will be evaluated in the subsequent study of efficacy. Once the combination dose is determined, patients meeting phase II eligibility criteria will be accrued.

12.2 **Phase I study**

The 3+3 design will be used to identify the MTD of nivolumab. The following table lists out the 3 dosage levels that will be used in the study, and the starting dose is 1mg/kg IV

of Nivolumab With 3 doses, the maximum total number of patients for phase I part will be 12 patients.

The dose of treatment agent, that is, Nivolumab, will be escalated in successive cohorts of patients. Patients will be entered sequentially to each dose level. If none of the first 3 patients at a dose level experience first cycle dose-limiting toxicity (DLT), new patients may be entered at the next higher dose level. If 1 of 3 patients experience first cycle DLT, up to 3 more patients are started at that same dose level. If 1of 6 experience DLT, then new patients may be entered at the next higher dose level. If 2 or more experience first cycle DLT, no further patients are started at that dose. The MTD is the highest dose level in which <2 patients of 6 develop first cycle DLT.

Table 13.1 Dose levels of nivolumab

Dose level	Nivolumab (mg/kg IV)
-1	0.3
0	1
1	3

Prior to advancing/changing dose levels, a cohort summary will be completed and submitted to the IND Office Medical Monitor for review and approval.

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12.3 Phase 2 study

The primary outcome of this trial is event-free survival (EFS) which is defined as the time from the treatment start till treatment failure, relapse, or death whichever comes first.. The treatment failure is defined as not achieving CR after two cycles of treatment. If the patient achieves remission after the treatment, the relapse occurred in the later time would be considered as “event”. We will monitor the EFS as patients accrue and are evaluated. The chemo-naïve patients under MTD in phase I will be included in the phase 2 study.

The monitoring uses the Bayesian method of Thall, et al [2005]. It will be assumed that EFS follows an exponential distribution with median m_T under the current treatment. The historical median of EFS is denoted by m_H given an historical (H) treatment. For priors, we assume the conjugate inverse gamma (IG) priors $m_T \sim IG(a_T,b_T) = IG(3.2,15.6)$ and $m_H \sim IG(a_H,b_H) = IG(124.5, 864.5)$. Both priors have mean of 7 months while var(m_T) =

40 and var(m_H) = 0.40. That is, the prior on m_T is non-informative while the prior on m_H is informative. The trial will be monitored and will be stopped early if, based on the data available at the time, it is unlikely that the median EFS rate will be at least 7 months. The monitoring is continuous monitoring starting from the 1st patient.

Pr(median EFS under treatment ≥ median EFS under historical treatment | data from the trial) < 0.03.

The operating characteristics of this rule for Nmax = 75 patients, computed assuming a 5 patient/month accrual rate and 24 months of follow up after the last patient is accrued, *The* operating characteristics are given in the following table.

Table 13.2 Operating characteristics. *The* operating characteristics for the EFS monitoring rule are summarized in the following table.

Simulation Results		
Median months to death or relapse	Pr(Stop early)	Mean # pats. (25%, 75% percentiles)
5	0.8	51.3 (31,75)
7	0.11	70.5 (75,75)
9	0.02	73.9 (75,75)

The Department of Biostatistics at MD Anderson will provide and maintain a website ("Clinical Trial Conduct": https://biostatistics.mdanderson.org/ClinicalTrialConduct/) for patients enrolled on this study. The Clinical Trial Conduct website resides on a secure server, and access is gained through usernames and passwords provided to personnel responsible for enrolling patients and updating patient data. The website is accessed through a browser using secure socket layer (SSL) technology. Personnel responsible for enrolling patients on trials, which includes the principal investigator(s), research nurse(s), and data coordinator(s), will be trained by members of the Department of Biostatistics in the use of the trial website; the importance of timely updating of follow-up times and recording of events will be emphasized in training.

We will also monitor the unacceptable nivolumab grade 3 or 4 drug attributable toxicity rate by 12 months, and we will stop the trial if we have statistical evidence that this unacceptable toxicity rate is more than 10%. The method of Thall, Simon and Estey [1995] will be used for toxicity monitoring for this study. The software Multc Lean.Version 2.1 was used to run the simulation.
We will stop the trial early if

P(unacceptable toxicity by 12 months > 10% | data from the trial) > 0.95.

That is, given the outcomes from the patients who have already been evaluated, if we determine that there is more than a 95% chance that the unacceptable toxicity rate is more than 10%, we will stop the trial. This decision rule gives the following stopping rule. We assume a beta(0.2, 1.8) prior distribution for the unacceptable toxicity rate.

The operating characteristics of this decision rule are shown in Table 2. When the trial is completed we will report the posterior probability that the unacceptable toxicity rate by 12 months is more than 10%, and we will give a 90% credible interval for this rate.

Table 13.3. toxicity stopping boundaries in cohort size of 5.

Number of patients	Stop the trial if there are this many patients achieving toxicity
5	3-5
10	4-10
15-20	5-20
25	6-25
30	7-30
35-40	8-40
45	9-45
50-55	10-55
60	11-60
65-70	12-70

Table 13.4: Operating characteristics for monitoring of toxicity rate.

True toxicity Rate	Early Stopping Probability	Average number of patients treated
0.05	0.01	75
0.1	0.11	70
0.15	0.47	56
0.2	0.83	38

0.25	0.97	25

12.4 Analysis plan:

Demographic and disease characteristics of the patients at registration will be summarized using descriptive statistics such as mean, standard deviation (SD), median and range. Frequency tables will be used to summarize categorical variables. The EFS will be estimated by Kaplan-Merier method, along with the 95% confidence intervals, and logrank test will be used to assess the EFS differences under different patient subgroups. The Cox proportional hazards model will be used to analyze the effects of treatments and other covariates.

Data from all subjects who receive any study drug will be included in the safety analyses.

Subjects who entered the study and did not take any of the study drugs and had this confirmed will not be evaluated for safety. The severity of the toxicities will be graded according to the NCI CTCAE v4.03 whenever possible. We will follow standard reporting guidelines for adverse events. Safety data will be summarized by category, severity and frequency. The proportion of patients with AEs will be estimated, along with the Bayesian 95% credible interval.

13.0 Background Drug Information

13.1 **Nivolumab**

13.1.1 Physical and Chemical Properties

BMS-936558-01 was selected for dosage form development and is also referred to as nivolumab or BMS-936558. Nivolumab is a soluble protein consisting of 4 polypeptide chains, which include 2 identical heavy chains and 2 identical light chains.

BMS Number BMS-936558-01
Other Names Nivolumab, BMS-936558, MDX-1106, ONO-4538, anti-PD-1
Molecular Weight 143,599 daltons
Appearance Clear to opalescent, colorless to pale yellow liquid, light (few) particulates
Solution pH 5.5 to 6.5

13.1.2 Pharmaceutical Properties and Formulation

BMS-936558-01 Injection 100 mg/Vial (10 mg/mL)

13.1.3 Description of the Dosage Form

BMS-936558-01 Injection, 100 mg/Vial (10 mg/mL) is a clear to opalescent, colorless to pale yellow liquid, light (few) particulates may be present. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate, sodium chloride, mannitol, diethylenetriamine pentacetic acid (pentetic acid) and polysorbate 80 (Tween□ 80), pH 6.0 and includes a 7% overfill to account for VNS (vial, needle, syringe) loss.
It is supplied in 10-cc type I flint glass vials, stoppered with butyl stoppers and sealed with aluminum seals.

13.1.4 Drug Product Preparation

BMS-936558-01 Injection 100 mg/Vial (10 mg/mL)
BMS-936558-01 injection is to be administered as an IV infusion, using a volumetric pump with a 0.2/0.22 micron pore size, low-protein binding polyethersulfone membrane in-line filter at the protocol-specified doses. It is not to be administered as an IV push or bolus injection.
BMS-936558-01 injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP to protein concentrations no lower than 0.35 mg/mL. Instructions for dilution and infusion of BMS-936558-01 injection may be provided in the clinical protocol, pharmacy binder, or pharmacy reference sheet. Care must be taken to assure sterility of the prepared solution as the product does not contain any anti-microbial preservative or bacteriostatic agent. No incompatibilities between BMS-936558-01 injection and polyolefin bags have been observed.

13.1.5Recommended Storage and Use Conditions

BMS-936558-01 Injection, 100 mg/Vial (10 mg/mL)
Vials of BMS-936558-01 injection must be stored at 2□-8□C (36□-46F) and protected from light and freezing.
Undiluted BMS-936558-01 Injection and Diluted BMS-936558-01 Injection in the IV Bag
IV bags containing undiluted and diluted solutions of BMS-936558-01 injection prepared for dosing may be stored up to 20 hours in a refrigerator at 2°-8°C (36°-46°F) and used within 4 hours at room temperature 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 should be inclusive of the product administration period.

PRODUCT INFORMATION

Drug ordering and accountability:

BMS is supplying study drug, information in this section may include how to order study drug from BMS or from the Investigator pharmacy. Or this information may be included in a pharmacy manual.

Please see Appendix D 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. If commercial investigational product is used, it should be stored in accordance with the appropriate local labeling

- If the study drug(s) are to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for disposal, and that procedures for proper disposal have been established according to applicable regulations, guidelines, and institutional procedures

  Product description and dosage form

PRODUCT INFORMATION TABLE: Please also see Drug Information Appendix D

Product Description:(Other names = MDX-1106, ONO-4538, anti-PD-1

Product Description and Dosage Form	**Potency**	**Primary Packaging (Volume)/ Label Type**	**Secondary Packaging (Qty) /Label Type**	**Appearance**	**Storage Conditions (per label)**
Nivolumab (BMS-936558-01)* Injection drug product is a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL	100 mg/Vial (10 mg/mL).	Carton of 5 or 10 vials	10-cc Type 1 flint glass vials stoppered with butyl stoppers and sealed with aluminum seals.	Clear to opalescent, colorless to pale yellow liquid. May contain particles	**BMS-936558-01 Injection** must be stored at 2 to 8 degrees C (36 to 46 degrees F) and protected from light and freezing

*Nivolumab may be labeled as BMS-936558-01 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 include laboratory coats and gloves.

For additional details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to the BMS-936558 (nivolumab) Investigator Brochure section for “Recommended Storage and Use Conditions”

Handling and Dispensing

The investigator should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as per product information and the Investigator Brochure and per local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Please refer to the current version of the Investigator Brochure and/or shipment reference sheets for additional information on storage, handling, dispensing, and infusion information for nivolumab.

Destruction of study drug

The drug will be disposed of on-site per MD Anderson Cancer Center Drug Disposal Policy

13.1.6Dose calculations and administration

Describe timing of first dose from registration/randomization. For further preparation and administration details please refer to the current Investigator Brochure and/or **pharmacy reference Appendix.**

Nivolumab will be given every two weeks at a target dose of 3mg/kg (as confirmed by the phase I portion of the study). Patients may be dosed no less than 12 days from the previous dose of drug.

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

13.2 **Idarubicin**

Idarubicin is commercially available. Please see package insert for further information.

13.2.1 **Synonyms**

4-Demethoxydaunorubicin; 4-DMDR, Idarubicin Hydrochloride, IDR: IMI30; NSC256439, SC 33428

13.2.2 **Use**

Treatment of acute leukemias (AML, ANLL, ALL), accelerated phase or blast crisis of chronic myelogenous leukemia (CML).

13.2.3 **Contraindications**

Hypersensitivity to idarubicin, other anthracyclines, or any component of the formulation; bilirubin >5 mg/dl; pregnancy

13.2.4 **Warnings/Precautions**
The U.S. Food and Drug Administration (FDA) currently recommends that procedures for proper handling and disposal of antineoplastic agents be considered. Can cause myocardial toxicity and is more common in patients who have previously received anthracyclines or have pre-existing cardiac disease; reduce dose in patients with impaired hepatic function.

13.2.5 **Adverse Reactions**

>10%

Cardiovascular: Transient EKG abnormalities (supraventricular tachycardia, S-T wave changes, atrial or ventricular extrasystoles); generally asymptomatic and self-limiting. Congestive heart failure, dose-related. The relative cardiotoxicity of idarubicin compared to doxorubicin is unclear. Some investigators report no increase in cardiac toxicity at cumulative oral idarubicin doses up to 540 mg/m_2; other reports suggest a maximum cumulative intravenous dose of 150 mg/m_2.
Central nervous system: Headache
Dermatologic: Alopecia (25% to 30%), radiation recall, skin rash (11%), urticaria
Gastrointestinal: Nausea, vomiting (30% to 60%); diarrhea (9% to 22%); stomatitis (11%); GI hemorrhage (30%)
Genitourinary: Discoloration of urine (darker yellow)
Hematologic: Myelosuppression, primarily leukopenia; thrombocytopenia and anemia. Effects are generally less severe with oral dosing
Nadir: 10-15 days
Recovery: 21-28 days
Hepatic: Elevations of bilirubin and transaminases (44%)

1% to 10%

Central nervous system: Seizures
Neuromuscular & skeletal: Peripheral neuropathy

<1%: Hyperuricemia

13.2.6 **Overdosage/Toxicology** Symptoms of overdose include severe myelosuppression and increased GI toxicity. Treatment is supportive. It is unlikely that therapeutic efficacy or toxicity would be altered by conventional peritoneal or hemodialysis.

13.2.7 **Drug Interactions** Patients may experience impaired imune response to vaccines; possible infection after administration of live vaccines in patients receiving immunosuppressants

13.2.8 **Stability** Store intact vials of solution under refrigeration at 2°C to 8°C (36°F to 46°F). Protect from light. Solutions diluted in D5W or NS for infusion are stable for 4 weeks at room temperature, protected from light. Syringe and IBPB

solutions are stable for 72 hours at room temperature and 7 days under refrigeration.

13.2.9 **Mechanism of Action** Similar to doxorubicin and daunorubicin; inhibition of DNA and RNA synthesis by intercalation between DNA base pairs

13.2.10 **Pharmacodynamics/Kinetics**
Absorption: Oral: Variable (4% to 77%; mean: ~30%)
Distribution: V_d: 64 L/kg (some reports indicate 2250 L)
Metabolism: Hepatic to idarubicinol (pharmacologically active)
Half-life elimination: Oral: 14-35 hours; I.V.: 12-27 hours
Time to peak, serum: 1-5 hours
Excretion:
Oral: Urine (~5% of dose; 0.5% to 0.7% as unchanged drug, 4% as idarubicinol); hepatic (8%)
I.V.: Urine (13% as idarubicinol, 3% as unchanged drug); hepatic (17%)

13.2.11 **Extravasation management:** Topical cooling may be achieved using ice packsor cooling with circulating ice water. Cooling of site for 24 hours as tolerated by the patient. Elevate and rest extremity 24-48 hours, then resume normal activity as tolerated. Application of cold inhibits vesicant's cytotoxicity. Application of heat can be harmful and is contraindicated. If pain, erythema, and/or swelling persist beyond 48 hours, refer patient immediately to plastic surgeon for consultation and possible debridement.

13.3 **Cytarabine**
Cytarabine is commercial available.

13.3.1Synonyms
Arabinosylcytosine; Ara-C; Cytarabine Hydrochloride; Cytosine Arabinosine Hydrochloride; NSC-63878

13.3.2 Use
Cytarabine is one of the most active agents in leukemia; also active against lymphoma, meningeal leukemia, and meningeal lymphoma; has little use in the treatment of solid tumors

13.3.3 Contraindications
Hypersensivity to cytarabine or any component of the formulation; pregnancy

13.3.4 Warnings/Precautions
The U.S. Food and Drug Administration (FDA) currently recommends that procedures for proper handling and disposal of antineoplastic agents be considered. Use with caution in pregnant women or women of childbearing age and in infants

13.3.5 **Adverse Reactions**

>10%:

Central nervous system: Fever (>80%)
Dermatologic: Alopecia
Gastrointestinal: Nausea, vomiting, diarrhea, and mucositis which subside quickly after discontinuing the drug; GI effects may be more pronounced with divided I.V. bolus doses than with continuous infusion
Hematologic: Myelosuppression; neutropenia and thrombocytopenia are severe, anemia may also occur
Onset: 4-7 days
Nadir: 14-18 days
Recovery: 21-28 days
Hepatic: Hepatic dysfunction, mild jaundice, and acute increases in transaminases can be produced
Ocular: Tearing, ocular pain, foreign body sensation, photophobia, and blurred vision may occur with high-dose therapy; ophthalmic corticosteroids usually prevent or relieve the condition

1% to 10%:

Cardiovascular: Thrombophlebitis, cardiomegaly
Central nervous system: Dizziness, headache, somnolence, confusion, malaise; a severe cerebellar toxicity occurs in about 8% of patients receiving a high dose (>36-48 g/m2/cycle); it is irreversible or fatal in about 1%
Dermatologic: Skin freckling, itching, cellulitis at injection site; rash, pain, erythema, and skin sloughing of the palmar and plantar surfaces may occur with high-dose therapy. Prophylactic topical steroids and/or skin moisturizers may be useful.
Genitourinary: Urinary retention
Neuromuscular & skeletal: Myalgia, bone pain
Respiratory: Syndrome of sudden respiratory distress, including tachypnea, hypoxemia, interstitial and alveolar infiltrates progressing to pulmonary edema, pneumonia

<1%:

Increases in amylase and lipase levels; isolated cases of pancreatitis have been reported; dysphagia (reported with intrathecal use); peripheral neuropathy, neuritis; accessory nerve paralysis (reported with intrathecal use); diplopia (reported with intrathecal use); cough, hoarseness (reported with intrathecal use); aphonia (reported with intrathecal use)

13.3.6 Overdosage/Toxicology

Symptoms of overdose include myelosuppression, megalobastosis, nausea, vomiting, respiratory distress, and pulmonary edema. A syndrome of sudden

respiratory distress progressing to pulmonary edema and cardiomegaly has been reported following high doses. Treatment is symptomatic and supportive.

13.3.7 **Drug Interactions**
Decreased effect of gentamicin, flucytosine; decreases digoxin oral tablet absorption Increased toxicity: Alkylating agents and radiation; purine analogs; methotrexiate

13.3.8 **Stability**
Store intact vials of powder at room temperature 15°C to 30°C (59°F to 86°F). Reconstitute with SWI, D5W or NS; reconstituted solutions are stable for up to 8 days at room temperature. Use preservative free cytarabine solution within 24 hours of reconstitution. Further dilution in D5W or NS is stable for 8 days at room temperature (25°C).
Standard IV infusion dilution: Dose/250-1000 mL D5W or NS.

13.3.9 **Mechanism of Action**
Inhibition of DNA synthesis. Cytosine gains entry into cells by a carrier process, and then must be converted to its active compound, aracytidine triphosphate. Cytosine is a purine analog and is incorporated into DNA; however, the primary action is inhibition of DNA polymerase resulting in decreased DNA synthesis and repair. The degree of cytotoxicity correlates linearly with incorporation into DNA; therefore, incorporation into DNA is responsible for drug activity and toxicity. Cytarabine is specific for the S phase of the cell cycle.

13.3.10 **Pharmacodynamics/Kinetics**
Distribution: V6: Total body water; widely and rapidly since it enters the cells readily; crosses blood-brain barrier with CSF levels of 40% to 50% of plasma level
Metabolism: Primarily hepatic; aracytidine triphosphaste is the active moiety; about 86% to 96% of dose is metabolized to inactive uracil arabinoside
Half-life elimination: Initial: 7-20 minutes; Terminal: 0.5-2.6 hours
Excretion: Urine (~80% as metabolites) within 24-36 hours

13.3.11 **Administration**
Can be administered at a concentration not to exceed 100 mg/mL.
I.V. doses of >1.5 g/m_2 may produce conjuctivitis which can be ameliorated with prophylactic use of corticosteroid (0.1% dexamethasone) eye drops. Dexamethasone eye drops should be administered at 1-2 drops every 6 hours during and for 2-7 days after cytarabine is done.

14.0 Correlative Studies (Optional)

The objective of this portion of the study is to correlate systemic serum markers, obtainable by peripheral venous access to patient responses and observed toxicities. Voluntary participation in this portion of the protocol is optional for all study participants.

Systemic lymphocyte counts obtained from routine CBC with differential will be analyzed and associated with clinical outcomes and toxicities from the lab draws obtained throughout this protocol.

Tumor-specific antigens that can elicit cellular and humoral immunity, are expressed on leukemia cells and can be identified for development of immunotherapy in these patients. Patient serum will be analyzed to assess candidate tumor-associated antigens or genes that elicit cellular and humoral immune responses. This analysis will correlate antigen-expression and immune responses with patient data such as cytogenetics, treatment response, and clinical outcome of patients.

This study will be done in collaboration with Dr. Padmanee Sharma, MD/PhD, and Dr. James Allison, PhD and covered by the immunotherapy platform supported by MD Anderson Laboratory Protocol PA13-0291. All samples will be collected using procedures characterized in this protocol and all patients will be consented for procedures done under this protocol separately. Specifically, this study will allow for the collection of up to 10 cc of blood, to be drawn at the time of routine blood-draw, to be used for biomarker analysis. Serum samples will be collected in red top tubes and PBMC cycle of chemotherapy, in 10 cc green top, heparin tubes for biomarker analysis before initiation of first cycle of chemotherapy, before every subsequent course of chemotherapy ($\pm$ 1 week), and approximately every 3 months until completion of nivolumab therapy, relapse, or discontinuation of therapy ($\pm$ 1 week) whichever comes first. Further samples will be obtained at the end of study visit.

Bone marrow aspirate samples will be obtained at diagnosis and at the time of any follow-up bone marrow assessment for molecular analysis of genomic aberrations as a part of the AML moonshot program and will be submitted to the laboratories of Dr. Lynda Chin and Andrew Futreal under the approved protocol LAB01-473.

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APPENDIX D SAMPLE OF DRUG ORDERING AND PHARMACY REFERENCE MATERIAL

Nivolumab (BMS-936558) Pharmacy Reference Material

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

Initial Orders

- *Following submission and approval of the required regulatory documents, a supply of nivolumab may be ordered from by completing a Drug Request Form provided by BMS for this specific trial. The first request may take place upon screening of the first patient*
- *The initial order should be limited to 20 vials. 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 product 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. <u>It is imperative that only drug product designated for this protocol number be used for this study.</u>*
- *<u>Pharmacy supplies not provided by BMS:</u> Empty IV bags/containers, approved diluents, In-line filters and infusion tubing*

Re-Supply

- *Drug re-supply request form should be submitted electronically 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 Investigator Brochure for additional information.

<u>Storage Conditions & Handling:</u>

- 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 section 3.2.3 of the current Investigator Brochure. Due to parameters surrounding the use time of Nivolumab, 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 4for up to 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 should be inclusive of the 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 paticulate 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.*

   Note: Nivolumab infusion concentration must be at or above the minimum allowable concentration of 1 mg/mL.

   Note: It is not recommended that so-called "channel" or tube systems are used to transport prepared infusions of nivolumab.
4. Attach the IV bag containing the nivolumab solution to the infusion set and filter.
5. At the end of the infusion period, flush the line with a sufficient quantity of approved diluents.

Example Dose Calculation [at 3mg/kg]

Total dose should be calculated as follows (assuming total dose volume of 210 mL, 70 kg pt, dose of 3 mg/kg):

- Subject body weight in kg x 3 mg (for the 3 mg/kg cohort) = total dose (mg)
  70 kg x 3 mg/kg = 210 mg
- Total dose (mg) ÷ 10 mg/mL = Amount of solution to be withdrawn from vials
  210 mg ÷ 10 mg/mL = **21 mL**

Example of Total volume of solution to infuse (mL) for a minimum conc solution. – Volume of 10 mg/mL solution (mL) = Volume of Diluent (mL) to add

210 mL – 21 mL = 189 mL

Please note it is perfectly acceptable to dose Nivolumab at a higher drug concentrations, **as long as the total volume of diluted solution is <u>at or above</u> the minimum allowable concentration of 1 mg/mL, below is the calculation based on the above example. Please double check.**

Total dose in mg ÷ Total volume to infuse in mL = Overall drug concentration, mg/mL

210 mg ÷ 210mL = 1 mg/mL