NRG ONCOLOGY

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SUMMARY OF CHANGES

For Protocol Amendment #3 to: NRG-GY002

NCI Protocol #: NRG-GY002
Local Protocol #: NRG-GY002

NCI Version Date: 01/31/2017
Protocol Date:

This amendment is being submitted in response to an RRA from Dr. Howard Streicher (streicherh@ctep.nci.nih.gov):

#	Section	Page(s)	Change
1	Title Page	1, 2	• NCI Version Date is now 01/31/2017. • Includes Amendments #1-3. • Amendment Date has been added to the Document History table.
	4.2	17	The *note now reads: "*As clinically indicated during treatment for symptoms or physical signs of congestive heart failure or cardiomyopathy."
2	6.312 and 6.3.13	26, 27	• Drug modification table for Cardiac Toxicities has been added as Section 6.3.12. • All Other Events is now Section 6.3.13.

3	7.31	29-36	Updated BMS-936558 CAEPR, Version 2.2, November 15, 2016, has been inserted:
			• Added New Risk:
			  • Less Likely: Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome)
			  • Rare but Serious: Immune system disorders - Other (GVHD in the setting of allotransplant); Myositis; Nervous system disorders - Other (encephalitis)
			  • Also Reported on BMS-936558 Trials But With Insufficient Evidence for Attribution: Immune system disorders - Other (autoimmune thrombotic microangiopathy)
			• Increase in Risk Attribution:
			  • Changed to Less Likely from Rare But Serious: Infusion related reaction

#	Section	Page(s)	Change
			• <u>Changed to Rare but Serious from Also Reported on BMS-936558 Trials But With Insufficient Evidence for Attribution:</u> Pericarditis • <u>Deleted Risk:</u> • <u>Also Reported on BMS-936558 Trials But With Insufficient Evidence for Attribution:</u> Alkaline phosphatase increased; Arthritis; CPK increased; Encephalitis infection; Endocrine disorders - Other (autoimmune thyroiditis); Endocrine disorders - Other (hypopituitarism); Enterocolitis; Hepatobiliary disorders - Other (autoimmune hepatitis); Investigations - Other (CRP increased); Investigations - Other (eosinophil count increased); Investigations - Other (thyroxine free increased); Investigations - Other (tri-iodothyronine free decreased); Nervous system disorders - Other (autoimmune neuropathy); Renal and urinary disorders - Other (nephritis); Respiratory failure; Respiratory, thoracic and mediastinal disorders - Other (interstitial lung disease); Respiratory, thoracic and mediastinal disorders - Other (lung infiltration); Stroke; Wheezing; White blood cell decreased • <u>Provided Further Clarification:</u> • The following footnote #7 was added: "Complications including hyperacute graft-versus-host disease (GVHD), some fatal, have occurred in patients receiving allo stem cell transplant (SCT) after receiving BMS-936558 (Nivolumab, MDX-1106). These complications may occur despite intervening therapy between receiving BMS-936558 (Nivolumab, MDX-1106) and allo-SCT."
	IC		Additional changes have been made to the IC document.

NRG ONCOLOGY

NRG-GY002
(ClinicalTrials.gov NCT #02257528)

A Phase II Evaluation of Nivolumab, a Fully Human Antibody against PD-1, in the Treatment of Persistent or Recurrent Cervical Cancer

NCI Version Date 01/31/2017
Includes Amendments #1-3

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI).

Lead Organization: NRG / NRG Oncology
This study is limited to NRG Oncology participation

Coordinating Center:
NRG Oncology
Four Penn Center, 1600 JFK Blvd., Suite 1020
Philadelphia, PA 19103

Study Team	
Study Chair	**Study Co-Chair**
Alessandro D. Santin, M.D./Gynecologic Oncology	**Michael Frumovitz, M.D., M.P.H.**
Yale University School of Medicine	MD Anderson Cancer Center
Department of Obstetrics and Gynecology	Dept of Gynecologic Oncology and
LSOG Bld. Room 305, 333 Cedar Street, PO Box 208063	Reproductive Medicine
New Haven, CT 06520-8063	Unit 1362, CPB 6.3562
203-737-4450/FAX: 203-737-4339	1515 Holcombe Blvd
Alessandro.santin@yale.edu	Houston, TX 77030
	713-792-9599/FAX: 713-792-7586
	mfrumovitz@mdanderson.org
Translational Science Co-Chair	
Samir Khleif, MD	**Translational Scientist**
Georgia Health Sciences Center	**Heather A Lankes, PhD, MPH**
Cancer Research Center	NRG SDMC-Buffalo Office
1120 15th St, CN 2133	Roswell Park Cancer Institute
Augusta, GA 30912	Elm & Carlton Streets
706-721-0570	Buffalo NY 14263
khleif@gru.edu	716-845-8508/FAX: 716-845-8393
	lankesh@nrgoncology.org

Correlative Scientists	
Warner Huh, MD	**Michael Birrer, MD, PhD**
University of Alabama at Birmingham	Massachusetts General Hospital
Department of OB/GYN	Yawkey 9072
618 20th St S, 538 OHB	55 Fruit St
Birmingham, AL 35233	Boston, MA 02114
205-934-4986	317-724-4800
whuh@uab.edu	mbirrer@partners.org
Data Manager and/or Data Operations Center	**Statistician**
Sandra Dascomb, MS, MT (ASCP)	Wei Deng, Ph.D.
NRG SDMC-Buffalo Office	NRG SDMC-Buffalo Office
Roswell Park Cancer Institute	Roswell Park Cancer Institute
Elm and Carlton Streets	Elm and Carlton Streets
Buffalo, NY 14263-0001	Buffalo, NY 14263-0001
716-845-5702/FAX: 716-845-8393	716-845-5702/FAX: 716-845-8393
sdascomb@gogstats.org	wdeng@gogstats.org
Protocol Coordinator	**Research Nurse**
Meg Colahan, M.A.	Lisa D. Baker, RN, BSN, OCN
NRG Oncology	Yale University School of Medicine
Four Penn Ctr, 1600 JFK Blvd, Ste 1020	Gyn Oncology
Philadelphia, PA 19103	333 Cedar Street, FMB340
215-854-0770/FAX: 215-854-0716	New Haven, CT 06520
mcolahan@gog.org	203-785-6398/FAX: 203-785-7480
	Lisa.baker@yale.edu

Protocol Agent

Agent	Supply	NSC #	IND #	IND Sponsor
Nivolumab	CTEP	748726	125336	DCTD, NCI

Participating Sites

☒ U.S.
☐ Canada
☐ Approved International Member Sites

Document History

	Version/Update Date	Broadcast Date
Amendment 3	**01/31/2017**	
Closure	**04/01/2016**	**06/09/2016**
Re-Activation and Amendment 2	**04/01/2016**	**04/25/2016**
Amendment 1	**03/07/2016**	**03/21/2016**
Temporary Closure	**04/24/2015**	**08/24/2015**
Activation	**04/24/2015**	**05/18/2015**

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NRG-GY002
SCHEMA

Patients must have persistent, recurrent or metastatic squamous cell carcinoma, adenosquamous carcinoma or adenocarcinoma of the cervix with documented disease progression (disease not amendable to curative therapy).

Patients must have had one prior systemic chemotherapeutic regimen for management of persistent, recurrent or metastatic disease

Nivolumab 3 mg/kg IV every 2 weeks (+/- 2 days) for 4 doses followed by an additional 42 doses 3mg/kg IV q 2 weeks for a maximum of 46 doses over 92 weeks until disease progression or adverse effects prohibit therapy, whichever comes first.

One Cycle = 2 doses (Day 1 Dose and Day 15 Dose) (03/21/2016)

1. OBJECTIVES

1.1 Primary Objectives

1.1.1 To assess the antitumor activity (proportion of objective response by RECIST 1.1 criteria) of nivolumab with objective tumor response in patients with persistent, recurrent or metastatic carcinoma of the cervix

1.1.2 To determine the nature and degree of toxicity of nivolumab as assessed by CTCAE in patients with persistent, recurrent or metastatic carcinoma of the cervix

1.2 Secondary Objective

To estimate the duration of progression-free survival (PFS) and overall survival (OS).

1.3 Translational Science Objectives

1.3.1 To systematically evaluate PD-1 and B7-H1 (i.e., PD-1 Ligand) expression in tumor infiltrating lymphocytes (TILs) and cervical cancer cells and explore their correlations with objective response, PFS, and OS in nivolumab-treated patients with PD-1 and B7-H1 scoring results.

1.3.2 To explore the composition of immune infiltrates in tumor specimens/biopsies from primary and/or metastatic/recurrent sites with selected markers including (but not limited) to CD4+,CD8+, FoxP3, CD25, LAG-3, TIM-3, and ICOS and their correlations to objective response, PFS and OS in nivolumab-treated patients.

1.3.3 To evaluate HPV status and to explore the changes of pre- and post-immune therapy responses to HPV16/18/31/35/45 E7 antigens in patients peripheral blood lymphocytes (PBL) and serum using proliferative and IFN-gamma ELISPOT (cellular immunity) and serological (ELISA) assays.

1.3.4 To explore the levels of circulating tumor cells (CTCs) pre-treatment and at 8 and 12 weeks and their association with patient outcome.

2. BACKGROUND

The usual treatment for recurrent or metastatic cervical cancer is a combination of paclitaxel and cisplatin or paclitaxel, cisplatin and bevacizumab.(Monk et al, 2009; Tewari et al, 2014) This treatment, although not curative, results in median survival times of approximately one to 1.5 years. Once patients progress after this initial therapy for recurrent or metastatic disease, options are limited (there are no FDA approved or NCCN level 1 or 2A therapies available).

Human Papillomavirus (HPV) DNA is detected in more than 99% of cervical cancer specimens and a large portion of these tumors are associated with HPV types 16 and 18. E6 and E7 play a major role in the transformation of HPV-infected cervical keratinocytes and these viral antigens are consistently expressed in HPV-associated neoplasms and may represent ideal targets for cervical cancer immunotherapy.(Santin et al, 1999; Santin et al, 2006; Santin et al, 2008) However, despite the great potential of immunotherapeutic approaches to treat chemotherapy/radiation resistant cervical cancer, tumor immunity is hindered by the expression of a series of cell surface molecules known as immune checkpoints in the suppressive tumor microenvironment.(Mellman et al, 2011)

Compelling evidence indicates that B7 molecules (i.e., B7-1/CD80, B7-2/CD86, B7-H1/PDL1, B7-H2/L-ICOS, B7-DC, B7-H3 and B7-H4) and their ligands (i.e., CTLA-4, CD28, PD-1, ICOS) not only provide crucial positive signals to stimulate and support T-cell activation, but can also offer negative signals that control and suppress potentially protective T-cell responses against spontaneously arising and virally-induced human tumors.(Mellman et al, 2011) Expression of these molecules on the surface of cervical tumor cells, tumor associated macrophages (TAM) and/or dendritic cells (DC), may attenuate or abrogate the ability of the immune system to successfully eliminate strongly antigenic (i.e., virus-infected) tumors such as cervical cancer.(Mellman et al, 2011)

Because these negative signals in multiple human solid tumors have been shown to be largely provided by programmed death-1 (PD-1), blockade of PD-1/PD-L1 co-inhibitory pathways by novel monoclonal antibodies may represent an innovative, potentially highly effective therapeutic approach to reverse immune suppression while inducing tumor-specific immunity in cervical cancer patients. Consistent with this hypothesis, exciting results have recently been reported in the clinical setting against multiple human cancers by the use of a fully-human antibody that targets the inhibitory receptor PD1 expressed on activated T-cells.(Topalian et al, 2012) In this study, objective response rates (ORs) across dose cohorts, as measured by standard RECIST criteria, ranged from 6% to 32% in non–small-cell lung cancer, 19% to 41% in metastatic melanoma and 24% to 31% in renal-cell cancer. Most of the responses were durable in these patients and the toxicity profile of nivolumab was found to be safer than that of ipilimumab (i.e., a monoclonal antibody targeting CTLA4, another crucial inhibitory molecule expressed on activated T cells, recently approved by the FDA for treatment of advanced melanoma patients).(6, 7) Importantly, an additional study targeting the blockade of PD-L1 (i.e., B7H1 or PD1-ligand) also induced durable tumor regression (objective response rate of 6 to 17%) and prolonged stabilization of disease (rates of 12 to 41% at 24 weeks) in patients with advanced cancers, including non–small-cell lung cancer, melanoma, and renal-cell cancer. (Brahmer et al, 2012)

PD-1 and PD-L1 expression on cervical T cells and DCs, respectively, has been recently reported to be associated with high risk-HPV positivity and to be increased in parallel with increasing cervical intraepithelial neoplasia (CIN) grade.(Yang et al, 2013) Furthermore, increased expression of PD-1 and its ligand PD-L1 correlates with impaired cell-mediated immunity in high-risk HPV-related CIN.(Yang et al, 2013) Finally, in cervical cancer, PD-1 is expressed by a vast number of infiltrating CD8 T cells, suggesting that blocking of PD-1 could have therapeutic potential in cervical cancer patients with recurrent and/or metastatic disease unresponsive to treatment.(Karim et al, 2009)

Taken together, these studies strongly validate the importance of the PD-1-PD-L1 pathway for the treatment of patients harboring multiple human solid tumors, including virally-infected tumors such as cervical cancer.

2.1 Nivolumab

Nivolumab (BMS-936558, MDX-1106, and ONO-4538) is a fully human monoclonal immunoglobulin G4 (IgG4) antibody (HuMAb) that is specific for human programmed death-1 (PD-1, cluster of differentiation 279 [CD279]) cell surface membrane receptor

(Investigator Brochure, 2013). PD-1 is a negative regulatory molecule that is expressed transiently following T-cell activation and on chronically stimulated T cells characterized by an "exhausted" phenotype. Nivolumab binds to cynomolgus monkey PD-1 but not mouse, rat, or rabbit molecules. Clinical activity of nivolumab has been observed in patients with melanoma, non-small cell lung cancer (NSCLC), and renal cell carcinoma (RCC). The combination of nivolumab and ipilimumab (anti-cytotoxic T lymphocyte associated antigen-4 [anti-CTLA-4]) in a phase 1/2 trial showed markedly enhanced clinical activity with an acceptable safety profile in melanoma patients (Wolchok et al., 2013).

The clinical use of monoclonal antibodies to T-cell inhibitory receptors has provided transformative information on the nature of the immune system and cancer. An emerging picture suggests that endogenous immune responses can mediate effective tumor regression and/or improved survival even in patients with large volume tumors resistant to other forms of therapy. Some of the unique features of this type of therapy, based largely on experience in advanced melanoma, include: improved overall survival (OS) with or without radiographic responses or improved progression-free survival (PFS); responses that may be delayed or occur after radiographic disease progression; combinations of immune modulators with enhanced or novel activities (in the example of ipilimumab and nivolumab); and toxicity that is almost exclusively immune or inflammatory in nature. It is not yet clear what factors determine responses and which components of the immune system are needed for this to occur. It seems likely that both memory helper and effector cells would be needed to sustain long-term responses. Increasing emphasis has been placed on understanding the relationships of the tumor, cellular infiltrate, and immunologic milieu surrounding each tumor.

PD-1, a 55-kDa type 1 transmembrane protein, is a member of the CD28 family of T-cell co-stimulatory receptors that include Ig super family member CD28, CTLA-4, inducible co-stimulator (ICOS), and B and T lymphocyte attenuator (BTLA) (Investigator Brochure, 2013). PD-1 is transiently but highly expressed on activated T cells functioning to limit immune effectors at the site of activation. Chronic stimulation may prevent the re-methylation of the PD-1 gene leading to continuous expression and characterizes a state of "exhausted" T cells that lose function and proliferative capacity while enhancing a suppressive tumor microenvironment. PD-1 may act together with other T-cell modulating molecules, including CTLA-4, TIM-3, lymphocyte-activation gene 3 (LAG-3) as well as indoleamine-pyrrole 23-dioxygenase 1 (IDO-1), cytokines, and transforming growth factor beta (TGF-beta).

Two ligands specific for PD-1 have been identified: PD-ligand 1 (PD-L1, also known as B7-H1 or CD274, expressed on tumor, antigen-presenting cells [APCs], and dendritic cells [DCs]) and PD-L2 (also known as B7-DC or CD273, expressed on endothelial cells). The interaction of PD-1 with PD-L1 and PD-L2 results in negative regulatory stimuli that down-modulate the activated T-cell immune response through SHP-1 phosphastase.

PD-1 knockout mice develop strain-specific lupus-like glomerulonephritis (C57BL/6)

and cardiomyopathy (BALB/c). In transplantable tumor models that expressed PD-1 and LAG-3 on tumor-infiltrating CD4+ and CD8+ T cells dual anti-LAG-3/anti-PD-1 antibody treatment cured most mice of established tumors that were largely resistant to single antibody treatment (Woo et al., 2012). Despite minimal immunopathologic sequelae in PD-1 and LAG-3 single knockout mice, dual knockout mice abrogated self-tolerance with resultant autoimmune infiltrates in multiple organs, leading to eventual lethality.

PD-L1 expression is found on a number of tumors, and is associated with poor prognoses based on OS in many tumors, including melanoma (Taube et al., 2012), renal (Thompson et al., 2004; Thompson et al., 2005; Thompson et al., 2006), esophageal (Ohigashi, et al. 2005), gastric (Wu et al., 2006), ovarian (Dong et al., 2003), pancreatic (Nomi, et al., 2007), lung (Zitvogel, et al., 2006), and other cancers (Investigator Brochure, 2013).

The PD-1/PD-L1 axis plays a role in human infections, particularly in hepatitis C virus (HCV) and human immunodeficiency virus (HIV). In these cases, high expression levels of PD-1 were found in viral-specific CD8+ T cells that also display a non-responsive or exhausted phenotype. Non-responsive PD-1-high T cells were observed in simian immunodeficiency virus (SIV) infection in rhesus macaques. Treatment of SIV-infected macaques with an anti-PD-1 mAb (3 mg/kg x4) resulted in decreased viral loads and increased survival along with expanded T cells with increased T-cell functionality.

2.1.1 Nonclinical Development of Nivolumab

In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, nivolumab alone was well tolerated (Investigator Brochure, 2013). Combination studies have highlighted the potential for toxicity when combined with ipilimumab, MDX-1408, and BMS-986016. Nivolumab bound specifically to PD-1 (and not to related members of the CD28 family such as CD28, ICOS, CTLA-4, and BTLA) with a Kd = 3.06 nM. A surrogate rat anti-mouse PD-1 antibody (4H2) was derived and expressed as chimeric IgG1 murine antibody. Antitumor activity was seen for several tumor models, including colon carcinoma and fibrosarcoma.

2.1.2 Clinical Development of Nivolumab

Nivolumab is being evaluated as monotherapy and in combination with cytotoxic chemotherapy, other immunotherapy (such as ipilimumab), anti-angiogenesis therapy, and targeted therapies in completed and ongoing BMS-sponsored clinical trials in NSCLC, melanoma, RCC, hepatocellular carcinoma (HCC), gastrointestinal (GI) malignancies including microsatellite instability (MSI) in colorectal cancer, and triple-negative breast cancer (TNBC) with an expanding group of indications (Investigator Brochure, 2013). In addition, two investigator-sponsored trials (ISTs) of nivolumab in combination with a peptide vaccine in melanoma are being conducted in the adjuvant setting and advanced disease.

Seven nivolumab studies were conducted in Japan, including six studies in advanced solid tumors and recurrent or unresectable stage III/IV melanoma sponsored by Ono Pharmaceuticals Co. Ltd., and one IST in recurrent or advanced platinum-refractory

ovarian cancer.

2.1.2.1 Pharmacokinetics

Pharmacokinetics (PK) of nivolumab was linear in the range of 0.3 to 10 mg/kg, with dose-proportional increases in maximum serum concentration (Cmax) and area under the concentration-time curve from time zero to infinity (AUC0-∞), with low to moderate inter-subject variability observed at each dose level (Investigator Brochure, 2013). Clearance of nivolumab is independent of dose in the dose range (0.1 to 10 mg/kg) and tumor types studied. Body weight normalized dosing showed approximately constant trough concentrations over a wide range of body weights. The mean terminal elimination half-life of BMS-936558 is 17 to 25 days consistent with the half-life of endogenous IgG4.

2.1.2.2 Efficacy

In a phase 1 (1, 3, and 10 mg/kg nivolumab doses) dose-escalation study the 3 mg/kg dose was chosen for expanded cohorts. Among 236 patients, objective responses (ORs) (complete or partial responses [CR or PR]) were seen in NSCLC, melanoma, and RCC. ORs were observed at all doses (Sznol et al., 2013). Median OS was 16.8 months across doses and 20.3 months at the 3 mg/kg dose. Median OS across all dose cohorts was 9.2 months and 9.6 months for squamous and non-squamous NSCLC, respectively (Brahmer et al., 2013). In the RCC cohort, median duration of response was 12.9 months for both doses with 5 of the 10 responses lasting ≥1 year (Drake et al., 2013).

In an advanced melanoma phase 1 study, nivolumab and ipilimumab were administered IV every 3 weeks for 4 doses followed by nivolumab alone every 3 weeks for 4 doses (concurrent regimen) (Wolchok et al., 2013). The combined treatment was subsequently administered every 12 weeks for up to 8 doses. In a sequenced regimen, patients previously treated with ipilimumab received nivolumab every 2 weeks for up to 48 doses. In the concurrent regimen (53 patients), 53% of patients had an OR at doses 1 mg/kg nivolumab and 3 mg/kg ipilimumab, with tumor reduction of 80% or more (modified World Health Organization [mWHO] criteria). In the sequenced-regimen (33 patients), the objective response rate (ORR) was 20%.

In a phase 1 study of nivolumab plus platinum-based doublet chemotherapy (PT-doublet) in chemotherapy-naïve NSCLC patients, 43 patients were treated with nivolumab + PT-doublet (Rizvi et al., 2013). No dose-limiting toxicities (DLTs) were reported and total/confirmed ORRs were 43/33%, 40/33%, and 31/31% in nivolumab/gemcitabine/cisplatin, nivolumab/pemetrexed/cisplatin, and nivolumab/carboplatin/paclitaxel arms, respectively.

2.1.2.3 Toxicology

A maximum tolerated dose (MTD) of nivolumab was not defined (Topalian et al., 2012). Serious adverse events (SAEs) occurred in 32 of 296 patients (11%) similar to the immune-related inflammatory events seen with ipilimumab: pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis (with noted pulmonary toxicity resulting in 3 deaths. Renal failure, symptomatic pancreatic and DM, neurologic events, and vasculitis have also been reported.). In combination with ipilimumab in the concurrent-regimen group (Wolchok et al., 2013), grade 3 or 4 treatment-related events were noted in 53% of patients. Skin rash represents the majority of these event.

2.1.2.4 Pharmacodynamics/Biomarkers

Tumor-cell expression (melanoma) of PD-L1 was characterized in combination with ipilimumab with the use of IHC staining and pharmacodynamics changes in the peripheral-blood absolute lymphocyte count (Wolchok et al., 2013). With PD-L1 positivity defined as expression in at least 5% of tumor cells, biopsy specimens from 21 of 56 patients (38%) were PD-L1–positive. Among patients treated with the concurrent regimen of nivolumab and ipilimumab, ORs were observed in patients with either PD-L1–positive tumor samples (6 of 13 patients) or PD-L1–negative tumor samples (9 of 22). In the sequenced regimen cohorts, a higher number of overall responses was seen among patients with PD-L1–positive tumor samples (4 of 8 patients) than among patients with PD-L1–negative tumor samples (1 of 13) suggesting the possibility that these tumors have higher response rates to the combination. The relationship between PDL-1 expression and responses may not be present in patients treated with the combination. Tissue expression of PDL-2, interferon-γ (IFN- γ), IDO, and T cell CD8+ are of current interest. Until more reliable data based on standardized procedures for tissue collection and assays are available, PD-L1 status cannot be used to select patients for treatment at this time.

2.1.2.5 **Translational Science Background**

A variety of factors may potentially predict clinical response to nivolumab in cervical cancer patients. Accordingly, an exploratory objective of this study is to investigate in tumor specimens obtained at screening, and in peripheral blood taken both at screening (prior to the first dose of study drug) and during the study, biomarkers and their association with nivolumab treatment and treatment outcome (as outlined in section 11 and Appendix IV).

Briefly, PD-L1 expression has been reported in a number of human tumors, and associated with poor prognoses based on OS. However, limited information is available regarding PD-1 and PD-L1 expression on cervical HPV-infected tumor cells and T cells infiltrating cervical cancers (TIL). Accordingly, this study will systematically evaluate PD-1 and B7-H1 (i.e., PD-1 Ligand) expression in tumor infiltrating lymphocytes (TILs) and cervical cancer cells using standardized immunohistochemistry (IHC) techniques (Velcheti et al., 2014) and explore their correlations with objective response, PFS, and OS in nivolumab-treated patients with PD-1 and B7-H1 scoring results. We will explore the composition of immune infiltrates in tumor specimens/biopsies from primary and/or metastatic/recurrent sites with selected markers including (but not limited) to CD4+,CD8+, FoxP3, CD25, LAG-3, TIM-3, and ICOS and their correlations to objective response, PFS and OS in nivolumab-treated patients (Velcheti et al., 2014). We are also planning to evaluate HPV status and to explore the changes of pre- and post-immune therapy responses to HPV16/18/31/35/45 E7 antigens in patients peripheral blood lymphocytes (PBL) and serum using proliferative and IFN-gamma ELISPOT (cellular immunity) assays and a new streptavidin-biotin capture ELISA method to investigate anti-HPV E7 antibody prevalence in serum (Ravaggi et al., 2006). These explorative assays have previously been validated in studies using reagents obtained from both healthy women as well as cervical cancer patients vaccinated within Phase I clinical studies with HPV type 16 and 18 E7 antigen-loaded autologous dendritic

cells (DC) as a therapeutic cellular vaccine (Santin et al., 1999, Ravaggi et al., 2006, Santin et al., 2006, Santin et al., 2008). Finally, the levels of circulating tumor cells (CTCs) pre-treatment and at 8 and 12 weeks and their association with patient outcome we will be explored using multi-marker μ-nuclear magnetic resonance, as recently described (Ghazani et al, 2014).

2.2 Inclusion of Women and Minorities

NRG Oncology and NRG participating institutions will not exclude potential subjects from participating in this or any study solely on the basis of ethnic origin of socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the entire cervical cancer population treated by participating institutions.

3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILTY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the NRG Statistical and Data Management Center-Buffalo Office (716-845-5702).

3.1 Eligibility Criteria

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

3.1.1 Patients must have persistent, recurrent or metastatic squamous cell carcinoma, adenosquamous carcinoma or adenocarcinoma of the cervix with documented disease progression (disease not amendable to curative therapy). NOTE: the following cervical tumors are not eligible: minimal deviation/adenoma malignum, gastric type adenocarcinoma, clear cell carcinoma and mesonephric carcinoma. Histologic confirmation of the original primary tumor is required via the pathology report. **(04/25/2016)**

3.1.2 All patents must have measurable disease as defined by RECIST 1.1. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be ≥ 10 mm when measured by CT, MRI or caliper measurement by clinical exam; or ≥ 20 mm when measured by chest x-ray. Lymph nodes must be ≥ 15 mm in short axis when measured by CT or MRI.

3.1.3 Patients must have at least one "target" lesion" to be used to assess response on this protocol as defined by RECIST 1.1. Tumors within a previously irradiated field will be designated as "non-target" lesions unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

3.1.4 Appropriate for study entry based on the following diagnostic workup:

- History/physical examination within 28 days prior to registration;
- Imaging of target lesion(s) within 28 days prior to registration;
- Further protocol-specific assessments:
  - Recovery from adverse effects of recent surgery, radiotherapy or chemotherapy
  - Any other prior therapy directed at the malignant tumor including chemotherapy, biologic/targeted agents and immunologic agents must be discontinued at least three weeks prior to registration.

- Investigation agents must be discontinued for at least 30 days prior to registration.
- Any prior radiation therapy must be completed at least 4 weeks prior to registration.
- At least 4 weeks must have elapsed since any major surgery prior to registration.

3.1.5 **Prior Therapy**
Patients must have had one prior systemic chemotherapeutic regimen for management of persistent, recurrent or metastatic carcinoma of the cervix (e.g.; paclitaxel/cisplatin, paclitaxel/cisplatin/bevacizumab). Chemotherapy administered concurrent with primary radiation (e.g.; weekly cisplatin) is not counted as a systemic chemotherapy regimen. Adjuvant chemotherapy given following the completion of radiation therapy (or concurrent chemotherapy and radiation therapy) is not counted as a systemic chemotherapy regimen (e.g.; paclitaxel and carboplatin for up to 4 cycles). NOTE: Patients who have received more than one prior regimen are NOT eligible.

3.1.6 Age ≥ 18; because no dosing or adverse event data are currently available on the use of nivolumab in patients <18 years of age, children are excluded from this study, but will be eligible for future pediatric trials.

3.1.7 The trial is open to females only.

3.1.8 Performance Status of 0 or 1.

3.1.9 Adequate hematologic function within 14 days prior to registration defined as follows:
- ANC ≥ 1,500/ul
- Platelets ≥ 100,000/ul

3.1.10 Adequate renal function within 14 days prior to registration defined as follows:
- Creatinine ≤ 1.5 x institutional upper limit of normal (ULN) or CrCl ≥ 40mL/min using Cockcroft-Gault formula

3.1.11 Adequate hepatic function within 14 days prior to registration defined as follows:
- Bilirubin ≤ 1.5 x ULN
- ALT and AST ≤ 3 x ULN

3.1.12 **Normal thyroid function testing (TSH)** within 14 days prior to registration

3.1.13 The patient or a legally authorized representative must provide study-specific informed consent and authorization permitting release of personal health information prior to study entry.

3.2 **Ineligibility Criteria**
Patients with one or more of the following conditions are NOT eligible for this study.

3.2.1 Patients who have had prior therapy with nivolumab or with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune check point pathways.

3.2.2 History of severe hypersensitivity reaction to any monoclonal antibody.

3.2.3 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years.

3.2.4 Patients with uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure and unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.5 Patients who are pregnant or nursing. The effects of nivolumab on the developing

human fetus are unknown. For this reason, women of child-bearing potential (WOCBP) must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. WOCBP should use an adequate method to avoid pregnancy for 23 weeks after the last dose of investigational drug. WOCBP must have a negative serum or urine pregnancy test (minimum sensitivity 25 IV/L or equivalent units of HCG) within 24 hours prior to the start of nivolumab. Women must not be breastfeeding.

Women who are not of childbearing potential (i.e., who are postmenopausal or surgically sterile or have undergone definitive radiation) do not require contraception.

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

WOCBP receiving nivolumab will be instructed to adhere to contraception for a period of 23 weeks after the last dose of investigational product. This duration has been calculated using the upper limit of the half-life of nivolumab (25 days) and are based on the protocol requirement that WOCBP use contraception for 5 half-lives plus 30 days.

Should a woman become pregnant or suspect she is pregnant while she is participating in this study, she should inform the treating physician immediately.

3.2.6 Patients with known brain metastases or leptomeningeal metastases are excluded unless the following conditions are met:

- Metastases have been treated and there is no magnetic resonance imaging (MRI) evidence of progression for at least 4 weeks after treatment is complete (must be confirmed within 28 days prior to the first dose of nivolumab administration)
- There must also be no requirement for immunosuppressive doses of systemic corticosteroids (>10 mg/day prednisone equivalents) for at least 2 weeks prior to study drug administration.

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

Cervical cancer patients on combination antiretroviral therapy and those with other acquired/inherited immunodeficiencies are excluded from this protocol secondary to the possibility the immune condition and medications may affect tumor response to nivolumab as well as the higher risk of active opportunistic infections.
Patients should be excluded if they have a positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection.

Autoimmune hepatotoxicity is a side effect of immune checkpoint inhibitors as a class.

Hepatitis B and C subjects with active/chronic disease may have an increased risk for development of nivolumab-induced liver-autoimmunity and for this reason are excluded from this protocol.

3.2.8 Patients with active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including systemic corticosteroids, should be excluded. These include but are not limited to patients with a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as SLE, connective tissue diseases, scleroderma, inflammatory bowel disease (IRB), Crohn's, ulcerative colitis, hepatitis; and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome should be excluded because of the risk of recurrence or exacerbation of disease. Patient with vitiligo, endocrine deficiencies including thyroiditis managed with replacement hormones including physiologic corticosteroids are eligible. Patients with rheumatoid arthritis and other arthropathies, Sjogren's syndrome and psoriasis controlled with topical medication and patients with positive serology, such as antinuclear antibodies (ANA), anti-thyroid antibodies should be evaluated for the presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible.
NOTE: Patients are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger (precipitating event).

3.2.9 Patients should be excluded if they have a condition requiring systemic treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses ≤10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease. Patients are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if ≤10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (*e.g.*, contrast dye allergy) or for treatment of non-autoimmune conditions (*e.g.*, delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

3.2.10 Patients who have had evidence of active or acute diverticulitis, intra-abdominal abscess, abdominal/pelvic fistula, gastrointestinal perforation, GI obstruction and/or who require parenteral hydration and/or nutrition.

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP

4.1 PRE-TREATMENT ASSESSMENTS (03/21/2016) (04/25/2016)

Assessments	Prior to Registration (calendar days)	Prior to Treatment (Cycle 1, Day 1)
History and Physical	≤ 28 days	≤ 28 days
Vital Signs (heart rate, temperature, blood pressure)	≤ 28 days	≤ 28 days
Height	Any prior documentation on adult medical record of treating site	
Weight	≤ 28 days	≤ 28 days
Performance Status	≤ 28 days	≤ 28 days
Toxicity Assessment	≤ 14 days	≤ 14 days
Concurrent Medications	≤ 14 days	≤ 14 days
CBC/Differential/Platelets	≤ 14 days	≤ 14 days
Chemistries (including Sodium, Potassium, Chloride, bicarbonate, Calcium, Glucose, BUN, Creatinine (and/or Creatinine Clearance), Total Bilirubin, Total Protein, ALT, AST, Alkaline Phosphatase, Albumin)	≤ 14 days	≤ 14 days
TSH	≤ 14 days	≤ 14 days
Testing for hepatitis C (HCV) and hepatitis B (HBV)	≤ 14 days	≤ 14 days
Pregnancy Test (for patients of child bearing potential)	≤ 14 days	≤ 24 hours
Chest imaging (X-ray or CT scan of the chest)	≤ 28 days	≤ 28 days
Radiographic Tumor Measurement (CT or MRI of the abdomen and pelvis)	≤ 28 days	≤ 28 days
ECG	≤ 28 days	

4.2 ASSESSMENTS DURING TREATMENT (03/21/2016) (04/25/2016)

Assessments	**Prior to Each Nivolumab Dose (Cycle 1, Day 15 Dose and Forward)**	**Prior to Day 1 of each Cycle (Cycle 2 and Forward)**	**Every 8 weeks x 6 months and then every 12 weeks (+/- 7 days)**
History and Physical	X		
Vital Signs (heart rate, temperature, blood pressure)	X		
Weight	X		
Performance Status	X		
Toxicity Assessment	X		
Concurrent Medications	X		
CBC/Differential/Platelets	X (within 72 hours)		
Chemistries (including Sodium, Potassium, Chloride, bicarbonate, Calcium, Glucose, BUN/Creatinine, Total Bilirubin, Total Protein, ALT, AST, Alkaline Phosphatase, Albumin)	X (within 72 hours)		
Amylase/Lipase		X (within 72 hours)	
TSH		X (within 72 hours)	
Chest imaging if initially abnormal or required to monitor tumor response			X (see Excel tool)
Radiographic tumor measurement			X (see Excel tool)
ECG*			

*As clinically indicated during treatment for symptoms or physical signs of congestive heart failure or cardiomyopathy. **( )**

4.3 ASSESSMENTS IN FOLLOW UP (03/21/2016)

Assessments	**From end of treatment: q3 mos. x 2 yrs.; q6 mos. x 3 years** until disease progression or until patient initiates a subsequent cancer therapy**.** Follow-up forms (Q forms) are collected for the 5 year follow-up period or until study termination.
Vital Status	X
Toxicity Assessment	X (Report all adverse events that occur within 100 days of last protocol treatment on Follow-Up Adverse Event Reporting Form. For reporting delayed toxicity, see section 7.
Chest imaging if initially abnormal or required to monitor tumor response	Every three months until disease progression or until patient initiates a subsequent cancer therapy
Radiography tumor measurement	Every three months until disease progression or until patient initiates a subsequent cancer therapy

Patients will be followed for 100 days from last dose of nivolumab. Patients who discontinue treatment for unacceptable adverse events(s) will be followed until resolution or stabilization of the adverse event.

5. TREATMENT PLAN/REGIMEN DESCRIPTION

5.1 NIVOLUMAB Therapy

Nivolumab 3 mg/kg IV every 2 weeks (+/- 2 days) for 4 doses followed by an additional 42 doses 3mg/kg IV q 2 weeks for a total of 46 doses over 92 weeks unless adverse effects prohibit therapy. Patients may be dosed no less than 12 days from the previous dose of drug.

During maintenance, a patient will be permitted to have an infusion delayed up to 7 days (without this being considered to be a protocol violation) for major life events (e.g., serious illness in a family member, major holiday, vacation which is unable to be re-scheduled). Documentation to justify this decision should be provided.

The dosing calculations should be based on the actual body weight. If the patient's weight on the day of dosing differs by >10% from the weight used to calculate the original (or most recent) dose, the dose must be recalculated. All doses should be rounded to the nearest milligram or as per institutional guidelines. There will be no dose modifications allowed. **(03/21/2016)**

Nivolumab is to be administered over approximately 60-minutes as an IV infusion, using a volumetric pump with a 0.2-1.2 micron filter at the protocol-specified dose. The drug can be diluted with 0.9% normal saline for delivery but the total drug concentration of the solution cannot be below 0.35 mg/mL. It is not to be administered as an IV push

or bolus injection. At the end of the infusion, flush the line with a sufficient quantity of normal saline.

5.2 General Concomitant Medication and Supportive Care Guidelines

5.2.1 Permitted Supportive/Ancillary Care and Concomitant Medications

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol.

5.3 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue as specified or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s) , which include the following (see also section 6 and specific algorithms in Appendix III): **(04/25/2016)**
    - Any dosing interruption lasting >6 weeks, with the following exceptions:
        - Patients being tapered after high dose corticosteroids over one month followed by a two-week observation period will be allowed an additional two weeks to restart treatment (a maximum eight week interruption).
        - Dosing interruptions >6 weeks that occur for non-drug-related reasons may be allowed if approved by the Investigator.
        - Prior to re-initiating treatment in a subject with a dosing interruption lasting >6 weeks, the Principal Investigator must be consulted.
    - Tumor assessments should continue as per protocol even if dosing is interrupted.
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6. TREATMENT MODIFICATIONS/MANAGEMENT (04/25/2016)

No dose reductions or escalations for nivolumab are permitted or specified. In the case of adverse effects, please see guidelines below and Appendix III for treatment delay/discontinuation and for management.

NOTE: Management algorithms for endocrinopathy, gastrointestinal, hepatic, neurological, pulmonary, renal and skin adverse events are detailed in Appendix III.

6.1 Criteria to Resume Treatment (04/25/2016)

Some patients may continue to benefit from treatment, maintaining or improving responses, including those treated with steroids.

For non-autoimmune or non-inflammatory events patients may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤1 or baseline value, with the following exceptions:

- Evaluation to exclude any additional immune mediated events endocrine, GI, and

liver/pancreas function as clinically indicated must be made prior to restarting.

- Non-drug-related toxicity including hepatic, pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed.

If the criteria to resume treatment are met, the patient should restart treatment no sooner than the next scheduled time point per protocol. However, if the treatment is delayed past the next scheduled time point per protocol the treatment should resume at the earliest convenient point that is within the six week delay period.

For patients treated with high dose steroids: Must resolve to baseline within 6 weeks of treatment.

Must be off steroids for at least 2 weeks with no recurrence or new events. New immune related events or exacerbation of existing events during steroid treatment or taper suggest the presence of ongoing immune activation and require permanent discontinuation of nivolumab.

Must have had no recurrence of symptoms or new symptoms during steroid taper.

6.2 Treatment of Nivolumab-Related Infusion Reactions (04/25/2016)

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

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE version 4.0 guidelines.

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

Remain at bedside and monitor subject until recovery from symptoms.

For Grade 1 symptoms: (Mild reaction; infusion interruption not indicated; intervention not indicated)

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 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations, slowing infusion rate as above.

For Grade 2 symptoms: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [*e.g.*, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; close observation for recurrence and treatment medications may need to be continued for 24-48 hours).

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor 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, re-administer diphenhydramine 50 mg IV, and remain at bedside and monitor the patient until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF).

The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and acetaminophen (or paracetamol) 325 to 1000 mg should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

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

Grade 4 symptoms: (life threatening; pressor or ventilatory support indicated).

Nivolumab will be permanently discontinued.

Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and treat the subject as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Patient should be monitored until the investigator is comfortable that the symptoms will not recur. 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 pruritus 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.

6.3 Treatment Delay and Discontinuation and Toxicity Management (04/25/2016)

Please refer to the Nivolumab Investigator Brochure or Appendix III to the protocol for toxicity management algorithms which include specific treatment guidelines. These algorithms should be followed unless there are specific clinical circumstances for which the treating physician decides an alternative treatment approach is clinically appropriate. Consultation with the study PI is recommended.

In several places there are differences from the algorithms regarding protocol directed drug modifications and these are identified with (#). In these cases please follow the protocol specific guidelines in this section.

Generally we strongly encourage early evaluation while withholding drug, and appropriate treatment as indicated in the management tables and event specific guidelines.

6.3.1 Skin Rash and Oral Lesions (see Appendix III: Skin Adverse Event Management Algorithm) (04/25/2016)

Skin Rash and Oral Lesions	**Management/Next Dose for Nivolumab**
≤ Grade 1	Continue therapy per protocol*
Grade 2	**Hold* until ≤ Grade 1 (#)**
Grade 3	Hold* until ≤ Grade 1. Resume at investigator discretion
Grade 4	Off protocol therapy
*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/pemphigoid. 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 Appendix III	

6.3.2 Liver Function/AST/ALT and Bilirubin (see Appendix III: Hepatic Adverse Event Management Algorithm) (04/25/2016)

Liver Function AST/ALT/Bilirubin	**Management/Next Dose for Nivolumab**
≤ Grade 1	Hold until ≤ UNL or baseline **(#)**
Grade 2	Hold until ≤ UNL or baseline
Grade 3	Off protocol therapy
Grade 4	Off protocol therapy
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 Appendix III	

6.3.3 Diarrhea/Colitis (see Appendix III: GI Adverse Event Management Algorithm) (04/25/2016)

Diarrhea/ Colitis	**Management/Next Dose for Nivolumab**
≤ Grade 1	**Hold until baseline (#)**
Grade 2	**Hold until baseline**
Grade 3	Off protocol therapy
Grade 4	Off protocol therapy
See GI AE Management Algorithm (Appendix III) for management of symptomatic colitis. Patients with grade 2 symptoms but normal colonoscopy and biopsies may be retreated after resolution. 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 Appendix III	

6.3.4 Pancreatitis-Amylase/Lipase (04/25/2016)

Pancreatitis Amylase/Lipase	**Management/Next Dose for Nivolumab**
≤ Grade 1	Hold until baseline. Resume if asymptomatic
Grade 2	Hold until baseline. Resume if asymptomatic
Grade 3	Hold until baseline. Resume if asymptomatic. Patients who develop symptomatic pancreatitis or DM should be taken off protocol therapy.
Grade 4	Hold until baseline. Resume if asymptomatic. Patients who develop symptomatic pancreatitis or DM should be taken off protocol therapy.
Patients may develop symptomatic and radiologic evidence of pancreatitis as well as	

Pancreatitis Amylase/Lipase	**Management/Next Dose for Nivolumab**
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 (Appendix III).	

6.3.5 Pneumonitis (see Appendix III: Pulmonary Adverse Event Management Algorithm) (04/25/2016)

Pneumonitis	**Management/Next Dose for Nivolumab**
≤ Grade 1	**Hold** dose pending evaluation and resolution to baseline including baseline pO2. Resume after pulmonary and/or ID consultation excludes lymphocytic pneumonitis. (#)
Grade 2	Hold dose pending evaluation. Resume after pulmonary and/or ID consultation excludes lymphocytic pneumonitis. **Off protocol therapy if steroids are required. (#)**
Grade 3	Hold dose pending evaluation. Resume after pulmonary and/or ID consultation excludes lymphocytic pneumonitis. **Off protocol therapy if steroids are required. (#)**
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 Appendix III	

6.3.6 Other GI/Nausea and Vomiting (04/25/2016)

Other GI N-V	**Management/Next Dose for Nivolumab**
≤ Grade 1	Continue therapy per protocol
Grade 2	Hold pending evaluation for gastritis, duodenitis and other immune adverse events or other causes. Resume after resolution to ≤ Grade 1.
Grade 3	Hold pending evaluation and until ≤ Grade 1. If symptoms do not resolve within 7 days with symptomatic treatment patients should go off protocol therapy
Grade 4	Off protocol therapy
Patients with grade 2 or 3 N-V should be evaluated for upper GI inflammation and other immune related events.	

6.3.7 Fatigue (04/25/2016)

Fatigue	**Management/Next Dose for Nivolumab**
≤ Grade 1	Continue therapy per protocol
Grade 2	Continue therapy per protocol
Grade 3	Hold until ≤ Grade 2
Grade 4	Off protocol therapy
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, hepatic, and/or muscle (CPK) inflammation	

6.3.8 Neurologic Events (see Appendix III: Neurological Adverse Event Management Algorithm) (04/25/2016)

Neurologic events	**Management/Next Dose for Nivolumab**
≤ Grade 1	**Hold pending evaluation and observation.** (#) Resume when resolved to baseline.
Grade 2	Hold pending evaluation and observation. (#) Hold until ≤ Grade 1. **Off protocol therapy if treatment with steroids is required. Resume for peripheral isolated n. VII (Bell's palsy)** (#)
Grade 3	Off protocol therapy
Grade 4	Off protocol therapy
Patients with any CNS events including aseptic meningitis, encephalitis, symptomatic hypophysitis, myopathy, peripheral demyelinating neuropathy, cranial neuropathy (other than peripheral n. VII), GB syndrome, and myasthenia gravis should be off study.	
Recommended management: See Appendix III	

6.3.9 Endocrine Hypophysitis/Adrenal Insufficiency (see Appendix III: Endocrinopathy Management Guidelines) (04/25/2016)

Endocrine Hypophysitis Adrenal Insufficiency	**Management/Next Dose for Nivolumab**
≤ Grade 1	Asymptomatic TSH elevation * **Hold pending evaluation, consider endocrine consult (#)**
Grade 2	Hold until patients are on a stable replacement hormone regimen. If treated with steroids patients must be stable off steroids for two weeks.
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	

Endocrine Hypophysitis Adrenal Insufficiency	**Management/Next Dose for Nivolumab**
associated deficiencies and adrenal function is monitored. Please evaluate pituitary function before beginning steroid therapy or replacement therapy of any kind. *Note patients with thyroiditis may be retreated on replacement therapy. Patients must be evaluated to rule out pituitary disease prior to initiating thyroid replacement.	
Recommended management: See Appendix III	

6.3.10 Fever (04/25/2016)

Fever	**Management/Next Dose for Nivolumab**
≤ Grade 1	Evaluate and continue therapy per protocol
Grade 2	Evaluate. Hold until ≤ Grade 1
Grade 3	Evaluate. Hold until ≤ Grade 1
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	
See section 6.2 "Treatment of Nivolumab-Related Infusion Reactions"	

6.3.11 Renal Adverse Event Management Algorithm) see Appendix III: Renal Management Guidelines) (4/25/2016)

Renal Adverse Events	**Management/Protocol Therapy Modifications**
Grade 1	Continue therapy per protocol and monitor creatinine weekly
Grade 2	Hold until ≤ Grade 1
Grade 3	Hold until ≤ Grade 1
Grade 4	Off protocol therapy
Recommended management: See Renal Adverse Event Management Algorithm in Appendix III	

6.3.12 Cardiac Adverse Event Management ( )

Cardiac *	**Management/Next Dose for BMS-936558 (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 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.	

6.3.13 All Other Events (04/25/2016)

ALL OTHER EVENTS	**Management/Next Dose for Nivolumab**
≤ Grade 1	Continue therapy per protocol
Grade 2	Hold until ≤ Grade 1 OR baseline (exceptions as noted below)
Grade 3	Off protocol therapy (exceptions as noted below)
Grade 4	Off protocol therapy
Recommended management: As clinically indicated	

- Any grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment should go off protocol treatment.

- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued study drug dosing should go off protocol treatment.

- Any grade 3 or 4 drug-related laboratory abnormality or electrolyte abnormality that can be managed with electrolyte replacement, hormone replacement, insulin, or that does not require treatment does **not** require discontinuation.

6.3.13 Treatment Delays

If treatment is delayed >6 weeks, >8 weeks for patients on high dose steroids with recommended 4 weeks taper and 2 week observation, the patient must be permanently discontinued from study therapy, except as specified in Section 6.1 (Criteria to Resume Treatment.)

Patients requiring > two dose delays for the same event should go off protocol therapy.

Prior to starting corticosteroids or hormone replacement for any reason, appropriate endocrine testing including cortisol, ACTH, TSH and T4 must be obtained to document baseline.

Patients may be dose-delayed for evaluation and restarted depending on results.

Any patient started on corticosteroids initially who is determined to not require steroids treatment for an autoimmune adverse event may resume therapy after a 2 week observation period without further symptoms at the discretion of the PI or investigator.

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents

Investigational Agents

The investigational agents administered in NRG-GY002 are:

Nivolumab: IND #125336; IND Sponsor: DCTD, NCI

For Nivolumab, determination of whether an adverse event meets expedited reporting criteria, see the reporting table in section 7.4.3 of the protocol.

7.2 Adverse Events and Serious Adverse Events

7.2.1 This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 for CTEP-AERS (CTEP Adverse Event Reporting System) CAERs reporting of adverse events (AEs), located on the CTEP web site, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0.

7.2.2 Definition of an Adverse Event (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

For multi-modality trials, adverse event reporting encompasses all aspects of protocol treatment including radiation therapy, surgery, device, and drug.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported via CTEP-AERS in an expedited manner.

7.3 Comprehensive Adverse Events and Potential Risks (CAEPR) List for CTEP Study Agents

7.3.1 Comprehensive Adverse Events and Potential Risks list (CAEPR) for BMS-936558 (Nivolumab, MDX-1106, NSC 748726) (03/21/2016) ( )

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

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

Version 2.2, November 15, 2016[1]

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 4.0 Term) [n= 2069]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 2)***
CARDIAC DISORDERS			
		Cardiac disorders - Other (cardiomyopathy)	
		Myocarditis	
		Pericardial tamponade[2]	
		Pericarditis	
ENDOCRINE DISORDERS			
	Adrenal insufficiency		
	Endocrine disorders - Other (hypophysitis)		
	Hyperthyroidism		
	Hypothyroidism		
EYE DISORDERS			
		Eye disorders - Other (diplopia)	
		Eye disorders - Other (Graves ophthalmopathy)	
		Eye disorders - Other (optic neuritis retrobulbar)	
	Uveitis		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 4.0 Term) [n= 2069]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Colitis		
		Colonic perforation	
	Diarrhea		***Diarrhea (Gr 2)***
	Dry mouth		***Dry mouth (Gr 2)***
		Gastritis	
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[3]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
	Fever		***Fever (Gr 2)***
	Infusion related reaction[4]		
	Injection site reaction		***Injection site reaction (Gr 2)***
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
		Autoimmune disorder[5]	
		Cytokine release syndrome[6]	
		Immune system disorders - Other (GVHD in the setting of allotransplant)[7]	
		Immune system disorders - Other (sarcoid granuloma)[5]	
INVESTIGATIONS			
	Alanine aminotransferase increased		***Alanine aminotransferase increased (Gr 2)***
	Aspartate aminotransferase increased		***Aspartate aminotransferase increased (Gr 2)***
	Blood bilirubin increased		***Blood bilirubin increased (Gr 2)***
	Creatinine increased		
	Lipase increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 2)***
	Neutrophil count decreased		
	Platelet count decreased		
	Serum amylase increased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
		Hyperglycemia	***Hyperglycemia (Gr 2)***
		Metabolism and nutrition disorders - Other (diabetes mellitus with ketoacidosis)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
		Musculoskeletal and connective tissue disorder - Other (polymyositis)	
		Musculoskeletal and connective tissue disorder - Other (rhabdomyolysis)	
		Myositis	
NERVOUS SYSTEM DISORDERS			

Adverse Events with Possible Relationship to BMS-936558 (Nivolumab, MDX-1106) (CTCAE 4.0 Term) [n= 2069]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Encephalopathy	
		Facial nerve disorder[5]	
		Nervous system disorders - Other (demyelination myasthenic syndrome)	
		Nervous system disorders - Other (encephalitis)	
		Nervous system disorders - Other (Guillain-Barre syndrome)[5]	
		Nervous system disorders - Other (meningoencephalitis)	
		Nervous system disorders - Other (meningoradiculitis)	
		Nervous system disorders - Other (myasthenia gravis)[5]	
		Nervous system disorders - Other (myasthenic syndrome)	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pleural effusion		
	Pneumonitis		
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme	
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 2)***
	Skin hypopigmentation		
	Skin and subcutaneous disorders - Other (Sweet's Syndrome)		

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

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

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

[4]Infusion reactions, including high-grade hypersensitivity reactions which have been observed following administration of nivolumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or

difficulty breathing during and immediately after administration of nivolumab.

[5]BMS-936558 (Nivolumab, MDX-1106) being a member of class of agents involved in the inhibition of "immune checkpoints", may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. This may result in autoimmune disorders that can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune nephritis, autoimmune neuropathy, autoimmune thyroiditis, bullous pemphigoid, exacerbation of Churg-Strauss Syndrome, drug rash with eosinophilia systemic symptoms [DRESS] syndrome, facial nerve disorder (facial nerve paralysis), limbic encephalitis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, thyrotoxicosis, and adrenal insufficiency), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome.

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

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

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

CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Heart failure; Ventricular arrhythmia
EAR AND LABYRINTH DISORDERS - Vestibular disorder
EYE DISORDERS - Eye disorders - Other (iridocyclitis); Optic nerve disorder
GASTROINTESTINAL DISORDERS - Constipation; Duodenal ulcer; Flatulence; Gastrointestinal disorders - Other (mouth sores); Mucositis oral; Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Pain
HEPATOBILIARY DISORDERS - Bile duct stenosis
IMMUNE SYSTEM DISORDERS - Anaphylaxis; Immune system disorders - Other (autoimmune thrombotic microangiopathy); Immune system disorders - Other (limbic encephalitis)
INFECTIONS AND INFESTATIONS - Bronchial infection; Lung infection; Sepsis; Upper respiratory infection
INVESTIGATIONS - GGT increased; Investigations - Other (blood LDH increased); Investigations - Other (protein total decreased); Investigations - Other (WBC count increased); Lymphocyte count increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Musculoskeletal and connective tissue disorder - Other (musculoskeletal pain); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (histiocytic necrotizing lymphadenitis)
NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Intracranial hemorrhage
PSYCHIATRIC DISORDERS - Insomnia

RENAL AND URINARY DISORDERS - Hematuria; Renal and urinary disorders - Other (tubulointerstitial nephritis)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchospasm; Cough; Dyspnea; Hypoxia
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Pain of skin; Periorbital edema; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (rosacea); Toxic epidermal necrolysis
VASCULAR DISORDERS - Flushing; Hypertension; Hypotension; Vasculitis

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

7.4 Expedited Reporting of Adverse Events

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the CTEP Adverse Event Reporting System, CTEP-AERS, accessed via the CTEP web site, https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613

Submitting a report via CTEP-AERS serves as notification to NRG and satisfies NRG requirements for expedited adverse event reporting.

CTEP-AERS provides a radiation therapy-only pathway for events experienced that involve radiation therapy only. These events must be reported via the CTEP-AERS radiation therapy-only pathway.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to the NRG Regulatory Affairs by phone at 215-854-0770. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

Note: A death on study requires both routine and expedited reporting regardless of causality, unless as noted below. Attribution to treatment or other cause must be provided.

Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (*e.g.*, radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

7.4.1 Expedited Reporting Methods

- CTEP-AERS-24 Hour Notification requires that a CTEP-AERS 24-hour notification is electronically submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a complete report within 3 days. Supporting source documentation is requested by NRG as needed to complete

adverse event review. When submitting supporting source documentation, include the protocol number, patient ID number, and CTEP-AERS ticket number on each page, and fax supporting documentation to the NRG Regulatory Affairs by phone at 215-854-0716.

- A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as "an action *not* recommended" must still be reported to fulfill NRG safety reporting obligations. Sites must bypass the "NOT recommended" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

7.4.2 Expedited Reporting Requirements for Adverse Events

Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under a CTEP IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

An adverse event is considered serious if it results in **ANY** of the following outcomes:

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

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

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days			24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		7 Calendar Days	

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

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur **more than** 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

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

7.4.3 Reporting to the Site IRB/REB

Investigators will report serious adverse events to the local Institutional Review Board (IRB) or Research Ethics Board (REB) responsible for oversight of the patient according to institutional policy.

7.4.4 Secondary Malignancy

Secondary Malignancy

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

CTEP requires all secondary malignancies that occur during or subsequent to treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. In addition, secondary malignancies following radiation therapy must be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy
  Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy:

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

8. REGISTRATION, STUDY ENTRY, AND WITHDRAWAL PROCEDURES

8.1 Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

8.1.1 CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

To obtain an active CTEP-IAM account, go to https://eapps-ctep.nci.nih.gov/iam.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

8.1.2 CTSU Registration Procedures

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

8.1.2.1 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. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU members' website by entering credentials at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Sites participating on the NCI CIRB initiative and that are approved by the CIRB for the study are not required to submit separate IRB approval documentation to the CTSU Regulatory Office for initial, continuing or amendment review. This information will be provided to the CTSU Regulatory Office from the CIRB at the time of the CIRB approval. The Signatory Institution must inform the CTSU which CIRB-approved institutions alighed with the Signatory Institution are participating in a given study so that the study approval can be applied to those institutions. Other site registration requirements (i.e., laboratory certifications, protocol-specific training certifications, or modality credentialing) must be submitted to the CTSU Regulatory Office or compliance communicated per protocol instructions.

8.1.2.2 Requirements for NRG-GY002 Site Registration:

- CTSU IRB Certification (for sites not participating via the NCI CIRB)
- CTSU IRB/Regulatory Approval Transmittal Sheet (for sites not participating via the NCI CIRB)

8.1.2.3 Submitting Regulatory Documents:

Submit completed forms along with a copy of your IRB Approval and Model Informed Consent to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-866-651-2878
Fax: 215-569-0206
E-mail: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

8.1.2.4 Checking Your Site's Registration Status:

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website. (Note: Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)
Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
Click on the Regulatory tab at the top of your screen
Click on the Site Registration tab
Enter your 5-character CTEP Institution Code and click on Go

8.2 Patient Enrollment

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

8.3 Oncology Patient Enrollment Network (OPEN)

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. All site staff (NRG and CTSU Sites) will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient position in the Rave database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' web site https://www.ctsu.org.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes. Site staff should use the registration forms provided on the group or CTSU web site as a tool to verify eligibility.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

Access requirements for OPEN:

- See Section 8.1.1 for information on obtaining a CTEP-IAM account.
- To perform registrations, the site user must have been assigned the 'Registrar' role on the relevant Group or CTSU roster.
- To perform registrations on protocols for which you are a member of the NRG, you must have an equivalent 'Registrar' role on the NRG roster. Role assignments are handled through the Groups in which you are a member.
- To perform registrations to trials accessed via the CTSU mechanism (i.e., non-Lead Group registrations) you must have the role of Registrar on the CTSU roster. Site and/or Data Administrators can manage CTSU roster roles via the new Site Roles maintenance feature under RSS on the CTSU members' web site. This will allow them to assign staff the "Registrar" role.

The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the OPEN tab located on the CTSU members' web site at https://www.ctsu.org or at https://open.ctsu.org. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

In the event that the OPEN system is not accessible, participating sites can contact NRG web support for assistance with web registration: [email to come] or call the NRG Registration Desk at [phone number to come], Monday through Friday, 8:30 a.m. to 5:00 p.m. ET. The registrar will ask the site to fax in the eligibility checklist and will need the registering individual's e-mail address and/or return fax number. This

information is required to assure that mechanisms usually triggered by the OPEN web registration system (e.g. drug shipment and confirmation of registration) will occur.

8.4 Agent Ordering and Agent Accountability

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

Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application (https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx). Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account (https://eapps-ctep.nci.nih.gov/iam/) and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

8.4.2 Agent Inventory Records – The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of all agents received from DCTD using the NCI Drug Accountability Record Form (DARF). (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

9. DRUG INFORMATION

9.1 Nivolumab (BMS-936558, MDX1106), NSC #748726

9.1.1 Amino Acid Sequence: 4 polypeptide chains, which include 2 identical heavy chains with 440 amino acids and 2 identical light chains.

9.1.2 Classification: Anti-PD-1MAb

9.1.3 M.W.: 126,211 daltons

9.1.4 Mode of Action: Nivolumab targets the programmed death–1 (PD-1, cluster of differentiation 279 [CD279]) cell surface membrane receptor. PD-1 is a negative regulatory receptor expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligand 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Nivolumab inhibits the binding of PD-1 to PD-L1 and PD-L2. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens.

9.1.5 Description: Nivolumab Injection is a clear to opalescent, colorless to pale yellow liquid; light (few) particulates may be present. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated in sodium citrate, sodium chloride, mannitol, diethylenetriamine pentacetic acid (pentetic acid) and polysorbate 80 (Tween® 80), pH 6.0.

9.1.6 How Supplied: Nivolumab is supplied by Bristol-Myers Squibb and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as 100 mg vials (10 mg/mL) with a 0.7 mL overfill. It is supplied in 10 mL type I flint glass vials, with butyl rubber stoppers and aluminum seals.

9.1.7 Preparation: Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose, USP to concentrations no less than 0.35 mg/mL. All vials must come from the same batch.

9.1.8 Storage: Vials of Nivolumab injection must be stored at 2°-8°C (36°-46°F) and protected from light, freezing and shaking.

9.1.9 Stability: Shelf-life surveillance of the intact vials is ongoing.
The administration of undiluted and diluted solutions of Nivolumab must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 24 hours in a refrigerator at 2°-8°C (36°-46°F) and a maximum of 4 hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and room light. The maximum 4-hour period under room temperature and room light conditions includes the product administration period.

CAUTION: The single-use dosage form contains no antibacterial preservative or bacteriostatic agent. Therefore, it is advised that the product be discarded 8 hours after initial entry.

9.1.10 Route of Administration: Intravenous infusion. Do not administer as an IV push or bolus injection.

9.1.11 Method of Administration: Administer through a 0.2 micron to 1.2 micron pore size, low-protein binding polyethersulfone membrane in-line filter.

9.1.12 Potential Drug Interactions: No incompatibilities between Nivolumab injection and polyvinyl chloride (PVC), non-PVC/non-DEHP (di[2-ethylhexyl]phthalate) IV components, or glass bottles have been observed.

9.1.13 Availability
Nivolumab is an investigational agent supplied to investigators by the Division of Cancer Treatment and Diagnosis (DCTD), NCI.

Nivolumab is provided to the NCI under a Collaborative Agreement between the Pharmaceutical Collaborator and the DCTD, NCI (see Appendix I).

9.1.14 **See Section 7.3.1 for the Nivolumab CAEPR.**

10. PATHOLOGY

No pathology is required for central pathology review, but pathology reports are required.

11. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

11.1 Reimbursement

See the Reimbursement and Case Credit Schedule found on the CTSU web site (www.ctsu.org).

11.2 Translational Science

Note: Testing of banked specimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

11.3 Specimen Requirements

If the patient gives permission to participate in this **optional** study component, then participating sites are required to submit the patient's specimens as outlined below.

Required Specimen (Specimen Code)	Collection Time Point	Sites Ship Specimens To
FFPE Primary Tumor (FP01)* 1st Choice: block 2nd Choice: 20 unstained slides (charged, 5µm)	Prior to all treatment *(Preferred FFPE)*	**NRG Oncology Biospecimen Bank-Columbus** within 8 weeks of registration[1]
FFPE Metastatic Tumor (FM01)* 1st Choice: block 2nd Choice: 20 unstained slides (charged, 5µm)	Prior to all treatment *(Optional if FP01, FRP01, FRM01, FPP01, or FPM01 is submitted)*	
FFPE **Recurrent Primary** Tumor (**FRP01**)* 1st Choice: block 2nd Choice: 20 unstained slides (charged, 5µm)	Prior to study treatment *(Optional if FP01, FM01, FRM01, FPP01, or FPM01 is submitted)*	
FFPE **Recurrent Metastatic** Tumor (**FRM01**)* 1st Choice: block 2nd Choice: 20 unstained slides (charged, 5µm)	Prior to study treatment *(Optional if FP01, FM01, FRP01, FPP01, or FPM01 is submitted)*	
FFPE **Persistent Primary** Tumor (**FPP01**)* 1st Choice: block 2nd Choice: 20 unstained slides (charged, 5µm)	Prior to study treatment *(Optional if FP01, FM01, FRP01, FRM01, or FPM01 is submitted)*	
FFPE **Persistent Metastatic** Tumor (**FPM01**)* 1st Choice: block 2nd Choice: 20 unstained slides (charged, 5µm)	Prior to study treatment *(Optional if FP01, FM01, FRP01, FRM01, or FPP01 is submitted)*	
Pre-treatment Serum (SB01) prepared from 7-10mL of blood drawn into plain red top tube(s)	Prior to study treatment	**NRG Oncology Biospecimen Bank-Columbus** within 14 weeks of registration[1]
Pre-treatment Immune Whole Blood (WB01) **30mL drawn into green top (sodium heparin) tube(s)**		**Yale University School of Medicine** the day the specimen is collected[2]
Pre-treatment CTC Whole Blood (WB02) **10mL drawn into purple top (EDTA) tube(s)**		**Massachusetts General Hospital** the day the specimen is collected[3]
8 Week Serum (SB02) **(03/21/2016)** prepared from 7-10mL of blood drawn into plain red top tube(s)	8 weeks after starting study treatment **(03/21/2016)**	**NRG Oncology Biospecimen Bank-Columbus** within 14 weeks of registration[1]
8 Week Immune Whole Blood (WB03) **(03/21/2016)** **30mL drawn into green top (sodium heparin) tube(s)**		**Yale University School of Medicine** the day the specimen is collected[2]

8 Week CTC Whole Blood (WB04) **(03/21/2016)** **10mL drawn into purple top (EDTA) tube(s)**		**Massachusetts General Hospital** the day the specimen is collected[3]
12 Week Serum (SB03) **(03/21/2016)** prepared from 7-10mL of blood drawn into plain red top tube(s)	12 weeks after starting study treatment **(03/21/2016)**	**NRG Oncology Biospecimen Bank-Columbus** within 14 weeks of registration[1]
12 Week Immune Whole Blood (WB05) **(03/21/2016)** **30mL drawn into green top (sodium heparin) tube(s)**		**Yale University School of Medicine** the day the specimen is collected[2]
12 Week CTC Whole Blood (WB06) **(03/21/2016)** **10mL drawn into purple top (EDTA) tube(s)**		**Massachusetts General Hospital** the day the specimen is collected[3]

* A copy of the corresponding pathology report must be shipped with all tissue specimens sent to the NRG Oncology Biospecimen Bank-Columbus

1 NRG Oncology Biospecimen Bank-Columbus / Protocol NRG GY002, Nationwide Children's Hospital, 700 Children's Drive, WA1340, Columbus, OH 43205, Phone: (614) 722-2865, FAX: (614) 722-2897, Email: BPCBank@nationwidechildrens.org

2 Dr. Alessandro Santin, c/o Lisa Patriub, Yale University School of Medicine, 330 Cedar St, LSOG 305, New Haven, CT 06520, Phone: 203-737-4450, Email: lisa.patriub@yale.edu

3 Dr. Michael Birrer, c/o Giulia Fulci, Massachusetts General Hospital, Jackson 9, 55 Fruit St, Boston, MA 02114, Phone: 617-726-6081, Email: gfulci@partners.org, wei.wei@mgh.harvard.edu. **Please email prior to shipping.**

11.3.1 Specimen Procedures

A detailed description of specimen procedures can be found in Appendix IV.

11.3.2 Laboratory Testing

Details regarding the distribution of translational science specimens to investigators can be found in Appendix IV.

11.3.2.1 PD-L1/B7-H1 and PD-1 Immunohistochemistry

Upon trial completion, the NRG Oncology Biospecimen Bank-Columbus will batch ship unstained sections of formalin-fixed, paraffin-embedded (FFPE) tumor to TBD for immunohistochemical analysis of PD-L1/B7-H1 and PD-1 IHC.

11.3.2.2 Tumor Infiltrating Lymphocytes

Upon trial completion, the NRG Oncology Biospecimen Bank-Columbus will batch ship unstained sections of FFPE tumor to Dr. Warner Huh (address below) for immunohistochemical analysis of tumor infiltrating lymphocytes (TILs).

Dr. Warner Huh
University of Alabama at Birmingham
176F RM 10250619
19th Street South
Birmingham, AL 35249
Phone: 205-934-4986
Email: whuh@uab.edu

11.3.2.3 HPV Typing

Upon trial completion, the NRG Oncology Biospecimen Bank-Columbus will batch ship unstained sections of FFPE tumor to Dr. Alessandro Santin (address below) for HPV typing.

Dr. Alessandro Santin
c/o Lisa Patriub
Yale University School of Medicine
330 Cedar St, LSOG 305
New Haven, CT 06520
Phone: 203-737-4450
Email: lisa.patriub@yale.edu

11.3.2.4 ELISPOT

Immune whole blood will be **shipped directly from sites** to Dr. Santin (address above) for analysis of HPV16/18/31/35/45 E7 antigens in peripheral blood lymphocytes (PBLs) by proliferative and IFN-gamma ELISPOT.

11.3.2.5 ELISA

Upon trial completion, the NRG Oncology Biospecimen Bank-Columbus will batch ship frozen serum from each time point to Dr. Santin (address above) for analysis of HPV16/18/31/35/45 E7 antigens in serum by ELISA.

11.3.2.6 CTC

CTC whole blood will be **shipped directly from sites** to Dr. Michael Birrer (address below) for analysis of circulating tumor cells (CTCs). **Please email prior to shipping.**

Dr. Michael Birrer
c/o Giulia Fulci
Massachusetts General Hospital
Jackson 9
55 Fruit St
Boston, MA 02114
Phone: 617-726-6081
Email: gfulci@partners.org, wei.wei@mgh.harvard.edu

11.3.3 Banking Specimens for Future Research

Details regarding the banking and use of specimens for future research can be found in Appendix IV.

11.4 Quality of Life

Not applicable.

12. DATA AND RECORDS

12.1 Data Management/Collection

Data collection for this study will be done exclusively through Medidata Rave®. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at https://eapps-ctep.nci.nih.give/iam/index.jsp) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Each person responsible for data entry must be on the NRG roster in order to receive access to Medidata Rave®.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata (iMedidata-Notification@mdsol.com) to activate their account. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Once an account is activated, eLearning modules will be available for Rave RDC instructions. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be listed in the upper right pane of the iMedidata screen.

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

12.2 NRG Data Management Forms

The following forms must be completed for all patients registered and submitted to the NRG Oncology Statistics and Data Management Center (SDMC) in Buffalo, NY, according to the schedule below. Electronic case report forms must be submitted through the Medidata Rave Electronic Data Entry System (www.imedidata.com). All amendments to forms must also be submitted through Medidata Rave. The pathology reports can be sent to the NRG Oncology SDMC in Buffalo, NY, via postal mail or uploaded in Medidata Rave. The upload option is an alternative method for submitting paper reports.

Form	Comments
Baseline Folder ***(Forms due within 2 weeks of registration)***	
Baseline/History Forms: - Visit Information – Baseline Form - Registration Form - Pre-Treatment Summary Form - Vitals Form - Concomitant Medications Form - ECG Information - Body Diagram Form Pre-Study History - History Information Form - Primary Surgery Form - Chemotherapy Information Form - Prior Radiation Therapy Form	The appropriate forms will load in the Baseline Folder based on the answers reported on the corresponding Baseline Visit Information form.

- Baseline Adverse Events Reporting - Baseline Adverse Event- Terms - Baseline Adverse Event AE Grades Solid Tumor Evaluation Forms: - Target Lesions Form - Non-Target Lesions Form - Specimen Consent	
Visit Folder ***(Forms due within 2 weeks of the completion of each cycle)***	
Cycle Information and Treatment Forms: - Visit Information Form - Cycle Patient Information Form - Cycle Drug Information Form - Labs and Chemistries Form - Vitals Form - Concomitant Medications Form - ECG Information Toxicity Forms: - Section 1 Form - NADIRS Form - Adverse Event Form - Adverse Event Grades Solid Tumor Evaluation Forms: - Target Lesions Form - Non-Target Form - New Target Lesions Form - Status and Response Form	The appropriate forms will load in the Visit Folder based on the answers reported on the corresponding Visit Information forms. Labs and Chemistries Forms will be collected prior to each dose of study drug
Pathology Folder ***(Reports and slides due within 6 weeks of registration)***	
Primary disease: Pathology Report Recurrent or Persistent Disease: Pathology Report	Submit one copy of the pathology report to SDC via postal mail or upload the pathology report online via RAVE.
Form	**Comments**

Translational Research Folder	
TR Forms: **(03/21/2016)** - FFPE Primary Tumor (FP01) - FFPE Metastatic Tumor (FM01) *optional* - FFPE Recurrent Primary Tumor (FRP01) *optional* - FFPE Recurrent Metastatic Tumor (FRM01) *optional* - FFPE Persistent Primary Tumor (FPP01) *optional* - FFPE Persistent Metastatic Tumor (FPM01) *optional* - Pre-treatment Serum (SB01) - 8 Week Serum (SB02) - 12 Week Serum (SB03) - Pre-treatment Immune Whole Blood (WB01) - Pre-treatment CTC Whole Blood (WB02) - 8 Week Immune Whole Blood (WB03) - 8 Week CTC Whole Blood (WB04) - 12 Week Immune Whole Blood (WB05) - 12 Week CTC Whole Blood (WB06)	An electronically-completed copy of Form TR must accompany each specimen shipped to the NRG Oncology Biospecimen Bank-Columbus (or alternate laboratory). Handwritten forms will not be accepted. FP01, FM01, FRP01, FRM01, FPP01, and FPM01 are due 8 weeks from registration. SB01-SB03 are due 14 weeks from registration. WB01 and WB02 are due 1 week from registration. WB03 and WB04 are due 9 weeks from registration. WB05 and WB06 are due 13 weeks from registration.
Treatment Completion Folder ***(Forms due within 2 weeks of treatment completion)***	
Treatment Completion Form	
Form	**Comments**
Follow-up Visit Folder ***(Forms due within 2 weeks of follow-up visits, disease progression or death)***	
Visit Information Follow-Up Form Follow-Up Form Follow-Up Period Adverse Event: - Follow-Up Adverse Event- Part 1 - Follow-Up Adverse Event- Terms - Follow-Up Adverse Event- AE Grades - Solid Tumor Evaluation:	Follow-up visits should be scheduled quarterly for 2 years, semi-annually for 3 more years The appropriate forms will load in the Follow-up Visit Folder based on the answers reported on the corresponding Follow-up Visit Information forms. Report all adverse events that occur within 100 days of last protocol treatment on Follow-Up Adverse Event Reporting form.

- Target Lesions Form - Non-Target Form - New Target Lesions Form - Status and Response Form	

12.3 Summary of Data Submission

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See Section 7 for information about expedited and routine reporting.

For reporting of secondary cancers or other report forms available in Rave:
Indicate form for reporting in Rave, time frames, add if loading of the pathology report is required.

12.4 Global Reporting/Monitoring

This study will be monitored by the Clinical Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly to CTEP by electronic means. Reports are due January 31, April 30, July 31, and October 31.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design

This is a single-arm, open-label phase II study using an optimal flexible two-stage design (Chen and Ng, 1998) to evaluate the efficacy of the study regimen through objective tumor response. There are no treatment comparisons involved and no known historical controls available. The study design will be primarily based on prior GOG experience in this disease entity.

The targeted accrual for the first stage of the study will be 12 eligible and evaluable patients but permitted to range from 8 to 15 for administrative reasons. The cumulative targeted accrual for the second stage will be 22 eligible and evaluable patients but permitted to range from 18 to 25 for administrative reasons.

If the true probability of tumor response is 5%, then the study has a 65% average probability of early termination and an expected probability of 10% of incorrectly declaring the study regimen interesting. If the true probability of tumor response is 25%, then the study has an expected 90% chance of correctly classifying the study regimen as being interesting.

13.1.1 Stratification

There are no stratification factors applied in this single-arm phase II study.

13.1.2 Randomization

This is a single-arm phase II study and hence, no randomization is involved.

13.1.3 Total Accrual

The planned total accrual of eligible and evaluable patients onto this study is 25.

13.1.4 Justification of Design:

This study will employ the optimal flexible two-stage design since it not only minimizes the average expected number of patient exposure to inactive regimen, but also allows the actual study accrual to slightly deviate from the targeted study accrual in a multi-center trial while maintaining the levels of the average type I and II errors.

13.2 Study Endpoints

13.2.1 Primary Endpoints

1) Frequency of objective tumor response as assessed by RECIST 1.1 criteria (Section 14).

2) Frequency and severity of adverse events as assessed by CTCAE v4.

13.2.2 Secondary Endpoints

1) Duration of progression-free survival (PFS) and overall survival (OS).

13.2.3 Translational Science Endpoints

1) Measures of PD-1 and PD-L1 expressions in tumor infiltrating lymphocytes and cervical cancer cells and objective tumor response, PFS and OS.

2) Measures of immune infiltration related biomarkers in tumor specimens with objective tumor response, PFS and OS.

3) Measures of HPV genotype/positivity and pre and post-treatment immune response to HPV 16/18/31/35/45 E7 antigen in peripheral blood lymphocytes and serum.

4) Pre and Post-treatment CTC counts and objective tumor response, PFS and OS.

13.3 Primary Objectives Study Design

13.3.1 Primary Hypothesis and Endpoints

Primary Hypothesis:

The intent of this study is to evaluate the efficacy of the study regimen measured by objective tumor response. Tumor response is dichotomized as response (i.e., complete or partial response) vs. non-response (i.e., stable disease, progressive disease, or indeterminate disease) and is assumed to have a Bernoulli distribution with a probability equal to π. Given a sample size, the number of tumor responses is binomially distributed with a given sample size and probability equal to π. Statistically, the evaluation of the study regimen efficacy measured by tumor response will be formulated through hypothesis testing via tumor response.

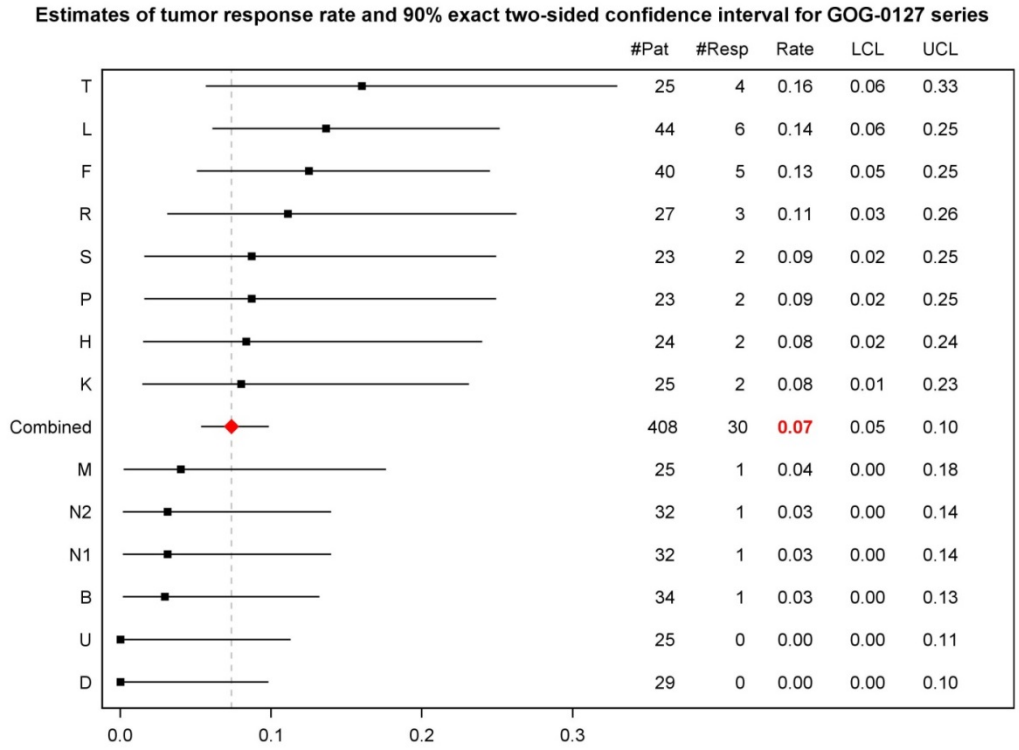
Since there is no known historical control available, a series of single-agent GOG-0127 studies were selected based on their similarity on this disease entity. The purpose of these studies was to evaluate several cytotoxic salvage regimens. These studies also implemented two-stage stopping guidelines. The conclusions from these studies are that the agents studied had at most modest activity. The estimated probability of responding is summarized in Figure 14.1. The average proportion of patients responding in these studies is 7% with a standard error of 0.014.

Figure 14.1 indicated that a probability of a true tumor response of 5% or less was uninteresting. Clinically a probability of a true tumor response of at least 25% is considered significant and important to detect. Therefore, the primary hypotheses for this study can be formulated as follow:

$$H_0: \pi \leq 0.05,$$
$$H_1: \pi \geq 0.25,$$

where π is the probability of true tumor response, H_0 is the null hypothesis and H_1 is the alternative hypothesis. The optimal flexible two-stage design with early stopping guidelines will be implemented to evaluate the primary hypotheses with average type I and type II errors at 0.1 level, respectively.

Figure 14.1



We will target an accrual of 12 eligible and evaluable patients in the first stage of the study, but permit the accrual to range from 8 to 15 for administration reasons. If there are more than 0 out of 8-13 or 1 out of 14-15 patients responding (complete or partial response) and medical judgment indicates, accrual to the second stage of the trial will be initiated. Otherwise, the study will be stopped and the treatment will be classified as clinically uninteresting. If the study advances to the second stage, then a cumulative accrual of 22 eligible and evaluable patients will be targeted, but permitted to range from 18 to 25 for administration reasons. If more than 1 out 18, or 2 out 19-25 patients respond and medical judgment indicates, then the study regimen will be considered worthy for further investigation.

Under the assumed accrual ranges of 8 to 15 (stage 1) and 18 to 25 (cumulatively after stage 2), if the true probability of tumor response is 5%, then the study has a 65% probability of early termination and a probability of 10% of incorrectly declaring the study regimen interesting; if the true probability of tumor response is 25%, then the study has a 90% chance of correctly classifying the study regimen as being interesting.

The following table summarizes the accrual and decision guideline.

Stage of Accrual	Targeted Cumulative Accrual	Limits of Actual Accrual	Max Number of Responses to Reject Study Regimen
1	12	8-15	0/(8-13), 1/14-15
2	22	18-25	1/(18), 2/(19-25)

Primary Endpoints: See Section 13.2.1.

13.3.2 Definitions of Primary Endpoints and How These Will Be Analyzed

1) Frequency of objective tumor response as assessed by RECIST 1.1 criteria.
See Section 13.3.1.
2) Frequency and severity of adverse events as assessed by CTCAE v4 and corresponding frequency table will be provided as descriptive statistics.

All eligible patients who receive any study therapy will be evaluated for both treatment efficacy and toxicity. Only those patients who are deemed "ineligible" or who receive no therapy will be eliminated from the efficacy analysis. All patients (eligible and ineligible) who receive any study therapy will be evaluated for safety and toxicity. While on occasion, circumstances may prevent the determination of treatment efficacy, such patients will be included in the analysis and labeled as "indeterminate." This category will be listed and be reflected in the calculation of the proportion responding.

13.3.3 Sample Size and Power Calculations:

The sample size and power calculations will be based on the optimal flexible two-stage method by Chen and Ng. This method assumes that the number of patients responding to the study regimen has binomial distribution and the accrual combination for stage 1 and 2 is uniformly distributed.

The minimum and maximum accruals for this study are 8 and 25 eligible and evaluable patients, respectively.

Under the assumed accrual ranges of 8 to 15 (stage 1) and 18 to 25 (cumulatively after stage 2), the study has an average 90% power to detect a 20% increase of the probability of tumor response from 5% at a significant level of 10%.

Details see Section 13.3.1

13.4 Study Monitoring of Primary Objectives

There will be one formal futility interim analysis for treatment efficacy in the study.

If the study has an accrual of 12 eligible and evaluable patients in the first stage since the study is activated, which is permitted to range from 8 to 15, the accrual of the study will be temporarily suspended until the data of primary endpoint is matured to make a decision on whether to go forward to second stage accrual according to the guidelines. That is, if there are 0 out of 8-13 or at most 1 out of 14-15 patients responding (complete or partial response) and medical judgment indicates, the study will be stopped and the

treatment will be classified as clinically uninteresting. Otherwise, accrual to the second stage of the trial will be initiated.

Data sheets from studies on this protocol will be reviewed before each semi-annual meeting and will also be reviewed by the Study Chairperson in conjunction with the NRG Statistical and Data Center. In some instances, because of unexpectedly severe toxicity, the NRG Statistical and Data Center may elect, after consultation with the Study Chairperson and the Medical Oncology Committee, to recommend early closure of a study.

The frequency and severity of all toxicities are tabulated from submitted case report forms and summarized for review by the study chairperson, Developmental Therapeutics Committee, and NRG Safety Review Committee (SRC) in conjunction with each semi-annual NRG meeting. For studies sponsored by the Cancer Therapy Evaluation Program (CTEP) of the National Cancer Institute (NCI), standardized toxicity reports are also submitted to the drug and disease monitors at the Investigational Drug Branch (IDB) and Clinical Investigation Branch (CIB). As this is a two-stage multi-institutional phase II protocol, the initial overall review of toxicity is usually performed after completion of the first stage of accrual, at which point accrual is generally suspended pending formal analysis of response.

All serious and/or unexpected events are communicated to the Study Chair, sponsor, and regulatory agencies as mandated in the protocol. These reports are reviewed by the Study Chair (or designated co-chair) within two working days for consideration of investigator notification, amendment, or immediate study suspension. All participating institutions will then receive notification of the toxicities and reason for study suspension. Under these circumstances, accrual cannot be re-activated until the study is reviewed by the NRG SRC. However, patients currently receiving treatment may continue to receive treatment in accordance with protocol guidelines at the discretion of their physicians, unless directed otherwise.

13.5 Accrual Considerations

13.5.1 Accrual Rate

The projected accrual rate for this study is approximately 1.1 patients per month based on historial GOG-0127 studies shown in Table 1.

Table 1. Estimated accrual rate (per month) in historical GOG-0127 studies

Protocol	Stage	Start Date	End Date	Number	Months	Accrual Rate
0127Q	1	10/2/2000	6/3/2002	32	20.0082	1.59934
0127R	1	6/3/2002	12/1/2003	27	17.9384	1.50515
0127S	1	6/2/2002	12/6/2004	23	30.1602	0.7626
0127T	1	7/6/2004	4/3/2006	25	20.8953	1.19644
0127U	1	1/3/2005	10/29/2007	25	33.807	0.73949
0127V	1	11/6/2006	3/19/2008	24	16.3943	1.46393
0127V	2	9/8/2009	2/1/2011	11	16.7885	0.65521
0127W	1	2/7/2011	1/17/2013	27	23.3265	1.15748

13.5.2 Accrual Goal

The projected minimum and maximum accruals for the study are 8 and 25 eligible and evaluable patients, respectively. The targeted accrual is 12 eligible and evaluable patients in the first stage of the study, and cumulatively 22 eligible and evaluable patients will be targeted in the second stage if the study advances.

13.5.3 Study Duration

1) Patients will receive therapy for a maximum of 46 doses (92 weeks), until disease progression or intolerable toxicity intervenes, whichever comes first.
The patient can refuse the study treatment at any time.
2) All patients will be treated (with completion of all required case report forms)with a maximum of 46 doses of study drug until disease progression, initiation of a subsequent cancer treatment or study withdrawal.
Patients will then be followed every three months for the first two years and then every six months for the next three years. Patients will be monitored for delayed toxicity and survival for this 5 year period with Follow-up Forms submitted to the NRG SDMC-Buffalo Office, unless consent is withdrawn. Follow-up Forms will no longer be required if the study is terminated prior to the completion of the 5-year follow-up period.
3) A patient is considered off study therapy when the patient has progressed or died, a non-protocol drug or therapy (directed at the disease) is initiated, or all study therapy is discontinued. Report all treatment received on Cycle Drug Information Forms and adverse events on Adverse Events Forms until the patient qualifies as being off study therapy.

13.5.4 Estimated Duration for Completion of Primary Endpoint: provision of timeframe, e.g. 24 months from activation

The projected accrual rate is 1.1 patients per month based on the GOG-0127 historical studies. Thus, the accrual duration will take approximate 11 months for the first stage and 9 months for the second stage, separately. Additionally, the evaluation of patients with complete/partial response takes at least 12 weeks, and it can take even longer to evaluate patients with stable disease to determine whether they respond or not. Therefore, the duration for completion of primary endpoint will be approximately 16 months from activation of the study for the first stage, and 14 months from activation of the second stage for the second stage if the study advances to the second stage.

However the study regimen is a very exciting new drug, it is reasonable to project that the actual study accrual rate can be as high as 3 patients per months. If the actual accrual rate is 3 patients per months, the duration for completion of primary endpoint will be approximately 9 months from activation of the study for the first stage, and 8.5 months from activation of the second stage for the second stage if the study advances to the second stage.

13.6 Dose Level Guidelines

Not Applicable.

13.7 Secondary or Exploratory Elements (including correlative science aims)

13.7.1 Secondary Hypotheses and Endpoints:

There are no specific secondary hypotheses regarding secondary objective. The purpose of secondary objective is to describe the survival functions for progression-free survival

(PFS) and overall survival (OS).

13.7.2 Definitions of Secondary Endpoints and How These Will Be Analyzed

Progression-free survival is defined as the duration of time from study entry to time of progression, death, or the date of last contact, whichever occurs first. PFS is censored in patients who are alive and have not progressed.

Overall survival is defined as the duration of time from study entry to time of death or the date of last contact. OS is censored in patients who are alive.

Kaplan-Meier median estimates and curves will be used to describe PFS and OS survival functions.

13.7.3 Interim Analysis for All Other Endpoints (Goals):

Not Applicable.

13.7.4 Power Calculations:

Not Applicable.

13.7.5 Expected Sample Size or Patient Cohorts:

Not Applicable.

13.8 Exploratory Hypothesis and Endpoints

The corresponding exploratory hypotheses for the study translational science objectives are:

1) Tumor expressions of PD-L1 and PD-1 will be associated respectively with objective response, PFS and OS in nivolumab-treated patients.
2) Immune infiltration related biomarkers (i.e., CD4+, CD8+, FoxP3) in tumor specimens will be associated with objective tumor response, PFS and OS in nivolumab-treated patients.
3) The study treatment will change the immune response to HPV 16/18/31/35/45 E7 antigen in peripheral blood lymphocytes and serum.
4) The study treatment will change the CTC count and the CTC count is associated with objective response, PFS and OS in nivolumab-treated patients.

The corresponding exploratory endpoints:
See Section 13.2.3.

Spearman's correlation coefficient will be used to explore the associations of tumor expressions of PD-L1, PD-1 and other interested biomarkers with tumor response. Cox proportional hazards (PH) model will be utilized to evaluate the associations of these tumor expressions with PFS and OS. These expressions may also be dichotomized into high versus low values (cut at the median). Log-rank tests will be used to assess the associations of these dichotomized tumor expressions with PFS and OS. The corresponding hazard rations will be estimated by Cox PH models. Wilcoxon signed rank test (for interval or ordinal data) or McNemar's test (for binary data) may be utilized to examine whether the study treatment will change immune response to HPV 16/18/31/35/45 E7 antigen in peripheral blood lymphocytes and serum by changes in the measures of pre- and post-treatment immune response to HPV 16/18/31/35/45 E7. Other statistical methods such as time dependent or landmark survival method, mixed model or logistic regression will be applied to evaluate the associations between the CTC count

and objective response, PFS or OS, and the hypothesis that the study treatment will change the CTS count, where it is appropriate.

The purpose of translation science objectives is to explore and possibly generate hypotheses for future study. Therefore there will be no adjustment for multiple tests. Due to small sample size of this study, exact testing procedure (i.e., exact Spearman correlation test, permutation-based log-rank test) may be used where it is appropriate.

13.9 Gender/Ethnicity/Race Distribution

	Gender		
Ethnic Category	**Females**	**Males**	**Total**
Hispanic or Latino	2	0	2
Not Hispanic or Latino	23	0	23
Ethnic Category: Total of all	25	0	**25**
	Gender		
Racial Category	**Females**	**Males**	**Total**
American Indian or Alaskan Native	0	0	0
Asian	0	0	0
Black or African American	5	0	5
Native Hawaiian or other Pacific	0	0	0
White	20	0	20
Racial Category: Total of all	25	0	**25**

14. EVALUATION CRITERIA

14.1 Response Assessment: RECIST 1.1

14.1.1 Antitumor Effect – Solid Tumors

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

14.1.1.1 Disease Parameters

Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥10 mm with CT scan, as ≥20 mm by chest x-ray, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in decimal fractions of centimeters.

Note: Tumor lesions that are situated in a previously irradiated area will not be considered measurable unless progression is documented or a biopsy is obtained to confirm persistence at least 90 days following completion of radiation therapy.

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 recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

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. Leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal/pelvic masses (identified by physical exam and not CT or MRI), are considered as non-measurable.

Notes:
Bone lesions: Lytic bone lesions or mixed lytic-blastic lesions, with identifiable soft tissue components, that can be evaluated by CT or MRI can be considered as measurable lesions if the soft tissue component meets the definition of measurability described above. Blastic bone lesions are non-measurable.

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.

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, and 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 which 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.

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.

14.1.1.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

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.

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.

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.

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), but NOT lung.
Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline, and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, subsequent image acquisitions should use the same type of scanner and follow the baseline imaging protocol as closely as possible. If possible, body scans should be performed with breath-hold scanning techniques.

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. PET-CT scans are not always done with oral and IV contrast. In addition, the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed. **For these reasons, NRG will not allow PET-CT use for RECIST 1.1 response criteria.**

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:
Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

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.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

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.

It is mandatory to obtain cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when measurable disease has met criteria for response or stable disease. This confirmation is necessary to differentiate response or stable disease versus progressive disease, as an effusion may be a side effect of the treatment.

14.1.1.3 Response Criteria

Determination of response should take into consideration all target (See 14.1.1.3.1) and non-target lesions (See 14.1.1.3.2).

14.1.1.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

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).

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.

Not Evaluable (NE): When at least one target lesion is not evaluated at a particular time point.

14.1.1.3.2 Evaluation of Non-Target Lesions

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

Non-CR/Non-PD: Persistence of one or more non-target lesion(s)

Progressive Disease (PD): Appearance of one or more new lesions 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.

Not evaluable (NE): When at least one non-target lesion is not evaluated at a particular time point.

Although a clear progression of only "non-target" lesions is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

14.1.1.3.3 Evaluation of Best Overall (unconfirmed) Response

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

Time Point Response for Patients with Measurable Disease at baseline (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions*	Time Point Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or NE	No	PR
SD	Non-PD or NE	No	SD
NE	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD**	Yes or No	PD
Any	Any	Yes	PD

Time Point Response for Patients with only Non-Measurable Disease at baseline (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions*	Time Point Response
CR	No	CR
CR	No	Non-CR/non-PD*
Non-CR/non-PD	No	Non-CR/non-PD*
NE	No	NE
Unequivocal PD	Yes or No	PD
Any	Yes	PD

14.1.1.3.4 Best Overall Confirmed Response

Confirmation of CR and PR for determination of best overall response is required for studies with a primary endpoint that includes response.

Confirmed CR and PR for best overall confirmed response

Time Point Response First time point	Time Point Response Subsequent time point	BEST overall confirmed response
CR	CR	CR
CR	PR	SD, PD or PR*
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

*If a CR is *truly* met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that point (since disease must have reappeared after CR). However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR or SD, not CR at the first time point. Under these circumstances, the original CR should be changed to PR or SD and the best response is PR or SD.

In non-randomized trials where response is part of the primary endpoint, confirmation of CR or PR is needed to deem either one the "best overall response." **Responses (CR and PR) require confirmation at greater than or equal to 4 weeks from initial documentation.**

For this study, the minimum criteria for SD duration is 8 weeks.

Patients with a global deterioration of health status requiring discontinuation of treatment or die without objective evidence of disease progression at that time should be reported to be off study treatment due to "symptomatic deterioration." Every effort should be made to document the objective progression even after discontinuation of treatment.

14.1.1.4 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.

14.1.1.5 Progression-Free Survival

Progression-Free Survival (PFS) is defined as the duration of time from study entry to time of progression, death, or the date of last contact, whichever occurs first.

14.1.1.6 Survival

Survival is defined as the duration of time from study entry to time of death or the date of last contact.

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APPENDIX I - COLLABORATIVE AGREEMENT

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

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

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

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

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

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

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

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

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

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

Email: ncicteppubs@mail.nih.gov

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

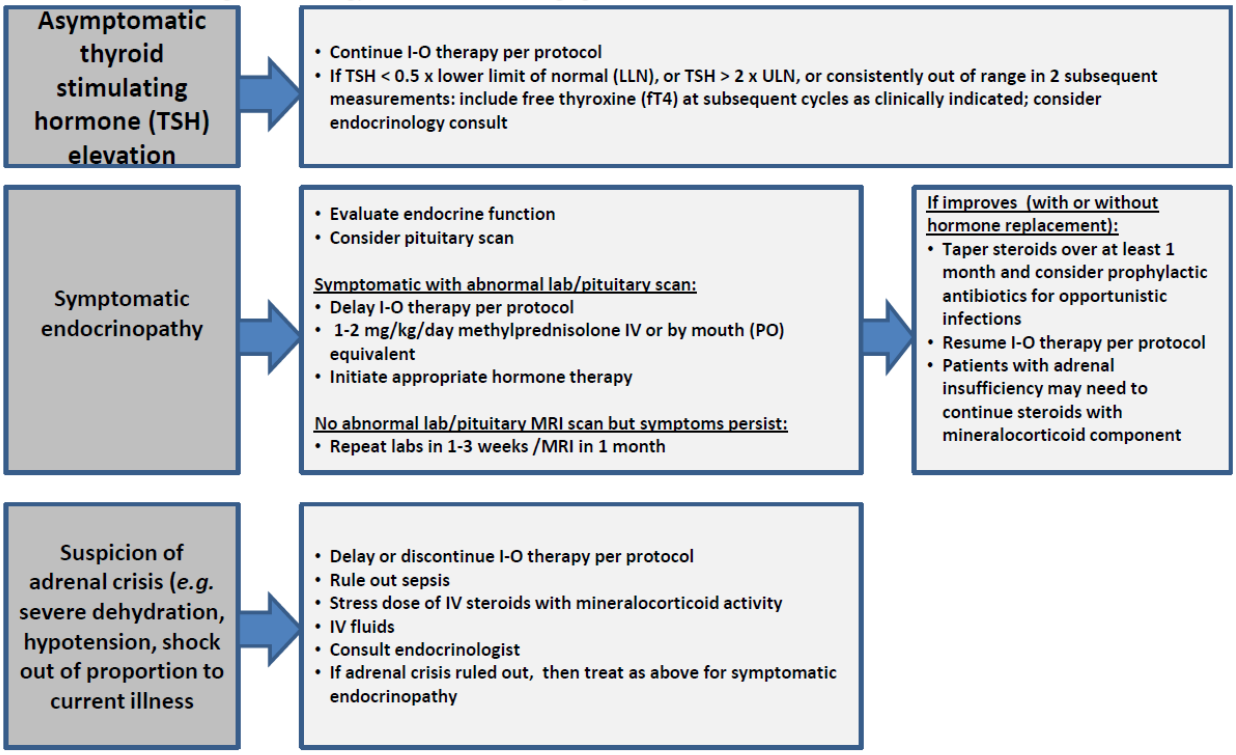
APPENDIX II **- PERFORMANCE STATUS CRITERIA**

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (*e.g.*, light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX III MANAGEMENT ALGORITHMS FOR ENDOCRINOPATHY, GASTROINTESTINAL, HEPATIC, NEUROLOGICAL, PULMONARY, RENAL, AND SKIN ADVERSE EVENTS

Endocrinopathy Management Algorithm

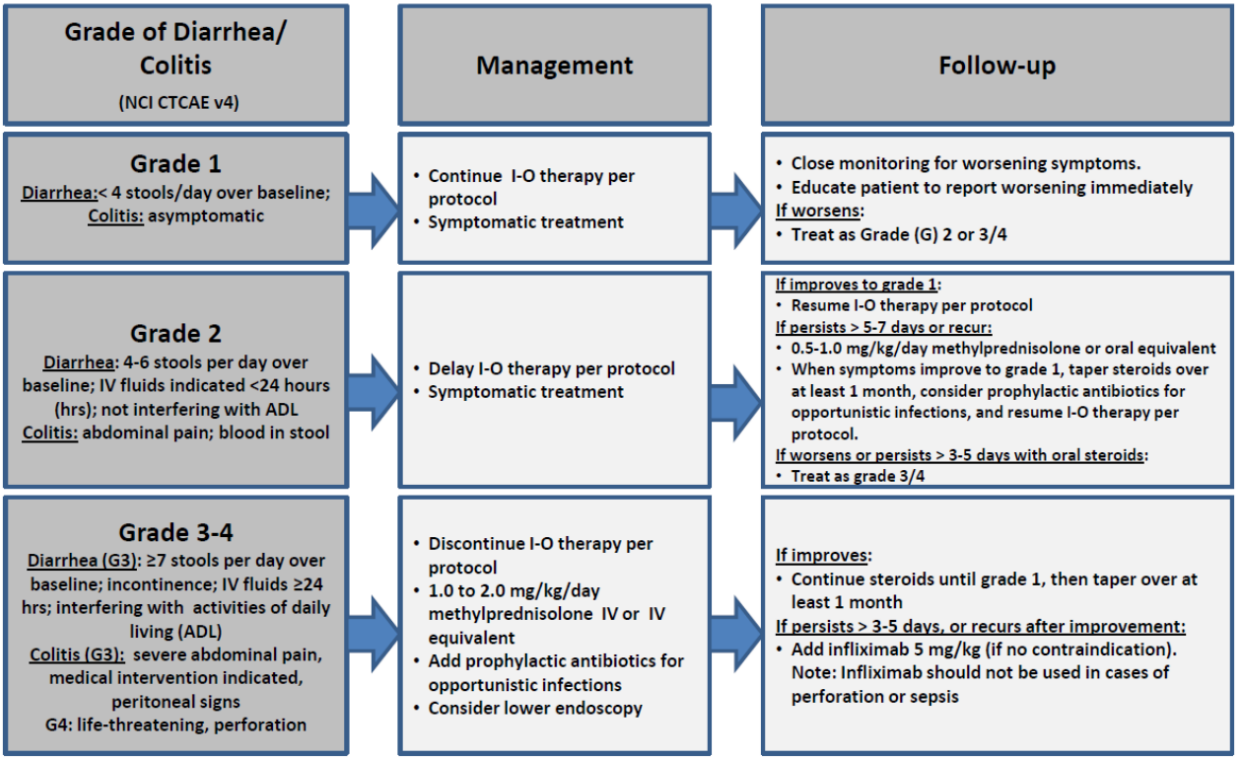
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue immuno-oncology (I-O) therapy.
Consider visual field testing, endocrinology consultation, and imaging.



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

GI Adverse Event Management Algorithm

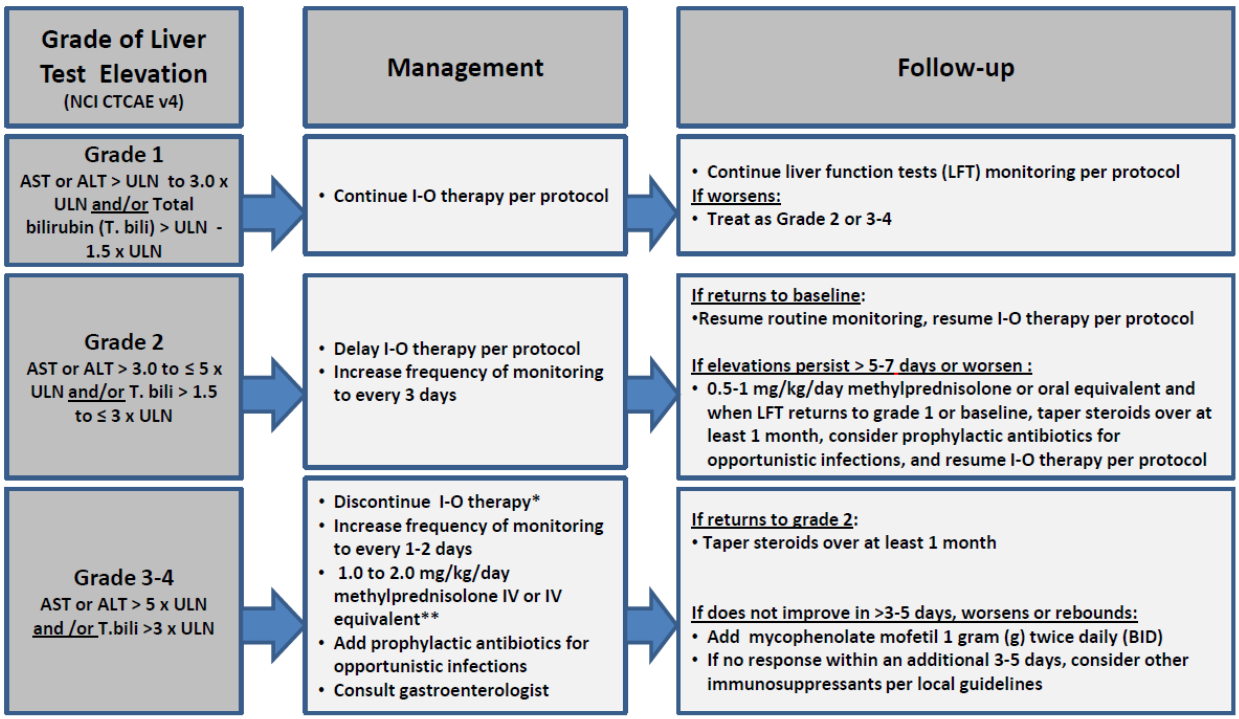
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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

Hepatic Adverse Event Management Algorithm

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



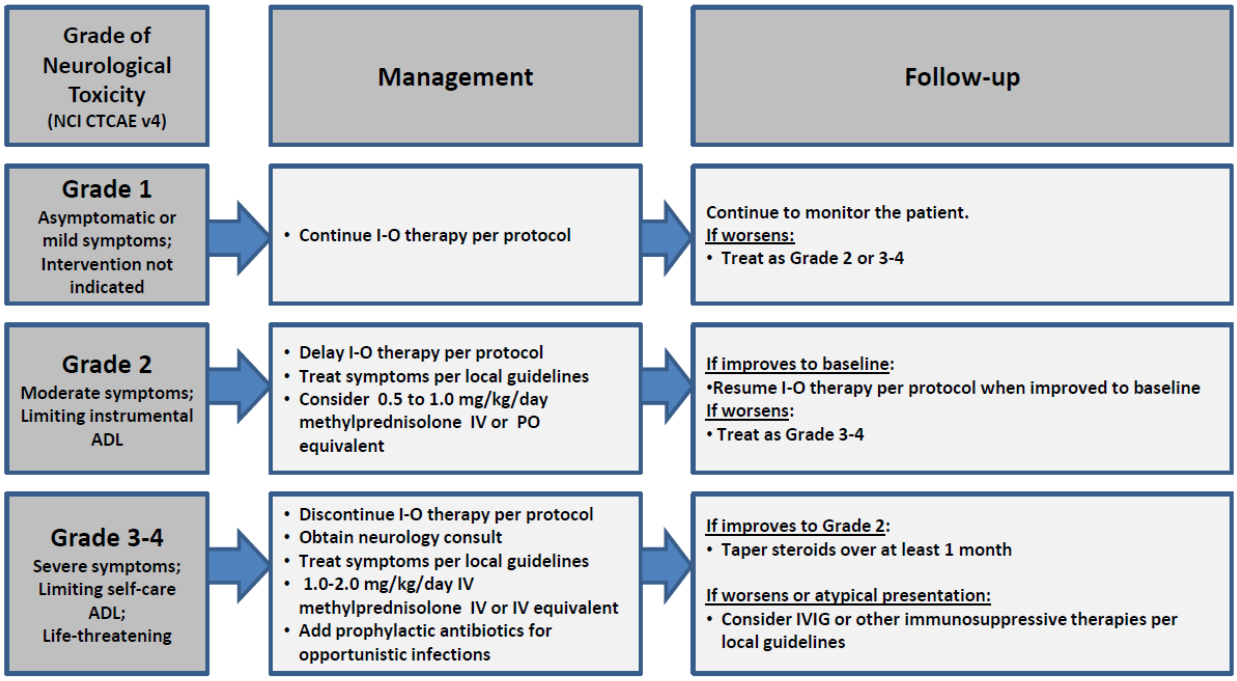
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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

Neurological Adverse Event Management Algorithm

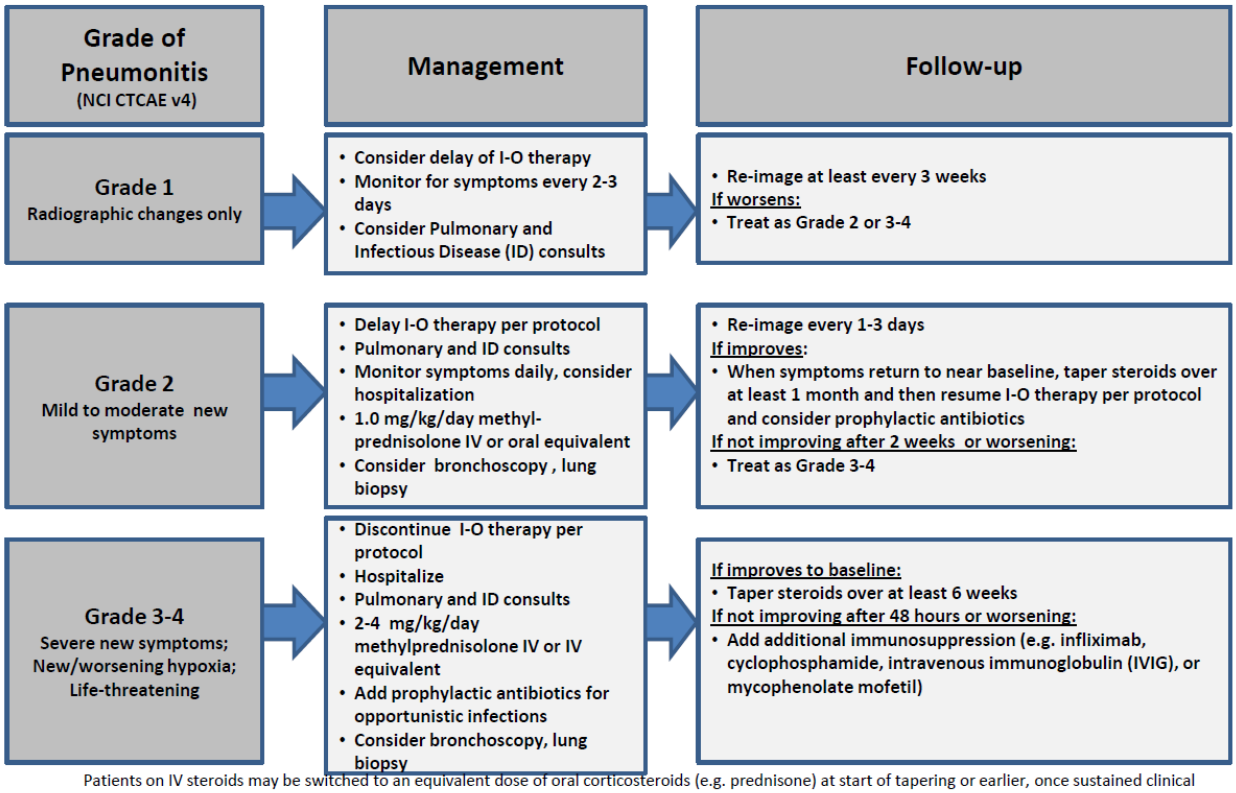
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

Pulmonary Adverse Event Management Algorithm

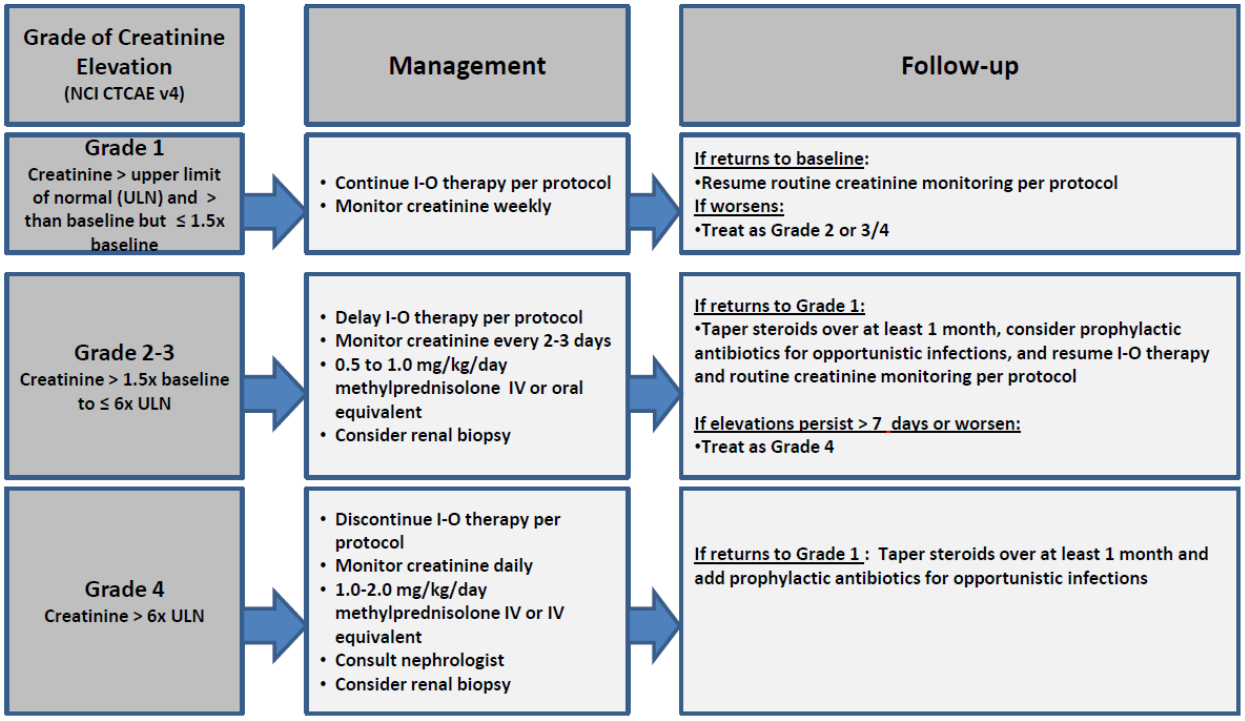
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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

Renal Adverse Event Management Algorithm

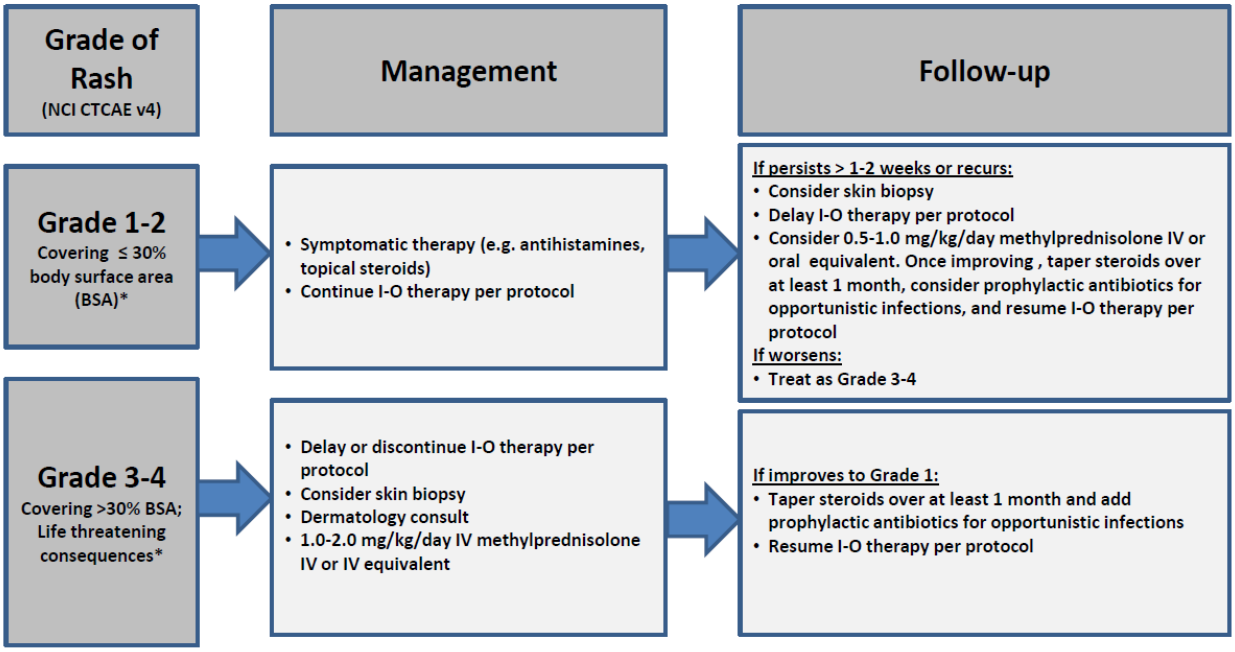
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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

Skin Adverse Event Management Algorithm

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



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.

APPENDIX IV - TRANSLATIONAL SCIENCE SPECIMEN PROCEDURES

I. Obtaining a Bank ID for Translational Science Specimens
Only one Bank ID (# # # # - # # - G # # #) is assigned per patient. All translational science specimens and accompanying paperwork must be labeled with this coded patient number.

A Bank ID is automatically assigned once the Specimen Consent is completed and indicates that a patient has agreed to participate in the translational science component.

A Bank ID can also be obtained online via the Tissue Bank Portal link on the NRG Oncology webpage. Obtain the patient's study ID for all protocols with translational science specimen requirements before requesting a Bank ID from the Tissue Bank Portal. **Be sure to indicate if the patient has a legacy GOG ID when registering.** This will ensure the patient is only assigned one Bank ID. The GOG ID – Bank ID Lookup on the Tissue Bank Portal can be used to search for an existing Bank ID.

Please contact User Support if you need assistance or have assigned more than one Bank ID to a patient (Email: support@gogstats.org; Phone: 716-845-7767).

II. Requesting Translational Science Specimen Kits (03/21/2016)
One single chamber kit will be provided per patient for the collection and shipment of frozen serum.

Sites can order kits online via the Kit Management link http://ricapps.nationwidechildrens.org/BPCKitManagement/. . Each site may order two kits per protocol per day (daily max = 6 kits).

Please contact the NRG Oncology Biospecimen Bank-Columbus if you need assistance (Email: BPCBank@nationwidechildrens.org; Phone: 866-464-2262).

Be sure to plan ahead and allow time for kits to be shipped by ground transportation.

Note: Unused materials and kits should be returned to the NRG Oncology Biospecimen Bank-Columbus.

III. Formalin-Fixed, Paraffin-Embedded Tissue Shipped to the NRG Oncology Biospecimen Bank-Columbus
Formalin-fixed, paraffin embedded (FFPE) tissue should be the most representative of the specimen type (primary, metastatic, recurrent). **Primary** and **metastatic** tumor should be collected prior to all treatment. **Recurrent** and **persistent** tumor should be collected prior to the study treatment. Recurrent or persistent tumor collected from the site of primary disease should be labeled **recurrent primary** or **persistent primary**, respectively. Recurrent or persistent tumor collected from a site other than the site of primary disease (e.g., lymph node) should be labeled **recurrent metastatic** or **persistent metastatic**, respectively. Only one block may be submitted per tissue type.

Every attempt should be made to provide a FFPE block; however, if a block cannot be provided on a permanent basis, then 20 unstained slides (charged, 5µm) should be submitted. All tissue sections should be cut sequentially from the same block.

The type of specimen (block or slides) should be specified on Form TR. If submitting slides, the slide type, thickness, and count should also be specified.

All FFPE tissue should be submitted with the corresponding pathology report.

Labeling Formalin-Fixed, Paraffin-Embedded Tissue
A waterproof permanent marker or printed label should be used to label each translational science specimen with:

Bank ID (# # # # - # # - G # # #)
protocol number (NRG-GY002)
specimen code (see protocol section 11)
collection date (mm/dd/yyyy)
surgical pathology accession number
block number

Note: If labeling slides, only label on the top, front portion of the slide. Do not place a label on the back of the slide or over the tissue. The label must fit on the slide and should not be wrapped around the slide or hang over the edge.

IV. Immune Whole Blood Shipped to Yale School of Medicine
Note: This protocol requires green top (sodium heparin) tubes to collect 30mL whole blood.

1. Label the green top (sodium heparin) collection tube(s) as described above. Multiple tubes may be used to collect the required amount.
2. Draw 30mL of blood into the labeled green top (sodium heparin) tube(s).
3. Immediately after collection, gently invert the tube 5-10 times to mix the blood and sodium heparin.
4. Whole blood specimens should be refrigerated (4°C) until the specimens can be shipped. Ship whole blood to Yale School of Medicine the day the specimen is collected. If the whole blood absolutely cannot be shipped the day it is collected, the tube(s) should be refrigerated (4°C) until the specimen can be shipped.

Labeling Immune Whole Blood
A waterproof permanent marker or printed label should be used to label each translational science specimen with:

Bank ID (# # # # - # # - G # # #)
protocol number (NRG-GY002)
specimen code (see protocol section 11)
collection date (mm/dd/yyyy)

V. CTC Whole Blood Shipped to Massachusetts General Hospital

Note: This protocol requires purple top (EDTA) tubes to collect 10mL whole blood.

1. Label the purple top (EDTA) collection tube(s) as described above. Multiple tubes may be used to collect the required amount.
2. Draw 10mL of blood into the labeled purple top (EDTA) tube(s).
3. Immediately after collection, gently invert the tube 5-10 times to mix the blood and purple top (EDTA).
4. Whole blood specimens should be refrigerated (4°C) until the specimens can be shipped. Ship whole blood to Massachusetts General Hospital the day the specimen is collected. If the whole blood absolutely cannot be shipped the day it is collected, the tube(s) should be refrigerated (4°C) until the specimen can be shipped.

Labeling CTC Whole Blood

A waterproof permanent marker or printed label should be used to label each translational science specimen with:

Bank ID (# # # # - # # - G # # #)
protocol number (NRG-GY002)
specimen code (see protocol section 11)
collection date (mm/dd/yyyy)

VI. Serum Shipped to the NRG Oncology Biospecimen Bank-Columbus

1. Label cryovials and a 15mL conical tube as described above. Use 2mL cryovials if serum will be shipped to the NRG Oncology Biospecimen Bank-Columbus.
2. Draw 7-10mL of blood into red top tube(s).
3. Allow the blood to clot at 4°C (or in a bucket with ice) for at least 30 minutes but no longer than 3 hours.
4. Centrifuge the blood at 1000g for 15 minutes at 4ºC (preferred) or room temperature to separate the serum (top, straw-colored layer) from the red blood cells (bottom, red layer).
5. Transfer the serum into a 15mL conical tube and gently mix.
6. Quickly, evenly dispense (aliquot) the serum into the pre-labeled cryovials and cap the tubes securely. Place a minimum of 0.25mL into each cryovial.
7. Immediately freeze the serum in an upright position in a -70ºC to -80ºC freezer or by direct exposure with dry ice until ready to ship. If a -70ºC to -80ºC freezer is not available for storage, store and ship on dry ice within 24 hours of collection.

Labeling Serum

A waterproof permanent marker or printed label should be used to label each translational science specimen with:

Bank ID (# # # # - # # - G # # #)
protocol number (NRG-GY002)
specimen code (see protocol section 11)
collection date (mm/dd/yyyy)

VII. Submitting Form TR

An electronically completed copy of Form TR must accompany each specimen shipped to the

NRG Oncology Biospecimen Bank-Columbus (or alternate laboratory). Handwritten forms will not be accepted.

Note: A copy does not need to be sent to the NRG Oncology Biospecimen Bank-Columbus (or alternate laboratory) if specimens are not collected.

Form TR should be printed from the Translational Research Form screen in Rave using the **"PDF File" link at the top of the form**. Clicking this link will generate a PDF of Form TR in a "SEDES style" format. Do not use the "Printable Version" or "View PDF" links at the bottom of the form or any other method to print the form, as these formats will not be accepted.

Retain a printout of the completed form for your records.

Please contact User Support if you need assistance (Email: support@gogstats.org; Phone: 716-845-7767).

VIII. Shipping Translational Science Specimens
An electronically completed copy of Form TR must be included for each translational science specimen.

A. FFPE Tissue
FFPE tissue, an electronically completed copy of Form TR, and a copy of the corresponding pathology report should be shipped using your own container at your own expense to:

NRG Oncology Biospecimen Bank-Columbus / Protocol NRG-GY002
Nationwide Children's Hospital
700 Children's Dr, WA1340
Columbus, OH 43205
Phone: 614-722-2865
FAX: 614-722-2897
Email: BPCBank@nationwidechildrens.org

Do not ship FFPE tissue for Saturday delivery.

B. Frozen Serum
Frozen serum should be shipped using the specimen kit provided to the NRG Oncology Biospecimen Bank-Columbus (address above).

Frozen specimens should be shipped **Monday through Thursday for Tuesday through Friday delivery**. Do not ship frozen specimens on Friday or the day before a holiday. Note: Saturday delivery is not available for frozen specimens.

Frozen specimens should be stored in an ultra-cold freezing/storage space (i.e., ultra-cold ≤-70ºC freezer, liquid nitrogen, or direct exposure with dry ice) until the specimens can be shipped.

Shipping Specimens in a Single Chamber Kit to the NRG Oncology Biospecimen Bank-

Columbus

1. Pre-fill the kit chamber about 1/3 full with dry ice.
2. Place the frozen specimens from each time point in a separate zip-lock bag.
3. Place the zip-lock bags in the biohazard envelope containing absorbent material. Do not put more than 25 cryovials in a single chamber kit. Put the secondary envelope into a Tyvek envelope. Expel as much air as possible before sealing both envelopes.
4. Place the Tyvek envelope containing the frozen specimens into the kit and fill the chamber to the top with dry ice.
5. Insert a copy of Form TR for each specimen.
6. Place the cover on top of the kit. Tape the outer box of the kit closed with filament or other durable sealing tape. Please do not tape the inner chamber.
7. Legacy GOG sites can print a pre-paid FedEx air bill using the Kit Management application (found under Data Entry on the Web Menu page). Non-legacy GOG sites should contact the NRG Oncology Biospecimen Bank-Columbus for a pre-paid FedEx air bill. Attach the air bill.
8. Attach the dry ice label (UN1845) and the Exempt Human Specimen sticker.
9. Arrange for FedEx pick-up through your site's usual procedure or by calling 800-238-5355.

C. Whole Blood

Immune whole blood specimens should be shipped to:

Dr. Alessandro Santin
c/o Lisa Patriub
Yale University School of Medicine
330 Cedar St, LSOG 305
New Haven, CT 06520
Phone: 203-737-4450
Email: lisa.patriub@yale.edu

CTC whole blood* specimens should be shipped to:
Dr. Michael Birrer
c/o Giulia Fulci
Massachusetts General Hospital
Jackson 9
55 Fruit St
Boston, MA 02114
Phone: 617-726-6081
Email: gfulci@partners.org, wei.wei@mgh.harvard.edu
***Please email MGH prior to shipping CTC whole blood specimens.**

Whole blood specimens can be shipped **Monday through Thursday for Tuesday through Friday delivery**. Do not ship whole blood the day before a holiday. Use your own shipping container to ship specimens via FedEx priority overnight.

When shipping whole blood specimens, your site must comply with IATA standards (www.iata.org). If you have questions regarding your **immune whole blood** shipment, contact Lisa Patriub (Phone: 203-737-4450; Email: lisa.patriub@yale.edu). If you have questions

regarding your **CTC whole blood** shipment, contact Giulia Fulci (Phone: 617-726-6081; Email: gfulci@partners.org, wei.wei@mgh.harvard.edu).

To ship whole blood specimens you will need (1) a sturdy shipping container (e.g., a cardboard or styrofoam box), (2) a leak proof biohazard envelope with absorbent material*, (3) a puncture and pressure resistant envelope (e.g. Tyvek envelope), (4) an Exempt Human Specimen sticker, and (5) a pre-paid FedEx air bill.

**If you will be shipping whole blood specimens from more than one patient, please put each specimen in a separate plastic zip-lock bag before placing the specimens in the shipping bag. You may include up to four different blood specimens in one biohazard envelope.*

If you do not have these materials available at your site, you may order them from any supplier (e.g., Saf-T-Pak; Phone: 800-814-7484; Website: www.saftpak.com).

Shipping Whole Blood Using Your Own Shipping Container to an Alternate Laboratory

1. Place the whole blood specimen in a biohazard envelope containing absorbent material. Expel as much air as possible before sealing the bag.
2. Wrap the biohazard envelope in bubble wrap or another padded material.
3. Place the padded tube(s) into a Tyvek envelope. Expel as much air as possible before sealing the envelope.
4. Place the Tyvek envelope in a sturdy shipping container (e.g., cardboard FedEx box).
5. Insert a copy of Form TR for each specimen.
6. Attach an Exempt Human Specimen sticker to the outside of the shipping container.
7. Attach the pre-paid FedEx air bill provided.
8. Make arrangements for FedEx pick-up through your site's usual procedure or by calling 800-238-5355.

IX. Distributing Translational Science Specimens

Note: Testing of banked specimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

The Statistics and Data Management Center-Buffalo Office and NRG Oncology Biospecimen Bank-Columbus (or alternate laboratory) will coordinate the distribution of translational science specimens to approved investigators.

Investigators will not be given access to any personal identifiers.

Investigators will be responsible for the direct supervision and oversight of the translational science and for keeping accurate records.

Investigators will ensure the results are linked to the appropriate translational science specimen-specific identifiers and are responsible for transferring relevant laboratory data to the Statistics and Data Management Center-Buffalo Office.

At the discretion of the Chair of the Translational Science-GYN Committee and the Director of the NRG Oncology Biospecimen Bank-Columbus, investigators may be required to ship any specimens (or by-products) remaining after the completion of the translational science to the NRG Oncology Biospecimen Bank-Columbus.

X. Banking Translational Science Specimens for Future Research

Specimens will remain in the NRG Oncology Biospecimen Bank-Columbus and made available for approved research projects if the patient has provided permission for the use of her specimens for future health research. The patient's choices will be recorded on the signed informed consent document and electronically via Specimen Consent. At the time of specimen selection for project distribution, the most recent consent information will be used.

Sites can amend a patient's choices regarding the future use of her specimens at any time if the patient changes her mind.

If the patient revokes permission to use her specimens, the NRG Oncology Biospecimen Bank-Columbus will destroy or return any remaining specimens. The patient's specimens will not be used for any <u>further</u> research; however, any specimens distributed for research prior to revoking consent cannot be returned or destroyed. In addition, the patient cannot be removed from any research that has been done with her specimens distributed prior to revoking consent.

Note: If return of specimens is requested, shipping will be at the site's expense.