CHILDREN'S ONCOLOGY GROUP

The world's childhood cancer experts

NCI Pediatric Early Phase Clinical Trials Network

A program funded by the National Cancer Institute of the National Institutes of Health


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A National Cancer Institute-supported member group of the National Clinical Trials Network


March 30, 2020

Martha Kruhm, MS, RAC
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Operations and Informatics Branch
Cancer Therapy Evaluation Program
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National Cancer Institute
Executive Plaza North Room 730
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Dear Ms. Kruhm,

Enclosed please find Amendment #11 to ADVL1412, *A Phase 1/2 Study of Nivolumab in Children, Adolescents, and Young Adults with Recurrent or Refractory Solid Tumors as a Single Agent and in Combination with Ipilimumab.*

This amendment is administrative in nature and includes the addition of off-study criteria for patients on Arm E.

Specific changes are detailed in the Summary of Changes table below. Minor administrative updates (such as the correction of typographical errors, spelling, or updates to the numbers of referenced sections) are tracked in the protocol but not specified.

Please let me know if you have any questions or need additional information.

Sincerely,

Patrice Navrude, MS, Protocol Coordinator for
Crystal Mackall, MD, ADVL1412 Study Chair, and
Brenda Weigel, MD, PEP-CTN Chair

**Changes to Protocol Document:**

| # | Section | Page | Change |
|---|---|---|---|
| 1. | Throughout | -- | The version date and amendment number has been updated |
| 2. | 10.2 | | 100 days after the last dose of the investigational agent (Patients on Part A or C that are not enrolled at the MTD**; Patients on Part E).** |

**Changes to Informed Consent Documents (Parts A& B; Parts C, D & E):**

| # | Section | Page | Change |
|---|---|---|---|
| 1. | Throughout | -- | The version date and amendment number has been updated |

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A program funded by the National Cancer Institute of the National Institutes of Health

Activated: February 2, 2015
Closed:

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Amendment #: 11

**CHILDREN'S ONCOLOGY GROUP**

**ADVL1412**

# A PHASE 1/2 STUDY OF NIVOLUMAB IN CHILDREN, ADOLESCENTS, AND YOUNG ADULTS WITH RECURRENT OR REFRACTORY SOLID TUMORS AS A SINGLE AGENT AND IN COMBINATION WITH IPILIMUMAB

**Lead Organization: COG Pediatric Early Phase Clinical Trials Network (PEP-CTN)**

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**AGENT NSC# AND IND#'s**
NCI-Supplied Agents*:
Nivolumab (BMS-936558, MDX-1106)
(NSC # 748726)
Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived) (NSC # 732442)

IND Sponsor: DCTD, NCI

**SEE SECTIONS 8.3.6, 8.4.1, 8.4.5, 8.5.6, 8.6.3, 8.7.3, and 8.8.5 FOR SPECIMEN SHIPPING ADDRESSES**

**This trial is covered by** a Certificate of Confidentiality from the federal government, which will help us protect the privacy of our research subjects. The Certificate protects against the involuntary release of information about subjects collected during the course of our covered studies. The researchers involved in the studies cannot be forced to disclose the identity or any information collected in the study in any legal proceedings at the federal, state, or local level, regardless of whether they are criminal, administrative, or legislative proceedings. However, the subject or the researcher may choose to voluntarily disclose the protected information under certain circumstances. For example, if the subject or his/her guardian requests the release of information in writing, the Certificate does not protect against that voluntary disclosure. Furthermore, federal agencies may review our records under limited circumstances, such as a DHHS request for information for an audit or program evaluation or an FDA request under the Food, Drug and Cosmetics Act.

The Certificate of Confidentiality will not protect against mandatory disclosure by the researchers of information on suspected child abuse, reportable communicable diseases, and/or possible threat of harm to self or others.

## ABSTRACT

The goal of Part A is to define the recommended phase 2 dose (RP2D), which is a tolerable dose of nivolumab that provides systemic exposure similar to that achieved by the RP2D in adults.

**Part A** will enroll at least six evaluable children with recurrent or refractory solid tumors, excluding brain tumors, and patients enrolled on Part A must have measurable or evaluable disease. Patients on Part A will receive 3 mg/kg nivolumab every 2 weeks until disease progression or until toxicity requires treatment interruption.

**Part B** will evaluate the activity of nivolumab at its RP2D in expanded cohorts for patients with neuroblastoma, osteosarcoma, rhabdomyosarcoma, Ewing sarcoma, Hodgkin lymphoma non-Hodgkin lymphoma, and melanoma. Measurable disease is required for enrollment on Parts B1-B6, measurable or evaluable disease is required for Part B7 (melanoma), and MIBG evaluable disease without measurable disease in patients with neuroblastoma (Part B8). The primary objective of Part B is to identify histologic subtypes where there is a signal for anti-tumor activity, using a Simon's optimal two-stage design, with the exception of Part B7, which will serve as a non-statistical access cohort for the rare diagnosis of melanoma, to remain open to enrollment until Parts B1-B6, B8 are complete.

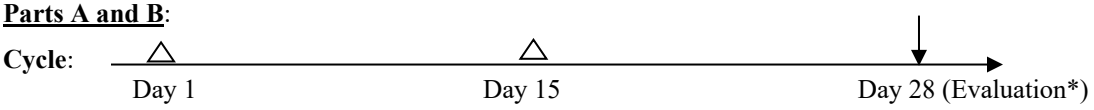
**Part C** will enroll all histologies with the same eligibility criteria required for enrollment on Part A with the goal of identifying the RP2D of the combination of nivolumab plus ipilimumab using a rolling 6 design. Patients will be monitored for response and toxicity using standard criteria.

**Part D** will evaluate nivolumab in combination with ipilimumab in selected disease cohorts (neuroblastoma, rhabdomyosarcoma, non-Hodgkin lymphoma, osteosarcoma, or Ewing sarcoma). Part D will open to accrual if there is insufficient activity in the initial stage of the Simon's optimal two-stage design in Part B. Part D will use a Simon's optimal two-stage design to evaluate the activity of nivolumab in combination with ipilimumab at the RP2D and schedule determined in Part C, nivolumab (3 mg/kg) in combination with ipilimumab (1 mg/kg) (See Section 11.6).

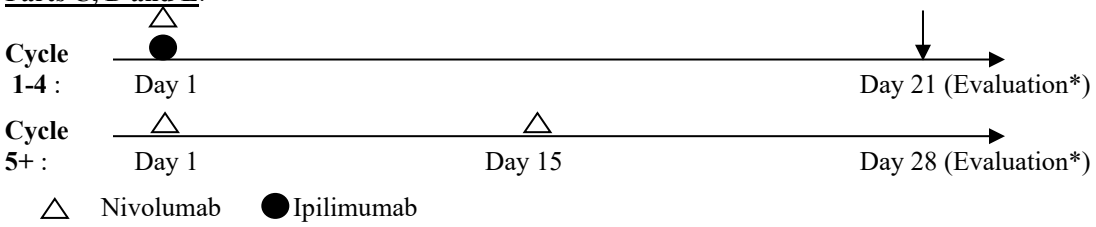
**Part E** will evaluate alternative dosing of nivolumab (1 mg/kg) in combination with ipilimumab (3 mg/kg) in rhabdomyosarcoma or Ewing sarcoma/Peripheral PNET.

## EXPERIMENTAL DESIGN SCHEMA

**Parts A and B**:



**Parts C, D and E**:




*See Table 8.1 for required disease evaluations. Therapy will be discontinued if there is evidence of progressive disease or drug related dose-limiting toxicity that requires removal from therapy. Cycle length for Parts A and B is 28 days. Cycle length for Parts C, D, and E in cycle 1-4 (combination therapy) is 21 days, and 28 days for subsequent cycles (nivolumab alone).

## 1.0 GOALS AND OBJECTIVES (SCIENTIFIC AIMS)

### 1.1 Primary Aims

Determine the tolerability, and define and describe the toxicities of nivolumab administered as a single agent in children with relapsed or refractory solid tumors at the adult recommended dose of 3 mg/kg.

Determine if systemic nivolumab exposure in children is similar to the systemic exposure in adults following a 3 mg/kg dose.

Determine the maximum tolerated dose (MTD) and/or recommended Phase 2 dose (RP2D) and define and describe the toxicities of nivolumab plus ipilimumab administered to children with relapsed or refractory solid tumors.

Assess antitumor effects of nivolumab across selected childhood solid tumors in seven expansion cohorts (Parts B1-B6, B8); neuroblastoma (2 cohorts: measurable disease; MIBG positive only non-measurable disease), osteosarcoma, rhabdomyosarcoma, Ewing sarcoma, Hodgkin lymphoma, and non-Hodgkin lymphoma. A non-statistical access cohort for the rare diagnosis of melanoma (Part B7) will remain open to enrollment until Parts B1-B6, B8 are complete B7 to preliminarily define the antitumor effects of nivolumab within the confines of a phase 1/2 study.

Assess antitumor effects of nivolumab in combination with ipilimumab across selected childhood solid tumors in two dose combinations (Part D and Part E).

Characterize the pharmacokinetics of nivolumab alone and in combination with ipilimumab, including AUC, Cmax, Cmin, using intensive sampling.

Assess immunogenicity of nivolumab alone and in combination with ipilimumab by measuring anti-drug antibody (ADA) levels

### 1.2 Secondary Aims

1.2.1 Conduct exploratory studies of the phenotypic and functional effects of nivolumab (alone and in combination with ipilimumab), as well as changes in antibodies to previously vaccinated viruses, in serum samples.

1.2.2 Explore whether correlations exist between PD-L1 expression on tumor and antitumor effects of nivolumab (alone and in combination with ipilimumab) in pediatric solid tumors and to conduct exploratory studies of potential tumor associated biomarkers of response in tumor tissue (at least five out of the

following markers: NRAS, BRAF, MEK, KIT, PDGF, TP53, RB1 and BRCA1, Akt phosphorylation, IL-17 or PD-L1).

1.2.3 Explore presence of tumor infiltrating lymphocytes and their association with antitumor effects of nivolumab (alone and in combination with ipilimumab).

1.2.4 Conduct exploratory studies of the effect of nivolumab (alone or in combination with ipilimumab) on cytokine levels in serum samples.

1.2.5 For Part E, determine tumor mutational burden of diagnostic specimens using FoundationOneCDx testing to explore immune-related gene expression or mutation and its association with antitumor response to nivolumab in combination with ipilimumab.

## 2.0 BACKGROUND

### 2.1 Introduction/Rationale for Development

*Checkpoint Inhibitors as a New Class of Immunotherapeutics*

Progressive optimization of cytotoxic regimens substantially improved cure rates for pediatric solid tumors between 1970 and 1995, but the rate of progress has diminished since then. Children with childhood cancer who present in many high risk groups, including those who are diagnosed with metastatic disease and those with disease recurrence after frontline therapy have poor survival rates, which have not changed substantially in many years. Current standard regimens for high-risk pediatric solid tumors already employ dose intensive cytotoxic therapy with significant short-term and long-term toxicity, thus further dose escalation of such regimens is unlikely to improve outcomes, but will almost certainly increase toxicity. For these reasons, there is an urgent need to develop new classes of therapeutics to treat childhood cancer, based upon biologic insights into the tumor itself or the host response to cancer.

Immunotherapy for cancer has recently demonstrated increasing success, evidenced by FDA approval of a therapeutic vaccine for prostate cancer[1], improved survival for patients with high risk neuroblastoma treated with an anti-GD2 based immunotherapy regimen following autologous stem cell transplant[2], dramatic anti-leukemia effects with adoptive therapy with genetically engineered T cells[3-6] and with bi-specific antibodies that activate host T cells.[4] Anti-CTLA4 (ipilimumab), the first of a new class of immunomodulatory agents, called checkpoint inhibitors, has been FDA approved for the treatment of metastatic melanoma.[7] Anti-PD1 is a second-generation checkpoint inhibitor, and blocking mAbs targeting PD-1 have shown antitumor effects in melanoma, renal cell carcinoma and lung cancer.[8,9] This trial will evaluate toxicity and potential antitumor activity of nivolumab, a PD1 blocking mAb being developed by BMS, in children with refractory solid tumors and will test a combination regimen of nivolumab plus ipilimumab, which has shown impressive activity in melanoma.[10]

Immunomodulatory "checkpoint inhibitors" induce antitumor effects by blocking inhibitory immune receptors. [11] Development of this class of agents for cancer is based on the hypothesis that anti-tumor immune responses exist in patients with cancer, but are inhibited by tonic activation of inhibitory pathways. Blockade of inhibitory receptors uncovers antitumor immune responses that can mediate antitumor effects. CTLA4 is considered the prototypic checkpoint molecule. Under normal circumstances, CTLA4

signaling broadly limits T cell responses to self-antigens and prevents autoimmunity. But blockade of CTLA4 results in increased activating signals via CD28, as both CTLA4 and CD28 bind to the same ligands (B7-1, B7-2) on antigen presenting cells. Experience gleaned during clinical development of anti-CTLA4 based therapeutics is informing development of nivolumab, and will be discussed in detail here.

Two antibodies which block CTLA4 signaling were tested in clinical trials: ipilimumab (Yervoy, BMS) and tremelimumab (Pfizer). Two randomized trials demonstrated prolonged survival in patients with metastatic melanoma treated with ipilimumab. In the first, ipilimumab (3 mg/kg) alone or ipilimumab plus anti-gp100 vaccine was compared to a gp100 vaccine alone arm, and both ipilimumab arms showed superior overall survival, with a median OS of 10.1 months for ipilimumab alone vs 6.4 months with vaccine alone.[12] This trial demonstrating a survival improvement for patients with metastatic melanoma served as the basis for FDA approval of ipilimumab, at the 3 mg/kg dose for metastatic melanoma. A subsequent trial demonstrated superior survival with ipilimumab (10 mg/kg) plus dacarbazine, compared to dacarbazine alone (11.1 months median OS vs. 9.2 months median OS) in metastatic melanoma. [13] Lessons learned from these studies were several:

1) At doses beyond 3 mg/kg, dose-response and dose-toxicity effects for ipilimumab remain unclear with similar response rates and toxicity rates observed at 3 mg/kg and 10 mg/kg. The current FDA approved dose is 3 mg/kg although results of ongoing Phase III trials evaluating 10 mg/kg are pending.

2) Objective responses were difficult to assess because patients not infrequently had clinical evidence of tumor progression that was subsequently followed by tumor shrinkage. Such "pseudoprogression" has been attributed to inflammation associated with immune mediated antitumor effects and has led to a consensus that patients with tumor progression (within well-defined limits) may remain on trial if they remain clinically stable and meet criteria to continue therapy. While RECIST remains the gold standard for defining an antitumor response, RECIST responses may ultimately occur in a delayed fashion after initial apparent tumor progression in patients treated with checkpoint blockade.

3) The adverse effect profile of anti-CTLA4 was significant but limited to immune mediated toxicity. In 15-45% of patients, autoimmune reactions occurred that typically involved one or two organs, and could be severe. Colitis, hypophysitis, hepatitis, rash, pancreatitis, thyroiditis and iritis were commonly observed and have been coined "immune related adverse events". Autoimmune related adverse events were treated by discontinuation of the anti-CTLA4 therapy with or without treatment with corticosteroids. Inflammation of endocrine glands, such as thyroid and pituitary typically resulted in irreversible dysfunction requiring long-term hormone replacement, whereas tissue damage in non-endocrine organs were typically reversible. In general, patients who developed autoimmune related adverse events had a higher response rate, suggesting that these syndromes are potential biomarkers of immune activity and that treatment with corticosteroid does not abrogate antitumor effects.

4) The optimal schedule for anti-CTLA4 remains unclear with most regimens using an induction phase administered every three weeks followed by maintenance dosing administered approximately every 3 months. However, the role for maintenance dosing is unclear and some investigators recommend induction therapy every 3 weeks x 4, followed by re-induction as necessary based upon disease activity. Tremelimumab did not show activity in randomized trials but was dosed every 3 months in the pivotal trial, raising the possibility that suboptimal dosing can limit efficacy of these agents.[14]

## 2.2 Preclinical Studies

Antitumor Activity

PD-1 (Programmed Death 1) is the second immune checkpoint receptor developed for cancer immunotherapy. Unlike CTLA4, which is expressed on nearly all regulatory T cells and appears to be important in controlling T cell proliferation during T cell development, PD-1 is upregulated on peripheral T cells following chronic activation. PD-1 signaling on T cells is induced following binding to either PD-L1 (B7-H1, CD274, considered widely expressed, especially on macrophages and some tumors) or PD-L2 (B7-DC, CD273, more limited expression, on antigen presenting cells). Murine studies showed impressive effects when blocking antibodies to PD-1 were administered to mice with chronic viral infection, resulting in recovery of antiviral immunity and reversal of "T cell exhaustion".[15] Furthermore, mice genetically induced to be deficient in PD-1 developed a variety of autoimmune-like diseases. Hence, PD-1 signaling has been associated with chronic T cell activation and T cell exhaustion and current concepts hold that blocking PD-1 may augment responses in the setting of chronic immune activation. The differences in the biology between CTLA4 and PD-1 leads to the prediction that PD-1 blockade is less likely to induce de novo autoimmunity and more likely to restore responses in the setting of chronic antigen exposure.

Several preclinical studies demonstrated antitumor effects of anti-PD1 in tumor models. A landmark manuscript by Dong et al. demonstrated robust tumor expression of PD-L1 as well as expression of PD-L1 on tumor-associated macrophages, but not on other normal tissues.[16] This group further demonstrated that interferon gamma induced upregulation of PD-L1 on tumor cell lines, thus providing a means for tumor immune escape through signaling of PD-1 on activated T cells, which induces suppressive signaling pathways. PD-1 signaling has been demonstrated to contribute to immune escape *in vivo* in murine myeloma[17], Sa1N fibrosarcoma, MC38 colorectal adenocarcinoma, and B16 melanoma.[18]

As discussed above, PD-1 has not been extensively studied in preclinical models of pediatric cancer. However recent work demonstrated expression of PD-L1 on two murine embryonal rhabdomyosarcoma cell lines including M3-9-M, which is derived from an HGFTgp53+/- genetically engineered mouse and 76-9, a spontaneous rhabdomyosarcoma.[19] In immunocompetent mice inoculated with either line, treatment with anti-PD1 prevented tumor growth if administered coincident with tumor inoculation. However, when anti-PD1 was administered in the presence of established tumors, anti-PD1 therapy had antitumor effects but was not curative. This work demonstrated that anti-PD1 therapy did augment immune responses to tumor antigens expressed on M3-9-M mice. Interestingly, this work demonstrated that co-treatment with anti-PD1 plus anti-CXCR2 antibodies, which prevent trafficking of myeloid derived suppressor cells into the tumor bed was more effective than treatment with anti-PD1 alone. These results implicate myeloid derived suppressor cells in tumor immune escape in rhabdomyosarcoma and suggest that a future clinical approach that combines anti-PD1 with other immunomodulators holds promise. PD-1 signaling has also been implicated in immune escape in acute myeloid leukemia,[20] and unpublished work has

demonstrated PD-L1 expression on tumor infiltrating myeloid cells in medulloblastoma tissue section and in medulloblastoma cell lines.

Preclinical Biomarker Studies (Amendment #10C)
A non-clinical biomarker study to characterize the expression levels of PD-L1 and presence of tumor-infiltrating lymphocytes in multiple pediatric tumor types and to identify tumor types likely to show response to nivolumab treatment was conducted as a measure for the nivolumab Pediatric Investigation Plan agreed upon by the Pediatric Committee of the European Medicines Agency.

In this study, high rates of PD-L1+ staining at a > 1% threshold (⩾1+ intensity, minimum 100 tumor cells evaluated) were observed in samples from NHL (Burkitt Lymphoma) (8/10; 80%) and glioblastoma (7/20; 35%). Positive PD-L1 staining was also observed in 16/114 (14%) neuroblastoma samples (including both whole slide sections and TMA samples), ganglioneuroblastoma (2/18; 11%), ependymoma (2/40; 5%) and rhabdomyosarcoma (2/54; 4%). Other tumor types demonstrating positive PD-L1 expression in at least one sample included osteosarcoma (1/20; 5%), supratentorial primitive neuroectodermal tumor (1/5; 20%) and the single synovial sarcoma sample (1/1, 100%).

No PD-L1 expression was observed in any medulloblastoma, ganglioneuroma or Ewing sarcoma tumor samples examined.

Immune cell infiltration was examined in a subset of the tumors assessed for PD L1 expression. CD45RO+ cells (memory T cells) were the most ubiquitously present immune cells, seen in 49/60 (81%) tumors. CD8+ cells (cytotoxic T cells) were commonly observed as well (46/60; 77%). PD-1+ and FoxP3+ expression were seen in 28 (47%) and 25 (42%) tumors, respectively. CD4+ staining was only observed in 13 (22%) of tumors assessed.

Regardless of presence or absence of PD-L1 expression, the presence of immune cells (macrophages and lymphocytes), and specifically CD45RO+ (memory) and CD8+ (cytotoxic) T cells in tumors was common, suggesting an presence of an immune active environment in tumors of pediatric cancer patients.[21] The clinical utility of PD-L1 expression and characteristics of tumor associated immune cells could not be determined in this study.

Animal Toxicology
None pertaining to this trial. The anti-PD1 mAb does not bind murine PD-1 or non-human primate PD-1 and therefore these are not informative for toxicity in humans.

Preclinical Pharmacokinetic Studies
Such studies do not significantly inform this trial as the pharmacokinetic studies from the adult early phase trials are more informative.

## 2.3 Adult Studies

Studies in Adults
Results of early phase clinical testing of two checkpoint inhibitors which block Programmed Death 1 (PD-1)/PD-L1 interactions in adult cancer patients have been

published. In general, these have demonstrated impressive antitumor activity is melanoma, lung cancer and renal cell cancer with less toxicity than that observed with ipilimumab.

Topalian et al. reported in June 2012 on 296 adult patients treated on a Phase I study of nivolumab (then called BMS-936558) a fully human IgG4 blocking mAb.[8] Patients received drug every 2 weeks for up to 2 years, unless they had a complete response, unacceptable side effects, progressive disease or they declined to continue therapy. Response was assessed every 8 weeks and due to concerns regarding pseudoprogression seen with other checkpoint inhibitors, patients were allowed to remain on study if they were clinically stable despite progression on routine restaging unless progression was confirmed on a subsequent restaging 8 weeks later. Doses tested were 0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg and 10 mg/kg using a standard 3+3 design. No MTD was identified.

A total of 5 expansion cohorts were then studied at 10 mg/kg comprising melanoma, non-small cell lung cancer, renal cell carcinoma, castration resistant prostate cancer and colorectal cancer. Because signs of clinical activity were observed, additional cohorts of melanoma, squamous and non-squamous lung cancer and renal cell cancer were studied. Five percent of patients discontinued treatment due to adverse events, Grade 3 or 4 treatment-related adverse events occurred in 14% and drug related SAEs occurred in 11%. Most common drug related immune adverse events were pneumonitis, vitiligo, colitis, hepatitis, hypophysitis and thyroiditis. In general, adverse events were similar in nature, severity and reversibility to that seen with ipilimumab, except that the incidence appeared to be less and pneumonitis was not observed with a significant frequency in studies with ipilimumab. There was no evidence that pneumonitis was more common in lung cancer or any other particular histology. There were 3 deaths associated with pneumonitis, two in patients with lung cancer and one in a patient with colorectal cancer.

**Table 1. Response rates associated with histology and dose[8]**

| Histology | Dose | Response rate (%) | Number treated |
|---|---|---|---|
| Melanoma | 0.1 mg/kg | 29 | 14 |
| Melanoma | 0.3 mg/kg | 19 | 16 |
| Melanoma | 1 mg/kg | 30 | 27 |
| Melanoma | 3 mg/kg | 41 | 17 |
| Melanoma | 10 mg/kg | 20 | 20 |
| Melanoma | All | 28 | 94 |
| Lung cancer | 1 mg/kg | 6 | 18 |
| Lung cancer | 3 mg/kg | 32 | 19 |
| Lung cancer | 10 mg/kg | 18 | 39 |
| Lung cancer | All | 18 | 76 |
| Renal cell cancer | 1 mg/kg | 24 | 17 |

| | | | |
|---|---|---|---|
| Renal cell cancer | 10 mg/kg | 31 | 16 |
| Renal cell cancer | All | 27 | 33 |

A substantial fraction of patients with objective responses who were followed for one year after initiation of therapy showed a prolonged duration of response (8/14 with lung cancer had responses lasting at least 24 weeks, 13/26 with melanoma had responses lasting at least one year and 5/8 with renal cancer had responses lasting at least one year).

In July 2013, Hamid et al reported results of a Phase I trial of lambrolizumab (previously MK-3475) a humanized IgG4 mAb that blocks PD-1. The drug was administered to 135 patients with advanced melanoma at a dose of 2 mg/kg or 10 mg/kg every 2-3 weeks. Using RECIST, a 38% response rate was observed combining all dose levels with a higher response rate (52%) in patients that received 10 mg/kg every 2 weeks. Overall, 77% of patients had a reduction in tumor burden during the study. Responses were durable in the majority of patients. Most common adverse events were fatigue, rash, pruritus and diarrhea and most were low grade. Patients (13%) with higher grade events (grades 3-5), included pneumonitis in 4%, which indirectly led to the death of one patient, a 96 year old man. Two cases of grade 3 renal failure were observed as well, both of which improved with discontinuation of therapy plus glucocorticoids. The pharmacokinetics showed linear relationships with dose and the half-life of the agent was judged to be 2-3 weeks. Biopsy of lesions from responding patients showed dense infiltration with CD8+ cytotoxic lymphocytes. There is an ongoing trial randomizing dosing between 10 mg/kg administered every 3 vs every 2 weeks.

Brahmer et al. reported results of anti-PD-L1 blocking antibody therapy in 207 patients with a variety of cancers.[22] The agent is an IgG4 subtype antibody, and therefore it is presumed that its effects would be mediated by blockade of PD-1/PD-L1 interactions, rather than by induction of ADCC or complement mediated cytotoxicity. Results were similar to that observed with anti-PD1. Objective response rates were observed in 6-17% of patient groups including melanoma, renal cell cancer and non-small cell lung cancer. Several patients also showed prolonged stabilization of disease and grade 3 or 4 toxic effects occurred in 9% of patients, and were primarily autoimmune in nature. No significant antitumor activity was not observed in cohorts of patients (n=16 patients each) with ovarian cancer, colorectal cancer, pancreatic cancer, breast cancer or gastric cancer.

As of June 2017, single agent nivolumab has been FDA approved for adults with locally advanced or metastatic urothelial carcinoma, hepatocellular carcinoma, microsatellite instability-high or mismatch repair deficient metastatic colorectal cancer, head and neck cancer, Hodgkin lymphoma, metastatic renal cell carcinoma, advanced lung cancer and melanoma.

Results of nivolumab administered in combination with ipilimumab for stage III or IV measurable, unresectable melanoma have recently been reported.[10] At the maximum tolerated combination dose (1 mg/kg anti-PD1 plus 3 mg/kg ipilimumab every three weeks administered concurrently), 53% of patients had an objective response, all with tumor reduction of 80% or more. Adverse effects observed with the combination therapy were qualitatively similar to those observed with

ipilimumab or nivolumab monotherapy, although at an increased rate; 53% of patients experienced Grade 3 or 4 AEs compared to ipilimumab alone (20% of patients) or nivolumab alone (15% of patients).[10] Sequential administration resulted in a lower response rate and lower toxicity rate. With regard to biomarkers previously associated with responses to anti-CTLA4 or anti-PD1, investigators evaluated PD-L1 expression in tumors and absolute lymphocyte counts and looked for relationships with response. In patients treated concurrently, 6/13 patients with PD-L1+ tumors responded whereas 9/22 patients with PD-L1– tumors responded (P>0.99 by Fisher's exact). Interestingly however, in the sequential group, 4/8 patients whose tumors were PD-L1+ responded whereas only 1/13 who had PD-L1- tumors responded. Absolute lymphocyte counts at weeks 5-7 were not associated with response in this study. In summary, the combination anti-CTLA4 plus anti-PD1 administered concurrently induces impressive durable response rates in metastatic melanoma which are higher than that reported with *any previous therapy*. Given that this is a non-randomized study however, the results must be interpreted with caution.

Nivolumab (1 mg/kg) in combination with ipilimumab (3 mg/kg) has been FDA approved for adults with BRAF wild-type melanoma. Approval was based on data from CheckMate 069 trial which randomized patients with previously untreated, unresectable stage III or IV melanoma to receive nivolumab (1 mg/kg) plus ipilimumab (3 mg/kg) vs. ipilimumab (3 mg/kg) plus placebo. Patients treated on the nivolumab plus ipilimumab received the combination every 3 weeks x 4 doses then received nivolumab single agent 3 mg/kg every 2 weeks. Treatment-related grade 3−4 adverse events were reported in 51 (54%) of 94 patients who received nivolumab plus ipilimumab compared with nine (20%) of 46 patients who received ipilimumab alone. The most common treatment-related grade 3−4 adverse events were colitis (12 [13%] of 94 patients) and increased alanine aminotransferase (ten [11%]) in the combination group and diarrhea (five [11%] of 46 patients) and hypophysitis (two [4%]) in the ipilimumab alone group. Serious grade 3−4 treatment-related adverse events were reported in 34 (36%) of 94 patients who received nivolumab plus ipilimumab (including colitis in ten [11%] of 94 patients, and diarrhea in five [5%]) compared with four (9%) of 46 patients who received ipilimumab alone (including diarrhea in two [4%] of 46 patients, colitis in one [2%], and hypophysitis in one [2%]) The 2-year overall survival was 63.8% (95% CI 53.3% (.6) for those assigned to nivolumab plus ipilimumab and 53.6% (95% CI 38.1% (.8) for those assigned to ipilimumab alone.[23]

Pharmacology/Pharmacokinetic Studies

Pharmacokinetic studies in adults in the Topalian study showed a median time to peak concentration of 1-4 hours after the start of the one hour infusion and a dose proportion increase in peak concentration and area under the curve with increasing dose across the dose range 0.1 mg/kg-10 mg/kg.[8] Half-life is 2-4 weeks, similar to other therapeutic antibodies. Minimum concentrations 15 days after the first dose 3 mg/kg of Nivolumab from 34 adults treated on CA209003 are shown in Table 2. Based upon this, the pediatric trial will seek to target a minimum exposure of 10 mcg/ml.

**Table 2. Trough Nivolumab Concentrations in Adults**

| Percentile | Cmin (mcg/ml) |
|---|---|
| Min | 6.9 |
| 5 | 8.9 |
| 10 | 11.0 |
| 15 | 11.3 |
| 20 | 12.4 |
| 25 | 13.0 |
| 30 | 14.3 |
| 35 | 15.0 |
| 40 | 17.0 |
| 45 | 17.2 |
| 50 | 17.6 |
| 55 | 18.0 |
| 60 | 19.9 |
| 65 | 21.0 |
| 70 | 22.1 |
| 75 | 24.1 |
| 80 | 24.5 |
| 85 | 25.4 |
| 90 | 28.6 |
| 95 | 31.2 |
| Max | 38.1 |

Pharmacodynamic analysis of PD-1 receptor occupancy revealed 64-70% occupancy across the range of dose levels tested. Tumors were analyzed for PD-L1 expression from archival samples in 42 patients. Of these, samples from 25 patients showed PD-L1 expression by immunohistochemical analysis (cutoff for positivity being > 5% of cells expressing PD-L1). Responses were observed in 9/25 patients with PD-L1 expression by IHC, whereas 0/17 patients without PD-L1 expression showed antitumor responses with anti-PD1 therapy. More recent data from Grosso and colleagues assessed objective response rates to nivolumab in patients with melanoma using a cutoff of 5% PD-L1 expression. In this study, 14% of patients with PD-L1 negative tumors had objective antitumor responses compared to 41% of patients with PD-L1+ tumors. [24]

In summary, anti-PD1 mAbs demonstrate response rates of 30-50% in patients with melanoma and 20-30% in patients with renal cell carcinoma and non-small cell lung cancer. Toxicities associated with checkpoint inhibition are primarily limited to autoimmune reactions. These occur in approximately 30% of adults and children treated with anti-CTLA4, but in <10% of patients treated with anti-PD1. Thus, compared to anti-

CTLA4, anti-PD1 based checkpoint inhibitors demonstrate more potent antitumor effects across a wider range of histologies, with less toxicity. Preliminary studies in adults have demonstrated higher response rates in patients with tumors expressing of the PD-L1, the major ligand for PD1, although antitumor responses have also been seen in patients with PD-L1 negative tumors. Thus, there is currently no accurate biomarker to predict tumor response to anti-PD1 therapy. In a single arm, non-randomized study, combination therapy with anti-PD1 plus anti-CTLA4 resulted in higher response rates for metastatic melanoma than observed with either agent alone, with a similar toxicity profile to that observed with anti-CLTA4 mAb therapy.[10] Preclinical studies have demonstrated antitumor effects of anti-PD1 in a murine model of rhabdomyosarcoma, but there is currently limited information about PD-L1 expression in pediatric tumors.

## 2.4 Pediatric Studies

Prior Experience in Children

A pediatric Phase I trial of ipilimumab, sponsored by CTEP and led by the Pediatric Oncology Branch of the NCI is nearing completion. Ipilimumab was administered to patients 2-21years old with refractory solid tumors. Dose cohorts included 1, 3, 5, and 10 mg/kg IV in a standard 3 + 3 design with 4 doses of induction therapy every 3 weeks followed by maintenance every 3 months until disease progression or unacceptable toxicity. Tumors were measured after 6 weeks, 12 weeks, and then every 3 months. Thirty patients with pediatric solid tumors (melanoma n=10, osteosarcoma n=8, soft tissue sarcomas n=7, renal malignancies n=3 and neuroblastoma n=2) have been enrolled. Subjects >12 years of tolerated the highest dose of 10 mg/kg tested. For subjects < 12 years of age, 3 mg/kg was tolerated without DLT, however DLT was observed in 2 subjects < 12 years treated at 10 mg/kg. In children < 12 years, the MTD was 5mg/kg. Grade 3/4 immune related adverse events (IrAE) included colitis (3) transaminitis (2), autoimmune thyroiditis (1), pancreatitis (1), and hypophysitis (1). Except for a lesser incidence of rash, this frequency and spectrum of IrAE appears similar to that observed in adults treated with ipilimumab. IrAE developed as early as week 1 and as late as 36 weeks, but the majority occurred in the first three weeks. Confirmed stable disease (stable disease at both 6 and 12 week scans) was the best response in 5 patients with melanoma, clear cell sarcoma or osteosarcoma, with a duration of 3 -18 months. Pharmacokinetics revealed no significant differences related to age and the exposure to ipilimumab in children was essentially the same as that for adults given the equivalent mg/kg dose. Although this study raises the prospect that younger children may have lesser tolerance to anti-CTLA4 therapy as compared to adolescents, this is based upon very small numbers and may not be truly related to differences in biology.

We have demonstrated tolerability of the combination at nivolumab 3 mg/kg and ipilimumab 1 mg/kg in Part C. An open question remains if the combination dosing is optimal as delivered in Part D. Reports have suggested improved efficacy at a higher ipilimumab dose. Antonia et al. demonstrated tolerability and potential survival benefit in patients treated with 1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab in patients with small cell lung cancer.[25] Other studies at this dose combination are ongoing. In order to test this dose combination, we will test in Part E and limit to children with rhabdomyosarcoma or Ewing sarcoma/Peripheral PNET. The rationale for including children with rhabdomyosarcoma is that in Part D, out of all the histologic cohorts treated with

combination, we observed one PR to the combination at the Part D dose in a patient with rhabdomyosarcoma. Thus, we will test the combination of nivolumab (1 mg/kg) with ipilimumab (3 mg/kg) to determine if the increased dose of ipilimumab demonstrates improved efficacy in a cohort of pediatric patients with rhabdomyosarcoma or Ewing sarcoma/Peripheral PNET.

## 2.5 Overview of Proposed Pediatric Study

Initially the study opened with 3 parts (Part A, Part B, and Part C) and has been amended to add parts D and E.

Part A will aim to define the recommended phase 2 dose (RP2D), which is a tolerable dose of nivolumab that provides systemic exposure similar to that achieved by the RP2D in adults. The goal of Part A will be to enroll at least 6 children with recurrent or refractory solid tumors, excluding CNS tumors. Patients enrolled on Part A must have measurable or evaluable disease. Part A will enroll at 3 mg/kg nivolumab every 14 days until disease progression or until toxicity requires treatment discontinuation. A cycle will be considered 28 days (2 doses) and the DLT monitoring period will be 28 days. Patients will be monitored for toxicity using standard CTCAE v.5 criteria. If DLT is observed in 2 or greater patients, the dose will be de-escalated to 1 mg/kg every 2 weeks and an additional cohort will be evaluated for toxicity and exposure at that dose level.

Part A will seek to ascertain that children treated at the 3 mg/kg dose (or 1 mg/kg dose if de-escalation occurs) do not experience significantly less drug exposure than adults treated at the 3 mg/kg dose level. Table 2 demonstrates the 95% confidence interval for nivolumab Cmin after the first dose is approximately 10-30 mcg/ml. Therefore, Cmin levels for patients treated in Part A will be evaluated prior to initiation of Part B. If at least 5 of 6 patients achieve a Cmin of at least 10 mcg/ml, we will conclude that children are not experiencing significantly less exposure than adults treated at the same dose. If however, < 5 of 6 patients achieve a Cmin of at least 10 mcg/ml, consideration will be given to a protocol amendment to test a higher dose level in Part A. Note that Cmin levels > 30 mcg/ml will not, in and of itself result in a change in protocol design, unless excess toxicity is observed.

Except for patients with neuroblastoma and MIBG only disease, response assessment will use standard RECIST criteria. Determination of progression will use target selection and single dimension measurements according to RECIST criteria. Patients will be removed from study if tumor size increases from baseline in target lesions selected according to RECIST criteria. However, because a minority of subjects treated with immunotherapy may derive clinical benefit despite initial evidence of progressive disease (e.g. pseudoprogression) patients will be allowed to remain on study if the magnitude of increase in tumor size is <40% and the bulleted criteria below are met. Patients who develop a new lesion while on study are eligible to remain on study if they meet the criteria bulleted below and the sum of the total tumor burden remains < 40% according to RECIST criteria. These are adapted from similar criteria already in place in trials of checkpoint inhibitors in adults with cancer and have been utilized in the Phase I trial of ipilimumab in children. Additional criteria required in order to allow a patient to remain on study despite an increase in tumor size of > 20% but < 40% are the following:

- In the judgment of the treating clinician, the patient does not show evidence for rapid disease progression and/or the patient has shown evidence for clinical benefit.

- There is no decrease in performance status.
- The patient is tolerating the study drug and has not experienced a DLT.
- Continued treatment with nivolumab alone or in combination with ipilimumab will not delay an imminent intervention required to prevent a serious complications (e.g. CNS metastases which require radiation therapy or surgery).

For patients who remain on study despite increase in tumor size of > 20%, imaging to include target lesions must occur following every cycle if clinically indicated, and the same radiographic and clinical criteria must be met in order to remain on study. If tumor size subsequently diminishes to < 20% increase from baseline, the patient may be followed according to the standard protocol guidelines which will involve less frequent imaging. The decision to continue treatment beyond radiographic evidence for disease progression should be discussed with the Study Chair and/or her designee and documented in the study record.

Response for patients with MIBG only neuroblastoma will be assessed according to Section 12.4.2.

Once a RP2D is identified in Part A, an expansion cohort of up to 6 additional patients will be treated at the nivolumab monotherapy RP2D to acquire PK data in a representative number of young patients (i.e. 6 patients < 12 years of age and 6 patients ≥ 12 years).

Twelve evaluable patients were enrolled to Part A (June 2017). None had dose limiting toxicity, the RP2D of single agent nivolumab was determined to be 3 mg/kg IV q14 days. Pharmacokinetic parameters were similar to adults. In children (n=11), the nivolumab Cmax (n=11) was 63.2 ± 15.7 mg/mL, half-life was 10.7±1.8 days and clearance was 0.196 ± 0.075 mL/h/kg.[26]

Part B and Part C will open simultaneously. Part B will evaluate the activity of nivolumab at its RP2D in expanded cohorts with the goal of enrolling at least 10 patients per tumor type: neuroblastoma, osteosarcoma, rhabdomyosarcoma, Ewing sarcoma, Hodgkin lymphoma, and non-Hodgkin lymphoma. Measurable disease is required for enrollment on Parts B1-B6, measurable or evaluable disease is required for Part B7 (melanoma) and MIBG evaluable disease without measurable disease in patients with neuroblastoma (Part B8). Patients aged 1-30 years may enroll on Parts B1-B6, B8; patients < 18 years may enroll on Part B7. The primary objective of Part B is to identify histologic subtypes where there is a signal for anti-tumor activity, using a Simon's optimal two-stage design, with the exception of Part B7, which will serve as a non-statistical access cohort (without minimum or maximum accrual limits) for the rare diagnosis of melanoma, to remain open to enrollment until Parts B1-B6, B8 are complete. Note that patients who have an initial increase in target lesions but eventually show a response according to RECIST criteria will be considered responders for the purpose of defining response in Cohort B. Parameters for response and progression are measured in relation to baseline measurements.

Preliminary data from Part B (June 2017, nivolumab 3 mg/kg every 14 days) for osteosarcoma (n=10), Ewing sarcoma (n=10), and rhabdomyosarcoma (n=10) was presented at ASCO 2017.[26] There were no objective responses. Enrollment to first stage of Hodgkin lymphoma, neuroblastoma measurable disease, and neuroblastoma MIBG evaluable disease cohorts is completed and response assessment pending.

Part C will aim to enroll at least 15 patients with the same eligibility criteria required for

enrollment on Part A, with the goal of identifying the MTD or RP2D of the combination of nivolumab plus ipilimumab. The first dose level will be nivolumab at 1 mg/kg and ipilimumab at 1 mg/kg with the goal of enrolling at least 3 patients at this dose level, with both agents administered every three weeks x 4 followed by nivolumab 3 mg/kg every 2 weeks until disease progression or toxicity. The second dose level will be nivolumab at 3 mg/kg and ipilimumab at 1 mg/kg on the same schedule, with the goal of enrolling at least 12 patients at this dose level. An expansion cohort of up to 6 additional patients will be treated at the nivolumab/ipilimumab combination RP2D to acquire PK data in a representative number of young patients (i.e. 6 patients < 12 years of age and 6 patients ≥ 12 years in Part C). If dose level 1 is not tolerated due to toxicity there will be no de-escalated dose studied.

Except for patients with neuroblastoma and MIBG only disease, response assessment will use standard RECIST, with the caveats regarding pseudo-progression noted above.
Patients with primary brain tumors or active CNS metastases will be excluded from this trial due to concerns regarding pseudo-progression in the CNS. Patients with a history of CNS metastases that have been previously treated may enroll if sequential imaging shows no evidence for active disease. Patients with extra axial disease [e.g. skull (bone) metastasis that do not invade the dura] may enroll if there is no evidence for CNS edema associated with the lesion. Patients on systemic corticosteroids and/or with a history of autoimmunity or previous allogeneic stem cell transplant will also be excluded. Management of autoimmune toxicities will be guided by algorithms (Appendix VIII) developed for nivolumab in adults and for ipilimumab in children with cancer, where autoimmune toxicity was also observed.

In Part C (June 2017) of the study, five evaluable patients enrolled at dose level 1 (nivolumab 1 mg/kg) in combination with ipilimumab (1 mg/kg), none had dose limiting toxicity. At dose level 2, nivolumab (3 mg/kg) in combination with ipilimumab (1 mg/kg), twelve patients were evaluable and one had grade 2 creatinine elevation that met criteria for dose limiting toxicity. Part C has demonstrated that nivolumab (3 mg/kg) in combination with ipilimumab (1 mg/kg) is tolerated in children and adolescents.[26]

### 2.6 Rationale for Inclusion of Melanoma Cohort (Amendment #2B)

With Amendment #2A, a non-statistical cohort for melanoma patients was added. Nivolumab is approved for metastatic or unresectable melanoma based upon an objective response rate of 32% and a duration of response greater than 6 months in approximately one third of responders. Currently, there is no treatment FDA approved for pediatric patients with melanoma. Other agents approved for adult melanoma include interferon alpha, anti-CTLA4 (ipilimumab), BRAF inhibitors (vemurafenib, dabrafenib), and a MEK inhibitor (trametinib) approved for combination therapy with BRAF inhibitors. Notably, BRAF inhibitors require a BRAF mutation for activity and this occurs in only approximately 50% of pediatric and adult melanomas. Furthermore, responses to BRAF inhibition have been short lived. A Phase 2 trial of BRAF inhibition in pediatric melanoma has been initiated but has not been completed. A Phase 1 trial of ipilimumab was completed in children and enrolled 11 patients with melanoma, but there were no objective responses and substantial autoimmune toxicity was observed.[27] Interferon alpha has a low response rate in adult melanoma and significant side effects. Thus, there are currently limited options for children with metastatic or unresectable melanoma. It is important that information be gleaned on the efficacy and toxicity of nivolumab in the pediatric melanoma population given the likelihood that children with melanoma will be offered this agent. Although the rarity of the disease limits the likelihood that a statistically complete cohort

can be achieved, enrollment of even limited numbers of patients could potential provide important information regarding the activity and tolerability of nivolumab in pediatric melanoma.

### 2.7 Rationale for Inclusion of Neuroblastoma- MIBG Evaluable Cohort (Amendment #2C)

Anti-GD2 mAb therapy is the only immunotherapy with demonstrated antitumor activity in solid tumors of childhood. An unconjugated chimeric anti-GD2 mAb (ch14.18) demonstrated significant improvements in event free and overall survival when administered to patients following autologous stem cell transplantation.[2] Importantly however, this same therapy demonstrated very limited evidence for antitumor activity in a Phase I trial when it was tested in patients with neuroblastoma measurable with standard radiographic imaging.[28] Similarly, an anti-GD2 mAb conjugated with IL-2 (hu14.18-IL2) showed very limited activity in patients with radiographically measurable neuroblastoma.[29] However, when the agent was tested in a Phase II trial enrolling both a radiographically measurable strata and a limited disease burden strata, 0/13 patients with disease measurable using standard radiographic criteria showed antitumor response following treatment with hu14.18-IL2, whereas 5/23 patients enrolled in the non-radiographically measurable cohort experienced complete responses to this immunotherapy.[30] All responders to hu14.18-IL2 were patients with limited disease burden. Preclinical data demonstrates evidence for an immunosuppressive microenvironment that may be responsible for limited benefit of immune based therapies for neuroblastoma in the setting of bulk disease.[31] Based upon these data, there is reason to hypothesize that immunotherapy for neuroblastoma may be more effective if undertaken in the setting of limited disease burdens. In an effort to capture a neuroblastoma cohort with more limited disease burden in this study of nivolumab, we will enroll patients with MIBG evaluable lesions (without measurable disease by RECIST), which is expected to accrue patients with more limited disease burdens than patients who will be enrolled on the neuroblastoma cohort comprising patients with radiographically measurable disease. Standard response criteria are already validated for MIBG only neuroblastoma and will be used to measured response for this cohort.

### 2.8 Incidence and Proposed Management of Pleural Effusions in Patients Treated with Nivolumab

As of October 22, 42 patients have been accrued to ADVL1412 and 5 cases of pleural effusion were reported. All involved patients with sarcoma (osteosarcoma n=2, rhabdomyosarcoma n=1, Ewing sarcoma n=1, epithelioid sarcoma n=1). Four patients received nivolumab alone whereas one patient received a combination of nivolumab and ipilimumab. In all cases, the effusion was associated with radiographic evidence of enlargement of the underlying lung mass(es) suggesting disease progression. Five of five patients for whom data is available did have baseline pleural disease associated with the malignancy, although twenty six other patients enrolled on ADVL1412 also had pleural disease at the time of enrollment and did not develop evidence of pleural effusion. In two cases pleural fluid was studied for the presence of tumor cells, and tumor cells were not identified, although one case was a bloody effusion. Two cases were treated with comfort measures only based upon the premise that the pleural effusion represented disease progression. These were associated with patient deaths, which were not attributed to the study drug. Based upon this experience, the possibility that the pleural effusions may be associated with nivolumab ± ipilumumab and could represent an inflammatory response was considered. The protocol has been modified in Section 6.8 to recommend aggressive supportive care for all patients who present with pleural effusion and a trial of corticosteroids for patients who present with pleural effusions of Grade 2 or greater.

2.9 **Rationale for Inclusion of Part D (Amendment #4)**

Part C of the study has demonstrated that nivolumab (3 mg/kg) in combination with ipilumumab (1 mg/kg) is tolerated in children and adolescents. As of June, 2016, some disease specific cohorts included in Part B, specifically the sarcoma subtypes have met first stage accrual or are near to accrual to the initial stage of the Simon's optimal two-stage (osteosarcoma, rhabdomyosarcoma, Ewing's sarcoma). As recently presented in abstract form, single agent PD-1 blockade with pembrolizumab has shown little activity in osteosarcoma and Ewing's sarcoma.[32] In melanoma, response rates to combination nivolumab/ipilimumab are higher in melanoma than with single agent nivolumab; therefore, it is important to determine if the combination regimen might show activity in pediatric solid tumors. Hence, for select disease cohorts which will not progress beyond the initial stage in Part B due to lack of objective responses to single agent nivolumab, we will evaluate the combination of nivolumab with ipilumimab using the RP2D of nivolumab 3 mg/kg and ipilumimab 1mg/kg at the same schedule as utilized in Part C.

As of April 2018, 46 patients have been treated with the combination of nivolumab (3 mg/kg) and ipilimumab (1 mg/kg) either on Part C or Part D of ADVL1412. The combination and doses have been well tolerated.

2.10 **Rationale for Inclusion of relapsed lymphoma patients post-allogeneic transplant (AMD#4)**

Given the promising data in adults treated with nivolumab for relapsed or refractory lymphoma (NHL and Hodgkin's disease)[33] and the May 2016 FDA approval of nivolumab for patients with Hodgkin's Disease, we propose to extend eligibility for patients with lymphoma to include those who have previously received an allogeneic stem cell transplant. For patients with an available donor, allo-SCT is commonly administered in the relapse setting. Thus exclusion of these patients is likely to provide a significant limitation to enrollment for the lymphoma disease specific arms.[34] Reports have demonstrated safety of targeting PD-1 in the post allo-SCT setting.[35,36] Given these reports of safety, we will extend eligibility to include lymphoma patients meet the following criteria: at least 100 days post allo-SCT, no evidence for GVHD at the time of enrollment and no requirement for immunosuppression.

Depending on the response to single agent Nivolumab as seen in cohort B6 (non-Hodgkin lymphoma), it is possible that a cohort D5 will open which will administer a combination of ipilimumab and nivolumab in the post-allogeneic transplant setting. This combination of checkpoint therapy has not previously been used within 180 days of allogeneic SCT. Both agents have been used as single agents in the post-allogeneic SCT setting, ipilimumab has shown safety and efficacy in this setting at higher dosing levels (3 mg/kg and 10 mg/kg).[37]

As of April 2018, ten evaluable patients with Hodgkin lymphoma have enrolled to part B (single agent nivolumab) and several have shown reduction in the size of tumors following treatment with nivolumab. Formal evaluation of response rate is ongoing and some patients remain on study. However, based upon this data and data from a pediatric study evaluating pembrolizumab in Hodgkin lymphoma as well as reports of children treated off-study, it appears clear that nivolumab as a single agent, has activity in pediatric Hodgkin lymphoma. Thus far, there is no evidence that activity in children or adolescents is distinct from that observed in adults.[33] Future studies are planned to incorporate nivolumab into multiagent regimens for pediatric Hodgkin lymphoma. For this reason, we plan to close the Hodgkin lymphoma strata on this trial and refer those patients to other open trials.

2.11 **Rationale for Inclusion of Part E (Amendment #8B)**

Nivolumab in combination with ipilimumab remains an open question. We have demonstrated tolerability with the combination at nivolumab 3 mg/kg and ipilimumab 1 mg/kg. An open question remains if the dosing in this combination, as delivered in Part D is optimal as the FDA approved dose for metastatic melanoma employs a higher dose of ipilimumab (3 mg/kg) with nivolumab (1 mg/kg).[38] Similarly, Antonia et al. demonstrated tolerability and potential survival benefit in patients treated with 1 mg/kg nivolumab in combination with 3 mg/kg ipilimumab in patients with small cell lung cancer and testing with this dosing regimen is ongoing in advanced small cell lung cancer.[25] Furthermore, in urothelial carcinoma, ipilimumab 3 mg/kg with nivolumab 1 mg/kg appears to be equally safe and more effective than an ipilimumab 1 mg/kg with nivolumab 3 mg/kg regimen.[39]

In contrast, the higher dose of ipilimumab (3 mg/kg) with 1 mg/kg nivolumab exceeded the DLT in adults with advanced non-small cell lung cancer[40]. Similarly, the FDA approved dosing regimen for combination therapy in renal cell cancer is ipilimumab 1 mg/kg and nivolumab 3 mg/kg, Thus, the optimal dosing regimen for combination therapies may vary with disease and patient population treated.

The response rate of nivolumab (3 mg/kg) alone and nivolumab (3 mg/kg) in combination with ipilimumab (1 mg/kg) has been low in this pediatric study providing rationale to study a different dose combination in Part E. Part D (nivolumab 3 mg/kg and ipilimumab 1 mg/kg) will close to accrual with this amendment. To determine if the increased dose of ipilimumab demonstrates efficacy in pediatric solid tumor histologies, we will launch Part E to look for a signal of efficacy with the regimen of ipilimumab 3 mg/kg plus nivolumab 1 mg/kg. Part E will look for evidence of a response in patients with rhabdomyosarcoma (E3) or Ewing sarcoma/Peripheral PNET (E4). A 10+10 Simon two-stage design will be used for Part E. All patients enrolled into Parts E3 or E4 will be combined into a single cohort for evaluation of response and toxicity. Assuming that the study does not close due to toxicity, enrollment will include at least 4 rhabdomyosarcoma patients and 4 Ewing sarcoma/Peripheral PNET patients in stage 1. If the study continues to stage 2, then the overall study will include at least 8 patients in each of the two disease cohorts. If at least one Cycle 1 dose limiting toxicity occurs among the first 10 patients or 4 dose limiting toxicities among 20 patients, then the study will close and conclude that the dose level is too toxic. Otherwise, the study will plan to enroll a total of 20 response-evaluable pediatric patients.

Ipilimumab at 3 mg/kg as single agent has been tested in pediatric patients and found to be tolerable.[41] Data from Part A and Part C of this study have demonstrated tolerability and safety of both single agent nivolumab at 3 mg/kg, also when used in combination with 1 mg/kg of ipilimumab. Thus, we anticipate the combination regimen of ipilimumab 3 mg/kg and nivolumab 1 mg/kg to be well tolerated.

2.12 **Rationale for Secondary Aims 1.2.3-1.2.5 (Amendment #8B)**

Clinical response to targeted checkpoint inhibitors has been associated with upregulation of the target protein on the tumor tissue.[42,43] Mazjner et al. performed a large survey of primary pediatric tumor samples (400+) for presence of tumor infiltrating immune cells and expression of PD-L1 on the tumor cells themselves.[44,45] This survey included primary samples comprising multiple tumors including osteosarcoma, Ewing sarcoma, rhabdomyosarcoma, neuroblastoma, soft tissue sarcomas, non-Hodgkin's lymphoma, Wilms tumor, and brain tumors in pediatric patients. Seventy-two percent of tissue sections

did stain positive for the presence of tumor infiltrating lymphocytes (TILs) and 20% positive for macrophages. The role of tumor infiltrating T-cells and their subsets has been well established in solid tumors. Thus, we will use immunohistochemistry on diagnostic tissue submitted to assess presence of TILs for patients enrolled on study.

Clinical success with checkpoint inhibitors has been associated with the degree of genetic instability that occurs due to mutations in tumors resulting in expression of unique neoantigens which can be recognized by the immune system. Neoantigens are peptides not normally found in healthy cells since they result from somatic alterations only present in the tumor [46]. It has been shown that a higher level of mutations or neoantigens is associated with higher response rates by check–point inhibitors supporting the immunosuppression mediated by the PD-1 pathway. Indeed, checkpoint inhibition as a therapeutic approach has been most successful in tumors with high burdens of non-synonymous somatic mutations including melanoma, non-small cell lung cancer, renal cell carcinoma and bladder cancer. [47] By contrast, pediatric tumors and in general hematological malignancies are relatively genomically stable and driven by single translocations or gene amplifications (e.g. myc-n in neuroblastoma). Thus, these tumors may be less responsive to checkpoint inhibition due to a lower number of antigenic peptides which to mount an immune response. However, the mutation burden and its correlation with checkpoint inhibition in pediatric hematological malignancies needs to be studied further. To address tumor mutational burden, we will perform FoundationOneCDx testing, to determine the presence of somatic mutations and determine if there is an association with response to nivolumab, either as a single agent or in combination with ipilimumab.

Adults treated with nivolumab alone and in combination with ipilimumab show an induction in IFNgamma-induced cytokines in serum (personal communication with BMS). This study will generate cytokine data that could be used to compare adult and pediatric populations with respect to a functional parameter of immune system-related effects (e.g. such as induction of IFNgamma-induced cytokines) of nivolumab alone and in combination with ipilimumab.

## 3.0 SCREENING AND STUDY ENROLLMENT PROCEDURES

Patient enrollment for this study will be facilitated using the Slot-Reservation System in conjunction with the Oncology Patient Enrollment Network (OPEN), a web-based registration system available on a 24/7 basis. It is integrated with the NCI Cancer Trials Support Unit (CTSU) Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the RAVE database.

**Access requirements for OPEN**:
Investigators and site staff will need to be registered with CTEP and have a valid and active CTEP-IAM account (check at < https://ctepcore.nci.nih.gov/iam/index.jsp >). This is the same account (user id and password) used for credentialing in the CTSU members' web site (refer to Appendix X for CTEP and CTSU registration procedures). To perform registrations in OPEN, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating,

crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

## 3.1 Current Study Status

Investigators should refer to the COG website to determine if the study is currently open for accrual. If the study is listed as active, investigators should then access the Studies Requiring Reservations page to ensure that a reservation for the study is available. To access the Studies Requiring Reservations page:

1. Log in to https://open.ctsu.org/open/
2. Click the **Slot Reservation** Tab. *The Site Patient page opens.*
3. Click the **Report** Tab. *The Slot Reservation Report opens. Available Slots are detailed per study strata.*

## 3.2 IRB Approval

NCI Pediatric CIRB or local IRB approval of this study must be obtained by a site prior to enrolling patients. Sites must submit CIRB/IRB approvals to the NCI's Cancer Trials Support Unit (CTSU) Regulatory Office and allow 3 business days for processing. The CTSU IRB Certification Form may be submitted in lieu of the signed IRB approval letter. All CTSU forms can be located on the CTSU web page (www.ctsu.org). Any other regulatory documents needed for access to the study enrollment screens will be listed for the study on the CTSU Member's Website under the Regulatory Tab.

Sites participating on the NCI CIRB initiative and accepting CIRB approval for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. This information will be provided to the CTSU Regulatory Office from the CIRB at the time the site's Signatory Institution accepts the CIRB approval. The Signatory site may be contacted by the CTSU Regulatory Office or asked to complete information verifying the participating institutions on the study.

**Submitting Regulatory Documents:**

Submit required forms and documents to the CTSU Regulatory Office via the Regulatory Submission Portal, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab → Regulatory Submission
When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.
For general (non-regulatory) questions, call the CTSU General Helpdesk at 1-888-823-5923 or contact CTSU by email at ctsucontact@westat.com.

Study centers can check the status of their registration packets by accessing the Site

Registration Status page on the CTSU Member's Website under the Regulatory Tab. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

### 3.3 Patient Registration in the COG Registry

Prior to enrollment on study, patients must be assigned a COG patient ID number. This number is obtained via the COG Registry system once authorization for the release of protected health information (PHI) has been obtained.

### 3.4 Reservation and Contact Requirements

Once a slot-reservation confirmation is obtained after making a reservation in OPEN, the Study Chair or Vice Chair should be notified and site staff may then proceed to enroll patients to this study. (The patient will need a COG patient ID number in order to obtain a reservation). Patients must be enrolled within 7 calendar days of making a reservation.

Reservations may be obtained 24-hours a day through the OPEN website.

### 3.5 Informed Consent/Assent

The investigational nature and objectives of the trial, the procedures and treatments involved and their attendant risks and discomforts, and potential alternative therapies will be carefully explained to the patient or the patient's parents or guardian if the patient is a child, and a signed informed consent and assent will be obtained according to institutional guidelines.

### 3.6 Screening Procedures

Diagnostic or laboratory studies performed exclusively to determine eligibility for this trial must only be done after obtaining written informed consent. This can be accomplished through one of the following mechanisms: a) the COG screening protocol, b) an IRB-approved institutional screening protocol or c) the study-specific protocol. Documentation of the informed consent for screening will be maintained in the patient's research chart. Studies or procedures that were performed for clinical indications (not exclusively to determine eligibility) may be used for baseline values even if the studies were done before informed consent was obtained.

### 3.7 Eligibility Checklist

Before the patient can be enrolled, the responsible institutional investigator must sign and date the completed eligibility checklist. A signed copy of the checklist will be uploaded into RAVE immediately following enrollment.

### 3.8 Institutional Pathology Report

Immediately following enrollment, the institutional pathology report for the diagnosis under which the patient is being enrolled must be uploaded into RAVE. The report must include the associated study number and COG patient registration and accession numbers. Personal identifiers, including the patient's name and initials must be removed from the institutional pathology report prior to submission.

### 3.9 Study Enrollment

Patients may be enrolled on the study once all eligibility requirements for the study have been met. Patients who give informed consent for the protocol in order to undergo

screening for eligibility are not considered enrolled and should not be enrolled until the screening is completed and they are determined to meet all eligibility criteria. Study enrollment is accomplished by going to the CTSU OPEN (Oncology Patient Enrollment Network) https://open.ctsu.org/open/. For questions, please contact the CTSU OPEN helpdesk at https://www.ctsu.org/CTSUContact.aspx. Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than five (5) calendar days after the date of study enrollment. **Patients must not receive any protocol therapy prior to enrollment.**

### 3.10 Dose Assignment

The dose level will be assigned via OPEN at the time of study enrollment.

## 4.0 PATIENT ELIGIBILITY

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility must be no older than seven (7) days at the start of therapy. Laboratory tests need **not** be repeated if therapy starts **within** seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are older than 7 days, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies must be obtained within 14 days prior to start of protocol therapy (repeat the tumor imaging if necessary).

Clarification in timing when counting days: As an example, please note that if the patient's last day of prior therapy is September 1st, and the protocol requires waiting at least 7 days for that type of prior therapy, then that patient cannot be enrolled until September 8th.

**Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical or research record which will serve as the source document for verification at the time of audit.**

### 4.1 Inclusion Criteria

4.1.1 Age:

4.1.1.1 **Parts A & C:** Patients must be ≥ 12 months and < 18 years of age at the time of study enrollment.

4.1.1.2 **Parts B1-B6, B8, D1-D6, E3, E4**: Patients must be ≥ 12 months and ≤ 30 years of age at the time of study enrollment.

4.1.1.3 **Part B7**: Patients must be ≥ 12 months and < 18 years of age at the time of study enrollment.

4.1.2 Diagnosis: Patients must have had histologic verification of malignancy at original diagnosis or relapse.

4.1.2.1 **Parts A & C**: Patients with recurrent or refractory solid tumors, without CNS tumors or known CNS metastases are eligible. Note: CNS imaging

for patients without a known history of CNS disease is only required if clinically indicated.

4.1.2.2 **Part B1**: Patients with relapsed or refractory neuroblastoma

**Part B2**: Patients with relapsed or refractory osteosarcoma
**Part B3**: Patients with relapsed or refractory rhabdomyosarcoma
**Part B4**: Patients with relapsed or refractory Ewing Sarcoma or Peripheral PNET
**Part B5**: Patients with relapsed or refractory Hodgkin Lymphoma
**Part B6**: Patients with relapsed or refractory Non-Hodgkin Lymphoma
**Part B7**: Patients with unresectable melanoma or metastatic melanoma or relapsed melanoma or refractory melanoma
**Part B8**: Patients with relapsed or refractory neuroblastoma (MIBG evaluable disease without RECIST measurable lesion)

Once the dose-escalation portion of Part A is completed, cohorts that are open concurrently for eligible patients (including Parts B and C and potential PK expansion cohorts) may be selected at the treating physician's discretion pending slot availability. In the event a disease group cohort in Part B is completed after the initial stage of Simon's optimal two-stage design (Section 11.4), for selected disease cohorts (Section 4.1.2.3), a corresponding cohort in the same disease group for select disease types will be open in Part D:

4.1.2.3 **Part D1**: Patients with relapsed or refractory neuroblastoma

**Part D2**: Patients with relapsed or refractory osteosarcoma
**Part D3**: Patients with relapsed or refractory rhabdomyosarcoma
**Part D4**: Patients with relapsed or refractory Ewing Sarcoma or Peripheral PNET
**Part D5**: Patients with relapsed or refractory Non-Hodgkin Lymphoma
**Part D6**: Patients with relapsed or refractory neuroblastoma (MIBG evaluable disease without RECIST measurable lesion)

4.1.2.4 **Part E3**: Patients with relapsed or refractory rhabdomyosarcoma

**Part E4**: Patients with relapsed or refractory Ewing Sarcoma or Peripheral PNET

4.1.3 Disease Status:

4.1.3.1 **Parts A & C**: Patients must have either measurable or evaluable disease (see Sections 12.2 and 12.3 for definitions).

4.1.3.2 **Parts B, D, & E**: Patients must have measurable disease (see Section 12.2 for definitions) for Parts B1-B6, D1-D5, E3 and E4. Melanoma patients in Part B7 must have either measurable or evaluable disease. Neuroblastoma patients in Parts B8 and D6 must be evaluable for MIBG response without evidence of RECIST measurable lesions (see Section 12.4 for definitions).

4.1.4 Therapeutic Options: Patient's current disease state must be one for which there is no known curative therapy or therapy proven to prolong survival with an acceptable quality of life.

4.1.5 Performance Level: Karnofsky ≥ 50% for patients > 16 years of age and Lansky ≥ 60 for patients ≤ 16 years of age (See Appendix I). Patients who are

unable to walk because of paralysis, but who are up in a wheelchair, will be considered ambulatory for the purpose of assessing the performance score.

4.1.6 Prior Therapy

4.1.6.1 Patients must have fully recovered from the acute toxic effects of all prior anti-cancer therapy and must meet the following minimum duration from prior anti-cancer directed therapy prior to enrollment. If after the required timeframe, the defined eligibility criteria are met, e.g. blood count criteria, the patient is considered to have recovered adequately.

a. Cytotoxic chemotherapy or other anti-cancer agents known to be myelosuppressive. See DVL homepage for commercial and Phase 1 investigational agent classifications. For agents not listed, the duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator prior to enrollment.
   *i.* At least 21 days after the last dose of cytotoxic or myelosuppressive chemotherapy (42 days if prior nitrosourea).
b. Hematopoietic growth factors: At least 14 days after the last dose of a long-acting growth factor (e.g. pegfilgrastim) or 7 days for short-acting growth factor. For agents that have known adverse events occurring beyond 7 days after administration, this period must be extended beyond the time during which adverse events are known to occur. The duration of this interval must be discussed with the study chair.
c. Anti-cancer agents not known to be myelosuppressive (e.g. not associated with reduced platelet or ANC counts): At least 7 days after the last dose of agent. See DVL homepage for commercial and Phase 1 investigational agent classifications. For agents not listed, the duration of this interval must be discussed with the study chair and the study-assigned Research Coordinator prior to enrollment.
d. Interleukins, Interferons and Cytokines (other than Hematopoetic Growth Factors): ≥ 21 days after the completion of interleukins, interferon or cytokines (other than Hematopoetic Growth Factors)
e. Antibodies: ≥ 21 days must have elapsed from infusion of last dose of antibody, and toxicity related to prior antibody therapy must be recovered to Grade ≤ 1.
f. XRT/External Beam Irradiation including Protons: ≥ 14 days after local XRT; ≥ 150 days after TBI, craniospinal XRT or if radiation to ≥ 50% of the pelvis; ≥ 42 days if other substantial BM radiation.
g. Radiopharmaceutical therapy (e.g., radiolabeled antibody, $^{131}$I-MIBG): ≥ 42 days must have elapsed since systemically administered radiopharmaceutical therapy.
h. Cellular Therapy: ≥ 42 days must have elapsed since the completion of any type of cellular therapy (e.g. modified T cells, NK cells, dendritic cells, etc.).
i. Patients must not have received prior exposure to nivolumab. For patients enrolled in Parts C, D, and E patients must not have received prior nivolumab or ipilimumab.

4.1.7 Organ Function Requirements

4.1.7.1 Adequate Bone Marrow Function Defined as:

a. For patients with solid tumors without known bone marrow involvement:
   - Peripheral absolute neutrophil count (ANC) ≥ 750/mm$^3$
   - Platelet count ≥ 75,000/mm$^3$ (transfusion independent, defined as not receiving platelet transfusions for at least 7 days prior to enrollment)

b. Patients with known bone marrow metastatic disease will be eligible for study provided they meet the blood counts in 4.1.7.1.a (may receive transfusions provided they are not known to be refractory to red cell or platelet transfusions). These patients will not be evaluable for hematologic toxicity. At least 5 of every cohort of 6 patients with a solid tumor must be evaluable for hematologic toxicity, for Parts A and C. If dose-limiting hematologic toxicity is observed on either Part A or C, all subsequent patients enrolled must be evaluable for hematologic toxicity on that Part.

4.1.7.2 Adequate Renal Function Defined as:

- Creatinine clearance or radioisotope GFR ≥ 70 ml/min/1.73 m$^2$ or
- A serum creatinine based on age/gender as follows:

| Age | Maximum Serum Creatinine (mg/dL) | |
|---|---|---|
| | Male | Female |
| 1 to < 2 years | 0.6 | 0.6 |
| 2 to < 6 years | 0.8 | 0.8 |
| 6 to < 10 years | 1 | 1 |
| 10 to < 13 years | 1.2 | 1.2 |
| 13 to < 16 years | 1.5 | 1.4 |
| ≥ 16 years | 1.7 | 1.4 |

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

4.1.7.3 Adequate Liver Function Defined as:

- Bilirubin (sum of conjugated + unconjugated) ≤ 1.5 x upper limit of normal (ULN) for age
- SGPT (ALT) ≤ 135 U/L. For the purpose of this study, the ULN for SGPT is 45 U/L.

4.1.7.4 Adequate Pulmonary Function Defined as:

- No evidence of dyspnea at rest, no exercise intolerance due to pulmonary insufficiency, and a pulse oximetry > 92% while breathing room air.

4.1.7.5 Adequate Pancreatic Function Defined as:

- Serum lipase ≤ ULN at baseline. Patients with glucose intolerance should be on a stable regimen and be monitored.

4.1.8 Informed Consent: All patients and/or their parents or legally authorized

representatives must sign a written informed consent. Assent, when appropriate, will be obtained according to institutional guidelines.

4.1.9 Tissue blocks or slides must be sent for all patients per Section 8.6. If tissue blocks or slides are unavailable, the study chair must be notified prior to enrollment.

## 4.2 Exclusion Criteria

4.2.1 Pregnancy or Breast-Feeding

Pregnant or breast-feeding women will not be entered on this study due to risks of fetal and teratogenic adverse events as there is yet no available information regarding human fetal or teratogenic toxicities. Pregnancy tests must be obtained in girls who are post-menarchal. Women of childbearing potential (WOCBP) receiving nivolumab will be instructed to adhere to contraception for a period of 5 months after the last dose of nivolumab. Men receiving nivolumab and who are sexually active with WOCBP will be instructed to adhere to contraception for a period of 7 months after the last dose of nivolumab.

4.2.2 Concomitant Medications

4.2.2.1 Corticosteroids: Patients requiring daily systemic corticosteroids are not eligible. Patients must not have received systemic corticosteroids within 7 days prior to enrollment. If used to modify **immune adverse events** related to prior therapy, ≥ 14 days must have elapsed since last dose of corticosteroid. Note: Use of topical or inhaled corticosteroids will not render a patient ineligible.

4.2.2.2 Investigational Drugs: Patients who are currently receiving another investigational drug are not eligible.

4.2.2.3 Anti-cancer Agents: Patients who are currently receiving other anti-cancer agents are not eligible.

4.2.3 Patients with CNS tumors or known CNS metastases will be excluded from this trial due to concerns regarding pseudo-progression in the CNS. Patients with a history of CNS metastases that have been previously treated may enroll if sequential imaging shows not evidence for active disease. Patients with extra axial disease [e.g. skull (bone) metastasis that do not invade the dura] may enroll if there is no evidence for CNS edema associated with the lesion.

4.2.4 Patients with a history of any Grade autoimmune disorder are not eligible. Asymptomatic laboratory abnormalities (e.g. ANA, rheumatoid factor, altered thyroid function studies) will not render a patient ineligible in the absence of a diagnosis of an autoimmune disorder.

4.2.5 Patients with ≥ Grade 2 hypothyroidism due to history of autoimmunity are not eligible. Note: Hypothyroidism due to previous irradiation or thyroidectomy will not impact eligibility.

4.2.6 Infection: Patients who have an uncontrolled infection are not eligible.

4.2.7 Patients with a history of CHF or are at risk because of underlying cardiovascular disease or exposure to cardiotoxic drugs must have adequate cardiac function as clinically indicated:

- QTC ⩽ 480 msec;
- Shortening fraction of ≥ 27% by echocardiogram or ejection fraction of ≥ 50% by gated radionuclide study

4.2.8 Patients with known HIV or hepatitis B or C are excluded.

4.2.9 Patients who have received prior solid organ transplantation are not eligible.

4.2.10 Patient who have received allotransplantation are not eligible.

4.2.11 Patients who in the opinion of the investigator may not be able to comply with the safety monitoring requirements of the study are not eligible.

4.2.12 Patients who have received prior anti-PD1 directed therapy (mAb or small molecule) are not eligible.

4.2.13 Parts C, D, and E: Patients who have received prior ipilimumab are not eligible.

## 5.0 TREATMENT PROGRAM

### 5.1 Overview of Treatment Plan

This trial will consist of Parts A-E as described below. Once the dose-escalation portion of Part A is completed, cohorts that are open concurrently for eligible patients (including Parts B and C and potential PK expansion cohorts) may be selected at the treating physician's discretion pending slot availability. Part B will be completed for all cohorts after the initial stage of Simon's optimal two-stage design (Section 11.4). Upon opening Part E to accrual, no additional patients will be enrolled to Part D.

Once enrolled, patients continue on the part of the study assigned at enrollment until they meet criteria in Section 10.1 or Section 10.2.

Pre-medication is not required as infusional reactions are rare, but anaphylactic precautions should be observed during each infusion of nivolumab. If ≥ Grade 2 infusional reaction occurs, the infusion should be stopped and supportive care given as per institutional guidelines. See Section 6.3 for management and dose modification guidelines for infusional reactions. Investigators are advised to monitor for fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of nivolumab.

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

5.1.1 Part A (COMPLETED)

Nivolumab of 3 mg/kg IV infused over 60 minutes every 14 days. A cycle will be considered 28 days. If Dose Level 1 is not tolerable, then the 3 mg/kg dose will be deescalated to 1 mg/kg and a similar cohort of patients will be evaluated for tolerability at this dose. Note: In the event that dose-limiting immune-related toxicities are observed in two patients enrolled on Part A that would potentially define the MTD as less than the adult RP2D, a review by COG, CTEP, and BMS

will be scheduled before proceeding with dosing changes.

| Dose Level | Nivolumab (mg/kg) IV over 60 min. | Day(s) of Administration |
|---|---|---|
| -1 | 1 | 1, 15 |
| 1* | 3 | 1, 15 |

*Starting dose

Update: The single-agent recommended Phase 2 dose of Part A was determined to be 3 mg/kg nivolumab.

5.1.2 Part B (COMPLETED)

Part B will evaluate the activity of nivolumab at its RP2D in expanded cohorts for patients with neuroblastoma, osteosarcoma, rhabdomyosarcoma, Ewing sarcoma, Hodgkin lymphoma, non-Hodgkin lymphoma. In the melanoma cohort (Part B7), toxicities and disease response will be reported descriptively within the confines of a Phase 1/2 study.

| Dose Level | Nivolumab (mg/kg) IV over 60 min. | Day(s) of Administration |
|---|---|---|
| 1 | 3 | 1, 15 |

5.1.3 Part C (COMPLETED)

Part C will enroll all histologies with the goal of identifying the MTD or RP2D of the combination of nivolumab and ipilimumab. The combination of nivolumab and ipilimumab will be administered every 3 weeks X 4 followed by nivolumab given every 2 weeks until off protocol criteria in Section 10.1 are met. **Note that cycle length is 21 days for the first 4 cycles of Part C, whereas reverts to 28 days for subsequent cycles which comprises two doses of nivolumab, and is the same regimen used in Part A and B.**

| Dose Level | Cycles 1-4 | Cycles 5+ |
|---|---|---|
| 1 | Nivolumab (IV over 60 min)<br>1 mg/kg on Day 1<br><br>Ipilimumab (IV over 90 min)<br>1 mg/kg on Day 1 | Nivolumab (IV over 60 min)<br>3 mg/kg on Days 1 and 15 |
| 2 | Nivolumab (IV over 60 min)<br>3 mg/kg on Day 1<br><br>Ipilimumab (IV over 90 min)<br>1 mg/kg on Day 1 | Nivolumab (IV over 60 min)<br>3 mg/kg on Days 1 and 15 |

Infusion of ipilimumab (over 90 minutes) should be initiated no sooner than 30 minutes after completion of the nivolumab infusion.

Vital signs (temperature, pulse, blood pressure and respirations) will be monitored closely baseline then every 15 minutes x 2, then every 30 minutes x 3 beginning at the initiation of administration of ipilimumab infusion. Patients who develop symptoms or signs of hypotension (≥ 25% decrease in systolic or diastolic blood pressures from baseline) that are temporally related to ipilimumab infusion will receive additional IV fluids as appropriate until the signs and symptoms resolve. During cycle 1, patients must remain for observation for a total of 6 hours following completion of ipilimumab. The post administration observation period may be extended to 24 hours and the patient admitted if clinically indicated. If the patient

tolerates the first infusion of ipilimumab without incident, the observation period may be reduced to 90 minutes following completion of the drug infusion with subsequent cycles. Any patient who develops Grade 3 or 4 anaphylaxis felt to be primarily related to administration of ipilimumab will be removed from protocol therapy.

Protocol therapy will continue to be administered until patient meets one of the off protocol criteria in Section 10.1.

Update: The recommended Phase 2 dose of nivolumab in combination with ipilimumab from Part C was determined to be 3 mg/kg nivolumab and 1 mg/kg ipilimumab.

5.1.4 Part D (COMPLETED)

If criteria for accrual to Part D are met, the combination of nivolumab and ipilimumab will be administered every 3 weeks X 4 followed by nivolumab given every 2 weeks until off protocol criteria in Section 10.1 are met. **Note that cycle length is 21 days for the first 4 cycles of Part D, whereas reverts to 28 days for subsequent cycles which comprises two doses of nivolumab, and is the same regimen used in Part A and B.**

| Dose Level | Cycles 1-4 | Cycles 5+ |
|---|---|---|
| **1** | Nivolumab (IV over 60 min)<br>3 mg/kg on Day 1<br><br>Ipilimumab (IV over 90 min)<br>1 mg/kg on Day 1 | Nivolumab (IV over 60 min)<br>3 mg/kg on Days 1 and 15 |

Infusion of ipilimumab (over 90 minutes) should be initiated no sooner than 30 minutes after completion of the nivolumab infusion.

Vital signs (temperature, pulse, blood pressure and respirations) will be monitored closely baseline then every 15 minutes x 2, then every 30 minutes x 3 beginning at the initiation of administration of ipilimumab infusion. Patients who develop symptoms or signs of hypotension (≥ 25% decrease in systolic or diastolic blood pressures from baseline) that are temporally related to ipilimumab infusion will receive additional IV fluids as appropriate until the signs and symptoms resolve. During cycle 1, patients must remain for observation for a total of 6 hours following completion of ipilimumab. The post administration observation period may be extended to 24 hours and the patient admitted if clinically indicated. If the patient tolerates the first infusion of ipilimumab without incident, the observation period may be reduced to 90 minutes following completion of the drug infusion with subsequent cycles. Any patient who develops Grade 3 or 4 anaphylaxis felt to be primarily related to administration of ipilimumab will be removed from protocol therapy.

5.1.5 Part E

The combination of nivolumab 1 mg/kg and ipilimumab 3 mg/kg will be administered every 3 weeks X 4 followed by nivolumab 3 mg/kg administered every 2 weeks until off protocol criteria in Section 10.1 are met. Note that cycle length is 21 days for the first 4 cycles of Part E; in cycle 5 and for subsequent cycles, cycle length will be 28 days and nivolumab 3 mg/kg will be administered

on days 1 and 15 of each cycle.

| Dose Level | Cycles 1-4 (21-day Cycles) | Cycles 5+ (28-day Cycles) |
|---|---|---|
| **1** | Nivolumab (IV over 30 min)<br>1 mg/kg on Day 1<br><br>Ipilimumab (IV over 90 min)<br>3 mg/kg on Day 1 | Nivolumab (IV over 30 min)<br>3 mg/kg on Days 1 and 15 |

Infusion of ipilimumab (over 90 minutes) should be initiated no sooner than 30 minutes after completion of the nivolumab infusion. If nivolumab therapy is withheld, ipilimumab should also be withheld.

Vital signs (temperature, pulse, blood pressure and respirations) will be monitored closely baseline then every 15 minutes x 2, then every 30 minutes x 3 beginning at the initiation of administration of ipilimumab infusion. Patients who develop symptoms or signs of hypotension (≥ 25% decrease in systolic or diastolic blood pressures from baseline) that are temporally related to ipilimumab infusion will receive additional IV fluids as appropriate until the signs and symptoms resolve. During cycle 1, patients must remain for observation for a total of 6 hours following completion of ipilimumab. The post administration observation period may be extended to 24 hours and the patient admitted if clinically indicated. If the patient tolerates the first infusion of ipilimumab without incident, the observation period may be reduced to 90 minutes following completion of the drug infusion with subsequent cycles. Any patient who develops Grade 3 or 4 anaphylaxis felt to be primarily related to administration of ipilimumab will be removed from protocol therapy.

5.2 **Protocol therapy will continue to be administered until patient meets one of the off protocol criteria in Section 10.1.Criteria for Starting Subsequent Cycles**

A cycle may be repeated every 28 days for Parts A and B (and either every 21 days or 28 days for Parts C, D, and E) if the patient has again met the parameters as defined in the eligibility section, Section 4.0, has not met any of the criteria for removal from therapy per Section 10.1, and has not experienced a dose-limiting toxicity. A delay of up to 7 days from the date of the next scheduled treatment dose may be allowed. Please note the following exceptions:

- Patients may continue on to the next cycle if Pancreatic Function is ≤ Grade 1 (See Section 6.5)
- Patients who experience pleural effusion may continue onto the next cycle upon resolution as per Section 6.8.

5.3 **Grading of Adverse Events**

Adverse events (toxicities) will be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Any suspected or confirmed dose-limiting toxicity should be reported immediately (within 24 hours) to the Study Chair.

5.4 **Definition of Dose-Limiting Toxicity (DLT)**

DLT will be defined as any of the following events that are possibly, probably, or definitely attributable to protocol therapy. DLT definitions will be the same for all parts. The DLT

observation period for the purposes of dose-escalation in Part C or dose de-escalation in Part A will be the first cycle of therapy. Toxicities with subsequent cycles will be monitored carefully and if significant numbers of delayed toxicities are observed, consideration will be given to a protocol amendment to focus on delayed toxicities in assessing the MTD.

5.4.1 Non-Hematological DLT:

- Any Grade 3 or Grade 4 non-hematological toxicity attributable to protocol therapy with the specific exclusion of:
    a. Grade 3 ALT that returns to levels that meet initial eligibility criteria or baseline within 7 days and does not require systemic immunosuppression. **Note:** For the purposes of this study the ULN for ALT is defined as 45 U/L. Adverse event grades will be based on increases above the upper limit of normal, regardless of the subject's baseline. See Appendix IX for toxicity grading table.
    b. Grade 3 liver enzyme elevation, including AST/GGT that returns to baseline within 7 days and does not require systemic immunosuppression.
    c. Grade 3 or 4 serum electrolyte or mineral abnormalities responsive to supplementation.
    d. Grade 3 or 4 amylase or lipase abnormalities that are not associated with diabetes mellitus (DM), associated liver or gall bladder inflammation clinical manifestations of pancreatitis and which decrease to ≤ Grade 2 within 7 days.
    e. Grade 3 rash/oral lesions that resolves to Grade ≤ 1 within 7 days
    f. Fever greater than 40°C of ≤ 24 hr duration
    g. Grade 3 fatigue that resolves to Grade ≤ 2 within 7 days
    h. Grade 3 creatinine increased that resolves to Grade ≤ 1 or baseline within 7 days
    i. Grade 3 pleural effusion that resolves per Section 6.8
- Grade 2 fever that does not resolve to Grade ≤ 1 within 7 days
- Grade 2 uveitis, eye pain, or blurred vision that does not respond to topical therapy and does not improve to Grade 1 prior to next scheduled dose
- Grade 2 non-hematological toxicity requiring systemic immunosuppressive therapy, including but not limited to, autoimmunity of the lung, heart, kidney, bowel, CNS, pituitary or eye, with the specific exclusion of:
    a. Grade 2 pleural effusion that resolves per Section 6.8
    b. Drugs will be held for grade 2 cardiac dysfunction pending evaluation.
- Grade 2 endocrine toxicity requiring hormone replacement, with the exception of Grade 2 hypothyroidism, thyroiditis and thyroid dysfunction adequately managed with thyroid hormone replacement (see Section 6.11)
- Grade 2 adrenal insufficiency
- Parts A and B: Grade 2 colitis or Grade 2 diarrhea attributable to protocol therapy that persists for > 7 days will be considered a DLT.
- Parts C, D, and E: Grade 2 colitis or Grade 2 diarrhea attributable to protocol therapy of any duration will be considered a DLT.
- Any non-hematological toxicity requiring > 7 days delay in therapy will be considered a DLT

- Note: Allergic reactions that necessitate discontinuation of study drug will not be considered a dose-limiting toxicity.

5.4.2 Hematological DLT:

In patients evaluable for hematological toxicity (see Section 4.1.7.1) DLT is defined as:

- Grade 4 thrombocytopenia (platelet count < 25,000/mm$^3$) or Grade 4 neutropenia lasting at least five days.
  - **Note:** Grade 3 or 4 febrile neutropenia will not be considered a dose-limiting toxicity. Any grade lymphopenia will not be considered DLT.

## 6.0 DOSE MODIFICATIONS FOR ADVERSE EVENTS

**The Study Chair must be notified of any dosage modification or use of myeloid growth factor.**

### 6.1 Dose Modifications for Hematological Toxicity

Patients who experience dose-limiting hematological toxicity as defined in Section 5.4.2 will be removed from protocol therapy.

### 6.2 Dose Modifications for Non-Hematological Toxicity

Patients who have any dose-limiting non-hematological toxicity as defined in Section 5.4.1 will be removed from protocol therapy, except as outlined in Sections 6.3-6.12 below.

### 6.3 Dose Modifications for Infusion-Related Reactions

For patients who have allergic or acute infusion reactions to nivolumab or ipilimumab, therapy modifications based on grade should be as follows.

| Grade (CTCAE v.5) Infusion Reaction | Action |
|---|---|
| Grade 1 | • Monitor patient until recovery from symptoms; infusion rate may be slowed.<br>• 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 patient closely.<br><br>The following prophylactic premedications are recommended for future infusions: diphenhydramine 1 mg/kg with max 50 mg (or equivalent) and/or acetaminophen 10-15 mg/kg (max 1000 mg) at least 30 minutes before additional nivolumab or ipilimumab administrations, slowing infusion rate as above. |
| Grade 2 | • Stop infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 1 mg/kg with max 50 mg IV (or equivalent) and/or acetaminophen 10-15 mg/kg (max 1000 mg); remain at bedside and monitor patient until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate.<br>• 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 patient closely.<br>• If symptoms recur, then no further nivolumab or ipilimumab will be administered at that visit. Administer diphenhydramine 1 mg/kg with max 50 mg IV (or equivalent), and remain at bedside and monitor the patient until resolution of symptoms.<br><br>The following prophylactic premedications are recommended for future infusions: diphenhydramine 1 mg/kg with max 50 mg IV (or equivalent) and acetaminophen (10-15 mg/kg, max 1000 mg) should be administered at least 30 minutes before additional nivolumab or ipilimumab administrations. If clinically indicated, corticosteroids (recommended dose: 1-2 mg/kg/day methylprednisolone IV or equivalent) may be used. |
| Grade 3 or 4 | • Immediately discontinue infusion of nivolumab/ ipilimumab.<br>• 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 1 mg/kg with max 50 mg IV with 1-2 mg/kg/day methylprednisolone IV (or equivalent), as needed.<br>• Patient should be monitored until the investigator is comfortable that the symptoms will not recur.<br>• Nivolumab/ipilimumab will be permanently discontinued.<br><br>Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor patient until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (*e.g.*, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (*e.g.*, oral antihistamine, or corticosteroids).<br><br>Please note that late occurring events including isolated fever and fatigue may represent the presentation of systemic inflammation. Please evaluate accordingly. |

## 6.4 Dose Modifications for Skin Rash and Oral Lesions

| **Skin Rash and Oral Lesions** | **Management/Next Dose of Nivolumab ± Ipilimumab** |
|---|---|
| ≤ Grade 1 | No change in dose* |
| Grade 2 | Continue protocol therapy*; Topical steroids do not require protocol therapy discontinuation. If prolonged symptoms require systemic corticosteroids, decisions regarding whether protocol therapy may be reinstituted following weaning of immunosuppression must be made in consultation with Protocol Chair/Vice-Chair and DVL Leadership. |

| Skin Rash and Oral Lesions | Management/Next Dose of Nivolumab ± Ipilimumab |
|---|---|
| Grade 3 | Hold* until ≤ Grade 1; if resolves within 7 days, then resume at same dose level. Topical steroids do not require protocol therapy discontinuation. If prolonged symptoms require systemic corticosteroids, decisions regarding whether protocol therapy may be reinstituted following weaning of immunosuppression must be made in consultation with Protocol Chair/Vice-Chair and DVL Leadership. |
| Grade 4 | Discontinue therapy, Systemic corticosteroids indicated. |
| *Patients with purpuric or bullous lesions must be evaluated for vasculitis, Steven-Johnson syndrome, TEN, and autoimmune bullous disease including oral lesions of bullous pemphigus/pemphagoid. Pruritus may occur with or without skin rash and should be treated symptomatically if there is no associated liver or GI toxicity. Note skin rash typically occurs early and may be followed by additional events particularly during steroids tapering. | |
| Recommended management: See Skin AE Management Algorithm | |

6.4.1 BMS Recommended Skin Adverse Management Algorithm

These suggested management guidelines are taken from the BMS algorithms provided in the Investigator's Brochure.

| Toxicity (CTCAE v.5) | Management | Follow-up |
|---|---|---|
| **Grade 1/2 Rash** | • Symptomatic therapy (e.g. antihistamines, topical steroids)<br>• Continue protocol therapy | **If persists > 1-2 weeks or recurs:**<br>• Consider skin biopsy<br>• Hold protocol therapy<br>• Consider 0.5-1 mg/kg/day methylprednisolone IV or oral equivalent<br>• Once improving, taper steroids over at least 1 month<br>• Consider prophylactic antibiotics for opportunistic infections<br><br>**If worsens:**<br>Treat as Grade 3/4 |
| **Grade 3/4 Rash** | • Hold infusion<br>• Consider skin biopsy<br>• Dermatology consult<br>• 0.5-1 mg/kg/day methylprednisolone IV or IV equivalent | **If improves to Grade 1:**<br>• Taper steroids over at least 1 month,<br>• Add prophylactic antibiotics for opportunistic infections |

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

## 6.5 Dose modifications for Hepatic/Pancreatic Adverse Events

| Liver Function Elevation | Management/Next Dose of Nivolumab ± Ipilimumab |
|---|---|
| ≤ Grade 1 | Continue protocol therapy |
| Grade 2 | Hold until baseline. If resolves within 7 days, resume at same |

| Liver Function Elevation | Management/Next Dose of Nivolumab ± Ipilimumab |
|---|---|
| | dose level. |
| Grade 3 | Off protocol therapy unless DLT exception in Section 5.4.1 is met. |
| Grade 4 | Off protocol therapy unless DLT exception in Section 5.4.1 is met. |
| See Appendix IX for values that represent thresholds between CTCAE grades.<br>Continued treatment of active immune mediated hepatitis may exacerbate ongoing inflammation. Holding drug to evaluate LFT changes and early treatment are recommended.<br>LFT changes may occur during steroid tapers from other events and may occur together with other GI events including cholecystitis/pancreatitis. | |
| Recommended management: see for Hepatitic AE management algorithm | |

| Pancreatitis; Amylase/Lipase | Management/Next Dose of Nivolumab ± Ipilimumab |
|---|---|
| ≤ Grade 1 | Continue protocol therapy |
| Grade 2 Amylase | Continue protocol therapy |
| Grade 2 Pancreatitis/Lipase | Hold until resolution to ≤ Grade 1; Resume at same dose level if asymptomatic |
| Grade 3 | Off protocol therapy unless DLT exception in Section 5.4.1 is met. |
| Grade 4 | Off protocol therapy |
| Patients may develop symptomatic and radiologic evidence of pancreatitis as well as DM and DKA. Lipase elevation may occur during the period of steroid withdrawal and with other immune mediated events or associated with colitis, hepatitis, and patients who have asymptomatic lipase elevation typically have self-limited course and may be retreated.<br>For treatment management of symptomatic pancreatitis please follow the Hepatic Adverse Event Management Algorithm below | |

6.5.1 BMS Recommended Hepatic Adverse Event Management Algorithm

These suggested management guidelines are taken from the BMS algorithms provided in the Investigator's Brochure.

Consider imaging for obstruction.

| Toxicity (CTCAE v.5) | Management | Follow-up |
|---|---|---|
| **Grade 1***<br>**AST or ALT, and/or bilirubin increased** | • Continue protocol therapy | • Continue routine LFT monitoring per Table 8.1<br>**If worsens:**<br>• Treat as Grade 2 or 3/4 |

| Toxicity (CTCAE v.5) | Management | Follow-up |
|---|---|---|
| **Grade 2* AST or ALT, and/or bilirubin increased** | • Hold infusion<br>• Increase LFT monitoring to every 3 days | **If improves to baseline:**<br>• Continue routine LFT monitoring per Table 8.1<br>• Resume protocol therapy<br>**If elevations persist >5-7 days or worsen:**<br>• 0.5-1 mg/kg/day methylprednisolone IV or oral equivalent<br>• When LFT returns to grade 1 or baseline, taper steroids over at least 1 month<br>• Consider prophylactic antibiotics for opportunistic infections |
| **Grade 3 or 4* AST or ALT, and/or bilirubin increased** | • Discontinue protocol therapy<br>• Increase LFT monitoring to every 1-2 days<br>• 1-2 mg/kg/day methylprednisolone IV or oral equivalent**<br>• Add prophylactic antibiotics for opportunistic infections<br>• Consult gastroenterologist | **If improves to Grade 2:**<br>• Taper steroids over at least 1 month<br>**If does not improve in > 3-5 days, worsens or rebounds:**<br>• Add mycophenolate mofetil 600 mg/m$^2$/dose (max 1 g/dose) BID<br>• If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines |

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

*See Appendix IX for values that represent thresholds between CTCAE grades.

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

## 6.6 Dose modifications for Gastrointestinal Adverse Events

| Diarrhea/ Colitis | Management/Next Dose of Nivolumab± Ipilimumab |
|---|---|
| ≤ Grade 1 | Continue protocol therapy |
| Grade 2 | For Part A and B (Nivolumab alone), may observe and treat symptomatically for 7 days. If persists > 7d, then off protocol therapy. For Parts C, D, and E any grade 2 diarrhea/colitis results in discontinuation of protocol therapy. |
| Grade 3 | Off protocol therapy |

| Diarrhea/ Colitis | Management/Next Dose of Nivolumab± Ipilimumab |
|---|---|
| Grade 4 | Off protocol therapy |
| Patients who require steroids should be taken off study treatment.<br>Please evaluate pituitary function prior to starting steroids if possible without compromising acute care.<br>Evaluation for all patients for additional causes includes C. diff, acute and self-limited infectious and foodborne illness, ischemic bowel, diverticulitis, and IBD. | |
| Recommended management: see GI AE management Algorithm below | |

| Other GI N-V | Management/Next Dose of Nivolumab ± Ipilimumab |
|---|---|
| ≤ Grade 1 | No change in dose. |
| Grade 2 | Hold pending evaluation for gastritis duodenitis and other immune adverse events or other causes. Resume at same dose level if resolution to ≤ Grade 1 within 7 days. |
| Grade 3 | Hold pending evaluation until ≤ Grade 1. Resume at same dose level. If symptoms do not resolve within 7 days with symptomatic treatment patients should go off protocol therapy |
| Grade 4 | Off protocol therapy |
| Patients with grade 2 or 3 N-V should be evaluated for upper GI inflammation and other immune related events. | |

6.6.1 BMS Recommended Gastrointestinal Adverse Event Management Algorithm

These suggested management guidelines are taken from the BMS algorithms provided in the Investigator's Brochure.

Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

| Toxicity (CTCAE v.5) | Management | Follow-up |
|---|---|---|
| **Grade 1 Diarrhea or Colitis** | • Continue protocol therapy<br>• Symptomatic treatment | • Close monitoring for worsening symptoms<br>• Educate patient to report worsening immediately<br><br>**If worsens:**<br>• Treat as Grade 2 or 3/4 |
| **Grade 2 Diarrhea or Colitis** | • Part A or B (Nivolumab alone) symptomatic management. If persists for > 7 days, discontinue protocol therapy.<br>• Part C, D, or E discontinue protocol therapy Symptomatic treatment | **If persists > 5-7 days or recurs:**<br>• 0.5-1 mg/kg/day methylprednisolone or oral equivalent<br>• When symptoms improve to grade 1, taper steroids over at least 1 month<br>• Consider prophylactic antibiotics for opportunistic infections<br><br>**If worsens or persists > 3-5 days with oral steroids:**<br>• Treat as Grade 3 or 4 |

| Toxicity (CTCAE v.5) | Management | Follow-up |
|---|---|---|
| **Grade 3 or 4 Diarrhea or Colitis** | • Discontinue protocol therapy<br>• 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent<br>• Add antibiotics for opportunistic infections<br>• Consider lower endoscopy | **If improves:**<br>• Continue steroids until grade 1, then taper over at least 1 month<br><br>**If persists > 3-5 days or recurs after improvement:**<br>• Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis |

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

## 6.7 Dose Modifications for Pneumonitis

| **Pneumonitis** | **Management/Next Dose of Nivolumab ± Ipilimumab** |
|---|---|
| ≤ Grade 1 | Consider delay in protocol therapy. Resume no change in dose after pulmonary and/or ID consultation |
| Grade 2 | Hold dose pending evaluation and resolution to baseline. Resume no change in dose after pulmonary and/or ID consultation if lymphocytic pneumonitis is excluded. |
| Grade 3 | Off protocol therapy |
| Grade 4 | Off protocol therapy |
| Distinguishing inflammatory pneumonitis is often a diagnosis of exclusion for patients who do not respond to antibiotics and have no causal organism identified including influenza. Most patients with respiratory failure or hypoxia will be treated with steroids. Bronchoscopy may be required and analysis of lavage fluid for lymphocytic predominance may be helpful. Patients with new lung nodules should be evaluated for sarcoid like granuloma. Please consider recommending seasonal influenza killed vaccine for all patients. | |
| Recommended management: See Pulmonary Adverse Event Management Algorithm for Pneumonitis below | |

### 6.7.1 BMS Recommended Pulmonary Adverse Event Management Algorithm for Pneumonitis

These suggested management guidelines are taken from the BMS algorithms provided in the Investigator's Brochure.

Evaluate with imaging and pulmonary consultation.

| Toxicity (CTCAE v.5) | Management | Follow-up |
|---|---|---|
| **Grade 1 Pneumonitis** | • Consider delay of protocol therapy<br>• Monitor for symptoms ever 2-3 days<br>• Consider Pulmonary and ID consults | • Re-image at least every 3 weeks<br><br>**If worsens:**<br>• Treat as Grade 2 or 3/4 |
| **Grade 2 Pneumonitis** | • Hold infusion<br>• Pulmonary and ID consults<br>• Monitor symptoms daily, consider hospitalization<br>• 1 to 2 mg/kg/day methylprednisolone IV or oral equivalent<br>• Consider bronchoscopy, lung biopsy | • Re-image every 1-3 days<br><br>**If improves:**<br>• When symptoms return near baseline, taper steroids over at least 1 month<br>• Consider prophylactic antibiotics<br><br>**If not improving after 2 weeks or worsening:**<br>• Treat as Grade 3 or 4 |
| **Grade 3 or 4 Pneumonitis** | • Discontinue protocol therapy<br>• Hospitalize<br>• Pulmonary and ID consults<br>• 2-4 mg/kg/day methylprednisolone IV or IV equivalent<br>• Add prophylactic antibiotics for opportunistic infections<br>• Consider bronchoscopy, lung biopsy | **If improves to baseline:**<br>• Taper steroids over at least 6 weeks<br><br>**If not improving after 48 hours or worsening:**<br>• Add additional immunosuppression (e.g. infliximab, cyclophosphamide, IVIG, or mycophenolate mofetil) |

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.

## 6.8 Dose Modification and Adverse Event Management Algorithm for Pleural Effusion and Ascites

| | | |
|---|---|---|
| **Pleural effusion or ascites** | Non-life-threatening (Grade < 4) pleural effusion or ascites | • Treat with appropriate supportive care, which may include: non-investigational diuretics, thoracentesis, chest tube drainage, paracentesis or pleurodesis.<br>• For grade 1 pleural effusion or Grade 1 or 2 ascites, monitor with physical exam and consider additional imaging.<br>• For grade ≥ 2 pleural effusion or grade 3 ascites, initiate methylprednisolone (2 mg/kg/day IV) or oral equivalent with attempt to taper over 7-10 days after a minimum of 24 hours of treatment.<br>• If chest tube drainage, pleurodesis or paracentesis is required, protocol therapy should be held until at least two days after the procedure or chest tube removal and the patient's condition is stable.<br>• If pleural effusion or ascites resolves or is managed to achieve grade ≤ 1 and steroids are discontinued, protocol therapy may proceed without dose reduction. If pleural effusion or ascites is not resolved/managed to grade ≤ 1 and steroids are not discontinued within 28 days of next scheduled dose of nivolumab or ipilimumab, discontinue protocol therapy. |
| | Grade 4 or Life threatening pleural effusion or ascites | • Institute emergency measures per institutional guidelines<br>• Initiate methylprednisolone 2 mg/kg/day IV or oral equivalent with plan to taper as tolerated.<br>• Permanently discontinue protocol therapy |

### 6.9 Dose Modifications for Fatigue

| Fatigue | Management/Next Dose of Nivolumab ± Ipilimumab |
|---|---|
| ≤ Grade 1 | No change in dose. |
| Grade 2 | No change in dose |
| Grade 3 | Hold until ≤ Grade 2. If resolves within 7 days, resume at same dose level |
| Fatigue is the most common adverse event associated with immune checkpoint therapy. Grade 2 or greater fatigue should be evaluated for associated or underlying organ involvement including pituitary, thyroid, and hepatic, or muscle (CPK) inflammation | |

### 6.10 Dose Modifications for Neurologic Adverse Events

| Neurologic events | Management/Next Dose of Nivolumab ± Ipilimumab |
|---|---|
| ≤ Grade 1 | Continue protocol therapy* |
| Grade 2 | Hold until resolution to baseline.* Resume with no change in dose.* |
| Grade 3 | Off protocol therapy |
| Grade 4 | Off protocol therapy |
| *Patients with any CNS events including aseptic meningitis, encephalitis, symptomatic hypophysitis, or myopathy, peripheral demyelinating neuropathy, cranial neuropathy (other than peripheral n. VII), GB syndrome, myasthenia gravis should be taken off protocol therapy. | |
| Recommended management: See Neurologic Adverse Event Management Algorithm below | |

#### 6.10.1 BMS Recommended Neurologic Adverse Event Management Algorithm

These suggested management guidelines are taken from the BMS algorithms provided in the Investigator's Brochure.

| Toxicity (CTCAE v.5) | Management | Follow-up |
|---|---|---|
| **Grade 1 Neurological Toxicity** | • Continue protocol therapy | • Continue to monitor the patient<br><br>**If worsens:**<br>• Treat as Grade 2 or 3/4 |
| **Grade 2* Neurological Toxicity** | • Hold infusion<br>• Treat symptoms per local guidelines<br>• Consider 0.5 to 1 mg/kg/day methylprednisolone IV or oral equivalent | **If improves to baseline:**<br>• within 7 days resume protocol therapy, if persists >7 days discontinue protocol therapy<br><br>**If worsens:**<br>• Treat as Grade 3/4 |

| Toxicity (CTCAE v.5) | Management | Follow-up |
|---|---|---|
| **Grade 3/4 Neurological Toxicity**** | • Discontinue protocol therapy<br>• Obtain neurology consult<br>• Treat symptoms per local guidelines<br>• 1-2 mg/kg/day methylprednisolone IV or IV equivalent<br>• Add prophylactic antibiotics for opportunistic infections | **If improves to Grade 2:**<br>• Taper steroids over at least 1 month<br><br>**If worsens or atypical presentation:**<br>• Consider IVIG or other immunosuppressive therapies per local guidelines |

* Patients with any CNS events including aseptic meningitis, encephalitis, symptomatic hypophysitis, or myopathy, peripheral demyelinating neuropathy, cranial neuropathy (other than peripheral n. VII), GB syndrome, myasthenia gravis should be taken off protocol therapy.

** With the exception of decreased tendon reflex (DTR); any grade of DTR does not require a dose modification.

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.

## 6.11 Dose Modifications for Endocrine Adverse Events

| **Endocrine Hypophysitis; Adrenal Insufficiency** | **Management/Next Dose of Nivolumab ± Ipilimumab** |
|---|---|
| ≤ Grade 1 | Continue protocol therapy; See Endocrine Management Algorithm |
| Grade 2 | Off protocol therapy if DLT criteria in Section 5.4.1 is met. |
| Grade 3 | Off protocol therapy |
| Grade 4 | Off protocol therapy |
| Note all patients with symptomatic pituitary enlargement, exclusive of hormone deficiency, but including severe headache or enlarged pituitary on MRI should be considered grade 3 events. Isolated thyroid or testosterone deficiency may be treated as grade 2 if there are no other associated deficiencies and adrenal function is monitored.<br>Please evaluate pituitary function before beginning steroid therapy or replacement therapy of any kind. | |
| Recommended management: See Endocrine Management Algorithm | |

### 6.11.1 BMS Recommended Endocrine Adverse Event Management Algorithm

These suggested management guidelines are taken from the BMS algorithms provided in the Investigator's Brochure.

Consider visual field testing, endocrinology consultation, and imaging.

| Toxicity (CTCAE v.5) | Management | Follow-up |
|---|---|---|
| **Asymptomatic TSH elevation** | • Continue protocol therapy<br>• If TSH < 0.5 x LLN, or TSH > 2X ULN, or consistently out of range in 2 subsequent measurements: include fT4 at subsequent cycles as clinically indicated<br>• Consider endocrinology consult | |
| **Symptomatic Endocrinopathy** | • Evaluate endocrine function<br>• Consider pituitary scan<br><br>**Symptomatic with abnormal lab/pituitary scan:**<br>• Hold infusion<br>• 1-2 mg/kg/day methylprednisolone IV or oral equivalent<br>• Initiate appropriate hormone therapy<br><br>**No abnormal lab/pituitary MRI scan but symptoms persist:**<br>• Repeat labs in 1-3 weeks/ MRI in 1 month | **If improves (with or without hormone replacement):**<br>• Taper steroids over at least 1 month<br>• Consider prophylactic antibiotics for opportunistic infections<br>• Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component |
| **Suspicion of adrenal crisis (e.g. severe dehydration, hypotension, shock out of proportion to current illness)** | • Discontinue protocol therapy<br>• Rule out sepsis<br>• Stress dose of IV steroids with mineralocorticoid activity<br>• IV fluids<br>• Consult endocrinologist<br>• If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy | |

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.

### 6.12 Dose Modifications for Fever

| Fever | Management/Next Dose of Nivolumab ± Ipilimumab |
|---|---|
| ≤ Grade 1 | Continue protocol therapy |
| Grade 2 | Hold until ≤ Grade 1. If resolves to ≤ Grade 1 within 7 days, resume at same dose level. If fever does not resolve to ≤ Grade 1 within 7 days, discontinue protocol therapy. |
| Grade 3 | Hold until ≤ Grade 1. If resolves to ≤ Grade 1 within 24 hours, resume at same dose level. If fever does not resolve to ≤ Grade 1 within 24 hours, discontinue protocol therapy. |

| Fever | Management/Next Dose of Nivolumab ± Ipilimumab |
|---|---|
| Grade 4 | Off protocol therapy |
| Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever | |

## 6.13 Dose Modifications for Renal Adverse Events

Dose modifications for renal adverse events will be per Section 6.2 if DLT definition is met. Refer to algorithm below for recommended management guidelines.

### 6.13.1 BMS Recommended Renal Adverse Event Management Algorithm

These suggested management guidelines are taken from the BMS algorithms provided in the Investigator's Brochure.

| Toxicity (CTCAE v.5) | Management | Follow-up |
|---|---|---|
| **Grade 1 Creatinine Increased** | • Continue protocol therapy | **If worsens:**<br>• Treat as Grade 2/3 or 4 |
| **Grade 2 or 3 Creatinine Increased** | • Hold infusion<br>• Monitor creatinine every 2-3 days<br>• 0.5-1 mg/kg/day methylprednisolone or oral equivalent<br>• Consider renal biopsy | **If improves to Grade 1 or baseline:**<br>• Taper steroids over at least 1 month<br>• Consider prophylactic antibiotics for opportunistic infections.<br><br>**If elevations persists > 7 days or worsen:**<br>• Treat as Grade 4 |
| **Grade 4 Creatinine Increased** | • Discontinue protocol therapy<br>• Monitor creatinine weekly<br>• 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent<br>• Consult nephrologist<br>• Consider renal biopsy | **If improves to Grade 1:**<br>• Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections |

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

### 6.14 Dose Modifications for Nivolumab + Ipilimumab Cardiac Toxicities

| Cardiac Toxicities * | Nivolumab + Ipilimumab Cardiac Toxicities |
|---|---|
| ≤ Grade 1 | Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize may resume therapy. If labs worsen or symptoms develop then treat as below. Hold pending evaluation. |
| Grade ≥ 2 with suspected myocarditis | Hold dose.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone. If no improvement within 24 hours, add either infliximab, ATG or tacrolimus. Resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely. |
| Grade ≥ 2 with confirmed myocarditis | Off protocol therapy. Admit to CCU (consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone<br>Add antithymocyte globulin (ATG) or tacrolimus if no improvement. Off treatment. |
| | |
| **Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin*<br>***Patients with evidence of myositis without myocarditis may be treated according as "other event"*<br>Note: The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended. | |

## 7.0 SUPPORTIVE CARE AND OTHER CONCOMITANT THERAPY

### 7.1 Concurrent Anticancer Therapy

Concurrent cancer therapy, including chemotherapy, radiation therapy, immunotherapy, or biologic therapy may NOT be administered to patients receiving study drug. If these treatments are administered the patient will be removed from protocol therapy.

### 7.2 Investigational Agents

No other investigational agents may be given while the patient is on study.

### 7.3 Supportive Care

Appropriate antibiotics, blood products, antiemetics, fluids, electrolytes and general supportive care are to be used as necessary. Specific supportive care measures for

management of autoimmune reactions are detailed below:

Skin Related Toxicity

For skin-related Grade 3 autoimmune toxicity lasting > 7 days or Grade 4 autoimmune toxicity, including severe generalized pruritis or rash, symptomatic treatment will be given and patients will be removed from protocol therapy. Therapy will be as clinically indicated and may include local skin care, antihistamines, or corticosteroids (which can be local/topical or systemic). The use of topical corticosteroids for grades 1 -3 dermatitis will be allowed, and will not require patients to be removed from study. In the case of late-occurring hypersensitivity symptoms (e.g., appearance within one week after treatment of a localized or generalized pruritis), symptomatic treatment may be given (e.g., oral antihistamine, topical steroids for the skin). A dermatologist should evaluate persistent (lasting >7 days) and/or severe rashes or pruritus. A biopsy should be performed if appropriate and photos should be obtained.

Ocular Toxicity

Patients who report any new visual symptom, ocular findings on exam, or change in vision should be immediately referred to an ophthalmologist. Ophthalmologic evaluation should include but will not be limited to examination of the conjunctiva, anterior and posterior chambers and retina, normal and dilated slit-lamp examination. The patient will be treated as deemed appropriate by the ophthalmologist, including peri-ocular steroid injections or steroid eye drops if necessary.

Gastrointestinal Toxicity

Any patient experiencing diarrhea (which may be defined as watery stool, or increase in the frequency stools above grade 1 with urgency or nocturnal bowel movement, or melena or hematochezia) should be further evaluated for etiology that should include a search for an infectious etiology, C. Difficile colitis and other alternative infections as clinically indicated. Consideration should be given to discontinuing medications known to exacerbate colitis. Grade 2 or greater diarrhea attributable to protocol therapy is considered a DLT as outlined in Section 5.4.1.

It is recommended that colitis or enterocolitis of Grade 1 be evaluated as above for other non-immune mediated causes, then monitored closely and treated symptomatically without steroids, including a trial of loperamide may be used. For Grade ≥ 2 colitis or enterocolitis, recommendations include endoscopy. Even if colonoscopy does not reveal gross findings of colitis, biopsies should be performed and strong consideration should be given to upper endoscopy and biopsies. Patients with gross or biopsy proven colitis or enteritis should receive IV steroids (recommend 1 mg/kg methylprednisone daily x 7 days) followed by a minimum 30 day taper. In patients with Grade 3 or 4 enterocolitis that does not respond to high dose steroids after 7 days, further therapies should be administered as clinically indicated in consultation with gastroenterology subspecialists.

Concern for immune-mediated liver toxicity may be elicited following LFT elevation of 3 fold over baseline and/or right upper quadrant abdominal pain or unexplained nausea or vomiting. Other etiologies for transaminitis should be considered and evaluated and may include but are not limited to neoplastic, concurrent medications, viral hepatitis, and other toxic etiologies. Evaluation for autoimmune etiologies may be evaluated by ANA, pANC, and anti-smooth muscle antibody tests as well as hepatology consultation with possible biopsy.

Pancreatitis has rarely been associated with checkpoint inhibitors and should be considered in cases of abdominal pain associated with elevations of amylase and lipase. Treatment of pancreatitis should be supportive and may include consultation with gastroenterology subspecialists.

Endocrine Toxicity

Patients experiencing symptoms such as fatigue, myalgias, impotence, mental status changes, constipation, or other symptoms thought to be associated with endocrine abnormalities should be evaluated for thyroid, pituitary, or adrenal endocrinopathies and an endocrinologist should be consulted.

Patients with Grade 2 hypothyroidism should be evaluated by an endocrinologist for further management. Patients with Grade 2 hypothyroidism or Grade 2 hyperthyroidism adequately managed with thyroid hormone replacement or thyroid suppression may continue on protocol therapy. Patients with Grade 3 or greater hypothyroidism will be considered to have had a dose-limiting toxicity. These patients should be managed according to Section 6.11 and evaluation by an endocrinologist is recommended for further management. Patients who enter the study on thyroid replacement or suppression should have their thyroid medication adjusted to maintain TSH in the normal range.

Auto Immune or Immune System Disorders Effecting Other Organ Systems

Patients experiencing symptoms that may be associated with autoimmune or immune mediated adverse events possibly, probably or definitely related to protocol therapy should be evaluated and monitored closely. These may include but are not limited to pneumonitis, sarcoid-like granuloma and neurologic events including hypophysitis, encephalitis, aseptic meningitis, and cranial neuropathy especially nVII. Consideration should be given to subspecialty consultation particularly if systemic immune suppression is considered.

## 7.4 Growth Factors

Growth factors that support platelet or white cell number or function can only be administered for culture proven bacteremia or invasive fungal infection. Patients MUST NOT receive prophylactic myeloid growth factor in the first cycle of therapy. The Study Chair should be notified before growth factors are initiated.

## 8.0 EVALUATIONS/MATERIAL AND DATA TO BE ACCESSIONED

### 8.1 Required Clinical, Laboratory and Disease Evaluation

All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated. Laboratory values used to assess eligibility (see Section 4.0) must be no older than seven (7) days at the start of therapy. Laboratory tests need **not** be repeated if therapy starts **within** seven (7) days of obtaining labs to assess eligibility. If a post-enrollment lab value is outside the limits of eligibility, or laboratory values are older than 7 days, then the following laboratory evaluations must be re-checked within 48 hours prior to initiating therapy: CBC with differential, bilirubin, ALT (SGPT) and serum creatinine. If the recheck is outside the limits of eligibility, the patient may not receive protocol therapy and will be considered off protocol therapy. Imaging studies must be obtained within 14 days prior to start of protocol therapy (repeat the tumor imaging if necessary).

| STUDIES TO BE OBTAINED | Pre-Study | During Cycle 1 | Prior to Subsequent Cycles^ |
|---|---|---|---|
| History | X | Weekly | X |
| Physical Exam with vital signs | X | Weekly | X |
| Height, weight, BSA | X | | X |
| Performance Status | X | | X |
| Pregnancy Test[1] | X | | |
| CBC, differential, platelets | X | Weekly [2] | Weekly[3] |
| Urinalysis | X | | X |
| Electrolytes including $Ca^{++}$, Cl, $PO_4$, $Mg^{++}$ | X | Weekly | X |
| Creatinine, ALT*, AST*, bilirubin | X | Weekly | X |
| Amylase, lipase, CRP | X | | X |
| TSH[4] | X | End of Cycle 1 | X |
| Tumor Disease Evaluation- Parts A and B | X | End of Cycle 1 | End of cycle 2, then q 3 cycles [5] |
| Tumor Disease Evaluation- Parts C, D, and E | X | End of Cycle 2 | End of cycle 4, then q 3 cycles [5] |
| Pulse Oximetry | X | | With Tumor Disease Evaluation |
| Pharmacokinetics[6] (Required) | X | X[7] | X |
| Vaccine Antibody and Cytokine Studies[8] (Optional) | X | X | X |
| Anti-Drug Antibody (ADA)[9] (Required) | X | X | X |
| Tumor Tissue (Required, if available) | X[10] | | X[11] |
| EKG[12], ECHO[12, 13] | X | Clinically Indicated | |
| CPK and Troponin [13] | X | Clinically Indicated | |

^ Studies may be obtained within 72 hours prior to the start of the subsequent cycle.

* For the purpose of this study, the ULN for SGOT (AST) is 50 U/L and the ULN for SGPT (ALT) is 45 U/L.

1 Women of childbearing potential require a negative pregnancy test prior to starting treatment. Men and women must be willing to adhere to effective contraception during the study and for 5 months after the last dose of nivolumab for women of childbearing potential and 7 months after the last dose of nivolumab for men sexually active with women of childbearing potential. Abstinence is an acceptable method of birth control.

2 If patients have Grade 4 neutropenia then CBCs should be checked at least every other day until recovery to Grade 3 or until meeting the criteria for dose limiting toxicity.

[3] If patients develop Grade 4 neutropenia then CBCs should be checked every 3 to 4 days until recovery to Grade 3

[4] Free T4 should also be measured for patients with an abnormal TSH level. Guidance on the management of patients who develop hypothyroidism is included in Section 7.3.4.

[5] Tumor Disease Evaluation should be obtained on the next consecutive cycle after initial documentation of either a PR or CR. Please note that if the institutional investigator determines that the patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding radiographically. If tumor growth is > 20% but < 40%, imaging to include target lesions must occur every cycle if clinically indicated, or if "pseudoprogression" appears based on inflammatory response, and the same radiographic and clinical criteria must be met in order to remain on study (See Section 12.2.1).

[6] See Section 8.3.2 and Appendix III for timing of PK studies.

[7] Patients who are removed from therapy during Cycle 1 after receiving the dose of nivolumab on Day 15 should have their last PK sample collected on Day 28 of Cycle 1.

[8] See Section 8.4.2 and Appendix IV for timing of vaccine antibody and section 8.8.2 and Appendix VII for timing of cytokine studies.

[9] See Section 8.5.2 and Appendix V for timing of ADA studies.

[10] See Section 8.6 and Appendix VI for instructions for submitting tumor specimens. If tissue blocks or slides are unavailable, the study chair must be notified prior to study enrollment.

[11] In the event a subject requires a biopsy for surgery and tumor tissue is removed, tissue will be requested for PD-L1 and CD8 Expression analysis (required, if available).

[12] 12-lead EKG and ECHO to be obtained at baseline, in patients with a history of CHF or at risk because of underlying cardiovascular disease or exposure to cardiotoxic drugs Refer to section 4.2.7

[13] For patients with evidence of myocardial infarction (MI), cardiomyopathy, myositis, congestive heart failure (CHF) while on study, cardiac evaluations should be performed including lab tests, cardiology consultations as clinically indicated, including EKG, CPK, troponin, ECHO cardiogram. A CK-MB test may be used as a follow-up test to an elevated CK in order to determine whether the increase is due to heart damage or skeletal muscle damage. Refer to section 6.1.4, 5.4.1

### 8.1.1 Required Observations Following Completion of Protocol Therapy

The following studies are required until the patient is off study as defined in Section 10.2.

| STUDIES TO BE OBTAINED | ~100 Days After Last dose of Nivolumab | Every 6 months up to 24 Months | Annually up to 60 Months |
|---|---|---|---|
| History | X | X | X |
| Physical exam with vital signs | X | X | X |
| CBC, differential, platelets | X | X | X |
| Tumor disease evaluation | X | X | X |
| Treatment with stem cell transplant | X | X | X |
| Evidence of or history of GVHD | X | X | X |

## 8.2 Radiology Studies

Central Radiology Review for Response:

Patients who respond (CR, PR) to therapy, have pseudoprogression or have long term stable disease (SD) (≥ 6 cycles) on protocol therapy will be centrally reviewed. The response of MIBG lesions will also be assessed by central review (See Section 12.4). COG Operations Center will notify the Imaging Center of any patient requiring central review. The Imaging Center will then request that the

treating institution forward the requested images for central review. The central image evaluation results will be entered into RAVE for review by the COG Operations Center and for data analysis.

The images are to be forwarded electronically to the Imaging Research Center at Children's Hospital Los Angeles via the ImageInBox.

COG institutions that are not connected via the ImageInBox can send the images on hard copy film, CD ROM, USB flash drive or by FTP. Submitted imaging studies should be clearly marked with the COG patient ID, study number (ADVL1412) and date and shipped to Syed Aamer at the address below:

Syed Aamer, MBBS, CRP
Administrator, Imaging Research Center
Children's Hospital Los Angeles
4650 Sunset Boulevard, MS # 81
Los Angeles, CA 90027
Phone: (323) 361-3898
Fax: (323) 361-3054

## 8.3 Pharmacokinetics (Required)

### 8.3.1 Analysis

Serum samples will be collected for pharmacokinetic evaluation of nivolumab and/or ipilimumab by validated immunoassay by PPD - Pharmaceutical Product Development, LLC. PK parameters will include Cmax, Cmin, Tmax, $AUC_{(TAU)}$ and $AUC_{(0-21)}$.

### 8.3.2 Sampling Schedule

Blood samples will be obtained prior to drug administration and as outlined in Appendix IIIA for Parts A and B, and Appendix IIIB for Parts C, D, and E.

### 8.3.3 Sample Collection and Handling Instructions

Blood samples (2 ml for parts A and B and 2 x 2ml for parts C, D, and E) will be collected in SST Vacutainer tubes at a site distant from the infusion for pharmacokinetic evaluation. Samples cannot be drawn from the 2nd lumen of a multi-lumen catheter through which drug is being administered. Record the exact time that the sample is drawn along with the exact time that the drug is administered (including drug start and stop times).

1. For timepoints where both PK and ADA samples are collected, an 8.5mL SST tube is used.
2. For timepoints where only a PK sample is collected, the 4mL SST tube is used.

### 8.3.4 Sample Processing Instructions:

1. Immediately after collection, gently invert each blood sample 5-10 times and allow blood to clot for 30-45 minutes at room temperature (tube standing upright).
2. Centrifuge samples at room temperature for 10 minutes (swing out) or 15 minutes (fixed) at 1100-1300 x g until clot and serum are well separated.
3. Aliquot according to the following:
    a. PK-only timepoints- transfer all serum into one appropriately

labeled 2 mL screw-capped polypropylene tube
   b. PK and ADA- transfer serum equally into two appropriately labeled 3 mL screw-capped polypropylene tubes
4. Store the serum samples immediately (within 1 hour of collection) at approximately -20°C or -70°C (preferred) until they are shipped on dry ice to the address in Section 8.3.6.

8.3.5 Sample Labeling
Each tube must be labeled with the patient's study registration number, the study I.D., and the date and time the sample was drawn. Data should be recorded on the Pharmacokinetic Study Form, which must accompany the sample(s).

8.3.6 Sample Shipping Instructions:
Samples may be batched and shipped on dry ice at the end of each cycle (Monday, Tuesday, or Wednesday) to:

Richard Catlyn
PPD - Pharmaceutical Product Development, LLC
2244 Dabney Road, Richmond, VA. 23230-3323
Tel: (804) 977-8344
Email: Richard.catlyn@ppdi.com
Fax: (804) 977-8112

Shipment notification with tracking number should be sent to Maria Edwards along with a copy of the PK Study form (Appendix III-A or Appendix III-B).

## 8.4 Vaccinated Antibody Studies (optional)

8.4.1 Analysis
In consenting patients, PD analysis will be done by Covance on serum samples for retrospective analysis of changes in antibody titers to previously vaccinated antigens following treatment with nivolumab alone and in combination with ipilimumab.

8.4.2 Sampling Schedule
Blood samples will be obtained prior to drug administration and as outlined in Appendix IV.

8.4.3 Sample Collection and Handling Instructions
Blood samples (2 ml) will be collected in 4 mL SST Vacutainer tubes at a site distant from the infusion. Samples cannot be drawn from the 2nd lumen of a multi-lumen catheter through which drug is being administered. Record the exact time that the sample is drawn along with the exact time that the drug is administered (including drug start and stop times).

8.4.4 Sample Processing and Shipping Instructions:
1. Immediately after collection, gently invert each blood sample 5-10 times and allow blood to clot for 30-45 minutes at room temperature (tube standing upright).
2. Centrifuge samples at room temperature for 10 minutes (swing out) or 15

minutes (fixed) at 1100-1300 x g until clot and serum are well separated.
3. Transfer all serum into one appropriately labeled 2 mL screw-capped polypropylene tube
4. Store the serum samples immediately (within 1 hour of collection) at approximately -20°C or -70°C (preferred) until shipment.

Refer to the guidelines provided for sample shipping instructions.

8.4.5 Vaccinated Antibody Sample Shipping Instructions:

Samples may be batched and shipped on dry ice at the end of each cycle (Monday, Tuesday, or Wednesday) to:

Covance Central Laboratory Services
CenterlinX Receiving-Dock17
8211 SciCor Drive
Indianapolis, IN 46214
Email: monitoringUS@covance.com
Phone: 317-271-1200

Shipment notification with tracking number should be sent to Covance along with a copy of the Vaccinated Antibody Study form (Appendix IV).

8.4.6 Sample Labeling

Each tube must be labeled with the patient's study registration number, the study I.D., and the date and time the sample was drawn. Data should be recorded on the Vaccinated Antibody Study Form, which must accompany the sample(s).

8.5 **Anti-drug antibody (ADA) analysis (Required)**

Analysis: ADA analysis will be done by PPD - Pharmaceutical Product Development, LLC using an ELISA assay.

8.5.1 Sampling Schedule

Blood samples will be obtained as outlined in Appendix V.

8.5.2 Sample Collection and Handling Instructions

Blood samples (2 ml) will be collected in SST Vacutainer tubes at a site distant from the infusion. Samples cannot be drawn from the 2nd lumen of a multi-lumen catheter through which drug is being administered. Record the exact time that the sample is drawn along with the exact time that the drug is administered (including drug start and stop times).

1. For timepoints where both PK and ADA samples are collected, an 8.5 mL SST tube is used.
2. For timepoints where only an ADA sample is collected, the 4 mL SST tube is used.

8.5.3 Sample Processing Instructions:

1. Immediately after collection, gently invert each blood sample 5-10 times and allow blood to clot for 30-45 minutes at room temperature (tube standing upright).

2. Centrifuge samples at room temperature for 10 minutes (swing out) or 15 minutes (fixed) at 1100-1300 x g until clot and serum are well separated.
3. Aliquot according to the following:
    a. ADA-only timepoints- transfer all serum into one appropriately labeled 2 mL screw-capped polypropylene tube
    b. PK and ADA- transfer serum equally into two appropriately labeled 3 mL screw-capped polypropylene tubes
4. Store the serum samples immediately (within 1 hour of collection) at approximately -20°C or -70°C (preferred) until they are shipped on dry ice to the address in Section 8.5.6.

8.5.4 Sample Labeling

Each tube must be labeled with the patient's study registration number, the study I.D., and the date and time the sample was drawn. Data should be recorded on the Anti-drug Antibody (ADA) Study Form, which must accompany the sample(s).

8.5.5 Sample Shipping Instructions:

Samples may be batched and shipped on dry ice at the end of each cycle (Monday, Tuesday, or Wednesday) to:

Richard Catlyn
PPD - Pharmaceutical Product Development, LLC
2244 Dabney Road, Richmond, VA. 23230-3323
Tel: (804) 977-8344
Email: Richard.catlyn@ppdi.com
Fax: (804) 977-8112

Shipment notification with tracking number should be sent to Richard Catlyn along with a copy of the ADA Study form (Appendix V).

## 8.6 Tumor Assessment PD-L1 and CD8 (required, if available)

8.6.1 Description of Studies

Tumor PD-L1 and CD8 expression will be performed by immunohistochemistry. Archival tumor tissue should be submitted for all patients. If a patient does not have tissue available, the study chair must be notified prior to enrollment.

8.6.2 Sampling Schedule (See Appendix VI)

- Archival tumor tissue (Archival Formalin-Fixed Paraffin-Embedded (*FFPE*)) will be requested to be sent when available (15 slides requested, see Appendix VI for more information).
- In the event a subject requires a biopsy for surgery and tumor tissue is removed, tissue will be requested for PD-L1 and CD8 expression analysis (optional). Tumor biopsies will not be performed solely for research purposes.

8.6.3 Sample Labeling

Each specimen must be labeled with the patient's study registration number, the study I.D., and must be accompanied by a pathology report. Data should be recorded on the Tissue Studies Form, which must accompany the sample(s).

8.6.4 Sample Shipping Instructions: Tissue samples will be shipped to Mosaic Laboratories:

Attn: Lisa Dauffenbach
Mosaic Laboratories
12 Spectrum Pointe Drive
Lake Forest, CA 92630
Phone: (949) 472-8855

Shipment notification with tracking number should be sent to Lisa Dauffenbach (ldauffenbach@mosaiclabs.com) along with a copy of the Tissue Studies Form (Appendix VI). Please note: PD-L1, CD8, and FoundationOneCDx Tumor Assessments may be batched and shipped together.

## 8.7 Tumor Assessment FoundationOneCDx (Optional): Part E

8.7.1 Description of Studies

Genomic analysis of tumors will be performed by Foundation Medicine to explore immune related gene expression and its association with antitumor response (optional).

8.7.2 Sampling Schedule

8.7.2.1 Archival tumor tissue (Archival Formalin-Fixed Paraffin-Embedded (*FFPE*)) will be requested to be sent when available (15 slides requested, or paraffin-embedded block; see Appendix VI for more information).

8.7.3 Sample Labeling

Each specimen must be labeled with the patient's study registration number, the study I.D., and must be accompanied by a pathology report. Data should be recorded on the Tissue Studies Form, which must accompany the sample(s).

8.7.4 Sample Shipping Instructions: Tissue samples will be shipped to Mosaic Laboratories:

Attn: Lisa Dauffenbach
Mosaic Laboratories
12 Spectrum Pointe Drive
Lake Forest, CA 92630
Phone: (949) 472-8855

Shipment notification with tracking number should be sent to Lisa Dauffenbach (ldauffenbach@mosaiclabs.com) along with a copy of the Tissue Studies Form (Appendix VI). Please note: PD-L1, CD8, and FoundationOneCDx Tumor Assessments may be batched and shipped together.

## 8.8 Cytokine studies (optional)

8.8.1 Analysis

In consenting patients, PD analysis will be performed by Myriad RBM on serum samples for retrospective analysis of changes in cytokines following treatment with nivolumab alone and in combination with ipilimumab.

8.8.2 Sampling Schedule

Blood samples will be obtained prior to drug administration and as outlined in Appendix VII.

8.8.3 Sample Collection and Handling Instructions

Blood samples (2 ml) will be collected in 4 mL SST Vacutainer tubes at a site distant from the infusion. Samples cannot be drawn from the 2nd lumen of a multi-lumen catheter through which drug is being administered. Record the exact time that the sample is drawn along with the exact time that the drug is administered (including drug start and stop times).

8.8.4 Sample Processing and Shipping Instructions:

1. Immediately after collection, gently invert each blood sample 5-10 times and allow blood to clot for 30-45 minutes at room temperature (tube standing upright).
2. Centrifuge samples at room temperature for 10 minutes (swing out) or 15 minutes (fixed) at 1100-1300 x g until clot and serum are well separated.
3. Transfer all serum into one appropriately labeled 2 mL screw-capped polypropylene tube
4. Store the serum samples immediately (within 1 hour of collection) at approximately -20°C or -70°C (preferred) until shipment.

8.8.5 Sample Labeling

Each tube must be labeled with the patient's study registration number, the study I.D., and the date and time the sample was drawn. Data should be recorded on the Cytokine Study Form, which must accompany the sample(s).

8.8.6 Cytokine Sample Shipping Instructions:

Samples may be batched and shipped on dry ice at the end of each cycle (Monday, Tuesday, or Wednesday) to:

Bristol-Myers Squibb
BMS Biorepository
Attn: Karl Kammerhoff and/or designee
Room K1421
Route 206 & Provinceline Road
Princeton, NJ 08543
609-818-6398
bmsbiorepository@bms.com

Shipment notification with tracking number should be sent to BMS Biorepository and the study research coordinator via email, along with a copy of the Cytokine Study form (Appendix VII).

## 9.0 AGENT INFORMATION

### 9.1 Nivolumab

(BMS-936558, MDX1106, ONO-4538, anti-PD-1, Opdivo™) NSC#748726,

Structure and molecular weight

Nivolumab is a soluble protein consisting of 4 polypeptide chains, which include 2 identical heavy chains consisting of 440 amino acids and 2 identical light chains. Molecular weight is 146,221 daltons.

9.1.1 Supplied by:

Nivolumab will be supplied by Bristol-Myers Squibb (BMS) and distributed by the DCTD, NCI. **Do NOT use commercially available supply.**

9.1.2 Formulation

The agent is a clear to opalescent, colorless to pale yellow liquid, with light (few) particulates may be present. It is available in a 100 mg/10 mL vial containing a sterile, non-pyrogenic, single-use, isotonic aqueous solution formulated at 10 mg/mL in sodium citrate dihydrate, sodium chloride, mannitol, diethylenetriamine pentacetic acid (pentetic acid) and polysorbate 80 (Tween® 80), and water for injection. Dilute solutions of hydrochloric acid and/or sodium hydroxide may be used for pH adjustment (pH 5.5-6.5). A small amount of overfill (0.7 mL) is included with each vial to account for VNS (vial, needle, syringe) loss. The 10 mL type I flint glass vials are stoppered with fluoropolymer film-laminated rubber stoppers and sealed with aluminum seals.

9.1.3 Storage

Nivolumab vials for injection must be stored at 2°-8°C (36°-46°F) and protected from light, freezing and shaking. Unopened vials can be stored at room temperature (up to 25°C, 77°F) and room light for up to 48 hours.

If a storage temperature excursion is identified, promptly return Nivolumab to 2°C-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

9.1.4 Solution Preparation

Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose. When the dose is based on patient weight (i.e., mg/kg), nivolumab injection can be infused undiluted or diluted to protein concentrations as low as 0.35 mg/mL. When the dose is fixed (e.g., 240 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 mL. For patients weighing less than 40 kilograms (kg), the total volume of infusion must not exceed 4 mL per kg of patient weight. During drug product preparation and handling, vigorous mixing or shaking is to be avoided.

Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

9.1.5 Stability

Shelf life surveillance of the intact vials is ongoing.

The administration of undiluted and diluted nivolumab must be completed within 24 hours of preparation. If not used immediately, the infusion solution of

nivolumab injection prepared for dosing may be stored for up to 24 hours in a refrigerator at 2°-8°C (36°-46°F) and a maximum of 8 hours of the total 24 hours can be at room temperature (up to 25°C, 77°F) and under room light. The maximum 8-hour period under room temperature and room light conditions for nivolumab injection in IV bag includes the product administration period (30 minutes).

CAUTION: The single-use vials of nivolumab for injection do not contain preservatives or bacteriostatic agents and should be prepared as soon as possible prior to administration using aseptic technique. It is advised that the product be discarded 8 hours after initial entry.

9.1.6 Administration

See Treatment and Dose Modifications sections of the protocol.

Nivolumab should be administered as an intravenous infusion over 30 minutes through a 0.2 to 1.2 micron pore size, low-protein binding (polyethersulfone membrane) in-line filter. Nivolumab is not to be administered as an IV push or bolus injection. Do not administer other medications through the same IV line. Flush IV line at the end of the infusion.

Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

When administered in combination with ipilimumab, infuse nivolumab first followed by ipilimumab on the same day. Use separate infusion set and filters for each infusion.

9.1.7 Potential drug interactions

No formal pharmacokinetic drug-drug interaction studies have been conducted with nivolumab. The indirect drug-drug interaction potential of nivolumab was assessed using systemic cytokine modulation data for cytokines known to modulate CYP enzymes. There were no meaningful changes in cytokines known to have indirect effects on CYP enzymes across all dose levels of nivolumab. This lack of cytokine modulation suggests that nivolumab has no or low potential for modulating CYP enzymes, thereby indicating a low risk of therapeutic protein-drug interaction.

9.1.8 Patient Care Implications

Adverse events were observed in animal reproduction studies. Nivolumab may be expected to cross the placenta; effects to the fetus may be greater in the second and third trimesters. Based on its mechanism of action, nivolumab is expected to cause fetal harm if used during pregnancy. Women of childbearing potential (WOCBP) receiving nivolumab must continue contraception for a period of 5 months after the last dose of nivolumab. Men receiving nivolumab and who are sexually active with WOCBP must continue contraception for a period of 7 months after the last dose of nivolumab.

It is not known if nivolumab is present in breast milk. Due to the potential for serious adverse reactions in the breastfed infant, the manufacturer recommends to discontinue breastfeeding during treatment.

9.1.9 Nivolumab Toxicities

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Frequency is provided based on 2069 patients. Below is the CAEPR for BMS-936558 (Nivolumab, MDX-1106).

**NOTE:** Report AEs on the SPEER ONLY IF they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

**Version 2.3, June 18, 2018[1]**

| **Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 5.0 Term) [n= 2069]** | | | **Specific Protocol Exceptions to Expedited Reporting (SPEER)** |
|---|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** | |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | | |
| | Anemia | | ***Anemia (Gr 2)*** |
| CARDIAC DISORDERS | | | |
| | | Cardiac disorders - Other (cardiomyopathy) | |
| | | Myocarditis | |
| | | Pericardial tamponade[2] | |
| | | Pericarditis | |
| ENDOCRINE DISORDERS | | | |
| | Adrenal insufficiency[3] | | |
| | Hypophysitis[3] | | |
| | Hyperthyroidism[3] | | |
| | Hypothyroidism[3] | | |
| EYE DISORDERS | | | |
| | | Blurred vision | |
| | | Dry eye | |
| | | Eye disorders - Other (diplopia) [3] | |
| | | Eye disorders - Other (Graves ophthalmopathy) [3] | |
| | | Eye disorders - Other (optic neuritis retrobulbar) [3] | |
| | Uveitis | | |
| GASTROINTESTINAL DISORDERS | | | |
| | Abdominal pain | | ***Abdominal pain (Gr 2)*** |
| | Colitis[3] | | |
| | | Colonic perforation[3] | |
| | Diarrhea | | ***Diarrhea (Gr 3)*** |
| | Dry mouth | | ***Dry mouth (Gr 2)*** |

| Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 5.0 Term) [n= 2069] | | | Specific Protocol Exceptions to Expedited Reporting (SPEER) |
|---|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** | |
| | | Gastritis | |
| | | Mucositis oral | |
| | Nausea | | ***Nausea (Gr 2)*** |
| | Pancreatitis[4] | | |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | | |
| Fatigue | | | ***Fatigue (Gr 3)*** |
| | Fever | | ***Fever (Gr 2)*** |
| | Injection site reaction | | ***Injection site reaction (Gr 2)*** |
| IMMUNE SYSTEM DISORDERS | | | |
| | | Allergic reaction[3] | |
| | | Autoimmune disorder[3] | |
| | | Cytokine release syndrome[5] | |
| | | Immune system disorders - Other (GVHD in the setting of allotransplant) [3, 6] | |
| | | Immune system disorders - Other (sarcoid granuloma) [3] | |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | | | |
| | Infusion related reaction[7] | | |
| INVESTIGATIONS | | | |
| | Alanine aminotransferase increased[3] | | ***Alanine aminotransferase increased[3] (Gr 3)*** |
| | Aspartate aminotransferase increased[3] | | ***Aspartate aminotransferase increased[3] (Gr 3)*** |
| | Blood bilirubin increased[3] | | ***Blood bilirubin increased[348484847] (Gr 2)*** |
| | Creatinine increased | | |
| | Lipase increased | | |
| | Lymphocyte count decreased | | ***Lymphocyte count decreased (Gr 2)*** |
| | Neutrophil count decreased | | |
| | Platelet count decreased | | |
| | Serum amylase increased | | |
| METABOLISM AND NUTRITION DISORDERS | | | |
| | Anorexia | | |
| | | Hyperglycemia | ***Hyperglycemia (Gr 2)*** |
| | | Metabolism and nutrition disorders - Other (diabetes mellitus with ketoacidosis) [3] | |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | | |
| | Arthralgia | | |
| | | Musculoskeletal and connective tissue disorder - Other (polymyositis) | |
| | | Myositis | |
| | | Rhabdomyolysis | |
| NERVOUS SYSTEM DISORDERS | | | |
| | | Encephalopathy[3] | |
| | | Facial nerve disorder[3] | |
| | | Guillain-Barre syndrome[3] | |

| Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 5.0 Term) [n= 2069] | | | Specific Protocol Exceptions to Expedited Reporting (SPEER) |
|---|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** | |
| | | Myasthenia gravis[3] | |
| | | Nervous system disorders - Other (demyelination myasthenic syndrome) | |
| | | Nervous system disorders - Other (encephalitis)[3] | |
| | | Nervous system disorders - Other (meningoencephalitis) | |
| | | Nervous system disorders - Other (meningoradiculitis)[3] | |
| | | Nervous system disorders - Other (myasthenic syndrome) | |
| | | Peripheral motor neuropathy | |
| | | Peripheral sensory neuropathy | |
| | | Reversible posterior leukoencephalopathy syndrome[3] | |
| RENAL AND URINARY DISORDERS | | | |
| | | Acute kidney injury[3] | |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | | |
| | Pleural effusion[3] | | |
| | Pneumonitis[3] | | |
| | | Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)[3] | |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | | |
| | | Erythema multiforme[3] | |
| | Pruritus[3] | | ***Pruritus*[3] *(Gr 2)*** |
| | Rash maculo-papular[3] | | ***Rash maculo-papular*[3] *(Gr 2)*** |
| | | Skin and subcutaneous disorders -Other (bullous pemphigoid) | |
| | Skin and subcutaneous disorders - Other (Sweet's Syndrome)[3] | | |
| | Skin hypopigmentation[3] | | |
| | | Stevens-Johnson syndrome | |
| | | Toxic epidermal necrolysis | |

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Pericardial tamponade may be related to possible inflammatory reaction at tumor site.

[3]BMS-936558 (Nivolumab, MDX-1106) being a member of class of agents involved in the inhibition of "immune checkpoints", may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. This may result in autoimmune disorders that can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune nephritis, autoimmune neuropathy, autoimmune

thyroiditis, bullous pemphigoid, exacerbation of Churg-Strauss Syndrome, drug rash with eosinophilia systemic symptoms [DRESS] syndrome, facial nerve disorder (facial nerve paralysis), limbic encephalitis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, thyrotoxicosis, and adrenal insufficiency), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome.

[4]Pancreatitis may result in increased serum amylase and/or more frequently lipase.

[5]Cytokine release syndrome may manifest as hemophagocytic lymphohistiocytosis with accompanying fever and pancytopenia.

[6]Complications including hyperacute graft-versus-host disease (GVHD), some fatal, have occurred in patients receiving allo stem cell transplant (SCT) after receiving BMS-936558 (Nivolumab, MDX-1106). These complications may occur despite intervening therapy between receiving BMS-936558 (Nivolumab, MDX-1106) and allo-SCT.

[7]Infusion reactions, including high-grade hypersensitivity reactions which have been observed following administration of nivolumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of nivolumab.

**Adverse events reported on BMS-936558 (Nivolumab, MDX-1106) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that BMS-936558 (Nivolumab, MDX-1106) caused the adverse event:**

**BLOOD AND LYMPHATIC SYSTEM DISORDERS** - Leukocytosis
**CARDIAC DISORDERS** - Atrial fibrillation; Atrioventricular block complete; Heart failure; Ventricular arrhythmia
**EAR AND LABYRINTH DISORDERS** - Vestibular disorder
**EYE DISORDERS** - Eye disorders - Other (iridocyclitis); Optic nerve disorder; Periorbital edema
**GASTROINTESTINAL DISORDERS** - Constipation; Duodenal ulcer; Flatulence; Gastrointestinal disorders - Other (mouth sores); Vomiting
**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Chills; Edema limbs; Malaise; Pain
**HEPATOBILIARY DISORDERS** - Bile duct stenosis
**IMMUNE SYSTEM DISORDERS** - Anaphylaxis; Immune system disorders - Other (autoimmune thrombotic microangiopathy); Immune system disorders - Other (limbic encephalitis)
**INFECTIONS AND INFESTATIONS** - Bronchial infection; Lung infection; Sepsis; Upper respiratory infection
**INVESTIGATIONS** - Blood lactate dehydrogenase increased; GGT increased; Investigations - Other (protein total decreased); Lymphocyte count increased; Weight loss
**METABOLISM AND NUTRITION DISORDERS** - Dehydration; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Hypophosphatemia
**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Back pain; Musculoskeletal and connective tissue disorder - Other (musculoskeletal pain); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Myalgia; Pain in extremity
**NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)** - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (histiocytic necrotizing lymphadenitis)
**NERVOUS SYSTEM DISORDERS** - Dizziness; Headache; Intracranial hemorrhage
**PSYCHIATRIC DISORDERS** - Insomnia
**RENAL AND URINARY DISORDERS** - Hematuria; Renal and urinary disorders - Other (tubulointerstitial nephritis)
**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Bronchospasm; Cough; Dyspnea; Hypoxia
**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Alopecia; Dry skin; Hyperhidrosis; Pain of skin; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (rosacea)

**VASCULAR DISORDERS** - Flushing; Hypertension; Hypotension; Vasculitis

**Note**: BMS-936558 (Nivolumab, MDX-1106) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

9.1.10 Agent Ordering and Agent Accountability

NCI supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

9.1.11 **Clinical Drug Request and Investigator Brochure Availability**

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password and active person registration status. For questions about drug orders, transfers, returns, or accountability call or email PMB anytime. Refer to the PMB's website for specific policies and guidelines related to agent management. Questions about IB access may be directed to the PMB IB coordinator via email.

The current version(s) of the IB(s) for the agent will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Questions about IB access may be directed to the PMB IB coordinator via email.

9.1.12 **Agent Inventory Records**

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

9.1.13 **Useful Links and Contacts**

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP/
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/

- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575
  Monday through Friday between 8:30 am and 4:30 pm (ET)
- Registration and Credential Repository (RCR): https://ctepcore.nci.nih.gov/rcr/

## 9.2 Ipilimumab

(MDX-010, anti-CTLA-4 antibody, Yervoy™) NSC#732442,

### 9.2.1 Description

Ipilimumab is a fully human immunoglobulin (IgG1κ) specific for human CTLA-4 antigen (CD152). It consists of 4 polypeptide chains, 2 identical heavy chains with 447 amino acids and 2 identical light chains consisting of 215 amino acids. Current NCI sponsored protocols utilize ipilimumab produced and formulated from a transfectoma, Chinese hamster ovary [CHO] cell line. Ipilimumab monoclonal antibody is specific for the CTLA-4 antigen (CD152) expressed on a subset of activated T-cells. CTLA-4 interaction with the B7 molecule, one of its ligands expressed on professional antigen presenting cells, can down-regulate a T-cell response. Ipilimumab is thought to act by blocking the interaction of CTLA-4 with the B7 ligand, resulting in a blockade of the inhibitory effect of T-cell activation that is created by the CTLA-4/B7 interaction.

### 9.2.2 Supplied by:

Ipilimumab is an investigational agent provided by Bristol-Myers Squibb and supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), Cancer Therapy Evaluation Program (CTEP), National Cancer Institute (NCI). **Do NOT use commercially available supply.**

### 9.2.3 Formulation

Ipilimumab injection is supplied as 200 mg/40 mL (5 mg/mL), formulated as a clear to slightly opalescent, colorless to pale yellow, sterile, isotonic aqueous solution (pH of 7) that may contains particles. Each vial contains a small amount of overfill. All vials are Type 1 flint glass vials with gray butyl stoppers and aluminum seals. Inactive ingredients include sodium chloride, TRIS-hydrochloride, diethylenetriamine pentacetic acid, mannitol, polysorbate 80, sodium hydroxide, hydrochloric acid, water for injection, and a small amount of nitrogen as a processing agent.

### 9.2.4 Storage

Store intact vials of ipilimumab refrigerated at 2-8 °C (36-46°F). Protect from light. DO NOT FREEZE OR SHAKE. The formulation contains no preservatives.

If a storage temperature excursion is identified, promptly return ipilimumab to 2°C-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

9.2.5 Solution Preparation

Ipilimumab may be dispensed undiluted or further diluted in 0.9% NaCl Injection, USP or 5% Dextrose Injection, USP to a concentration between 1 mg/mL and 4 mg/mL. Ipilimumab is stable in polyvinyl chloride (PVC), non-PVC/non DEHP (di-(2-ethylhexyl) phthalate) IV bag or glass container. Ipilimumab diluted between 1 mg/mL and 4 mg/mL is stable in polypropylene syringes. Mix GENTLY by inverting several times. **Do not shake.** Vials of ipilimumab for injection do not contain preservatives; the product should be prepared as soon as possible prior to administration using aseptic technique.

9.2.6 Stability

Shelf-life surveillance of the intact vials is ongoing. Prepared solutions of ipilimumab undiluted (5 mg/mL) or diluted with 0.9% sodium chloride are stable for up to 24 hours refrigerated (2 – 8° C) or at room temperature (under room light).

9.2.7 Administration

See Treatment and Dose Modifications sections of the protocol.
Ipilimumab is administered as a 90-minute intravenous infusion using a volumetric pump and a PVC IV infusion set with an in-line, sterile, non-pyrogenic, low-protein-binding filter (0.2 micron to 1.2 micron). Do NOT administer as an intravenous push or bolus. **For administration by syringe pump, the concentration of Ipilimumab must be within the range of 1 mg/mL and 4 mg/mL.**

When administered in combination with nivolumab, infuse nivolumab first followed by ipilimumab on the same day. Use separate infusion set and filters for each infusion.

9.2.8 Ipilimumab Toxicities

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2678 patients.* Below is the CAEPR for Ipilimumab (MDX-010).

**NOTE**: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

| Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678] | | | Specific Protocol Exceptions to Expedited Reporting (SPEER) |
|---|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** | |
| BLOOD AND LYMPHATIC SYSTEM DISORDERS | | | |
| | | Blood and lymphatic system disorders - Other (acquired hemophilia) | |
| CARDIAC DISORDERS | | | |
| | Atrial fibrillation | | |
| | | Myocarditis[50] | |
| | | Pericardial effusion | |
| EAR AND LABYRINTH DISORDERS | | | |
| | Hearing impaired | | |
| ENDOCRINE DISORDERS | | | |
| | Adrenal insufficiency[50] | | |
| | Hyperthyroidism[50] | | |
| | Hypophysitis[50] | | |
| | Hypopituitarism[50] | | |
| | Hypothyroidism[50] | | |
| | Testosterone deficiency[50] | | |
| EYE DISORDERS | | | |
| | Eye disorders - Other (episcleritis)[50] | | |
| | Uveitis[50] | | |
| GASTROINTESTINAL DISORDERS | | | |
| | Abdominal pain | | |
| | Colitis[50] | | ***Colitis[50] (Gr 3)*** |
| | | Colonic perforation[51] | |
| | Constipation | | |
| Diarrhea | | | ***Diarrhea (Gr 3)*** |
| | Enterocolitis | | |
| | Esophagitis | | |
| | | Ileus | |
| Nausea | | | ***Nausea (Gr 3)*** |
| | Pancreatitis[50] | | |
| | Vomiting | | |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | | | |
| | Chills | | |
| Fatigue | | | ***Fatigue (Gr 3)*** |
| | Fever | | ***Fever (Gr 2)*** |
| | | General disorders and administration site conditions - Other (Systemic inflammatory response syndrome [SIRS]) | |
| | | Multi-organ failure | |
| HEPATOBILIARY DISORDERS | | | |
| | Hepatobiliary disorders - Other (hepatitis)[50] | | |
| IMMUNE SYSTEM DISORDERS | | | |
| | Autoimmune disorder[50] | | |
| | | Immune system disorders - Other (GVHD in the setting of allotransplant)[52] | |

| Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678] | | | Specific Protocol Exceptions to Expedited Reporting (SPEER) |
|---|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** | |
| INFECTIONS AND INFESTATIONS | | | |
| | | Infections and infestations - Other (aseptic meningitis)[50] | |
| INJURY, POISONING AND PROCEDURAL COMPLICATIONS | | | |
| | Infusion related reaction | | |
| INVESTIGATIONS | | | |
| | Alanine aminotransferase increased | | |
| | Aspartate aminotransferase increased | | |
| | | Lymphocyte count decreased | |
| | Neutrophil count decreased | | |
| | Weight loss | | |
| METABOLISM AND NUTRITION DISORDERS | | | |
| | Anorexia | | |
| | Dehydration | | |
| | Hyperglycemia | | |
| | | Metabolism and nutrition disorders - Other (exacerbation of pre-existing diabetes mellitus) | |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | | | |
| | Arthralgia | | |
| | Arthritis | | |
| | | Generalized muscle weakness | |
| | Musculoskeletal and connective tissue disorder - Other (polymyositis)[50] | | |
| NERVOUS SYSTEM DISORDERS | | | |
| | | Ataxia | |
| | Facial nerve disorder[50] | | |
| | Guillain-Barre syndrome[50] | | |
| | Headache | | |
| | Myasthenia gravis[50] | | |
| | | Nervous system disorders - Other (immune-mediated encephalitis)[50] | |
| | | Peripheral motor neuropathy | |
| | | Peripheral sensory neuropathy | |
| | Trigeminal nerve disorder | | |
| PSYCHIATRIC DISORDERS | | | |
| | | Psychiatric disorders - Other (mental status changes) | |
| RENAL AND URINARY DISORDERS | | | |
| | Acute kidney injury | | |
| | Renal and urinary disorders - Other (granulomatous tubulointerstitial nephritis) | | |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | | | |
| | Pneumonitis | | |
| | | Respiratory failure | |

| Adverse Events with Possible Relationship to Ipilimumab (MDX-010) (CTCAE 5.0 Term) [n= 2678] | | | Specific Protocol Exceptions to Expedited Reporting (SPEER) |
|---|---|---|---|
| **Likely (>20%)** | **Less Likely (<=20%)** | **Rare but Serious (<3%)** | |
| | | Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia) | |
| | | Respiratory, thoracic and mediastinal disorders - Other (lung infiltration) | |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | | |
| | | Erythema multiforme | |
| | Pruritus | | ***Pruritus (Gr 3)*** |
| Rash maculo-papular | | | ***Rash maculo-papular (Gr 3)*** |
| | Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome) | | |
| | | Stevens-Johnson syndrome | |
| | | Toxic epidermal necrolysis | |
| | Urticaria | | |
| VASCULAR DISORDERS | | | |
| | Hypotension | | |

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Ipilimumab can result in severe and fatal immune-mediated adverse events probably due to T-cell activation and proliferation. These can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune thyroiditis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, and adrenal insufficiency), ocular manifestations (e.g., uveitis, iritis, conjunctivitis, blepharitis, and episcleritis), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome. The majority of these reactions manifested early during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab especially with the initiation of additional treatments.

[3]Late bowel perforations have been noted in patients receiving MDX-010 (ipilimumab) in association with subsequent IL-2 therapy.

[4]Complications including hyperacute graft-versus-host disease (GVHD), may occur in patients receving allo stem cell transplant (SCT) after receiving Ipilimumab (MDX-010). These complications may occur despite intervening therapy between receiving Ipilimumab (MDX-010) and allo-SCT.

[5]In rare cases diplopia (double vision) has occurred as a result of muscle weakness (Myasthenia gravis).

[6]Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL

DISORDERS SOC.

[7]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

**Adverse events reported on Ipilimumab (MDX-010) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Ipilimumab (MDX-010) caused the adverse event:**

**BLOOD AND LYMPHATIC SYSTEM DISORDERS** - Anemia; Blood and lymphatic system disorders - Other (pure red cell aplasia)[50]; Febrile neutropenia
**CARDIAC DISORDERS** - Conduction disorder; Restrictive cardiomyopathy
**EYE DISORDERS** - Extraocular muscle paresis[53]; Eye disorders - Other (retinal pigment changes)
**GASTROINTESTINAL DISORDERS** - Colonic ulcer; Dyspepsia; Dysphagia; Gastrointestinal disorders - Other (gastroenteritis); Gastrointestinal hemorrhage[54]; Proctitis
**GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS** - Flu like symptoms; Non-cardiac chest pain
**HEPATOBILIARY DISORDERS** - Hepatic failure[50]
**IMMUNE SYSTEM DISORDERS** - Allergic reaction
**INFECTIONS AND INFESTATIONS** - Infection[55]
**INVESTIGATIONS** - Creatinine increased; Investigations - Other (rheumatoid factor); Lipase increased; Platelet count decreased; Serum amylase increased; White blood cell decreased
**METABOLISM AND NUTRITION DISORDERS** - Tumor lysis syndrome
**MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS** - Back pain; Joint range of motion decreased; Myalgia; Pain in extremity
**NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)** - Tumor pain
**NERVOUS SYSTEM DISORDERS** - Dizziness; Dysphasia; Ischemia cerebrovascular; Seizure
**PSYCHIATRIC DISORDERS** - Anxiety; Confusion; Depression; Insomnia
**RENAL AND URINARY DISORDERS** - Proteinuria
**RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS** - Allergic rhinitis; Cough; Dyspnea; Laryngospasm
**SKIN AND SUBCUTANEOUS TISSUE DISORDERS** - Alopecia; Dry skin; Hyperhidrosis; Skin hypopigmentation
**VASCULAR DISORDERS** - Flushing; Hypertension; Vascular disorders - Other (temporal arteritis)

**Note**: Ipilimumab (BMS-734016; MDX-010 Transfectoma-derived) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

### 9.2.9 Agent Ordering and Agent Accountability

NCI supplied agents may be requested by the eligible participating investigator (or their authorized designee) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that agent be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained.) The CTEP assigned protocol number must be used for ordering all CTEP supplied investigational agents. The responsible investigator at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

### 9.2.10 Clinical Drug Request and Investigator Brochure Availability

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability call or email PMB anytime. Refer to the PMB's website for specific policies and guidelines related to agent management. Questions about IB access may be directed to the PMB IB coordinator via email.

The current versions of the IBs for the agents will also be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Questions about IB access may be directed to the PMB IB coordinator via email.

#### 9.2.11 Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

#### 9.2.12 Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB policies and guidelines: http://ctep.cancer.gov/branches/pmb/agent_management.htm
- PMB Online Agent Order Processing (OAOP) application: https://ctepcore.nci.nih.gov/OAOP
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP Associate Registration and IAM account help: ctepreghelp@ctep.nci.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575
  Monday through Friday between 8:30 am and 4:30 pm (ET)
- PMB IB Coordinator: IBcoordinator@mail.nih.gov
- Registration and Credential Repository (RCR): https://ctepcore.nci.nih.gov/rcr/

## 10.0 CRITERIA FOR REMOVAL FROM PROTOCOL THERAPY AND OFF STUDY CRITERIA

### 10.1 Criteria for Removal from Protocol Therapy

a) Clinical (including physical examination or serum tumor markers) or radiographic evidence of progressive disease of greater than 40% increase from baseline target lesions selected according to RECIST criteria (See Section 12.0).
b) Clinical (including physical examination or serum tumor markers) or radiographic evidence of progressive disease > 12 weeks after start of protocol therapy.
c) Adverse Events requiring removal from protocol therapy (See Sections 5.4 and 6.0).
d) Immune adverse events requiring removal from protocol therapy (See Section 5.4

and Section 6.0) which in the opinion of the treating physician are consistent with acute or chronic GVHD requiring systemic immunosuppression.

e) Refusal of further protocol therapy by patient/parent/guardian
f) Non-compliance that in the opinion of the investigator does not allow for ongoing participation.
g) Physician determines it is not in the patient's best interest.
h) Repeated eligibility laboratory studies (CBC with differential, bilirubin, ALT (SGPT) or serum creatinine) are outside the parameters required for eligibility prior to the start of protocol therapy (See Section 8.1).
i) Study is terminated by Sponsor.
j) Pregnancy

**Patients who are removed from protocol therapy during cycle 1 (Part A and B) or during cycles 1 and 2 (Parts C, D, or E) should continue to have the required observations in Section 8.1 until the originally planned end of the cycle or until all adverse events have resolved per Section 13.4.4, whichever happens LATER. The only exception is with documentation of the patient's withdrawal of consent. Patients who are removed from protocol therapy in subsequent cycles should have the necessary observations to ensure adequate clinical care.**

Patients who are off protocol therapy are to be followed as described in Section 8.1.1 until they meet the criteria for Off Study (see below). Ongoing adverse events, or adverse events that emerge after the patient is removed from protocol therapy, but within 100 days of the last dose of investigational agent, must be followed and reported via RAVE and CTEP-AERS (if applicable). Serious adverse events that occur during the follow-up period (more than 30 days after the last administration of investigational agent) and have an attribution of possible, probable, or definite require reporting per Footnote 1 of Table A. Follow-up data will be required unless consent is withdrawn.

### 10.2 Off Study Criteria

a) 100 days after the last dose of the investigational agent (Patients on Part A or C that are not enrolled at the MTD; Patients on Part E).
b) The fifth anniversary of the date the patient was enrolled on this study (All patients enrolled at the determined MTD)
c) Death
d) Lost to follow-up
e) Withdrawal of consent for any further required observations or data submission.
f) Enrollment onto another COG therapeutic (anti-cancer) study
g) Patient did not receive protocol treatment after study enrollment

## 11.0 STATISTICAL AND ETHICAL CONSIDERATIONS

### 11.1 Sample Size and Study Duration

Part A: Phase 1 (single agent) - patients with solid tumors, excluding brain and CNS tumors
Part B: Patients with relapsed or refractory neuroblastoma (B1)
Patients with relapsed or refractory osteosarcoma (B2)
Patients with relapsed or refractory rhabdomyosarcoma (B3)
Patients with relapsed or refractory Ewing Sarcoma or Peripheral PNET (B4)

Patients with relapsed or refractory Hodgkin Lymphoma (B5)
Patients with relapsed or refractory Non-Hodgkin Lymphoma (B6)
Patients with unresectable melanoma or metastatic melanoma or relapsed melanoma or refractory melanoma (B7)
Patients with relapsed or refractory neuroblastoma (MIBG evaluable without RECIST evaluable disease) (B8)

Part C: Phase 1 (combination) - patients with solid tumors, excluding brain and CNS tumors

Part D: Patients with relapsed or refractory neuroblastoma (D1)
Patients with relapsed or refractory osteosarcoma (D2)
Patients with relapsed or refractory rhabdomyosarcoma (D3)
Patients with relapsed or refractory Ewing Sarcoma or Peripheral PNET (D4)
Patients with relapsed or refractory Non-Hodgkin Lymphoma (D5)
Patients with relapsed or refractory neuroblastoma (MIBG evaluable without RECIST evaluable disease) (D6)

Part E: Patients with relapsed or refractory rhabdomyosarcoma (E3)
Patients with relapsed or refractory Ewing Sarcoma or Peripheral PNET (E4)

| Part | Minimum | Maximum | Estimated Duration |
|---|---|---|---|
| A | 4 | 36 (20% inevaluable) | 2-36 months |
| B | 60 | 170 (10% inevaluable) | 1-2.75 years |
| C | 2 | 36 (20% inevaluable | 2-36 months |
| D | 0 | 110 (10% inevaluable) | 1-2.75 years |
| E | 2 | 23 (10% inevaluable) | 1-23 months |

Part A will enroll a minimum of 2 evaluable patients at each dose level for determination of MTD/Recommended Phase 2 dose (RP2D) of single agent nivolumab. Once the MTD or recommended Phase 2 dose has been defined in Part A, Parts B and C will open concurrently. Part C will enroll a minimum of 2 evaluable patients at each dose level for determination of MTD/Recommended Phase 2 dose (RP2D) of the combination nivolumab plus ipilumumab. Up to 6 additional patients with relapsed/refractory solid tumors without restrictions on heme evaluability may be enrolled at the RP2D determined in Part A and Part C to acquire PK data in a representative number of young patients (i.e. patients < 12 years old) at the MTD/RP2D in each Part. Once the dose-escalation portion of Part A is completed, cohorts that are open concurrently for eligible patients (including Parts B and C and potential PK expansion cohorts) may be selected at the treating physician's discretion pending slot availability.

The single-agent recommended Phase 2 dose of Part A was determined to be 3 mg/kg nivolumab.

The recommended Phase 2 dose of nivolumab in combination with ipilimumab from Part C was determined to be 3 mg/kg nivolumab and 1 mg/kg ipilimumab.

In the event a cohort in a given disease group in Part B is completed after Stage 1, a corresponding cohort in the same disease group will open for select disease types in Part D at the RP2D determined in Part C.

A minimum of 4 patients will be enrolled in Part A, and a maximum of 36 patients are possible. A maximum of 36 patients could occur in the unlikely scenario that each dose level is expanded to 12 patients per Section 11.2.2, and a 20% inevaluable rate occurs. A minimum of 2 patients will be enrolled in Part C, and a maximum of 36 patients is possible similar to Part A. Review of the enrollment rate into previous COG new agent studies

indicates that 1-2 patients per month are available, which will permit completion of Part A within 11-22 months and Part C within 14-29 months.

Review of patient accrual onto recent Phase 2 solid tumor studies indicates the following entry rates for the various tumors under study can be achieved for Parts B, D and E:

| **Disease Group/Part** | **Patients/ Year** |
|---|---|
| Neuroblastoma | 10-12 |
| Osteosarcoma | 10-12 |
| Rhabdomyosarcoma | 8-10 |
| Ewing Sarcoma | 10-12 |
| Hodgkin Lymphoma | 10-12 |
| Non-Hodgkin Lymphoma | 10-12 |
| Melanoma | 3-4 |

A minimum of 10 evaluable patients per disease group will be enrolled in Parts B1-B6 and B8 and Parts D1-6. A maximum 22 per disease group will be enrolled in these cohorts. A non-statistical access cohort for the rare diagnosis of melanoma (Part B7) will remain open to enrollment until Parts B1-B6, B8 and Parts D1-6 are complete. If at any time after enrollment of three patients, cycle 1 DLT occurs in ≥ 33% in the melanoma cohort, enrollment to that cohort will be closed. There will be no required minimum or maximum accrual limits for Part B7; however, given the accrual rate of 3-4 patients/year a minimum of 0 evaluable patients and a maximum of 16 patients is anticipated to enroll in this disease group assuming the maximum study duration of 4 years. The maximum enrollment assumes a 10% inevaluable rate. Therefore, a minimum of 60 patients and a maximum of 170 patients will be enrolled in Part B. A maximum of 110 patients will be enrolled in Part D.

As cohort D5 investigates the combination of nivolumab and ipilimumab in patients who may be post-allogeneic BMT, if at any time after 3 enrollments, acute or chronic GVHD requiring systemic immunosuppression occurs in ≥ 33% of patients, the strata will be closed to accrual.

A minimum of 6 children < 12 years of age and at least 6 children ≥ 12 years of age will be evaluated for tolerability and systemic exposure of single agent nivolumab RP2D in Parts A and B. If less than 6 patients < 12 years of age are enrolled upon completion of accrual to Part B, additional children (any histology) will be added to Part A studied to reach the 6 patient minimum.

Update: As of Amendment #8 a total of 132 patients have been enrolled:
Part A: 13 patients
Part B: B1: 10 patients
B2: 10 patients
B3: 11 patients
B4: 10 patients
B5: 12 patients
B6: 10 patients
B7: 1 patient
B8: 8 patients
Part C: 18 patients
Part D: D2: 10 patients

D3: 10 patients
D4: 9 patients

A total 132 patients have enrolled into ADVL1412 to date. A minimum of 3 evaluable patients will be enrolled in Part E, and a maximum of 23 patients will be enrolled overall. The maximum enrollment assumes a 10% inevaluable rate, and this part of the study is anticipated to be completed within 2-23 months. Therefore, the maximum number of patients for the entire study is expected to be 155 with amendment 8, and this entire protocol will have been completed within 5.5 years.

## 11.2 Definitions

### 11.2.1 Evaluable For Adverse Events

For all parts of the study, any patient who receives at least one dose of the study drug(s) and who experiences a dose-limiting toxicity is considered evaluable for Adverse Events. In addition, for the dose-escalation portions (Parts A and C), during Cycle 1, patients must have the appropriate toxicity monitoring studies performed to be considered evaluable for dose limiting toxicity. In Parts A and C, patients who do not have DLT and do not receive at least 85% of the prescribed dose within the first 28 days (the DLT observation period) for reasons other than toxicities (e.g. progressive disease) will not be considered evaluable for toxicity and will be replaced.

### 11.2.2 Maximum Tolerated Dose

- The MTD will be the maximum dose at which fewer than one-third of patients experience DLT (See Section 5.4) during Cycle 1 of therapy.
- In the unlikely event that two DLTs observed out of 6 evaluable patients are different classes of Adverse Effects (e.g. hepatotoxicity and myelosuppression), AND all of the following conditions are met, expansion of the cohort to 12 patients will be considered:
  - One of the DLTs does not appear to be dose-related
  - The Adverse Effects are readily reversible
  - The study chair, DVL statistician, DVL committee chair or vice chair, and IND sponsor all agree that expansion of the cohort is acceptable

  If fewer than 1/3 of patients in the expanded cohort experience dose-limiting toxicities, the dose escalation can proceed.
- The DLTs observed in the pharmacokinetic (PK) expansion cohort will be counted towards the total number of DLTs observed at the MTD during the dose escalation portion of the study. If ≥ 1/3 of the cohort of patients at the MTD (during the dose escalation plus the PK expansion) experience DLT then the MTD will be exceeded.

### 11.2.3 Evaluability for Response

Any patient who is enrolled who meets eligibility criteria for Parts B, D or E and receives at least one dose of protocol therapy will be considered evaluable for response provided: (1) the patient demonstrates progressive disease or death while on protocol therapy (note: if the institutional investigator determines that the

patient has progressed based on clinical or laboratory evidence, he/she may opt not to confirm this finding radiographically); or (2) the patient is observed on protocol therapy for at least one cycle and the tumor is not removed surgically prior to the time complete response or partial response is confirmed, or (3) the patient demonstrates a complete or partial response as confirmed according to protocol criteria. Patients who demonstrate a complete or partial response confirmed by central review will be considered to have experienced a response for the application of the rule given in Section 11.4. Two objective status determinations are required to confirm best response (Section 12.6). All other patients will be considered non-responders. All patients considered to have a response (CR or PR) must have imaging studies reviewed centrally at the COG. Centers will be notified by the COG about requests for scans of patients with stable disease. See Section 8.2 regarding image submission instructions. The central review by COG will be provided as the final reviewed assessment of response when such becomes available. Patients inevaluable for response will be considered for replacement.

## 11.3 Determination of Recommended Phase 2 Dose for Nivolumab as a Single Agent (Part A):

- Part A will evaluate a single dose level (3 mg/kg). If 1 or fewer of 6 evaluable patients experience DLT and at least 5/6 of patients achieve a Cmin of at least 10 mcg/ml, the 3 mg/kg dose level will be the RP2D and we will conclude that children are not experiencing significantly less exposure than adults treated at the same dose. If however, < 5 of 6 patients achieve a Cmin of at least 10 mcg/ml, consideration will be given to a protocol amendment to test a higher dose level in Part A. Note that Cmin levels > 30 mcg/ml will not, in and of itself result in a change in protocol design, unless excess toxicity is observed.
- If 2 or more of the 6 patients experience DLT at the 3 mg/kg dose level, then the MTD has been exceeded and the 1 mg/kg dose level will be evaluated. If 1 or fewer of 6 patients experience DLT at the 1 mg/kg dose level and at least 5/6 of patients achieve a Cmin of at least 10 mcg/ml, then this dose level will be the RP2D. Once the RP2D for nivolumab as a single agent is determined, Part B and Part C will open simultaneously.

Update: The single-agent recommended Phase 2 dose of Part A was determined to be 3 mg/kg nivolumab.

## 11.4 Phase 2 Evaluation of Nivolumab (for Part B):

Study Design

The best response of disease to nivolumab will be examined separately for each of the tumor strata: neuroblastoma, osteosarcoma, rhabdomyosarcoma, ewing sarcoma, Hodgkin lymphoma, and non-Hodgkin lymphoma with the goal of enrolling at least evaluable 10 patients per tumor type. Given the activity seen in adult patients with melanoma, an additional non-statistical cohort for patients with unresectable, metastatic, relapsed or refractory melanoma will be open to accrual as Part B7 to preliminarily define the antitumor effects of nivolumab within the confines of a phase 1/2 study and will remain open for enrollment until Parts B1-B6, B8 are complete. Given the rarity of the disease in the pediatric population the study will not remain open to complete this cohort if all other strata have completed accrual. If at any time after enrollment of three patients, cycle 1 DLT occurs in ≥

33% in the melanoma cohort, enrollment to that cohort will be closed. If at least 12 patients are treated at Part B7, evaluation of accrual rate and toxicities may be discussed with the sponsor to determine if any changes in study design are required. The following Simon's optimal two stage design[56] will be used for Parts B1-B6, B8.

| | Cumulative Number of Responses | Decision |
|---|---|---|
| Stage 1: Enter 10 patients | 0 | Terminate the stratum: agent ineffective |
| | 1 or more | Inconclusive result, continue stratum (proceed to stage 2) |
| Stage 2: Enter 10 additional patients | 2 or less | Terminate the stratum: agent ineffective |
| | 3 or more | Terminate the stratum: agent effective |

In the event that a cohort in a given disease group in Part B is completed after Stage 1 because no responses are observed, a cohort in the same disease group will open to up to 10 evaluable patients in Part D, at the RP2D of nivolumab in combination with ipilimumab as determined in Part C: 3 mg/kg nivolumab and 1 mg/kg ipilimumab (See Section 11.6).

Nivolumab will not be considered of sufficient interest for further evaluation in a disease category if the true response rate is 5% and of sufficient activity if the true response rate is 25%. If nivolumab has a true response rate of 5%, the rule described above will identify it of sufficient activity for further study with probability 0.07 (type I error), and the trial will have an expected sample size of 14 with 60% probability of early termination. If nivolumab has a true response rate of 25%, the rule described above will identify it of sufficient activity for further study with probability 0.88 (power against the alternative hypothesis P = 0.25).

Children with a target diagnosis and measurable or MIBG evaluable disease who are enrolled on Part A and receive the RP2D will be considered evaluable for disease response in Part B.

If cycle 1 DLT occurs in ≥ 33% of evaluable patients in a cohort of Part B with at least 3 evaluable patients, the maximum tolerated dose will have been exceeded in this tumor type and the cohort will be closed to further enrollment.

Response in all patients with solid tumors will be determined according to RECIST as defined in the protocol as either complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD), or as described in Section 12.0 for other categories of responses assessment, and reported as final results. A report on the efficacy assessment will be posted on the completed disease stratum as part of the semi-annual study committee meeting book report.

Method of Analysis

Response criteria are described in Section 12.0. Response rates will be calculated separately for each of the tumor strata as the percent of patients whose best response is a CR or PR and confidence intervals will be constructed according to the method of Chang.[57] A responder is defined as a patient who achieves a best confirmed response (as defined in Section 12.6) of PR or CR on the study and includes pseudo-progressive disease. Response is defined relative to baseline disease.

11.5 **Dose Escalation and Determination of Recommended Phase 2 Dose for Nivolumab plus Ipilimumab (Part C):**

The rolling six phase 1 trial design will be used for the conduct of Part C of this study.[49] Two to six patients can be concurrently enrolled onto a dose level, dependent upon (1) the number of patients enrolled at the current dose level, (2) the number of patients who have experienced DLT at the current dose level, and (3) the number of patients entered but with tolerability data pending at the current dose level. Accrual is suspended when a cohort of six has enrolled or when the study endpoints have been met.

Dose level assignment is based on the number of participants currently enrolled in the cohort, the number of DLTs observed, and the number of participants at risk for developing a DLT (i.e., participants enrolled but who are not yet assessable for toxicity). For example, when three participants are enrolled onto a dose cohort, if toxicity data is available for all three when the fourth participant entered and there are no DLTs, the dose is escalated and the fourth participant is enrolled to the subsequent dose level. If data is not yet available for one or more of the first three participants and no DLT has been observed, or if one DLT has been observed, the new participant is entered at the same dose level. Lastly, if two or more DLTs have been observed, the dose level is de-escalated. This process is repeated for participants five and six. In place of suspending accrual after every three participants, accrual is only suspended when a cohort of six is filled. When participants are inevaluable for toxicity, they are replaced with the next available participant if escalation or de-escalation rules have not been fulfilled at the time the next available participant is enrolled onto the study.

The following table provides the decision rules for enrolling a patient at (i) the current dose level (ii) at an escalated dose level, (iii) at a de-escalated dose level, or whether the study is suspended to accrual:

| # Pts Enrolled | # Pts with DLT | # Pts without DLT | # Pts with Data Pending | *Decision* |
|---|---|---|---|---|
| 2 | 0 or 1 | 0, 1 or 2 | 0, 1 or 2 | Same dose level |
| 2 | 2 | 0 | 0 | De-escalate* |
| 3 | 0 | 0, 1 or 2 | 1, 2 or 3 | Same dose level |
| 3 | 1 | 0, 1 or 2 | 0, 1 or 2 | Same dose level |
| 3 | 0 | 3 | 0 | Escalate** |
| 3 | ≥ 2 | 0 or 1 | 0 or 1 | De-escalate* |
| 4 | 0 | 0, 1, 2 or 3 | 1, 2, 3 or 4 | Same dose level |
| 4 | 1 | 0, 1, 2 or 3 | 0, 1, 2 or 3 | Same dose level |
| 4 | 0 | 4 | 0 | Escalate** |
| 4 | ≥ 2 | 0, 1 or 2 | 0, 1 or 2 | De-escalate* |
| 5 | 0 | 0, 1, 2, 3 or 4 | 1, 2, 3, 4 or 5 | Same dose level |

| | | | | |
|---|---|---|---|---|
| 5 | 1 | 0, 1, 2, 3 or 4 | 0, 1, 2, 3 or 4 | Same dose level |
| 5 | 0 | 5 | 0 | Escalate** |
| 5 | ≥ 2 | 0, 1, 2 or 3 | 0, 1, 2 or 3 | De-escalate* |
| 6 | 0 | 0, 1, 2, 3, or 4 | 2, 3, 4, 5 or 6 | Suspend |
| 6 | 1 | 0, 1, 2, 3 or 4 | 0, 1, 2, 3 or 4 | Suspend |
| 6 | 0 or 1 | 5 or 6 | 0 or 1 | Escalate** |
| 6 | ≥ 2 | 0, 1, 2, 3 or 4 | 0, 1, 2, 3 or 4 | De-escalate* |

* If six patients already entered at next lower dose level, the MTD has been defined. If the lowest dose level is not tolerated, that part will close to accrual and discussed with sponsor.
**If final dose level has been reached, the recommended dose has been reached.

If two or more of a cohort of up to six patients experience DLT at a given dose level, then the MTD has been exceeded and dose escalation will be stopped (see Section 11.2.2 for exception to rule).

In addition to determination of the MTD, a descriptive summary of all toxicities will be reported.

## 11.6 Phase 2 Evaluation of Nivolumab (3 mg/kg) in Combination with Ipilimumab (1 mg/kg) (for Part D):

In the event that a cohort in a given disease group in Part B is completed after Stage 1 because no responses are observed, a corresponding cohort will open in the same disease group for select disease types to an initial cohort of up to 10 evaluable patients in Part D, at the RP2D of nivolumab in combination with ipilimumab as determined in Part C: 3 mg/kg nivolumab and 1 mg/kg ipilimumab.

### 11.6.1 Study Design

The best response of disease to nivolumab in combination with ipilimumab will be examined separately for each of the tumor strata that are expanded from Part B. The following Simon's optimal two stage design[56] will be used for Parts D1-6.

| | Cumulative Number of Responses | Decision |
|---|---|---|
| Stage 1: Enter 10 patients | 0 | Terminate the stratum: agent ineffective |
| | 1 or more | Inconclusive result, continue stratum (proceed to stage 2) |
| Stage 2: Enter 10 additional patients | 2 or less | Terminate the stratum: agent ineffective |
| | 3 or more | Terminate the stratum: agent effective |

Nivolumab in combination with ipilimumab will not be considered of sufficient interest for further evaluation in a disease category if the true response rate is 5% and of sufficient activity if the true response rate is 25%. If nivolumab in combination with ipilimumab has a true response rate of 5%, the rule described above will identify it of sufficient activity for further study with probability 0.07 (type I error), and the trial will have an expected sample size of 14 with 60% probability of early termination. If nivolumab in combination with ipilimumab has a true response rate of 25%, the rule described above will identify it of sufficient activity for further study with probability 0.88 (power against the alternative hypothesis P = 0.25).

Children with a target diagnosis and measurable or MIBG evaluable disease who are enrolled on Part C and receive the RP2D will be considered evaluable for disease response in Part D. The number of patients needed to evaluate any cohort in part D would therefore be reduced by the number of patients treated and evaluable for response in part C,

If cycle 1 DLT occurs in ≥ 33% of evaluable patients in a cohort of Part D with at least 3 evaluable patients, the maximum tolerated dose will have been exceeded in this tumor type and the cohort will be closed to further enrollment.

Response in all patients with solid tumors will be determined according to RECIST as defined in the protocol as either complete response (CR), partial response (PR), stable disease (SD) or progressive disease (PD), or as described in Section 12.0 for other categories of responses assessment, and reported as final results. A report on the efficacy assessment will be posted on the completed disease stratum as part of the semi-annual study committee meeting book report.

Method of Analysis
Response criteria are described in Section 12.0. Response rates will be calculated separately for each of the tumor strata as the percent of patients whose best response is a CR or PR and confidence intervals will be constructed according to the method of Chang.[57] A responder is defined as a patient who achieves a best confirmed response (as defined in Section 12.6) of PR or CR on the study and includes pseudo-progressive disease. Response is defined relative to baseline disease.

## 11.7 Phase 2 Evaluation of Nivolumab (1 mg/kg) in Combination with Ipilimumab (3 mg/kg) (for Part E):

### 11.7.1 Study Design

The Simon's optimal two stage design[47] will be used for Part E to assess response in rhabdomyosarcoma (E3) and Ewing/Peripheral PNET pediatric patients (E4). All patients enrolled into either E3 or E4 will be combined for assessment of response and toxicity. Assuming that the study does not stop early for dose limiting toxicity, a total of 10 response-evaluable patients will be enrolled into Stage 1. This will include at least 4 patients each in parts E3 and E4. If at least 1 response is observed among 10 evaluable patients, then stage 2 will open for enrollment. A total of 10 more response-evaluable patients will then be enrolled into Stage 2 including at least 4 more patients each in parts E3 and E4. Otherwise, the study will close with stage 1 and the study will conclude that the agent does not elicit sufficient response.

The following Simon's optimal two-stage design will be used to assess response in Part E.

| | Cumulative Number of Responses | Decision |
|---|---|---|
| Stage 1: Enter 10 patients | 0 | Terminate the stratum: agent ineffective |
| | 1 or more | Inconclusive result, continue stratum |

| | | |
|---|---|---|
| | | (proceed to stage 2) |
| Stage 2: Enter 10 additional patients | 2 or less | Terminate the stratum: agent ineffective |
| | 3 or more | Terminate the stratum: agent effective |

The combination of Nivolumab (1 mg/kg) and Ipilimumab (3mg/kg) will not be considered of sufficient interest for further evaluation among Rhabdomyosarcoma and Ewing/Peripheral PNET patients if the true response rate is ≤ 5% and of sufficient activity if the true response rate is ≥25%. If this combination has a true response rate of 5%, the rule described above will identify it of sufficient activity for further study with probability 0.07 (type I error), and the trial will have an expected sample size of 14 with 60% probability of early termination. If the combination has a true response rate of 25%, the rule described above will identify it of sufficient activity for further study with probability 0.88 (power against the alternative hypothesis P = 0.25). A maximum of 23 patients will be enrolled into Part E allowing for 10% inevaluability.

If at least one Cycle 1 dose limiting toxicity occurs among the first 10 patients or 4 patients with dose limiting toxicities among 20 patients, then the study will close and conclude that the dose level is too toxic. This rule will provide >=89% power to terminate the study in stage 1 and >=90% power overall to terminate the study due to excessive Cycle 1 toxicity when the true cycle 1 toxicity is >=20%. Otherwise, the study will continue per the 10+10 Simon two-stage design. The overall type 1 error rate for this rule is 40% if the true Cycle 1 toxicity is 0.05 and 66% if the true toxicity is 0.10.

All grade 3, 4, and 5 toxicity attributed to protocol therapy will reviewed weekly by the study committee and discussed during the scheduled monthly sponsor calls in order to determine the need for any changes. Consideration to open the second stage will be discussed by all approved parties (i.e. DSMC, NCI) following the release of the aggregated data for all events.

### 11.7.2 Method of Analysis

Response criteria are described in Section 12.0. Response rates will be calculated for the combined cohort as the percent of patients whose best response is a CR or PR and confidence intervals will be constructed according to the method of Chang.[48] A responder is defined as a patient who achieves a best confirmed response (as defined in Section 12.6) of PR or CR on the study and includes pseudo-progressive disease. Response is defined relative to baseline disease.

## 11.8 Inclusion of Children, Women and Minorities

The study is open to all participants regardless of gender or ethnicity. Review of accrual to past COG studies of new agents demonstrates the accrual of both genders and all NIH-identified ethnicities to such studies. Efforts will be made to extend the accrual to a representative population, but in a Phase 1 trial which will accrue a limited number of patients, a balance must be struck between patient safety considerations and limitations on the number of individuals exposed to potentially toxic or ineffective treatments on the one hand and the need to explore gender, racial, and ethnic aspects of clinical research on the other. If differences in outcome that correlate to gender, racial, or ethnic identity are noted,

accrual may be expanded or additional studies may be performed to investigate those differences more fully.

### 11.9 Pharmacokinetic and Correlative Studies and Response Analysis

A descriptive analysis of pharmacokinetic (PK) parameters of nivolumab will be performed to define systemic exposure, drug clearance, and other pharmacokinetic parameters. The PK parameters will be summarized with simple summary statistics, including means, medians, ranges, and standard deviations (if numbers and distribution permit).

While the primary aim of this study is to define the recommended phase 2 dose of nivolumab (or nivolumab plus ipilimumab), patients will have disease evaluations performed as indicated in Section 8.1. Disease response will be assessed according to RECIST criteria for patients with solid tumors, and will be reported descriptively.

In addition, Part B will evaluate the activity of nivolumab in expanded cohorts of patients with neuroblastoma, osteosarcoma, rhabdomyosarcoma, Ewing sarcoma, Hodgkin lymphoma, non-Hodgkin lymphoma. In the melanoma cohort (Part B7), toxicities and disease response will be reported descriptively.

Pharmacodynamic studies will evaluate the degree of PD1 occupancy rate on peripheral blood T cells pre- and post-therapy using flow cytometry. Anti-drug antibody analyses will be measured by Bristol-Myers Squibb.

PD-L1 expression will be analyzed in an exploratory fashion, both using a binary scale and using a continuous scale to evaluate whether there are correlations between PD-L1 expression and antitumor effects.

Biomarkers, including those identified in the secondary objectives, will be evaluated for association with outcome, overall and by tumor type. All of these analyses will be descriptive and exploratory and hypotheses generating in nature.

## 12.0 EVALUATION CRITERIA

### 12.1 Common Terminology Criteria for Adverse Events (CTCAE)

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

### 12.2 Response Criteria for Patients with Solid Tumors

See the table in section 8.0 for the schedule of tumor evaluations. In addition to the scheduled scans, a confirmatory scan should be obtained at the end of the subsequent cycle following initial documentation of objective response.

Response and progression will be evaluated in this study using the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Key points are that 5 target lesions are identified and that changes in the *largest* diameter (unidimensional measurement) of the tumor lesions but the *shortest* diameter of malignant lymph nodes are used in the RECIST v 1.1 criteria.

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

- In the judgment of the treating clinician, the patient does not show evidence for rapid disease progression or the patient has shown evidence for clinical benefit.
- There is no decrease in performance status.
- The patient is tolerating the study drug and there has been no DLT.
- Continued treatment with nivolumab alone or in combination with ipilimumab will not delay an imminent intervention required to prevent a serious complications (e.g. CNS metastases which require radiation therapy or surgery).

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

Definitions

12.2.2.1 Evaluable for objective response:
Eligible patients who receive at least one dose of protocol therapy will be considered evaluable for response. Evaluable patients who demonstrate a complete or partial response confirmed by central review before receiving non-protocol anti-cancer therapy will be considered a responder. All other evaluable patients will be considered non-responders.

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

Disease Parameters

12.2.3.1 Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥ 20 mm by chest x-ray, as ≥ 10 mm with CT scan, or ≥10

mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

12.2.3.2 Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

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

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts. 'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

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

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

Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or

calipers.

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

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

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

12.2.4.3 Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans). Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans.

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

12.2.4.5 Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

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

Cytology should be obtained if an effusion appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease.

12.2.4.7 FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET

scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

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

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

Response Criteria for Patients with Solid Tumor and Measurable Disease

#### 12.2.5.1 Evaluation of Target Lesions

| | |
|---|---|
| Complete Response (CR): | Disappearance of all target and non-target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm. If immunocytology is available, no disease must be detected by that methodology. Normalization of urinary catecholamines or other tumor markers if elevated at study enrollment (for patients with neuroblastoma). |
| Partial Response (PR): | At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters |
| Progressive Disease (PD): | At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression. See Section 12.2.1 for exception). Note: in presence of SD or PR in target disease but unequivocal progression in non-target or non-measurable disease, the patient has PD if there is an overall level of substantial worsening in non-target disease such that the overall tumor burden has increased sufficiently to merit discontinuation of therapy. |
| Stable Disease (SD): | Neither sufficient shrinkage to qualify for PR nor |

sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

#### 12.2.5.2 **Evaluation of Non-Target Lesions**

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

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

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

Progressive Disease (PD): Appearance of one or more new lesions (. See Section 12.2.1 for exception) and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Overall Best Response Assessment
Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.6 from a sequence of overall response assessments.

### 12.3 **Response Criteria for Patients with Solid Tumors and Evaluable Disease**

Evaluable Disease
The presence of at least one lesion, with no lesion that can be accurately measured in at least one dimension. Such lesions may be evaluable by nuclear medicine techniques, immunocytochemistry techniques, tumor markers or other reliable measures.

Complete Response
Disappearance of all evaluable disease.

Partial response
Partial responses cannot be determined in patients with evaluable disease

Stable Disease (SD)
That which does not qualify as Complete Response (CR), Partial Response (PR), or Progressive Disease.

Progressive Disease
The appearance of one or more new lesions or evidence of laboratory, clinical, or radiographic progression. See Section 12.2.1 for exception.

Overall Best Response Assessment
Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined as outlined in Section 12.6 from a sequence of overall response assessments.

## 12.4 Response Criteria for Neuroblastoma Patients with MIBG Positive Lesions

### 12.4.1 MIBG Positive Lesions

Patients who have a positive MIBG scan at the start of therapy will be evaluable for MIBG response. The use of $^{123}$I for MIBG imaging is recommended for all scans. If the patient has only one MIBG positive lesion and that lesion was radiated, a biopsy must be done at least 28 days after radiation was completed and must show viable neuroblastoma.

### 12.4.2 The following criteria will be used to report MIBG response by the treating institution:

Complete response: Complete resolution of all MIBG positive lesions
Partial Response: Resolution of at least one MIBG positive lesion, with persistence of other MIBG positive lesions
Stable disease: No change in MIBG scan in number of positive lesions
Progressive disease: Development of new MIBG positive lesions

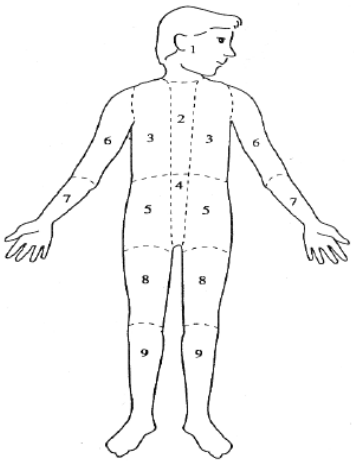
### 12.4.3 The response of MIBG lesions will be assessed on central review using the Curie scale[14] as outlined below. Central review responses will be used to assess efficacy for study endpoint. See Section 8.2.1 for details on transferring images to the Imaging Research Center.

NOTE: This scoring should also be done by the treating institution for end of course response assessments.

The body is divided into 9 anatomic sectors for osteomedullary lesions, with a 10$^{th}$ general sector allocated for any extra-osseous lesion visible on MIBG scan**.** In each region, the lesions are scored as follows. The **absolute extension score** is graded as:

0 = no site per segment,
1 = 1 site per segment,
2 = more than one site per segment,
3 = massive involvement (>50% of the segment).

The **absolute score** is obtained by adding the score of all the segments. See diagram of sectors below:




The **relative score** is calculated by dividing the absolute score at each time point by the corresponding pre-treatment absolute score. The relative score of each patient is calculated at each response assessment compared to baseline and classified as below:

1. **Complete response:** all areas of uptake on MIBG scan completely resolved. If morphological evidence of tumor cells in bone marrow biopsy or aspiration is present at enrollment, no tumor cells can be detected by routine morphology on two subsequent bilateral bone marrow aspirates and biopsies done at least 21 days apart to be considered a **Complete Response**.
2. **Partial response**: Relative score ≤ 0.2 (lesions almost disappeared) to ≤ 0.5 (lesions strongly reduced).
3. **Stable disease**: Relative score > 0.5 (lesions weakly but significantly reduced) to 1.0 (lesions not reduced).
4. **Progressive disease**: New lesions on MIBG scan.

12.4.4 Overall Best Response Assessment

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined from the sequence of the overall response assessments as described in Table 5 in Section 12.6.

## 12.5 Response Criteria for Neuroblastoma Patients with Bone Marrow Involvement

Bone Marrow Involvement

Bone marrow obtained within 28 days prior to study enrollment with tumor cells seen on routine morphology (not by immunohistochemical staining only) of bilateral aspirate or biopsy on one bone marrow sample.

Bone Marrow responses are determined by H&E Staining of bilateral bone marrow biopsies and aspirates.

Complete Response: No tumor cells detectable by routine morphology on 2 consecutive bilateral bone marrow aspirates and biopsies performed at least 21 days apart. Normalization of urinary catecholamines or other tumor markers if elevated at study enrollment.

Progressive Disease: Patients who enroll with neuroblastoma in bone marrow

by morphology have progressive disease if there is a doubling in the amount of tumor in the marrow AND a minimum of 25% tumor in bone marrow by morphology. (For example, a patient entering with 5% tumor in marrow by morphology must increase to ≥ 25% tumor to have progressive disease; a patient entering with 30% tumor must increase to > 60%).

Patients who enroll without evidence of neuroblastoma in bone marrow will be defined as having progressive disease if tumor is detected in 2 consecutive bone marrow biopsies or aspirations done at least 21 days apart.

Stable Disease: Persistence of tumor in bone marrow that does not meet the criteria for either complete response or progressive disease.

Overall Best Response Assessment

Each patient will be classified according to his "best response" for the purposes of analysis of treatment effect. Best response is determined from the sequence of the overall response assessments as described in Section 12.6.

## 12.6 Best Response

**Evaluation of Best Overall Response**

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

Table 1: For Patients with Measurable Disease (i.e., Target Disease)

| Target Lesions | Non-Target Lesions | New Lesions | Overall Response | Best Overall Response when Confirmation is Required* |
|---|---|---|---|---|
| CR | CR | No | CR | ≥ 28 days Confirmation** |
| CR | Non-CR/Non-PD | No | PR | ≥ 28 days Confirmation** |
| CR | Not evaluated | No | PR | |
| PR | Non-CR/Non-PD/not evaluated | No | PR | |
| SD | Non-CR/Non-PD/not evaluated | No | SD | documented at least once ≥ 28 days from baseline** |
| PD | Any | Yes or No | PD | no prior SD, PR or CR |
| Any | PD*** | Yes or No | PD | |
| Any | Any | Yes | PD | |
| * See RECIST 1.1 manuscript for further details on what is evidence of a new lesion. | | | | |

** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

Table 2: For Patients with Non-Measurable Disease (i.e., Non-Target Disease)

| Non-Target Lesions | New Lesions | Overall Response |
|---|---|---|
| CR | No | CR |
| Non-CR/non-PD | No | Non-CR/non-PD* |
| Not all evaluated | No | not evaluated |
| Unequivocal PD | Yes or No | PD |
| Any | Yes | PD |

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised

Table 3. Sequences of overall response assessments with corresponding best response.

| 1st Assessment | 2nd Assessment | Best Response |
|---|---|---|
| Progression | | Progressive disease |
| Stable, PR, CR | Progression | Progressive disease |
| Stable | Stable | Stable |
| Stable | PR, CR | Stable |
| Stable | Not done | Not RECIST classifiable |
| PR | PR | PR |
| PR | CR | PR |
| PR, CR | Not done | Not RECIST classifiable |
| CR | CR | CR |

Table 4: Overall Response for Patients with Neuroblastoma and Measurable Disease

| CT/MRI | MIBG | Bone Scan | Bone Marrow | Catechol | Overall |
|---|---|---|---|---|---|
| PD | Any | Any | Any | Any | PD |
| Any | PD | Any | Any | Any | PD |
| Any | Any | PD | Any | Any | PD |
| Any | Any | Any | PD | Any | PD |
| SD | CR/PR/SD | Non-PD | Non-PD | Any | SD |
| PR | CR/PR | Non-PD | Non-PD | Any | PR |
| CR/PR | PR | Non-PD | Non-PD | Any | PR |
| CR | CR | Non-PD | Non-PD | Elevated | PR |
| CR | CR | CR | CR | Normal | CR |

Table 5: Overall Response Evaluation for Neuroblastoma Patients and MIBG Positive Disease Only
If patients are enrolled without disease measurable by CT/MRI, any new or newly identified lesion by CT/MRI that occurs during therapy would be considered progressive disease.

| MIBG | CT/MRI | Bone Scan | Bone Marrow | Catechol | Overall |
|---|---|---|---|---|---|
| PD | Any | Any | Any | Any | PD |

| | | | | | |
|---|---|---|---|---|---|
| Any | New Lesion | Any | Any | Any | PD |
| Any | Any | PD | Any | Any | PD |
| Any | Any | Any | PD | Any | PD |
| SD | No New Lesion | Non-PD | Non-PD | Any | SD |
| PR | No New Lesion | Non-PD | Non-PD | Any | PR |
| CR | No New Lesion | Non-PD | Non-PD | Elevated | PR |
| CR | No New Lesion | CR | CR | Normal | CR |

**Duration of Response**

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

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

## 13.0 ADVERSE EVENT REPORTING REQUIREMENTS

Adverse event data collection and reporting which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. (Please follow directions for routine reporting provided in the data collection packet for this protocol). Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care. The following sections provide information about expedited reporting.

Reporting requirements may include the following considerations: 1) whether the patient has received an investigational or commercial agent; 2) whether the adverse event is considered serious; 3) the grade (severity); and 4) whether or not hospitalization or prolongation of hospitalization was associated with the event.

An investigational agent is a protocol drug administered under an Investigational New Drug Application (IND). In some instances, the investigational agent may be available commercially, but is actually being tested for indications not included in the approved package label.

Commercial agents are those agents not provided under an IND but obtained instead from a commercial source. The NCI, rather than a commercial distributor, may on some occasions distribute commercial agents for a trial.

### 13.1 Steps to Determine If an Adverse Event Is To Be Reported In an Expedited Manner

Step 1: Identify the type of adverse event using the NCI CTCAE version 5.0. All

appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Step 2: Grade the adverse event using the NCI CTCAE v.5.0.

Step 3: Review Table A in this section to determine if:

- the adverse event is considered serious;
- there are any protocol-specific requirements for expedited reporting of specific adverse events that require special monitoring; and/or
- there are any protocol-specific exceptions to the reporting requirements.

Note: This includes all events that occur within 30 days of the last dose of protocol treatment. Any event that occurs during the follow-up period (See Section 10.2) more than 30 days after the last dose of treatment and is attributed (possibly, probably, or definitely) to the agent(s) must also be reported according to the instructions in the table below. Attribution categories are as follows: Unrelated, Unlikely, Possible, Probable, and Definite.

**Table A: Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]**

**FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)**
**NOTE:** Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon 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. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

**ALL SERIOUS** adverse events that meet the above criteria MUST be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

| Hospitalization | Grade 1 and Grade 2 Timeframes | Grade 3-5 Timeframes |
|---|---|---|
| Resulting in Hospitalization ≥ 24 hrs | 7 Calendar Days | 24-Hour 5 Calendar Days |
| Not resulting in Hospitalization ≥ 24 hrs | Not required | |

**NOTE:** Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

**Expedited AE reporting timelines are defined as:**

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur during the follow up period (See Section 10.2) more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

**Expedited 24-hour notification followed by complete report within 5 calendar days for:**

- All Grade 3, 4, and Grade 5 AEs

**Expedited 7 calendar day reports for:**

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

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- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions.
- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via CTEP-AERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

Additional Instructions or Exceptions to Expedited Reporting Requirements for Phase 1 Trials Utilizing an Agent under a CTEP-IND or Non-CTEP IND:

- Any death that occurs more than 30 days after the last dose of treatment with an investigational agent which can be attributed (possibly, probably, or definitely) to the agent and is not clearly due to progressive disease must be reported via CTEP-AERS for an agent under a CTEP or non-CTEP IND agent per the timelines outlined in the table above.
- Adverse events associated with study drug overdose are to be reported via CTEP-AERS.
- Lymphopenia, does not require expedited reporting, unless it is associated with hospitalization.
- All cases of Graft versus host disease (GVDH) while patient is on study should be reported via CTEP AERS regardless of attribution to protocol therapy. This includes reporting during extended follow up periods
- Myelosuppression, (Grade 1 through Grade 4 adverse events as defined in the table below), does not require expedited reporting, unless it is associated with hospitalization.

| Category | Adverse Events |
|---|---|

| | |
|---|---|
| INVESTIGATIONS | Platelet count decreased |
| INVESTIGATIONS | White blood cell decreased |
| INVESTIGATIONS | Neutrophil count decreased |
| INVESTIGATIONS | Lymphocyte count decreased |
| BLOOD/LYMPHATICS DISORDERS | Anemia |

- Grade 1 and 2 adverse events listed in the table below do **not** require expedited reporting via CTEP-AERS, unless it is associated with hospitalization.

| Category | Adverse Events |
|---|---|
| GASTROINTESTINAL DISORDERS | Abdominal pain |
| GASTROINTESTINAL DISORDERS | Constipation |
| GASTROINTESTINAL DISORDERS | Dry Mouth |
| GASTROINTESTINAL DISORDERS | Nausea |
| GASTROINTESTINAL DISORDERS | Vomiting |
| GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS | Chills |
| INVESTIGATIONS | Alanine aminotransferase increased |
| INVESTIGATIONS | Aspartate aminotransferase increased |
| METABOLISM AND NUTRITION DISORDERS | Anorexia |
| METABOLISM AND NUTRITION DISORDERS | Dehydration |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | Arthralgia |
| MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS | Arthritis |
| NERVOUS SYSTEM DISORDERS | Headache |
| RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS | Dyspnea |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | Urticaria |

- See also the Specific Protocol Exceptions to Expedited Reporting (SPEER) in Section 9.1.8 and in Section 9.2.9 of the protocol.

As referenced in the CTEP Adverse Events Reporting Requirements, an AE that resolves and then recurs during a subsequent cycle does not require CTEP-AERS reporting unless (1) the Grade increases; or (2) hospitalization is associated with the recurring AE.

### 13.2 When to Report an Event in an Expedited Manner

- Some adverse events require notification **within 24 hours** (refer to Table A) to NCI via the web at http://ctep.cancer.gov (telephone CTEP at: **301-897-7497** within 24 hours of becoming aware of the event if the CTEP-AERS 24-Hour Notification web-based application is unavailable) and by telephone call to the Study Chair. Once internet connectivity is restored, a 24-hour notification phoned in must be entered electronically into CTEP-AERS by the original submitter at the site.

- When the adverse event requires expedited reporting, submit the report **within 5 or 7 calendar days** of learning of the event (refer to Table A).

- Expedited AE reporting for this study must only use CTEP-AERS, accessed via the

CTEP home page
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm.

### 13.3 Expedited Reporting Methods

CTEP-AERS Reporting
To report adverse events in an expedited fashion use the NCI's Adverse Event Reporting System that can be found at
https://ctepcore.nci.nih.gov/ctepaers/pages/task

A CTEP-AERS report must be submitted electronically via the system at https://ctepcore.nci.nih.gov/ctepaers/pages/task. If prompted to enter a sponsor email address, please type in: PEPCTNAERS@childrensoncologygroup.org

Send supporting documentation to the NCI by fax (fax# 301-897-7404) and by email to the ADVL1412 study assigned Research Coordinator. **ALWAYS include the ticket number on all faxed and emailed documents**.

### 13.4 Definition of Onset and Resolution of Adverse Events

**Note:** These guidelines below are for reporting adverse events on the COG data submission forms and do not alter the guidelines for CTEP-AERS reporting.

If an adverse event occurs more than once in a course (cycle) of therapy only the most severe grade of the event should be reported.

If an adverse event progresses through several grades during one course of therapy, only the most severe grade should be reported.

The duration of the AE is defined as the duration of the highest (most severe) grade of the Adverse Effects.

The resolution date of the AE is defined as the date at which the AE returns to baseline or less than Grade 1, whichever level is higher (note that the resolution date may therefore be different from the date at which the grade of the AE decreased from its highest grade). If the AE does not return to baseline the resolution date should be recorded as "ongoing."

An adverse event that persists from one course to another should only be reported once unless the grade becomes more severe in a subsequent course. An adverse event which resolves and then recurs during a different course, must be reported each course it recurs.

### 13.5 Other Recipients of Adverse Event Reports

Events that do not meet the criteria for CTEP-AERS reporting (Section 13.2) should be reported at the end of each cycle using the forms provided in the data form packet (See Section 14.1).

COG will forward reports and supporting documentation to the Study Chair, to

the FDA (when COG holds the IND) and to the pharmaceutical company (for industry sponsored trials).

Adverse events determined to be reportable must also be reported according to the local policy and procedures to the Institutional Review Board responsible for oversight of the patient.

### 13.6 Reporting Secondary AML/MDS

All cases of acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS) that occur in patients on NCI-sponsored trials following their chemotherapy for cancer must be reported to the Investigational Drug Branch (IDB) of the NCI Cancer Therapy Evaluation Program (CTEP) via CTEP-AERS and included as part of the second malignant neoplasm reporting requirements for this protocol (see data submission packet). Submit the completed CTEP-AERS report within 14 days of an AML/MDS diagnosis occurring after treatment for cancer on NCI-sponsored trials.

**Secondary Malignancy**:
A *secondary malignancy* is a cancer caused by treatment for a previous malignancy (*e.g.*, treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur following treatment with an agent under an NCI IND/IDE be reported via AdEERS. Three options are available to describe the event:

1) Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
2) Myelodysplastic syndrome (MDS)
3) Treatment-related secondary malignancy.

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

**Second Malignancy**:

A *second malignancy* is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine reporting via CDUS unless otherwise specified.

### 13.7 Reporting Pregnancy, Pregnancy Loss, and Death Neonatal

When submitting CTEP-AERS reports for "Pregnancy", "Pregnancy loss", or "Neonatal loss", the Pregnancy Information Form should be completed and emailed to the ADVL1412 COG Study Assigned Research Coordinator along with any additional medical information. The potential risk of exposure of the fetus to the investigational agent should be documented in the "Description of Event" section of the CTEP-AERS report.

<u>Pregnancy</u>

- Patients who become pregnant on study risk intrauterine exposure of the fetus to agents which may be teratogenic. For this reason, pregnancy occurring on study or within 6 months following the last dose of study therapy should be reported in an expedited manner via CTEP-AERS as **Grade 3 *"Pregnancy, puerperium and perinatal conditions - Other***

***(Pregnancy)***" under the ***"Pregnancy, puerperium and perinatal conditions"*** **System Organ Class (**SOC**)**.

- Pregnancy should be followed until the outcome is known. If the baby is born with a birth defect or anomaly, then a second CTEP-AERS report is required.

Pregnancy Loss (Fetal Death)

- Pregnancy loss is defined in CTCAE as "Death in utero."

- Any pregnancy loss should be reported expeditiously, as **Grade 4** ***"Pregnancy loss"*** under the ***"Pregnancy, puerperium and perinatal conditions"*** **SOC**. Do NOT report a pregnancy loss as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

Death Neonatal

- Neonatal death, defined in CTCAE as ***"Newborn deaths occurring during the first 28 days after birth"*** that is felt by the investigator to be at least possibly due to the investigational agent/intervention, should be reported expeditiously.

- A neonatal death should be reported expeditiously as Grade 4 "Death neonatal" under the "General disorders and administration" SOC **when the death is the result of a patient pregnancy or pregnancy in partners of men on study**

- Do NOT report a neonatal death resulting from a patient pregnancy or pregnancy in partners of men as a Grade 5 event since CTEP-AERS recognizes any Grade 5 event as a patient death.

Pregnancy should be followed up until the outcome of the pregnancy is known at intervals deemed appropriate by her physicians. The "Pregnancy Information Form" should be used for all necessary follow-ups. This form is available at http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf.

## 14.0 RECORDS, REPORTING, AND DATA AND SAFETY MONITORING PLAN

### 14.1 Categories of Research Records

Research records for this study can be divided into three categories

1. Non-computerized Information: *e.g.*, Roadmaps, Pathology Reports, Surgical Reports. These forms are uploaded into RAVE.
2. Reference Labs, Biopathology Reviews, and Imaging Center data: These data accompany submissions to these centers, which forward their data electronically to the COG Statistics & Data Center.
3. Computerized Information Electronically Submitted: All other data will be entered in RAVE with the aid of schedules and worksheets (essentially paper copies of the OPEN and RAVE screens) provided in the data form packet.

See separate Data Form Packet, which includes submission schedule.

14.2 **Access to Rave for Data Submission/ Data Reporting**

Data collection for this study will be done through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the COG or PEP-CTN roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings), and can be accessed by clicking on the link in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com, or by email to the COG Study Assigned Data Manager.

14.3 **CDUS**

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31 and October 31. Instructions for submitting data using the CDUS can be found on the CTEP website: http://ctep.cancer.gov/reporting/cdus.html. This is not a responsibility of institutions participating in this trial.

14.4 **CRADA/CTA/CSA**

Standard Language to Be Incorporated into All Protocols Involving Agent(s) Covered by a Clinical Trials Agreement (CTA) or a Cooperative Research and Development Agreement.

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor

can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements , the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

   a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

   b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.

   c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment

prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

## 14.5 Data and Safety Monitoring Plan

Data and safety is ensured by several integrated components including the COG Data and Safety Monitoring Committee.

Data and Safety Monitoring Committee

This study will be monitored in accordance with the Children's Oncology Group policy for data and safety monitoring of Phase 1 and 2 studies. In brief, the role of the COG Data and Safety Monitoring Committee is to protect the interests of patients and the scientific integrity for all Phase 1 and 2 studies. The DSMC consists of a chair; a statistician external to COG; one external member; one consumer representative; the lead statistician of the PEP-CTN scientific committee; and a member from the NCI. The DSMC meets at least every 6 months to review current study results, as well as data available to the DSMC from other related studies. Approximately 6 weeks before each meeting of the Phase 1 and 2 DSMC, study chairs will be responsible for working with the study statistician to prepare study reports for review by the DSMC. The DSMC will provide recommendations to the COG PEP-CTN Chair and the Group Chair for each study reviewed to change the study or to continue the study unchanged. Data and Safety Committee reports for institutional review boards can be prepared using the public data monitoring report as posted on the COG Web site.

Monitoring by the Study Chair and Developmental Therapeutics Leadership

The study chair will monitor the study regularly and enter evaluations of patients' eligibility, evaluability, and dose limiting toxicities into the study database. In addition, study data and the study chair's evaluations will be reviewed by the COG PEP-CTN Chair, Vice Chair and Statistician on a weekly conference call.

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49. This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.,
50. Ipilimumab can result in severe and fatal immune-mediated adverse events probably due to T-cell activation and proliferation. These can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune thyroiditis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, and adrenal insufficiency), ocular manifestations (e.g., uveitis, iritis, conjunctivitis, blepharitis, and episcleritis), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome. The majority of these reactions manifested early during treatment; however, a minority occurred weeks to months after discontinuation of ipilimumab especially with the initiation of additional treatments.,
51. Late bowel perforations have been noted in patients receiving MDX-010 (ipilimumab) in association with subsequent IL-2 therapy.,
52. Complications including hyperacute graft-versus-host disease (GVHD), may occur in patients receving allo stem cell transplant (SCT) after receiving Ipilimumab (MDX-010). These complications may occur despite intervening therapy between receiving Ipilimumab (MDX-010) and allo-SCT.,
53. In rare cases diplopia (double vision) has occurred as a result of muscle weakness (Myasthenia gravis).
54. Gastrointestinal hemorrhage includes Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric

hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.,

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## APPENDIX I: PERFORMANCE STATUS SCALES/SCORES

| **Karnofsky** | | **Lansky** | |
|---|---|---|---|
| Score | Description | Score | Description |
| 100 | Normal, no complaints, no evidence of disease | 100 | Fully active, normal. |
| 90 | Able to carry on normal activity, minor signs or symptoms of disease. | 90 | Minor restrictions in physically strenuous activity. |
| 80 | Normal activity with effort; some signs or symptoms of disease. | 80 | Active, but tires more quickly |
| 70 | Cares for self, unable to carry on normal activity or do active work. | 70 | Both greater restriction of and less time spent in play activity. |
| 60 | Required occasional assistance, but is able to care for most of his/her needs. | 60 | Up and around, but minimal active play; keeps busy with quieter activities. |
| 50 | Requires considerable assistance and frequent medical care. | 50 | Gets dressed, but lies around much of the day; no active play, able to participate in all quiet play and activities. |
| 40 | Disabled, requires special care and assistance. | 40 | Mostly in bed; participates in quiet activities. |
| 30 | Severely disabled, hospitalization indicated. Death not imminent. | 30 | In bed; needs assistance even for quiet play. |
| 20 | Very sick, hospitalization indicated. Death not imminent. | 20 | Often sleeping; play entirely limited to very passive activities. |
| 10 | Moribund, fatal processes progressing rapidly. | 10 | No play; does not get out of bed. |

## APPENDIX II: CORRELATIVE STUDIES GUIDE

| PARTS A and B: Correlative Study | Appx. | Tube Type | Blood Volume per Sample | Cycle 1 Volume |
|---|---|---|---|---|
| **Pharmacokinetics** | IIIA; | SST Vacutainer | 2 mL | 14 mL |
| **Anti-Drug Antibody (ADA) Studies** | V | SST Vacutainer | 2 mL | 2 mL |
| **Vaccinated Antibody Studies** | IV | SST Vacutainer | 2 mL | 2 mL |
| **Total Blood Volume in Cycle 1** | | | | **18 mL** |
| **Tumor Tissue** | VI | | | |

| PARTS C, D AND E: Correlative Study | Appx. | Tube Type | Blood Volume per Sample | Cycle 1 Volume |
|---|---|---|---|---|
| **Pharmacokinetics** | IIIB | SST Vacutainer | 4 mL | 8 mL |
| **Anti-Drug Antibody (ADA) Studies** | V | SST Vacutainer | 4 mL | 4 mL |
| **Vaccinated Antibody Studies** | IV | SST Vacutainer | 2 mL | 2 mL |
| **Cytokine Studies** | VII | SST Vacutainer | 2 mL | 4mL |
| **Total Blood Volume in Cycle 1: Parts C, D and E** | | | | **18 mL** |
| **Tumor Tissue** | VI | | | |

## APPENDIX IIIA: PHARMACOKINETIC STUDY FORM (PARTS A AND B)

COG Pt ID # _____ ACC # _____ Part of Study # _____
Please do not write patient names on this form or on samples.

Cycle 1, Day 1 Date: |__/__|__/__|__/__| Dose Level: _____mg/kg Dose Administered: _____mg

Serum samples (2 mL) will be collected for pharmacokinetic studies at a site distant from the infusion, prior to and at the end of infusion (EOI) on Days 1 and 15 of Cycle 1, and prior to and at EOI on Day 1 of Cycle 2. Samples cannot be drawn from the 2nd lumen of a multi-lumen catheter through which drug is being administered. Additional samples will be also obtained on Days 2, 4, and 8 of Cycles 1 and 2 as indicated below. Record the exact date and time each sample is drawn and the start and stop time of the nivolumab infusion.

| Blood Sample No. | Time Point | Scheduled Sample Collection Time | Scheduled Nivolumab Time Point | Actual Date Sample Collected or Dose Given | Actual Time Sample Collected or Dose Given (24-hr clock) |
|---|---|---|---|---|---|
| **1^** | **Cycle 1, Day 1** | **Prior to Cycle 1, Day 1 infusion** | | ___/___/___ | \|__\|__\| : \|__\|__\| |
| | | | **Cycle 1, Day 1** | ___/___/___ | Start: \|__\|__\|:\|__\|__\|<br>Stop: \|__\|__\|:\|__\|__\| |
| **2** | **Cycle 1, Day 1** | Immediately following EOI | | ___/___/___ | \|__\|__\| : \|__\|__\| |
| **3** | **Cycle 1, Day 2** | 24 (±2) hrs after EOI | | ___/___/___ | \|__\|__\| : \|__\|__\| |
| **4** | **Cycle 1, Day 4** | 72 (±2) hrs after EOI | | ___/___/___ | \|__\|__\| : \|__\|__\| |
| **5** | **Cycle 1, Day 8** | Any time point | | ___/___/___ | \|__\|__\| : \|__\|__\| |
| **6** | **Cycle 1, Day 15** | **Prior to Cycle 1, Day 15 infusion** | | ___/___/___ | \|__\|__\| : \|__\|__\| |
| | | | **Cycle 1, Day 15** | ___/___/___ | Start: \|__\|__\|:\|__\|__\|<br>Stop: \|__\|__\|:\|__\|__\| |
| **7** | **Cycle 1, Day 15** | Immediately following EOI | | ___/___/___ | \|__\|__\| : \|__\|__\| |
| **8^** | **Cycle 2, Day 1*** | **Prior to Cycle 2, Day 1 infusion** | | ___/___/___ | \|__\|__\| : \|__\|__\| |
| | | | **Cycle 2, Day 1** | ___/___/___ | Start: \|__\|__\|:\|__\|__\|<br>Stop: \|__\|__\|:\|__\|__\| |
| **9** | **Cycle 2, Day 1** | Immediately following EOI | | ___/___/___ | \|__\|__\| : \|__\|__\| |
| **10** | **Cycle 2, Day 2** | 24 (±2) hrs after EOI | | ___/___/___ | \|__\|__\| : \|__\|__\| |
| **11** | **Cycle 2, Day 4** | 72 (±2) hrs after EOI | | ___/___/___ | \|__\|__\| : \|__\|__\| |
| **12** | **Cycle 2, Day 8** | Any time point | | ___/___/___ | \|__\|__\| : \|__\|__\| |
| **13^** | **Cycle 4, Day 1** | **Prior to Cycle 4, Day 1 infusion** | | ___/___/___ | \|__\|__\| : \|__\|__\| |

* Patients who are removed from therapy during Cycle 1 after receiving the dose of nivolumab on Day 15 should have this sample collected on Day 28 of Cycle 1.
^ Note serum samples (2 mL) for ADA analysis will also be collected at these timepoints.

**Sample Processing Procedures:** One copy of this Pharmacokinetic Study Form should be uploaded into RAVE. Refer to Section 8.3 for instructions on packaging and shipping PK samples.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date: _____

## APPENDIX IIIB: PHARMACOKINETIC STUDY FORM (PARTS C, D AND E)

COG Pt ID # _____ ACC # _____ Part of Study # _____
Please do not write patient names on this form or on samples. Cycle 1, Day 1 Date: |__/__|__/__|__/__|

Nivolumab: _____mg/kg Dose Administered: _____mg Ipilimumab: _____mg/kg Dose Administered: _____mg

Serum samples (4 mL per sample aliquoted into two 4ml SST tubes) will be collected for pharmacokinetic studies at a site distant from the infusion, prior to the nivolumab infusion and at the end of the ipilimumab infusion (EOI) on Day 1 of Cycles 1-4. Samples cannot be drawn from the 2nd lumen of a multi-lumen catheter through which drug is being administered. Record the exact date and time each sample is drawn and the start and stop time of the nivolumab infusion.

| Blood Sample No. | Time Point | Scheduled Sample Collection Time | Scheduled Infusion Time Point | Actual Date Sample Collected or Dose Given | Actual Time Dose Given (24-hr clock) | Actual Time Sample Collected (24-hr clock) |
|---|---|---|---|---|---|---|
| 1^ | Cycle 1, Day 1 | Within 30 min prior to start of nivolumab infusion | | / / | | \|__\|__\| : \|__\|__\| |
| | | | Cycle 1, Day 1 | / / | Nivolumab Start: \|__\|__\| : \|__\|__\| | |
| | | | | / / | Nivolumab Stop: \|__\|__\| : \|__\|__\| | |
| | | | | / / | Ipilimumab Start: \|__\|__\|:\|__\|__\| | |
| 2 | Cycle 1, Day 1 | Immediately prior to ipilimumab EOI[a] (3 hr from start of nivolumab infusion) | | / / | | \|__\|__\| : \|__\|__\| |
| | | | Cycle 1, Day 1 | / / | Ipilimumab Stop: \|__\|__\|:\|__\|__\| | |
| 3^ | Cycle 2, Day 1 | Within 30 min prior to start of nivolumab infusion | | / / | | \|__\|__\| : \|__\|__\| |
| | | | Cycle 2, Day 1 | / / | Nivolumab Start: \|__\|__\| : \|__\|__\| | |
| | | | | / / | Nivolumab Stop: \|__\|__\| : \|__\|__\| | |
| | | | | / / | Ipilimumab Start: \|__\|__\|:\|__\|__\| | |
| 4 | Cycle 2, Day 1 | Immediately prior to ipilimumab EOI[a] (3 hr from start of nivolumab infusion) | | / / | | \|__\|__\| : \|__\|__\| |
| | | | Cycle 2, Day 1 | / / | Ipilimumab Stop: \|__\|__\|:\|__\|__\| | |
| 5^ | Cycle 3, Day 1 | Within 30 min prior to start of nivolumab infusion | | / / | | \|__\|__\| : \|__\|__\| |
| | | | Cycle 3, Day 1 | / / | Nivolumab Start: \|__\|__\| : \|__\|__\| | |
| | | | | / / | Nivolumab Stop: \|__\|__\| : \|__\|__\| | |
| | | | | / / | Ipilimumab Start: \|__\|__\|:\|__\|__\| | |
| 6 | Cycle 3, Day 1 | Immediately prior to ipilimumab EOI[a] (3 hr from start of nivolumab infusion) | | / / | | \|__\|__\| : \|__\|__\| |
| | | | Cycle 3, Day 1 | / / | Ipilimumab Stop: \|__\|__\|:\|__\|__\| | |
| 7^ | Cycle 4, Day 1 | Within 30 min prior to start of nivolumab infusion | | / / | | \|__\|__\| : \|__\|__\| |
| | | | Cycle 4, Day 1 | / / | Nivolumab Start: \|__\|__\| : \|__\|__\| | |
| | | | | / / | Nivolumab Stop: \|__\|__\| : \|__\|__\| | |
| | | | | / / | Ipilimumab Start: \|__\|__\|:\|__\|__\| | |
| 8 | Cycle 4, Day 1 | Immediately prior to ipilimumab EOI[a] (3 hr from start of Nivolumab infusion) | | / / | | \|__\|__\| : \|__\|__\| |
| | | | Cycle 4, Day 1 | / / | Ipilimumab Stop: \|__\|__\|:\|__\|__\| | |

a. EOI: This sample should be taken immediately prior to stopping the ipilimumab infusion. In the event of a delay beyond 1 hr, the sample should be taken at the END of the infusion.
^ Note serum samples (4 mL) for ADA analysis will also be collected at these timepoints.

**Sample Processing Procedures:** One copy of this Pharmacokinetic Study Form should be uploaded into RAVE. Refer to Section 8.3 for instructions on packaging and shipping PK samples.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date: _____

## APPENDIX IV: VACCINATED ANTIBODY STUDY FORM

COG Pt ID # _____ ACC # _____ Gender: _____ Age: _____
Please do not write patient names on this form or on samples.

Cycle 1, Day 1 Date: |__/__|__/__|__/__| Part of Study # _____

Dose Level: _____mg/kg Weight: _____ kg Nivolumab Dose Administered: _____mg

Serum samples (2 mL) will be collected in consenting patients at baseline and prior to Cycle 2, Day 1 nivolumab infusion. Record the exact date and time each sample is drawn. Refer to Section 8.4 for processing instructions.

| Blood Sample No. | Time Point | Scheduled Sample Collection Time | Scheduled Nivolumab Time Point | Actual Date Sample Collected or Dose Given | Actual Time Sample Collected or Dose Given (24-hr clock) |
|---|---|---|---|---|---|
| **1** | **Cycle 1, Day 1** | **Prior to Cycle 1, Day 1 nivolumab infusion** | | ___/___/___ | |__|__| : |__|__| |
| | | | **Cycle 1, Day 1** | ___/___/___ | Start: |__|__|:|__|__|<br>Stop: |__|__|:|__|__| |
| **2*** | **Cycle 2, Day 1** | **Prior to Cycle 2, Day 1 nivolumab infusion** | | ___/___/___ | |__|__| : |__|__| |

* Patients who are removed from therapy during Cycle 1 should have this sample collected on Day 28 (or Day 21) of Cycle 1.

One copy of this Vaccinated Antibody Study Form should uploaded into RAVE. Refer to the provided guidelines for instructions on shipping these samples.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date: _____

## APPENDIX V: ANTI-DRUG ANTIBODY (ADA) STUDY FORM

COG Pt ID # _____ ACC # _____ Part of Study # _____
Please do not write patient names on this form or on samples.

Cycle 1, Day 1 Date: |__/__|__/__|__/__|

Dose Level: _____mg/kg Weight: _____ kg Nivolumab Dose Administered: _____mg

In Parts A and B, serum samples (2 mL) will be collected in all patients prior to Day 1 nivolumab infusion in each cycle. Record the exact date and time each sample is drawn. In Parts C, D, and E serum samples (4 mL) will be collected in all patients prior to Day 1 nivolumab infusion in each cycle for ADA assessment of both Nivolumab and Ipilimumab.

| Cycle | Scheduled Sample Collection Time | Actual Date Sample Collected | Actual Time Sample Collected |
|---|---|---|---|
| **Cycle # 1** | Prior to Day 1 nivolumab infusion | ___/___/___ | \|__\|__\| : \|__\|__\| |

**Subsequent Cycles:**

| Cycle | Scheduled Sample Collection Time | Actual Date Sample Collected | Actual Time Sample Collected |
|---|---|---|---|
| **Cycle#_____** | Prior to Day 1 nivolumab infusion | ___/___/___ | \|__\|__\| : \|__\|__\| |

One copy of this ADA Study Form should be uploaded into RAVE
Refer to Section 8.5 for instructions on packaging and shipping ADA samples.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date: _____

## APPENDIX VI: TISSUE STUDIES FORM

**COG Pt ID #** _____ **ACC #** _____ **Date:**_____ Part of Study # ____
(Please do not write patient names on this form or on samples)

**Sample Labeling:**
Samples should be labeled with the following information:

Protocol number: **ADVL1412**
Institution: _____ ☐ E3: Rhabdomyosarcoma
Patient ID #: _____ ☐ E4: Ewing's Sarcoma
Accession #: _____
Sample Date: _____
Anatomical Site of Acquired Tissue: _____
Tissue obtained at (check one option below):
☐Diagnosis ☐Relapse ☐Subsequent Resection/Biopsy

Tissue sample is from a:
☐ Resection or ☐ Biopsy

**Shipment of Tumor Tissue:**
Tissue is requested from original diagnosis, relapse, or any subsequent resection or biopsy prior to treatment with nivolumab. Archived tissue samples should be in the form of a paraffin-embedded tissue block or at least 5 unstained slides (15 requested, 5 required) from the tissue block accompanied by a copy of the pathology report. Fine needle aspirate samples or other cytology samples are not acceptable and tumor samples obtained from bone metastases are generally not considered acceptable.

All blocks or slides must be labeled with the patient's study registration number (COG Patient ID #), the study I.D. (ADVL1412), and the sample collection date. Data should be recorded on this Tissue Studies Form, which must accompany the sample(s) to the address provided in Section 8.6.3.

1. **If sending paraffin block (PREFERRED):**
   a. Place appropriate sample ID label on back of cassette
   b. Place labeled cassette in a Zipper lock bag
   c. Paraffin blocks are shipped to the lab at **ambient temperature**. It is acceptable to send blocks refrigerated if sending blocks and slides together.

2. **If sending slides:**
   If slides will be cut from tissue block, they must be cut within one week of shipment. Recommended thickness of tissue sections for slides is 4 microns. Positively charged slides are required (Superfrost Plus is recommended). **After cutting, the slides should be kept in refrigerator (2-5°C)**.
   a. Place slides in the plastic slide holder and place sample ID label provided on the slide holder
   b. Place the slide holder in the Zipper lock bag and eliminate as much air (and therefore moisture) as possible prior to sealing the Zip-lock bag
   c. Slides are shipped to the lab **at refrigerated temperature on a cold gel pack**. It is acceptable to send blocks refrigerated if sending blocks and slides together.

One copy of this form should be uploaded into RAVE.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date:_____
(site personnel who collected samples)

## APPENDIX VII: CYTOKINE STUDY FORM

COG Pt ID # _____ ACC # _____ Gender: _____ Age: _____

**Please do not write patient names on this form or on samples**.

Cycle 1, Day 1 Date: |__/__|__/__|__/__| Part of Study # _____

Dose Level: _____mg/kg Weight: _____ kg Nivolumab Dose Administered: _____mg

Blood samples (2 mL) will be collected in consenting patients at baseline and prior to Cycle 2, Day 1 nivolumab infusion. Record the exact date and time each sample is drawn. Refer to Section 8.8 for processing instructions.

| Blood Sample No. | Time Point | Scheduled Sample Collection Time | Scheduled Nivolumab Time Point | Actual Date Sample Collected or Dose Given | Actual Time Sample Collected or Dose Given (24-hr clock) |
|---|---|---|---|---|---|
| **1** | **Cycle 1, Day 1** | **Prior to Cycle 1, Day 1 nivolumab infusion** | | ___/___/___ | \|__\|__\| : \|__\|__\| |
| | | | **Cycle 1, Day 1** | ___/___/___ | Start: \|__\|__\|:\|__\|__\|<br>Stop: \|__\|__\|:\|__\|__\| |
| **2*** | **Cycle 2, Day 1** | **Prior to Cycle 2, Day 1 nivolumab infusion** | | ___/___/___ | \|__\|__\| : \|__\|__\| |

* Patients who are removed from therapy during Cycle 1 should have this sample collected on Day 28 (or Day 21) of Cycle 1.

One copy of this Cytokine Study Form should uploaded into RAVE. Refer to the provided guidelines for instructions on shipping these samples.

If this form will be used as a source document, the site personnel who collected the samples must sign and date this form below:

Signature: _____ Date: _____

## APPENDIX VIII: MEDICATIONS ASSOCIATED WITH PROLONGED $QT_C$

The use of the following medications should be avoided during protocol therapy if reasonable alternatives exist. This is not an inclusive list. Because the lists of these agents are constantly changing, it is important to regularly consult frequently updated medical references. For the most current list of medications, please refer to the following reference:
Woosley, RL and Romero, KA, www.Crediblemeds.org, QTdrugs List, Accession Date December 2nd, 2016, AZCERT, Inc. 1822 Innovation Park Dr., Oro Valley, AZ 85755

| **Medications that prolong QTc** | |
|---|---|
| Amiodarone | Flecainide |
| Anagrelide | Fluconazole |
| Arsenic trioxide | Haloperidol |
| Azithromycin | Ibutilide |
| Chloroquine | Methadone |
| Chlorpromazine | Moxifloxacin |
| Ciprofloxacin | Ondansetron |
| Citalopram | Pentamidine |
| Clarithromycin | Pimozide |
| Disopyramide | Procainamide |
| Dofetilide | Propofol |
| Domperidone | Quinidine |
| Droperidol | Sevoflurane |
| Dronedarone | Sotalol |
| Erythromycin | Thioridazine |
| Escitalopram | Vandetanib |

| **Medications that MAY prolong QTc** | |
|---|---|
| Aripiprazole | Lapatinib |
| Bortezomib | Lenvatinib |
| Bosutinib | Leuprolide |
| Ceritinib | Mirtazapine |
| Clomipramine | Nicardipine |
| Crizotinib | Nilotinib |
| Dabrafenib | Olanzapine |
| Dasatinib | Osimertinib |
| Degarelix | Pazopanib |
| Desipramine | Promethazine |
| Dolasetron | Risperidone |
| Eribulin mesylate | Sorafenib |
| Famotidine | Sunitinib |
| Foscarnet | Tacrolimus |
| Gemifloxacin | Vemurafenib |
| Granisetron | Venlafaxine |
| Isradipine | Vorinostat |

## APPENDIX IX: TOXICITY-SPECIFIC GRADING

Bilirubin

| | |
|---|---|
| Grade 1: | >ULN - ≤ 1.5 x ULN |
| Grade 2: | > 1.5 x ULN - 3.0 x ULN |
| Grade 3: | > 3.0 x ULN -10.0 x ULN |
| Grade 4: | > 10.0 x ULN |

ALT: For the purpose of this study, the ULN for ALT is 45 U/L regardless of baseline.

| | |
|---|---|
| Grade 1: | > 45 U/L - ≤ 135 U/L |
| Grade 2: | 136 U/L – 225 U/L |
| Grade 3: | 226 U/L - 900 U/L |
| Grade 4: | > 900 U/L |

AST: For the purpose of this study, the ULN for AST is 50 U/L regardless of baseline.

| | |
|---|---|
| Grade 1: | > 50 U/L- ≤ 150 U/L |
| Grade 2: | 151 U/L -250 U/L |
| Grade 3: | 251 U/L -1000 U/L |
| Grade 4: | > 1000 U/L |

GGT:

| | |
|---|---|
| Grade 1: | > ULN- 2.5 x ULN |
| Grade 2: | > 2.5 x ULN - 5.0 x ULN |
| Grade 3: | > 5.0- x ULN 20.0 x ULN |
| Grade 4: | > 20.0 x ULN |

## APPENDIX X: CTEP AND CTSU REGISTRATION PROCEDURES

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account (https://ctepcore.nci.nih.gov/iam). In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) (i.e., clinical site staff requiring write access to OPEN, RAVE, or TRIAD or acting as a primary site contact) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) (https://ctepcore.nci.nih.gov/rcr). Documentation requirements per registration type are outlined in the table below.

| Documentation Required | IVR | NPIVR | AP | A |
|---|---|---|---|---|
| FDA Form 1572 | ✔ | ✔ | | |
| Financial Disclosure Form | ✔ | ✔ | ✔ | |
| NCI Biosketch (education, training, employment, license, and certification) | ✔ | ✔ | ✔ | |
| HSP/GCP training | ✔ | ✔ | ✔ | |
| Agent Shipment Form (if applicable) | ✔ | | | |
| CV (optional) | ✔ | ✔ | ✔ | |

An active CTEP-IAM user account and appropriate RCR registration is required to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and IRBs covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval
- Assigned the Clinical Investigator (CI) role on the Delegation of Tasks Log (DTL).

Additional information can be found on the CTEP website at < https://ctep.cancer.gov/investigatorResources/default.htm >. For questions, please contact the RCR ***Help Desk*** by email at < RCRHelpDesk@nih.gov >.

### CTSU Registration Procedures

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

**IRB Approval:**
Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Assignment of site registration status in the CTSU Regulatory Support System (RSS) uses extensive data to make a determination of whether a site has fulfilled all regulatory criteria including but not limited to the following:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Network or a participating organization
- A valid IRB approval
- Compliance with all protocol specific requirements.

In addition, the site-protocol Principal Investigator (PI) must meet the following criteria:

- Active registration status
- The IRB number of the site IRB of record listed on their Form FDA 1572
- An active status on a participating roster at the registering site.

Sites participating on the NCI CIRB initiative that are approved by the CIRB for this study are not required to submit IRB approval documentation to the CTSU Regulatory Office. For sites using the CIRB, IRB approval information is received from the CIRB and applied to the RSS in an automated process. Signatory Institutions must submit a Study Specific Worksheet for Local Context (SSW) to the CIRB via IRBManager to indicate their intent to open the study locally. The CIRB's approval of the SSW is then communicated to the CTSU Regulatory Office. In order for the SSW approval to be processed, the Signatory Institution must inform the CTSU which CIRB-approved institutions aligned with the Signatory Institution are participating in the study.

**Requirements for ADVL1412 Site Registration:**

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation, an IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form, or combination is accepted )
- For applicable studies with a radiation and/or imaging (RTI) component, the enrolling site must be aligned to a RTI provider. To manage provider associations access the Provider Association tab on the CTSU website at https://www.ctsu.org/RSS/RTFProviderAssociation, to add or remove associated providers. Sites must be linked to at least one IROC credentialed provider to participate on trials with an RT component. Enrolling sites are responsible for ensuring that the appropriate agreements are in place with their RTI provider, and that appropriate IRB approvals are in place.

**Submitting Regulatory Documents:**
Submit required forms and documents to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission
When applicable, original documents should be mailed to:
CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 in order to receive further instruction and support.