SUPPLEMENTARY MATERIALS

Supplementary Methods

Pharmacokinetic (PK) Evaluation

Samples for PK analysis were collected prior to and at the end of each nivolumab infusion on cycle 1, days 1 and 15 and cycle 2, day 1. During cycle 1 and 2, samples were also obtained on day 2 (24 hours post-infusion), day 4 (72 hours post-infusion) and day 8. A predose sample was also collected prior to the cycle 4, day 1 dose. Blood samples (2 ml) were collected in SST Vacutainer tubes at a site distant from the infusion and allowed to stand for 30-45 minutes at room temperature. Serum was isolated by centrifugation (1100-1300 x g), transferred to polypropylene tubes and stored frozen at less than -20°C until analysis. Nivolumab was measured in human serum using a validated ligand binding electrochemiluminescence immunoassay method. Briefly, samples (calibrators, quality controls, and specimens) were diluted in assay buffer and mixed with a reaction buffer containing biotin labeled capture anti-nivolumab-idiotype antibody and ruthenium labeled detection anti-nivolumab-idiotype antibody. The reaction mixture was incubated to allow the formation of an immuno-sandwich complex prior to transfer to a 96 well streptavidin-coated plate. The biotin-streptavidin interaction captured the complex onto the plate and the excess reactants were removed by a washing step. Addition of a tripropylamine containing buffer and an electric current produced a chemiluminescence signal that is directly proportional to the concentration of nivolumab in the sample. A nivolumab concentration-response curve was constructed using the calibrator data from which the quality control and specimen concentrations were calculated. Pharmacokinetic

parameters were calculated using standard non-compartmental analysis (Phoenix WinNonlin 6.4; Pharsight Corporation, Mountain View, CA).

Statistical Analysis

Power Calculations and Derivation of Sample Size

Part A

Part A is a Phase 1 dose finding study using the Rolling 6 study design. 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.

Part B

Part B used a 10+10 Simon two-stage design for each disease cohort separately. Nivolumab will not be considered of sufficient interest for further evaluation in a disease category if the true response proportion is 5% and of sufficient activity if the true response proportion is at least 25%. If nivolumab has a true response proportion 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 proportion 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).

Definitions of Population Assessed for Primary and Secondary Outcomes and Safety

Part A

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 Parts A, during Cycle 1, patients must have the appropriate toxicity monitoring studies performed to be considered evaluable for dose limiting toxicity. In Part A, 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. The rolling 6 study design was used for analysis of primary and secondary outcomes.

Part B

Any patient who is enrolled who meets eligibility criteria for Parts B 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 by the study design for Part B. Two objective status determinations are required to confirm best response. 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. 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. The Simon two-stage study design was used for analysis of primary and secondary outcomes.

Planned Interim Analyses

The rolling 6 study design uses interim analyses to determine whether to increase the dose level, decrease the dose level, or define the MTD/RP2D. Interim analyses occur after a cohort of 6 (or 3 in some cases) evaluable patients are assessed.

Yes, the Simon two-stage design uses an interim analysis to determine whether or not to continue enrolling patients into the second stage of the study. 10 patients were assessed for response in the first stage for each disease cohort. If at least 1 responder was observed, then the 2nd stage opened for enrollment. Otherwise, the disease cohort would close to enrollment and conclude insufficient evidence for response.

Table S1. Definitions of Dose Limiting Toxicities

Hematological DLT	Non-Hematological DLT
Grade 4 neutropenia > 5 days duration	Grade 2 fever not improved to ≤ Grade1 within 7days
Grade 4 thrombocytopenia > 5 days duration	Uveitis, eye pain, or blurred vision not improved with topical therapy and not improved to ≤ Grade 1 prior to the next scheduled dose of therapy
	Grade 2 adrenal insufficiency > 7 days duration
	Grade 2 colitis >7 days duration
	Grade 2 diarrhea >7 days duration
	Endocrine toxicity requiring hormone replacement Exceptions: • Grade 2 hypothyroidism, thyroiditis and thyroid dysfunction adequately managed by thyroid hormone replacement
	Grade 2 toxicity requiring immunosuppressive therapy (involving lung, heart, kidney, bowel, CNS, pituitary, eye) Exceptions: • Grade 2 or 3 pleural effusion
	Any Grade3 or 4 toxicity attributable to protocol therapy Exceptions: • Grade 3 rash, oral lesions, or hepatic transaminase elevation (ALT/AST/GGT) that returned to levels meeting protocol eligibility criteria or baseline within 7 days and did not require systemic immunosuppression, • Grade 3 or 4 serum electrolyte or mineral abnormalities responsive to supplementation, • Grade 3 or 4 amylase or lipase abnormalities that were not associated with diabetes mellitus, liver or gall bladder inflammation, or clinical manifestations of pancreatitis that resolved to grade ≤ 2 within 7 days, • Grade 3 fatigue that resolved to grade ≤ 2 within 7 days, Grade 3 creatinine increased that resolved to Grade ≤ 1 or baseline within 7 days

Table S2. Dose Limiting Toxicities

Treatment Level	Part	Patient ID	Type Of DLT	Grade of DLT
ADVL1412 DL 1	Part B	807824	Lipase increased	3
ADVL1412 DL 1	Part B	848650	Neutrophil count decreased	4
ADVL1412 DL 1	Part B	859483	Tumor pain	3
ADVL1412 DL 1	Part B	860049	Upper gastrointestinal hemorrhage	3
ADVL1412 DL 1	Part B	880130	Enterocolitis infectious	2
ADVL1412 DL 1	Part B	880130	Lipase increased	4

Table S3. Hematologic and Non-Hematologic toxicities stratified by grade and deemed related to protocol therapy (attributions definite, possible and probable) observed in evaluable patients (Part A and B, N=69). Grade 1 and 2 adverse events are those occurring in ≥10% of patients. All grade 3, 4, 5 events are listed.

	N events	N patients (%)	# of Patients with Maximum grade across all Cycles			
			Grade 1	Grade 2	Grade 3	Grade 4
White blood cell decreased	78	24 (35)	17	4	2	1
Neutrophil count decreased	64	22 (32)	8	10	1	3
Anemia	57	35 (51)	18	12	5	
Lymphocyte count decreased	52	22 (32)	7	5	7	3
Platelet count decreased	38	14 (20)	10	2		2
Investigations - Other, specify	36	20 (29)	19	1		
Aspartate aminotransferase increased	32	22 (32)	19	2	1	
Fatigue	31	28 (41)	20	8		
Alanine aminotransferase increased	25	18 (26)	16	1	1	
Nausea	19	14 (20)	9	5		
Anorexia	15	14 (20)	6	8		
Hypoalbuminemia	13	9 (13)	5	3	1	
Fever	13	11 (16)	4	7		
Hypokalemia	12	9 (13)	8		1	
Vomiting	12	9 (13)	7	2		
Abdominal pain	12	8 (12)	6	1	1	
Headache	12	11 (16)	8	3		
Hypothyroidism	12	10 (14)	7	3		
Hypocalcemia	11	10 (14)	10			
Hyponatremia	11	10 (14)	10			
Hypophosphatemia	10	8 (12)	8			
Rash maculo-papular	9	8 (12)	7	1		
Cough	8	8 (12)	5	3		
Sinus tachycardia	8	7 (10)	6	1		
Lipase increased	3	3 (4)			2	1
Febrile neutropenia	2	2 (3)			1	1
Pleural effusion	2	2 (3)			2	
Arthralgia	1	1 (1)			1	

	N events	N patients (%)	# of Patients with Maximum grade across all Cycles			
			Grade 1	Grade 2	Grade 3	Grade 4
Autoimmune disorder	1	1 (1)			1	
Dyspnea	1	1 (1)			1	
Gastritis	1	1 (1)			1	
Mucositis oral	1	1 (1)			1	
Central nervous system dysfunction	1	1 (1)			1	
Stevens-Johnson syndrome	1	1 (1)				1
Tumor pain	1	1 (1)			1	
Upper gastrointestinal hemorrhage	1	1 (1)			1	

Table S4. Nivolumab pharmacokinetic (PK) parameters [median (IQR)] by stratum

	Age (yrs)	Cycle 1						Cycle 2		Accumulation Ratio – AUC (Cycle 2/Cycle 1)
		Half-life (h)	C_{min} (mcg/ml)	Cl (ml/h)	Cl/kg (ml/h/kg)	C_{max} (mcg/ml)	$AUC_{0\text{-}168hr}$ (h•mcg/ml)	C_{max} (mcg/ml)	$AUC_{0\text{-}168hr}$ (h•mcg/ml)	
Part A; n=12 Relapsed solid tumors	11 (8.5 – 13)	285 (268.9 – 392.3)	19.0 (15.3 – 24.6)	6.4 (4.99 – 8.3)	0.16 (0.12 – 0.21)	63.9 (57.5 – 76.4)	6527 (5421 – 7356)	93.7 (83.4 – 113.5)	11530.6 (9301.3 – 13905.4)	1.74 (1.56 – 1.87)
Part B* –All; n=64	15 (8 – 17.5)	379.1 (279.6 – 496.65)	22.1 (17.1 – 25.65)	6.3 (3.10 – 10.53)	0.14 (0.11 – 0.18)	59.4 (49.3 – 73.15)	5645 (4754.9 – 6893.2)	90.9 (72.9 – 104)	9784 (8130.9 – 11202.2)	1.79 (1.61 – 1.88)
Neuroblastoma (B1); n=10	8.5 (5 – 10)	405 (268.8-1039.6)	22.4 (17.1 – 30.3)	3.05 (2.1 – 3.6)	0.13 (0.07 – 0.18)	58.7 (48.8 – 78.5)	5219.7 (4965.7 – 6974.03)	98.8 (88.9 – 103)	10139 (9409.2 – 10779.3)	1.71 (1.6 – 1.88)
Osteosarcoma (B2); n=10	16 (15 – 17)	293.7 (222.8 – 364.8)	21.3 (16.5 – 24.9)	10.7 (9.7 – 12)	0.18 (0.14 – 0.24)	69.7 (54.6 – 88.4)	5793.8 (5146.7 – 7500.7)	63.0 (62.8 – 87.8)	5376.5 (3866.1 – 8210.7)	1.63 (1.07 – 1.68)
Rhabdomyosarcoma (B3); n=10	5.5 (4 – 16)	351 (257.5 – 521.1)	17.7 (15.8 – 23.6)	4.11 (2.93 – 6.33)	0.17 (0.12 – 0.24)	46.4 (41.6 – 65.9)	4649 (3986.2 – 5792.6)	88.0 (52.9 – 123)	10057 (6409 – 13704)	1.83 (1.61 – 2.05)
Ewing sarcoma (B4); n=10	20 (17 – 22)	351 (324.1 – 439.5)	22.9 (15.7 – 27)	9.12 (7.9 – 12.1)	0.12 (0.12 – 0.16)	70.8 (61.3 – 79.1)	6606.6 (5648.1 – 7712.6)	72.8 (70.9 – 120)	8051 (7247.4 – 13999)	1.36 (1.28 – 1.82)
Hodgkin lymphoma (B5); n=9	17 (16 – 18)	400 (385.6 – 441.6)	22.2 (19.7 – 25.4)	8.22 (5.84 – 10.7)	0.12 (0.11 – 0.14)	59.1 (51.6 – 68.5)	5821 (5642.3 – 7304.3)	97.7 (78.3 – 127)	10858 (9778.2 – 13504.6)	1.81 (1.68 – 1.88)
Non-Hodgkin lymphoma (B6); n=8	15 (8 – 16)	387 (322.9 – 587.3)	24.8 (20.2 – 26.6)	9.13 (3.54 – 9.69)	0.15 (0.09 – 0.17)	57.5 (49.7 – 61.4)	5576.5 (4945.5 – 6292.6)	91.3 (90.5 – 110)	11333 (10781.4 – 14656.4)	1.88 (1.79 – 2.43)
Melanoma (B7); n=1	15	404	21.8	6.17	0.12	72.1	8219			
Neuroblastoma non-measureable (B8); n=6	8.5 (7 – 14)	467 (399.4 – 954.4)	20.8 (17.7 – 23.3)	3.45 (2.32 – 5.24)	0.14 (0.09 – 0.15)	50.8 (46.2 – 54.6)	4848 (4371.6-5654.2)	79.3 (73 – 92.55)	8914 (7300 – 9584.9)	2.01 (1.79 – 2.15)

* Part B1 (neuroblastoma measurable disease); Part B2 (osteosarcoma); Part B3 (rhabdomyosarcoma); Part B4 (Ewing Sarcoma or Peripheral PNET); Part B5 (Hodgkin Lymphoma); Part B6 (Non-Hodgkin Lymphoma); Part B7 (melanoma); Part B8 (neuroblastoma detectable by MIBG only)

Table S5. All Hematologic and Non-Hematologic toxicities related to protocol therapy observed in evaluable patients in Part B5, Hodgkin lymphoma

All Toxicities Summary (maximum grade), Overall Cycles (Part B5---Hodgkin lymphoma)		
	Dose Level and Toxicity Grade, No. (%)	
	All Dose Level (N=10)	
Toxicity Type	All	>=Grade 3
Lymphocyte count decreased	6 (32)	2 (11)
White blood cell decreased	5 (26)	1 (5)
Alanine aminotransferase increased	4 (21)	0 (0)
Anemia	4 (21)	1 (5)
Neutrophil count decreased	4 (21)	1 (5)
Platelet count decreased	4 (21)	1 (5)
Aspartate aminotransferase increased	3 (16)	0 (0)
Fatigue	3 (16)	0 (0)
Hypernatremia	2 (11)	0 (0)
Hypothyroidism	2 (11)	0 (0)
Infusion related reaction	2 (11)	0 (0)
Investigations - Other, specify	2 (11)	0 (0)
Rash maculo-papular	2 (11)	0 (0)
Autoimmune disorder	1 (5)	1 (5)
CPK increased	1 (5)	0 (0)
Cough	1 (5)	0 (0)
Creatinine increased	1 (5)	0 (0)
Eye disorders - Other, specify	1 (5)	0 (0)
Fever	1 (5)	0 (0)
Flushing	1 (5)	0 (0)
Headache	1 (5)	0 (0)
Hematuria	1 (5)	0 (0)
Hyperglycemia	1 (5)	0 (0)
Hyperthyroidism	1 (5)	0 (0)
Hypoalbuminemia	1 (5)	0 (0)
Hypocalcemia	1 (5)	0 (0)
Hypokalemia	1 (5)	0 (0)
Hyponatremia	1 (5)	0 (0)
Hypophosphatemia	1 (5)	0 (0)
Investigations - Other, INCREASED CRP	1 (5)	0 (0)
Lung infection	1 (5)	0 (0)
Lymphocyte count increased	1 (5)	0 (0)
Nausea	1 (5)	0 (0)
Pain	1 (5)	0 (0)
Proteinuria	1 (5)	0 (0)
Weight gain	1 (5)	0 (0)

Table S6. All Hematologic and Non-Hematologic toxicities related to protocol therapy observed in evaluable patients in Part B5, Non-Hodgkin lymphoma

All Toxicities Summary (maximum grade), Overall Cycles (Part B6---Non-Hodgkin lymphoma)		
	Dose Level and Toxicity Grade, No. (%)	
	All Dose Level (N=9)	
Toxicity Type	All	>=Grade 3
Anemia	6 (32)	2 (11)
Aspartate aminotransferase increased	6 (32)	0 (0)
Alanine aminotransferase increased	5 (26)	0 (0)
Fatigue	4 (21)	0 (0)
Hypocalcemia	4 (21)	0 (0)
White blood cell decreased	4 (21)	0 (0)
Abdominal pain	3 (16)	1 (5)
Headache	3 (16)	0 (0)
Hypoalbuminemia	3 (16)	1 (5)
Hypokalemia	3 (16)	1 (5)
Hypophosphatemia	3 (16)	0 (0)
Lymphocyte count decreased	3 (16)	2 (11)
Neutrophil count decreased	3 (16)	3 (16)
Platelet count decreased	3 (16)	1 (5)
Anorexia	2 (11)	0 (0)
Cough	2 (11)	0 (0)
Creatinine increased	2 (11)	0 (0)
Febrile neutropenia	2 (11)	2 (11)
Hypoglycemia	2 (11)	0 (0)
Hypomagnesemia	2 (11)	0 (0)
Mucositis oral	2 (11)	1 (5)
Vomiting	2 (11)	0 (0)
Constipation	1 (5)	0 (0)
Diarrhea	1 (5)	0 (0)
Electrocardiogram QT corrected interval prolonged	1 (5)	0 (0)
Enterocolitis infectious	1 (5)	0 (0)
Eye pain	1 (5)	0 (0)
Fever	1 (5)	0 (0)
Hyperglycemia	1 (5)	0 (0)
Hyperthyroidism	1 (5)	0 (0)
Hyponatremia	1 (5)	0 (0)
Hypothyroidism	1 (5)	0 (0)
Hypoxia	1 (5)	0 (0)
Insomnia	1 (5)	0 (0)
Investigations - Other, specify	1 (5)	0 (0)
Lipase increased	1 (5)	1 (5)
Nausea	1 (5)	0 (0)
Nervous system disorders - Other, Central nervous system dysfunction	1 (5)	1 (5)
Pain in extremity	1 (5)	0 (0)
Pericardial effusion	1 (5)	0 (0)
Rash maculo-papular	1 (5)	0 (0)
Respiratory, thoracic and mediastinal disorders - Other, specify	1 (5)	0 (0)
Sinus tachycardia	1 (5)	0 (0)
Stomach pain	1 (5)	0 (0)
Supraventricular tachycardia	1 (5)	0 (0)
Tumor pain	1 (5)	0 (0)

Table S7. Enrolling sites and principle investigators.

Institution	Principal Investigator	Patients Enrolled
Children's Healthcare of Atlanta - Egleston	Jason R. Fangusaro, MD	11
Baylor College of Medicine/Dan L Duncan Comprehensive Cancer Center	Jodi Muscal, MD	8
Riley Hospital for Children	Melissa K. Bear, MD	7
Children's Hospital of Philadelphia	Elizabeth Fox, MD	7
C S Mott Children's Hospital	Rajen Mody, MD	6
NYP/Columbia University/Herbert Irving Cancer Center	Alice Lee, MD	6
UCSF Medical Center-Mission Bay	Kieuhoa Tran Vo, MD MAS	5
Children's Hospital of Orange County	Josephine Hoatuyet Haduong, MD	4
Seattle Children's Hospital	Julie Ruggieri Park, MD	4
Children's National Medical Center	AeRang Kim, MD	3
National Institute of Health Clinical Center	Brigitte C. Widemann, MD	3
University of Minnesota/Masonic Cancer Center	Emily G. Greengard, MD	3
Cincinnati Children's Hospital Medical Center	Joseph G. Pressey, MD	3
Saint Jude Children's Research Hospital	Wayne Lee Furman, MD	3
Lucile Packard Children's Hospital Stanford University	Jay Michael S. Balagtas, MD	2
Ann and Robert H Lurie Children's Hospital of Chicago	Stewart Goldman, MD	2
Children's Hospital of Pittsburgh of UPMC	Jean M. Tersak, MD	2
Children's Hospital of Alabama	Gregory Kane Friedman, MD	1
Children's Hospital Colorado	Margaret Ellen Macy, MD	1
Dana-Farber/Harvard Cancer Center	Steven G. DuBois, MD	1
Washington University School of Medicine	Robert J. Hayashi, MD	1
Oregon Health and Science University	Linda Claudette Stork, MD	1
Children's Hospital of Wisconsin	Paul David Harker-Murray, MD PhD	1

Table S8. Table of Amendments

Amendment	Summary
Amendment 2B	Inclusion of non-statistical melanoma cohort
Amendment 2C	Inclusion of patients with non-measurable neuroblastoma to cohort B
Amendment 3	Recommendation for management of pleural effusions
Amendment 4	Inclusion of relapsed lymphoma patients post-allogeneic transplant

Children's Oncology Group Data Sharing Statement

The Children's Oncology Group Data Sharing policy describes the release and use of COG individual subject data for use in research projects in accordance with National Clinical Trials Network (NCTN) Program and NCI Community Oncology Research Program (NCORP) Guidelines. Only data expressly released from the oversight of the relevant COG Data and Safety Monitoring Committee (DSMC) are available to be shared. Data sharing will ordinarily be considered only after the primary study manuscript is accepted for publication. For phase 3 studies, individual-level de-identified datasets that would be sufficient to reproduce results provided in a publication containing the primary study analysis can be requested from the NCTN/NCORP Data Archive at https://nctn-data-archive.nci.nih.gov/. Data are available to researchers who wish to analyze the data in secondary studies to enhance the public health benefit of the original work and agree to the terms and conditions of use. For non-phase 3 studies, data are available following the primary publication. An individual-level de-identified dataset containing the variables analyzed in the primary results paper can be expected to be available upon request. Requests for access to COG protocol research data should be sent to: datarequest@childrensoncologygroup.org. Data are available to researchers whose proposed analysis is found by COG to be feasible and of scientific merit and who agree to the terms and conditions of use.

For all requests, no other study documents, including the protocol, will be made available and no end date exists for requests. In addition to above, release of data collected in a clinical trial conducted under a binding collaborative agreement between COG or the NCI Cancer Therapy Evaluation Program (CTEP) and a pharmaceutical/biotechnology company must comply with the data sharing terms of the binding collaborative/contractual agreement and must receive the proper approvals.

Activated: February 2, 2015
Closed:

Version Date: 05/23/2019
Amendment #: 9

CHILDREN'S ONCOLOGY GROUP

ADVL1412

A PHASE 1/2 STUDY OF NIVOLUMAB (IND# 124729) 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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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.

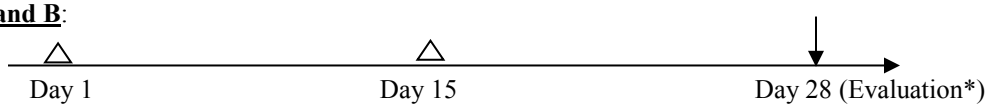
Part C will enroll all histologies with the same eligibility criteria required for enrollment on Part A with the goal of identifying the RP2D of the combination of nivolumab plus ipilimumab using a rolling 6 design. Patients will be monitored for response and toxicity using standard criteria.

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).

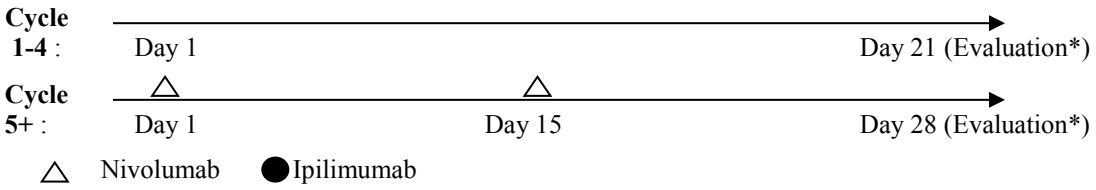
Part E will evaluate alternative dosing of nivolumab (1 mg/kg) in combination with ipilimumab (3 mg/kg) in rhabdomyosarcoma or Ewing sarcoma/Peripheral PNET.

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.

[redacted]

[redacted]

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

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. Stem Cell Infusion (with or without TBI):
   - Allogeneic (non-autologous) bone marrow or stem cell transplant, or any stem cell infusion including DLI or boost infusion: ≥ 100 days after infusion, no evidence of GVHD and no requirement for immunosuppression.
   - Autologous stem cell infusion including boost infusion: ≥ 42 days.

i. 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.).

j. 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 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.

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

4.2.12 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) 1 mg/kg on Day 1	Nivolumab (IV over 60 min) 3 mg/kg on Days 1 and 15

	Ipilimumab (IV over 90 min) 1 mg/kg on Day 1	
2	Nivolumab (IV over 60 min) 3 mg/kg on Day 1 Ipilimumab (IV over 90 min) 1 mg/kg on Day 1	Nivolumab (IV over 60 min) 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) 3 mg/kg on Day 1 Ipilimumab (IV over 90 min) 1 mg/kg on Day 1	Nivolumab (IV over 60 min) 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 [redacted]

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.

	• 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. 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. • 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. • 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. 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. • 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. • Patient should be monitored until the investigator is comfortable that the symptoms will not recur. • Nivolumab/ipilimumab will be permanently discontinued. 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). 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.
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) • Continue protocol therapy	**If persists > 1-2 weeks or recurs:** • Consider skin biopsy • Hold protocol therapy • Consider 0.5-1 mg/kg/day methylprednisolone IV or oral equivalent • Once improving, taper steroids over at least 1 month • Consider prophylactic antibiotics for opportunistic infections **If worsens:** Treat as Grade 3/4
Grade 3/4 Rash	• Hold infusion • Consider skin biopsy • Dermatology consult • 0.5-1 mg/kg/day methylprednisolone IV or IV equivalent	**If improves to Grade 1:** • Taper steroids over at least 1 month, • 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 dose level.
Grade 3	Off protocol therapy unless DLT exception in Section 5.4.1 is met.
Grade 4	Off protocol therapy
See Appendix IX for values that represent thresholds between CTCAE grades. Continued treatment of active immune mediated hepatitis may exacerbate ongoing inflammation. Holding drug to evaluate LFT changes and early treatment are recommended. 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.

Pancreatitis; Amylase/Lipase	**Management/Next Dose of Nivolumab ± Ipilimumab**
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. 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* AST or ALT, and/or bilirubin increased	• Continue protocol therapy	• Continue routine LFT monitoring per Table 8.1 **If worsens:** • Treat as Grade 2 or 3/4
Grade 2* AST or ALT, and/or bilirubin increased	• Hold infusion • Increase LFT monitoring to every 3 days	**If improves to baseline:** • Continue routine LFT monitoring per Table 8.1 • Resume protocol therapy **If elevations persist >5-7 days or worsen:** • 0.5-1 mg/kg/day methylprednisolone IV or oral equivalent • When LFT returns to grade 1 or baseline, taper steroids over at least 1 month • Consider prophylactic antibiotics for opportunistic infections

Toxicity (CTCAE v.5)	Management	Follow-up
Grade 3 or 4* AST or ALT, <u>and/or</u> bilirubin increased	• Discontinue protocol therapy • Increase LFT monitoring to every 1-2 days • 1-2 mg/kg/day methylprednisolone IV or oral equivalent** • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	**If improves to Grade 2:** • Taper steroids over at least 1 month **If does not improve in > 3-5 days, worsens or rebounds:** • Add mycophenolate mofetil 600 mg/m^2/dose (max 1 g/dose) BID • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

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

*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

<u>Diarrhea/ Colitis</u>	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
Grade 4	Off protocol therapy
Patients who require steroids should be taken off study treatment. Please evaluate pituitary function prior to starting steroids if possible without compromising acute care. 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	

<u>Other GI N-V</u>	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

Other GI N-V	Management/Next Dose of Nivolumab ± Ipilimumab
	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 • Symptomatic treatment	• Close monitoring for worsening symptoms • Educate patient to report worsening immediately **If worsens:** • 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. • Part C, D, or E discontinue protocol therapy Symptomatic treatment	**If persists > 5-7 days or recurs:** • 0.5-1 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month • Consider prophylactic antibiotics for opportunistic infections **If worsens or persists > 3-5 days with oral steroids:** • Treat as Grade 3 or 4
Grade 3 or 4 Diarrhea or Colitis	• Discontinue protocol therapy • 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent • Add antibiotics for opportunistic infections • Consider lower endoscopy	**If improves:** • Continue steroids until grade 1, then taper over at least 1 month **If persists > 3-5 days or recurs after improvement:** • 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 • Monitor for symptoms ever 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks **If worsens:** • Treat as Grade 2 or 3/4
Grade 2 Pneumonitis	• Hold infusion • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1 to 2 mg/kg/day methylprednisolone IV or oral equivalent • Consider bronchoscopy, lung biopsy	• Re-image every 1-3 days **If improves:** • When symptoms return near baseline, taper steroids over at least 1 month • Consider prophylactic antibiotics **If not improving after 2 weeks or worsening:** • Treat as Grade 3 or 4

Toxicity (CTCAE v.5)	Management	Follow-up
Grade 3 or 4 Pneumonitis	• Discontinue protocol therapy • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	**If improves to baseline:** • Taper steroids over at least 6 weeks **If not improving after 48 hours or worsening:** • 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. • For grade 1 pleural effusion or Grade 1 or 2 ascites, monitor with physical exam and consider additional imaging. • 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. • 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. • 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 • Initiate methylprednisolone 2 mg/kg/day IV or oral equivalent with plan to taper as tolerated. • 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 **If worsens:** • Treat as Grade 2 or 3/4
Grade 2* Neurological Toxicity	• Hold infusion • Treat symptoms per local guidelines • Consider 0.5 to 1 mg/kg/day methylprednisolone IV or oral equivalent	**If improves to baseline:** • within 7 days resume protocol therapy, if persists >7 days discontinue protocol therapy **If worsens:** • Treat as Grade 3/4

Toxicity (CTCAE v.5)	Management	Follow-up
Grade 3/4 Neurological Toxicity**	• Discontinue protocol therapy • Obtain neurology consult • Treat symptoms per local guidelines • 1-2 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	**If improves to Grade 2:** • Taper steroids over at least 1 month **If worsens or atypical presentation:** • 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. 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 • 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 • Consider endocrinology consult	
Symptomatic Endocrinopathy	• Evaluate endocrine function • Consider pituitary scan **Symptomatic with abnormal lab/pituitary scan:** • Hold infusion • 1-2 mg/kg/day methylprednisolone IV or oral equivalent • Initiate appropriate hormone therapy **No abnormal lab/pituitary MRI scan but symptoms persist:** • Repeat labs in 1-3 weeks/ MRI in 1 month	**If improves (with or without hormone replacement):** • Taper steroids over at least 1 month • Consider prophylactic antibiotics for opportunistic infections • 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 • Rule out sepsis • Stress dose of IV steroids with mineralocorticoid activity • IV fluids • Consult endocrinologist • 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:** • Treat as Grade 2/3 or 4
Grade 2 or 3 Creatinine Increased	• Hold infusion • Monitor creatinine every 2-3 days • 0.5-1 mg/kg/day methylprednisolone or oral equivalent • Consider renal biopsy	**If improves to Grade 1 or baseline:** • Taper steroids over at least 1 month • Consider prophylactic antibiotics for opportunistic infections. **If elevations persists > 7 days or worsen:** • Treat as Grade 4
Grade 4 Creatinine Increased	• Discontinue protocol therapy • Monitor creatinine weekly • 1 to 2 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	**If improves to Grade 1:** • 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 Add antithymocyte globulin (ATG) or tacrolimus if no improvement. Off treatment.
**Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin* ***Patients with evidence of myositis without myocarditis may be treated according as "other event"* 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 $AUC_{(0\text{-}21)}$.

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 and Cytokine 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, 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).

[redacted]

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).
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[52] 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.[53] 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[52] will be used for Parts D1-6.

	Cumulative Number	Decision

	of Responses	
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.[53] 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

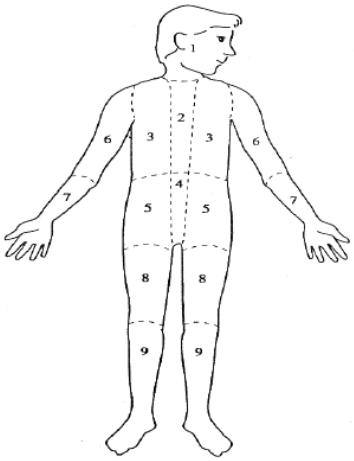
scale[14] as outlined below. Central review responses will be used to assess efficacy for study endpoint. See Section 8.2.1 for details on transferring images to the Imaging Research Center.

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 10th 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.

[redacted]

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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: |__|__|:|__|__| 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: |__|__|:|__|__| 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: |__|__|:|__|__| 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: |__|__|:|__|__| 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: _____
Patient ID #: _____
Accession #: _____
Sample Date: _____
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 3 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: |__|__|:|__|__| 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 QTc

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.