BrUOG 355
BMS: CA209-9LX

TITLE: BrUOG 355: A Pilot Feasibility study incorporating Nivolumab to tailored radiation therapy with concomitant cisplatin in the treatment of patients with cervical cancer

Coordinating Center: **Brown University Oncology Group (BrUOG)**

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Agent(s): Nivolumab (supplied by Bristol-Myers Squibb)

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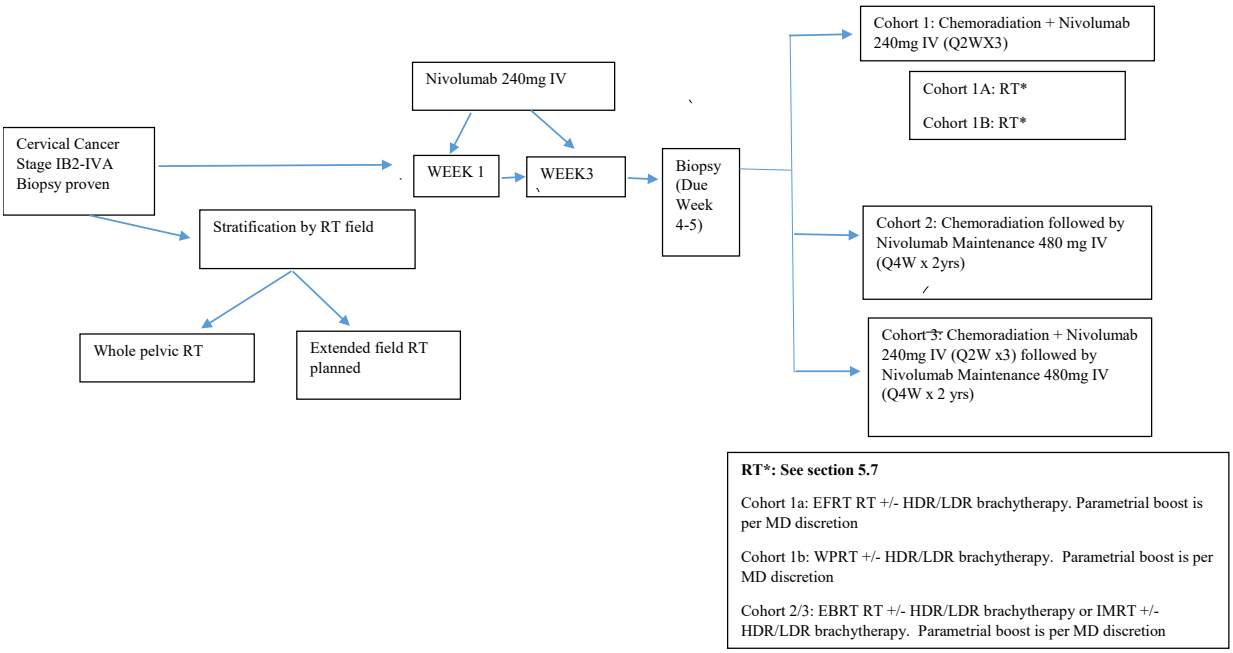
SCHEMA


Nivolumab 240mg IV
Cervical Cancer Stage IB2-IVA Biopsy proven
WEEK 1
WEEK3
Biopsy (Due Week 4-5)
Cohort 1: Chemoradiation + Nivolumab 240mg IV (Q2WX3)
Cohort 1A: RT*
Cohort 1B: RT*
Cohort 2: Chemoradiation followed by Nivolumab Maintenance 480 mg IV (Q4W x 2yrs)
Cohort 3: Chemoradiation + Nivolumab 240mg IV (Q2W x3) followed by Nivolumab Maintenance 480mg IV (Q4W x 2 yrs)
Stratification by RT field
Whole pelvic RT
Extended field RT planned
RT*: See section 5.7
Cohort 1a: EFRT RT +/- HDR/LDR brachytherapy. Parametrial boost is per MD discretion
Cohort 1b: WPRT +/- HDR/LDR brachytherapy. Parametrial boost is per MD discretion
Cohort 2/3: EBRT RT +/- HDR/LDR brachytherapy or IMRT +/- HDR/LDR brachytherapy. Parametrial boost is per MD discretion

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1 OBJECTIVES

1.1 Study Design

1.1.1 This is a pilot study to assess the feasibility and toxicity of incorporating nivolumab with definitive chemoradiation for newly diagnosed cervical cancer.

1.2 Primary Objectives

1.2.1 To determine the feasibility of the incorporation of nivolumab with weekly cisplatin and extended field (EFRT) or whole pelvic radiation therapy (WPRT) in women with cervical cancer.

1.2.2 To determine the feasibility of the regimen through assessment of acute toxicities.

1.2.3 Estimate the distribution of progression free survival for three years after study entry

1.3 Secondary Objectives

1.3.1 To determine site of recurrence, loco-regional versus distant within three years of study entry

1.3.2 To estimate the frequency of chronic toxicities experienced within three years after study entry.

1.4 Exploratory Objectives

1.4.1 To assess if there is an association between progression free survival, PD-L1 expression, and serum Chitinase 3-like 1 (Chi3l1) in cervical cancer treated with definitive chemoradiation and nivolumab.

2 BACKGROUND

2.1 Study Disease(s)

Women with locally advanced cervical cancer include those with FIGO stage IB2 (a clinically visible cervical lesion of 4cm or larger), stage II (invasion beyond the uterus but not to pelvic sidewall or lower third of the vagina), stage III (tumor extension to the pelvic sidewall and/or involvement of the lower third of the vagina, and/or associated with hydronephrosis or a nonfunctioning kidney), and stage IVA disease (tumor extension to the bladder, rectum, or beyond the true pelvis).[1] For these patients, prognosis ranges greatly with five-year overall survival ranging from 89% (with stage IB disease) to 22% (with stage IVA disease) using contemporary standard therapies.[2]

For these women, seminal trials defined that standard treatment requires cisplatin-based chemoradiation (chemo-RT).[3] Despite this, it is well recognized that prognosis following definitive chemo-RT remains very much dependent on disease stage and nodal involvement. In addition, the reality is that, despite the routine use of chemoradiation, many patients are not cured.

The prognostic impact of stage and nodal disease was shown in one recent review of 139 patients which included 48% had stage IIB disease and 18% had para-aortic node (PAN) involvement (PAN+), defined at laparoscopic lymphadenectomy.[4] Following definitive chemoradiation, the median OS for the whole group was 68 months. For PAN+ patients, however, median OS was 21 months (versus 77 months if PAN-). On regression analysis, PAN+ and large tumor size (T>5cm, which constitutes stage IB or IIB disease) both were found to be independent and significant risk factors for poor survival. In a 2010 individual patient meta-analysis conducted by the Cochrane group, the overall benefit of chemoradiation was confirmed, with a 19% relative reduction in the risk of death with chemoradiation compared to RT alone, translating in to an absolute survival benefit of 6% at five years.[5] However, in real-world terms, the estimates of overall survival at 5 years was 66% with chemoRT versus 60% with RT alone, indicating that almost 40% will die of their disease despite treatment. In addition, the magnitude of the benefit associated with chemoradiation was found to depend on FIGO stage: estimated absolute survival benefit was 10, 7, and 3% at five years for patients with stage 1b-2a, 2b, versus 3-4a (which includes those with PAN involvement), respectively.

These results illustrate the lack of advancement in the contemporary curative intent treatment strategies for newly diagnosed cervical cancer since 2000. It also illustrates that much progress is still needed to cure more patients of this disease.

The potential role of immunotherapy in cervical cancer is based on the causative role of HPV infection in this disease. There are data to support the theory that the host immunological status and HPV-induced immune evasion are responsible for persistent HPV infection and the subsequent development of cervical cancer.[6] HPV infection invokes a cellular immune response, and regulatory T cells appear to play a role in local immune suppression in HPV-associated tumors.[7] Finally, recent results from The Cancer Genome Atlas on cervical cancer has identified amplification of known immune targets, specifically CD274 (which encodes the PD-L1 checkpoint protein) and PDCD1LG2 (which encodes the PD-L2 immune checkpoint protein).[8]

2.2 Nivolumab

Nivolumab (also referred to as BMS-936558 or MDX1106) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes.1 Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of

lymphocyte activation. 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. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration. It is approved for use in multiple countries including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014).

The PK, clinical activity, and safety of nivolumab have been assessed in subjects with non-small cell lung cancer (NSCLC), melanoma, clear-cell renal cell carcinoma (RCC), and classical Hodgkin Lymphoma (cHL) in addition to other tumor types. This updated Investigator Brochure (IB) references the most recent US Prescribing Information (USPI) and EU Summary of Product Characteristics (SmPC) as the basis for the current state of knowledge on nivolumab for use in humans.

Nivolumab monotherapy is approved in multiple countries, including the US and EU, for unresectable or metastatic melanoma, previously treated metastatic NSCLC, and previously treated advanced RCC; it is also approved for the treatment of cHL in the US. Nivolumab is being investigated both as monotherapy and in combination with chemotherapy.

The overall safety experience with nivolumab, as a monotherapy or in combination with other therapeutics, is based on experience in approximately 12,300 subjects treated to date.
For monotherapy, the safety profile is similar across tumor types. There is no pattern in the incidence, severity, or causality of AEs to nivolumab dose level. In Phase 3 controlled studies, the safety profile of nivolumab monotherapy is acceptable in the context of the observed clinical efficacy, and manageable using established safety guidelines. Clinically relevant AEs typical of stimulation of the immune system were infrequent and manageable by delaying or stopping nivolumab treatment and timely immunosuppressive therapy or other supportive care.
In several ongoing clinical trials, the safety of nivolumab in combination with other therapeutics such as ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies is being explored. Most studies are ongoing and, as such, the safety profile of nivolumab combinations continues to evolve.

Nivolumab has demonstrated promising activity in refractory cervical cancer according to results from CheckMate 358 presented at the ASCO Annual Meeting, 2017.[9] Conventional second-line options for recurrent or metastatic cervical cancers results in a median PFS of around 2 to 4 months and an objective response rate of 0% to 14%. Hollebecque and colleagues evaluated data from 24 patients (median age, 51 years) with cervical (n = 19) or vaginal or vulvar cancer (n = 5) treated in CheckMate 358, an ongoing multicohort study of five virus-associated cancers. The study included PD-L1–unselected adults with relapsed and metastatic gynecologic cancers with an ECOG performance score of 0 to 1 who had received two or fewer prior systemic therapies All patients who underwent HPV testing were positive, with 41.7% of patients having an unreported HPV status. Ten patients had PD-L1 expression above 1%. Patients received 240 mg

nivolumab every 2 weeks until progression or unacceptable toxicity. ORR and safety served as primary endpoints; secondary endpoints included duration of response, PFS and OS. Median follow-up was 31 weeks (range, 6-38). Researchers reported an ORR of 20.8%, which included one complete response (4.2%) and four partial responses (16.7%). Twelve patients (50%) achieved stable disease, for a disease control rate of 70.8%. All response occurred in patients with cervical cancer (ORR, 26.3%) and occurred regardless of PD-L1 or HPV status.

2.3 Rationale

Given the emerging understanding on the importance of immune mechanisms in cervical cancer, including the recent findings in the TCGA project, we propose to evaluate the safety of adding nivolumab to definitive chemoradiation for cervical cancer.

2.4 Correlative Studies Background

All patients will have tumor tissue from the diagnosis (or else, obtained prior to treatment) available, prior to study treatment, for exploratory correlative studies, which will be performed at a later date. In order to evaluate the tumor and the surrounding microenvironment, an optional second tumor biopsy attempt as outlined in the Schema is built in to the study, following induction doses of nivolumab (prior to start of chemoradiation).

The aim of such studies will be to identify potentially predictive biomarkers of benefit for patients with cervical cancer treated with nivolumab and standard chemoradiation. Data from these investigations will be evaluated for associations with response, survival (OS, PFS) and/or safety (adverse event) data. Biomarkers analysis may include PD-L1 expression, and tumor mutation burden. We may explore the prognostic significance of Chitinase 3-like 1 (Chi3l1), which we have recently demonstrated to have prognostic significance following immune checkpoint inhibitors in lung cancer. It is anticipated that advances in the understanding of biomarkers for immune checkpoint inhibitors will be forthcoming over the next few years emphasizing the need for tissue storage for future collaborative studies.

3 PARTICIPANT SELECTION (3.1, 3.2, 3.3 MUST ALL BE CONFIRMED)

3.1 Eligibility Criteria

3.1.1 Age ≥ 18 years. Cervical cancer is rarely seen in women under 18 years.

3.1.2 ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A)

3.1.3 Patients with histologically confirmed advanced cervical cancer (any cell type): FIGO Clinical stages IB2, IIA, IIB, IIIA, IIIB, IVA. All patients must have tissue from the diagnostic biopsy submitted prior to enrollment for both pathologic confirmation of the diagnosis (if done

outside of a BrUOG institution) and for specimen collection. Pathology must be reviewed by gynecological pathologist. NOTE: Patients with positive or negative pelvic and/or para-aortic lymph nodes by histologic confirmation or by radiological evaluation are eligible.

NOTE: Histologic or cytologic evaluation of PA nodes is highly recommended in the presence of enlarged lymph nodes on imaging (CT or PET/CT). In such cases, FNA or laparoscopic sampling are acceptable.

3.1.4 Participants must have normal organ and marrow function as defined below:

- absolute neutrophil count ≥1,500/mcL
- platelets ≥100,000/mcL
  - total bilirubin within normal institutional limits. A value below the LLN is acceptable if confirmed appropriate by the treating MD
- AST(SGOT)/ALT(SGPT) ≤2.5 × institutional upper limit of normal
- creatinine Within normal institutional limits
- hemoglobin ≥9.0g/dL

3.1.5 Neuropathy (sensory and motor) ≤ CTCAE v4.0 grade 1

3.1.6 Patients with ureteral obstruction should undergo stent or nephrostomy tube placement prior to study entry. Any side effects or complications associated with stent placement that, in the opinion of the treating investigator, puts the patient at increased risk for treatment-related toxicity, must be resolved completely prior to study enrollment.

3.1.7 Patients of child-bearing potential must have a negative serum pregnancy test prior to study entry (within 7 days prior to initiation of study treatment) and be practicing an effective form of contraception during study treatment and for 24 months (2 years) thereafter.

3.1.8 Women should not breast-feed while on this study

3.1.9 Patients must not be receiving any other investigational agent

3.1.10 Ability to understand and the willingness to sign a written informed consent document.

3.1.11 All patients with a history of hearing loss are required to have an audiogram within 28 days prior to initiating protocol therapy. If patient does not have a history of hearing loss this must be documented by treating physician. Audiogram with results required to be submitted to BrUOG.

3.2 Exclusion Criteria

3.2.1 Participants with visceral metastases, including brain metastases.

3.2.2 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, hepatitis, active rheumatologic or collagen vascular disease, symptomatic congestive heart failure, unstable angina pectoris, clinically significant cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements. Patients with active HIV disease not controlled on antiretroviral therapy are also excluded.

NOTE: Participants with active or a history of Hepatitis B or C infection as follows:

- Active hepatitis B (positive hepatitis B surface antigen [HBsAg] or hepatitis C virus (HCV) (positive HCV RNA) are not eligible to participate.
- HBV carriers or those participants requiring antiviral therapy are not eligible to participate.
- Participants positive for HCV antibody are eligible only if PCR is negative for HCV RNA. If PCR is positive, they are not eligible to participate.
- Past HBV infection or resolved HBV infection are may be eligible on this trial provided the following criteria are met prior to randomization: Positive for hepatitis B core antibody (HBcAb), the absence of hepatitis B surface antigen (HBsAg), and no detectable HBV DNA in serum.

3.2.3 Patients who have received previous pelvic or abdominal radiation, cytotoxic chemotherapy, or previous therapy of any kind for this or any other malignancy.

3.2.4 Patients who have circumstances that will not permit completion of this study or the required follow-up as per the treating physician

3.2.5 Patients with a history of other invasive malignancies, with the exception of non-melanoma skin cancer are excluded if there is any evidence of other malignancy being present within the last three years (2 years for invasive breast cancer). However, patients with a malignancy that is non-likely to require treatment, as per the treating physician, in the next 2 years, such as a completely resected, early stage breast cancer, or other malignancies treated with curative intent are eligible. Patients are also excluded if their previous cancer treatment contraindicates this protocol therapy.

3.2.6 Prior treatment with immunotherapy for any cancer, including immune checkpoint inhibitors or anti-CTLA4 agents

3.2.7 Patients with renal abnormalities, such as pelvic kidney, horseshoe kidney, or renal transplantation, that would require modification of radiation fields as documented by treating physician

3.2.8 Participants with an active, known or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not

expected to recur in the absence of an external trigger are permitted to enroll.

3.2.9 Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of day 1 of treatment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease

3.3 Clinical Staging Evaluation: Each item below is required to be documented if done or not with reason by treating physician and all assessments/tests with results are required to be submitted with registration

Patients will undergo clinical staging as permitted by FIGO rules. To be documented by treating physician

Assessment of adenopathy demonstrated on CT or PET scans by fine needle aspiration (FNA), extraperitoneal lymph node biopsy, or laparoscopic sampling (see section 3.4) is recommended.

Cystoscopy, proctoscopy, and barium enema are optional prior to entry onto study, although they should be obtained in those patients with clinical symptoms and/or physical findings highly suspicious of recto-vaginal and/or vesico-vaginal fistula. To be documented by treating physician if done (submit) or if not done confirming not required.

3.4 Inclusion of Women and Minorities

Women of all races and ethnic groups are eligible for this trial.

4 REGISTRATION PROCEDURES

All patients will be registered through the Brown University Oncology Research Group Central Office. Eligibility Checklist with supporting documentation, On Study Form and the signed Patient Consent Form must be faxed to the BrUOG Central Office, Fax: (401) 863-3820, at the time of registration and prior to patient treatment.

Details of patient's study participation should be documented in clinic/file notes. The Brown University Oncology Research Group will provide case report forms, included in the appendix, for the recording and collection of data. In the event of corrections, each correction will be initialed and dated by the person making the correction. The investigator will sign the case reports to indicate that, to his/her knowledge, they are complete and accurate. Case report forms, flow sheets, off-study forms and follow-up forms should emailed to:

Brown University Oncology Research Group,
Brown University
Box G-R 001
Providence, RI 02912

BrUOG@brown.edu

All support data must be sent in with the corresponding BrUOG forms. It is the treating physician's responsibility to review all data submitted to the BrUOG Central Office for accuracy and completeness and he/she must sign the off study form. Sites are to be sure that elements to support all inclusion and exclusion criteria are submitted and that all assessments from the schedule of evaluations are submitted for registration.

5 TREATMENT PLAN

5.1 BIOPSY:

There are 2 specimens anticipated for collection, as outlined in the schema. NOTE: Only the diagnostic specimen is required. The second biopsy (following two doses of neoadjuvant therapy prior to start of planned chemoradiation) is optional.

The first specimen must be obtained or ordered (if from outside institution) prior to enrollment. This may consist of the biopsy obtained for diagnostic purposes. All tissue submitted from outside of a BrUOG institution must be reviewed at Rhode Island Hospital for pathologic confirmation of the diagnosis.

The second biopsy is an optional **research only core needle biopsy** and will not be required as part of participation in this trial. If patients agree to proceed, an **attempt** at the biopsy will be obtained following the first two doses of Nivolumab (see 5.3 below) in each patient, which must be scheduled (and attempted) within 2 weeks of the final Nivolumab dose (week 4-5). The type of biopsy will be determined by the treating physician. Note, if there is evidence of primary cervical lesion, the biopsy may be obtained at the discretion of the treating gynecologic oncologist. However, the treating physician may proceed with a biopsy in Interventional Radiology if determined to be a better modality of collection.

If the biopsy is non-diagnostic or otherwise not technically feasible, patients will be allowed to continue on study.

All collected specimens will be utilized for correlative testing for future exploratory analyses to assess biomarkers associated with treatment using nivolumab in cervical cancer.

5.2 ALL PATIENT TREATMENT

5.3 Nivolumab

All patients will receive two doses of nivolumab prior to the start of definitive chemoradiation. During induction and for those receiving concurrent nivolumab with chemoradiation, this study will use a fixed dose of nivolumab 240 mg every 2 weeks during RT, with each 2 week period constituting a cycle. The cycle window will be +/- 3 days (See section 5.5).

For patients assigned to maintenance nivolumab (cohorts 2 and 3), nivolumab will be administered at a fixed dose of 480 mg every 4 weeks, with each 4-week period constituting cycle. The cycle window will be +/- 3 days

5.4 COHORT ASSIGNMENT:

All patients will continue on treatment within 14 days (+/- 7 days) following the final dose of nivolumab pre-chemoradiation in one of three cohorts:

Cohorts will be enrolled consecutively with all patients being enrolled to cohort 1 (8 patients) after-which enrollment to cohort 2 will open (to enroll 4 patients). Once safety is confirmed in those cohorts, enrollment to cohort 3 will open and enroll the remaining patients up to a total of 24 evaluable patients.

- Cohort ONE: Nivolumab during chemoradiation (total, 8 patients)
    - Definitive radiation therapy fields will be determined by the treating radiation oncologist.
    - Two groups of patients (4/group) will be evaluated dependent on the chemoradiation field, with the field determined and documented in advance by the treating radiation oncologist:
        - COHORT 1A: Patients receiving EFRT +/- HDR/LDR brachytherapy. Parametrial boost is per MD discretion
        - COHORT IB: Patients receiving WPRT +/- HDR/LDR brachytherapy. Parametrial boost is per MD discretion
    - Nivolumab 240mg IV every 14 days (+/- 3 days) for 3 doses, administered concomitantly during chemoradiation and beginning day 1 of Radiation. Dosing days of nivolumab will be flexible to align with cisplatin dosing.
    - Standard cisplatin dosing will be utilized during treatment (40 mg/m2 weekly for maximum of 6 doses)
- Cohort TWO: Chemoradiation followed by Nivolumab maintenance for 2 years (total, four patients)
    - Patients will proceed with definitive chemoradiation alone.
    - 2-3 weeks following completion, patients will begin Nivolumab 480 mg IV every 4 weeks (+/- 3 days) for a planned duration of 2 years.
- Cohort THREE: Nivolumab 240mg IV during chemoradiation and then as nivolumab monotherapy 480mg IV (beginning no more than 4 weeks post CRT) for 2 years (total, approximately 12 patients to enroll allow for total study

enrollment of up to total 24 patients on study)

- Patients will receive nivolumab during definitive chemoradiation (as in cohort one) followed by nivolumab alone (as in cohort two). Pending safety data of cohort one, patients may be stratified by the radiation field, as in cohort One.

5.5 Nivolumab administration

Nivolumab is to be administered as an approximate 30-minute IV infusion. For details on prepared drug storage, preparation, and administration, please refer to the Nivolumab Investigator Brochure (IB).

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding polyethersulfone membrane in-line filter at 240 mg. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 1 mg/mL. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. At the end of the infusion, flush the line with an adequate amount of normal saline.

5.5.1 DOSE DELAYS FOR NIVOLUMAB (see section 6 for radiation and cisplatin dose modifications and requirements)

There will be no dose reduction of nivolumab in this protocol.
During Chemo/RT:

For patients receiving definitive chemoradiation plus nivolumab (cohorts one and three), standard treatment parameters will apply toward administration of weekly cisplatin and/or radiation therapy. **If a dose of cisplatin is held on a treatment week where nivolumab is scheduled, that dose of nivolumab should be <u>skipped</u> and not made up.**

Nivolumab (All Cohorts):

Non-Immune mediated: All toxicities- heme or non-heme- felt to have some causality to nivolumab must resolve to <u>≤</u> grade 2 (excluding weight loss, weight gain, and alopecia) or to baseline prior to a patient receiving a subsequent dose (of Nivolumab). Any dose of nivolumab not administered will be skipped and not made up.

Immune mediated: Adverse events (both serious and non-serious) associated with nivolumab may represent immunologic etiology. Nivolumab must be held for suspected immune-mediated toxicities or severe/life-threating AEs of particular interest (in Section 7.0) and immune-related toxicities (in Appendix D). Please review both Sections (7 and Appendix D) prior to infusion of nivolumab in any patient in whom immune-mediated toxicity is suspected.

If the investigator is unsure if a particular toxicity at least possibly represents an immune mediated toxicity to nivolumab, the treating physician should follow section 7 and appendix D and treat as immune mediated, until it is confirmed as not being immune mediated. Consultation with BrUOG is suggested in such situations. BrUOG will share information about the situation with the BrUOG Reviewer and PI and provide the site guidance, as available.

Removal from study (all cohorts):

Patients must discontinue nivolumab permanently for the following:

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding
- Any treatment delay resulting in no nivolumab dosing for > 6 weeks.
- Patients who discontinue nivolumab during definitive chemoradiation (cohorts one and three)
- Grade 4 drug-related endocrinopathy adverse events such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, hypophysitis.
- ≥ Grade 4 hepatic AEs
- ≥ Grade 4 skin toxicity (per Appendix D can delay or discontinue for grade 3. Must come off, as per this bullet for grade 4 skin)
- ALL OTHER treatment related grade 3/4 treatment related events with the following exceptions:
    - Grade 4 neutropenia ≤ 7 days;
    - Grade 4 lymphopenia or leukopenia;
    - isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/ appropriate management within 72 hours of their onset;
    - Grade 3 hepatic AEs that return to Grade 2 or less within 5 days Of note, this overrides Appendix D
    - Skin toxicity ≤ grade 3 that improves with steroid therapy. NOTE: Any rash consistent with Stevens-Johnson Syndrome or Toxic Epidermal Necrolysis requires permanent discontinuation of nivolumab.
    - Grade 3 renal toxicity (as per Appendix D)

If Nivolumab is discontinued, the patient is to be taken off study. The total treatment patient

received will be collected, but once patient is off study, all treatment is per standard of care and does not need to follow-BrUOG 355.

In situations when RT is not given (held for toxicity or other reasons (weather, machine is down, holiday), cisplatin and Nivolumab should not be given and should also be held.

If Nivolumab is held on a day Cisplatin is due and the patient meets criteria to receive Cisplatin and Radiation then every attempt should be made to administer Cisplatin and radiation, while holding Nivolumab.

Every attempt should be made for all patients to complete radiation therapy (even if cisplatin and nivolumab are held)

5.6 Definitive Chemoradiation Plan

Standard therapy guidelines for definitive chemoradiation in cervical cancer will be utilized during this trial. All patients will receive tailored pelvic (if para-aortic nodes are negative) and/or extended field, pelvis+para-aortic, radiation therapy (if para-aortic nodes are involved) with a plan for daily delivery of RT (Monday-Friday) for approximately 6 weeks (which may include brachytherapy).

Cisplatin:
40 mg/m2 of cisplatin (maximum total dose of 70 mg/week and maximum BSA=1.75m^2)

Dosing on Days: 1, 8, 15, 22, 29, 36 (preferably on Mondays or Tuesdays). The only exception allowed is to account for holidays or unexpected events that warrant closure of the radiation oncology or infusion center, in which case treatment is allowed within the next fully operational day. For example, if D8 falls on a holiday, treatment with cisplatin (and with nivolumab if scheduled) should occur on next day, which will be counted as D8 with all subsequent days rescheduled to allow for a 7-day interval between dosing.

- Cisplatin should be infused **over approximately 1 hour,** beginning on day 1 of radiation therapy.

One hour before cisplatin administration, 500-1000 ml of normal saline should be infused intravenously, as per institutional standard of care.

Appropriate antiemetics should be administered prior to cisplatin. Additional fluid may be given as needed for symptomatic support. Premedications for nausea and vomiting prophylaxis should follow institutional guidelines.

Immediately after completion of the cisplatin infusion, an additional 500-1000 ml normal saline should be infused over one hour. It is highly recommended that KCl 20-40 meq and MgSO4 2 grams be added to the normal saline in the post hydration fluid given that hypomagnesemia and

hypokalemia are associated with cisplatin therapy. **This is the minimum fluid administration recommendation and more fluid may be given at the discretion of the treating physician and institutional standard of care should be followed**.

On days when Cisplatin and Nivolumab are administered the same day, Nivolumab is to be administered first, followed by the normal saline flush of the line.

After Nivolumab administration, administer one hour of normal saline (500-1000 ml), 1 hour of Cisplatin, then 1 hour of normal saline (500-1000 ml). It is highly recommended KCl 20-40 meq and MgSO4 2 grams added. Radiation would then commence post completion of Cisplatin and normal saline.

5.7 Radiation specifications

This protocol requires photon external beam radiation therapy (EBRT), either 3D conventional radiation therapy (3D- CRT) or intensity modulated radiation therapy (IMRT) techniques followed by low dose rate (LDR) or high dose rate (HDR) brachytherapy. Radiation therapy must be completed within 60 days of initiation. Four-field box 3D-CRT and IMRT are pretreatment stratification variables.

- For 3D-CRT, the prescription dose is 45 Gy in 25 fractions at 1.8 Gy/fraction with an optional parametrial boost of 5.4 Gy in three fractions at 1.8 Gy/fraction. EBRT should be given once daily Monday-Friday, 5 fractions per week.

- For IMRT, the prescription dose is 45 Gy in 25 fractions at 1.8 Gy/fraction, unless a simultaneous integrated boost (SIB) is used for gross nodal disease. For SIB cases, the primary target will receive 47.6 Gy in 1.7 Gy/fraction and the gross nodal PTV (PTV_Boost) will receive 1.93-2.12 Gy per fraction, depending on bowel tolerance. IMRT should be given once daily Monday-Friday, 5 fractions per week.

- For brachytherapy, the prescription doses are 27.5 - 30 Gy for HDR.

Cohort 1A - Extended-Field Radiation Therapy (EFRT) - EFRT will be used for patients with any positive common iliac LN requiring extension of the superior border of the radiation field above the L4-L5 inter-space as detailed in Section 5.7.1.

Cohort 1B -Whole Pelvic Radiation Therapy (WPRT) - WPRT will be used for patients without evidence of high common iliac LN necessitating EFRT. The traditional whole pelvic radiation field borders are as detailed in Section 5.7.1.

5.7.1 Treatment technology

Conventional 3D RT (4-field box)

Conventional 3D plans will consist of a 4-field box arrangement using AP/PA and Right/Left lateral fields. Conventional RT must use 4-25 MV photons. It is permissible i) to use bone landmarks to draw field borders as described below or ii) to use 3D planning with explicit targets as outlined in section 5.2.3. Custom cerrobend blocks or MLCs are acceptable for field shaping.

If bone landmarks are used, use the following portals:

- Superior border: L4-L5 interspace. For patients with positive high common iliac LN, an extended field will be used such that the superior border will extend above L4-L5 inter-space to cover additional para-aortic LN at least 3cm above the superior-most extent of gross nodal disease.
- Lateral border: 1-2 cm lateral to the border of the true pelvis
- Inferior border: Obturator foramen or 3 cm inferior to the lowest extent of disease, whichever is lower
- Anterior border: line from pubic symphysis to 1.5 cm anterior to common iliac nodes at L4-5. At least 0.5 cm anterior of the L4-L5 vertebral bodies should be included in the field in order to adequately encompass the low para-aortic region.
- Posterior border: draw border 1.0 cm posterior to the sacrum from S1-S4
- Custom blocking to shield femoral heads. Do not block the obturator foramen or within 1 cm of the common iliac nodes

Opposed lateral pelvic fields are used using the same isocenter as the anterior and posterior pelvic fields. The superior and inferior borders will be the same as for the anterior and posterior fields.

The inferior extent or vaginal extension of disease should be marked so that the inferior border of disease can be documented. Uninvolved normal tissues may be blocked although the position of the uterus should be contoured to ensure adequate coverage.

For patients who underwent lymph node dissection: If clips are present to document the position of the lymph nodes, these should be used as a guide when anterior blocks are designed to shield small bowel. When shielding bowel, at least 3 cm should not be blocked anterior to the L4 and L5 vertebral bodies in order to adequately encompass the low para-aortic region.

IMRT

IMRT plans may include static field arrangements (e.g. 5-9 fields), modulated arc therapy, or Tomotherapy. Pseudo-step-wedge intensity modulation (PSWIM) or volumetric modulated arc therapy (VMAT) techniques are permitted. IMRT should use 6-15 MV photons.

Parametrial boost

After conventional RT or IMRT delivery, a parametrial boost can be delivered at the treating

physician's discretion. The parametrial boost will use an AP/PA field arrangement. The superior border should be reduced to include only the true pelvis and the upper border of the true pelvis is defined as 1 cm above the inferior aspect of the sacroiliac joint. The inferior border remains the same as in the pelvis fields. A parametrial central field block is a minimum of 4 cm wide.

Brachytherapy
Patients will be treated using HDR brachytherapy for all patients treated on this protocol. Tandem and ring or tandem and ovoids will be used for intact cervix brachytherapy. Interstitial brachytherapy such as with a Vienna applicator is allowed at the discretion of the treating physician. A tandem and cylinder or tandem alone is allowed only for patients where tandem and ring or ovoid application is not possible due to extent of disease or poor anatomy (e.g., obliterated fornices).

Use of IMRT or other external beam techniques in place of brachytherapy to boost gross cervical disease is discouraged. If deemed necessary or essential for the patient's care (e.g., if a patient refuses brachytherapy), reasons for not performing brachytherapy should be documented.

5.7.2 Immobilization and simulation

Conventional RT
CT simulation is required. Field outlines should be drawn electronically on Digitally Reconstructed Radiographs (DRRS) produced from the CT simulation information. Localization or block-check-images of simulated fields are to be obtained in a simulator and/or treatment machine. Digital pictures of all treatment portals with the patient in the treatment position are to be submitted for quality assurance review. All treatment fields, whether formed by cerrobend blocks or multi-leaf collimation, should be independently checked against the corresponding DRRs. Prone positioning with bowel exclusion devices (e.g. belly boards) is allowed.

3D planning is at the physician's discretion. If 3D planning is being done, a CT simulation scan is required with a slice thickness ≤ 3.0 mm for the regions extending at least 4cm above and below target volumes. Patients can be simulated supine or prone. All subjects will have a customized immobilization device (e.g., Alpha Cradle or Vac-Loc) fabricated at the time of simulation. A full bladder is required at the time of simulation and treatment. Intravenous contrast is recommended to visualize vessels better. Oral or rectal contrast is not recommended for treatment planning.

IMRT
All subjects will undergo a CT (or PET/CT) simulation scan in the supine position using a slice thickness ≤ 3.0 mm and large field-of-view pelvic protocol. A customized immobilization device fabricated at the time of simulation is required. It is recommended that CT scans be obtained from the T12 vertebral body to 5 cm below the ischial tuberosities. For patients undergoing CBCT with each fraction, it is recommended that the isocenter be placed along the patient's midline 1.5 cm caudal to the inferior border of the sacroiliac joint. Otherwise, isocenter

placement is left to the discretion of the treating physician. It is recommended to use a consistent bladder filling state (e.g. always full or always empty) for simulation and treatment. It is recommended for patients not to be simulated or treated with a full rectum as this may result in poor setup reproducibility. Bowel preparatory agents (enema, stool softeners, etc.) may be applied at the discretion of the physician. Oral contrast is optional. Radio-opaque cervical markers or implanted fiducials are optional
The volume irradiated will include the totality of the gross disease locally and regionally, as visualized by CT scan, the whole uterus, paracervical, parametrial and uterosacral ligaments as well as the areas of the obturator, hypogastric, external and internal iliac lymph nodes. In patients treated with extended fields the para-aortic regions with a minimum margin of 2 cm should be included. A margin of 2-3 cm should be given around the gross disease and 1.5-2 cm around uninvolved lymph nodes.

Brachytherapy
For 3D brachytherapy planning, all subjects will undergo a CT (or PET/CT) simulation scan using a slice thickness ≤ 3.0 mm with brachytherapy applicators and dummy sources in. It is recommended that CT scans contain the entire brachytherapy applicators and the critical structures such as bladder and rectum.

Maintaining applicator position is required from the time of applicator insertion to simulation and treatment. Before a CT scan, a Foley catheter is inserted into the bladder and the balloon must be filled with 7 cc of radio-opaque fluid to define the bladder reference point in treatment planning.

For volume-directed brachytherapy, pelvic MRI (≤ 3 mm slice thickness) is required with either the first or second insertion. An MRI-compatible applicator is required to perform volume-directed brachytherapy. Subsequent insertions may use CT or MRI for planning.

5.7.3 Target volumes, margins, and compliance criteria

The structures marked as “Required” in the table must be contoured and documented in the Radiation Oncology Treatment Plan.

Conventional RT (4-field box)
For a 4-field box treatment without 3D planning, contouring target volumes is not required. For 3D plans, target volumes and margins will be the same as for IMRT described below. The only difference between 3D plans and IMRT contours is that patients treated with 3D planning will not have an ITV option.

IMRT
Pelvic MRI and/or PET fusion with the CT simulation scan is recommended to aid target delineation. Fusion should be optimized to match the MRI/PET scans to the treatment position. The Gross Tumor Volume (GTV), Clinical Target Volume (CTV) and Planning Target Volume

(PTV) will be contoured on all CT slices in which the structures exist.

Standard	Description	Specification
Gross Tumor Volume (GTV)	Required dose = 45 Gy	The GTV is defined as all known gross disease determined from radiographic studies, clinical information, physical examination, endoscopic examination, and biopsy results.
Cervical Tumor Volume (CTV)	Required dose = 45 Gy	The CTV will be divided in to 3 sub regions: CTV1, CTV2, CTV3. CTV1 will consist of the gross tumor, cervix, and uterus. CTV2 will consist of the parametria and superior third of the vagina (or half of the vagina, if the vagina is clinically involved). CTV3 will include the common, external, and internal iliac and presacral lymph nodes. The upper border of the CTV3 should not extend above the confluence of the common iliac arteries with the aorta (i.e., aortic bifurcation), and should begin no lower than superior border of L5. The nodal CTV (CTV3) will be obtained by ensuring an approximately 7 mm margin around the vessels, plus extension to include any adjacent visible lymph nodes, lymphoceles, or pertinent surgical clips. The presacral nodes should be contoured until the superior border of the S3 vertebral body is reached; below this point the nodal volume can be separated into two structures. The external iliac nodes should be contoured to the superior aspect of the femoral head. CTV3 should be modified to exclude bone, muscle, and bowel. The CTV should not extend inferior to the ischial tuberosities.

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CTV (for SIB schemes)	Required dose = 47.6 Gy	Same as above
CTVn boost (for boost)	Required dose = 54.0 to 59.4 Gy	Gross pelvic nodes
ITV	Total dose = 45 Gy	Patients should be simulated with both a full and empty bladder (i.e., 2 simulation scans). CTV1-CTV3 and PTV1-PTV3 should be delineated as described above on the plan used for treatment (either the full or empty bladder scan), and CTV1 should be delineated on both scans. The CTV1 from both scans should be fused together to generate the ITV. A 7 mm margin should be applied to generate PTV4. PTV4 should be fused with PTV1-PTV3 to generate the final PTV.
Pelvic Tumor Volume (PTV)	Required dose = 45 Gy	Around CTV1, a 15 mm uniform expansion should be used. Around CTV2, a 10 mm uniform expansion should be used. Around CTV3 (and CTV_boost, if applicable), a 5 mm uniform expansion should be used. These expansions will generate PTV1, PTV2, and PTV3, respectively. PTV1-3 will be fused to generate the PTV .
PTV-skin	IF applicable only: PTV-3mm from skin surface	The PTV should be manually or automatically trimmed up to 3 mm from the skin surface, if necessary, to spare skin. However, the CTV still needs to be included entirely within the PTV .
PTV-boost	Required dose = 54 to 59.4 Gy	5 mm uniform expansion around CTV_Boost

<u>Brachytherapy (point-directed)</u>

The definition of all points (A, B, Bladder, Rectum and Vaginal Surface) will be in accordance with the 1985 ICRU Report #38: Dose and Volume Specifications for Reporting Intracavitary Therapy in Gynecology.

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Brachytherapy (volume-directed)
The MRI based target delineation can be reused by superimposition in the process of contouring on CT, if for subsequent fractions of brachytherapy only CT can be used with the applicator in place. No planning margins will be added to the CTV.

Standard name	Description	Specification
GTV	Required dose = 27.5-30 Gy	Macroscopic tumor (if present) at time of brachytherapy
CTV		GTV + whole cervix + presumed extra cervical tumor extension

Compliance criteria:

	Per protocol	Variation (Acceptable)	Deviation (Unacceptable)*
Overall Treatment time	≤ 60 days	≤ 66 days	>66 days

Patients who require a treatment delay of RT for 7 consecutive days or longer will be removed from this protocol. The decision to continue standard chemoradiation will be left to the treating physician. See Section 6.2.

5.7.4 Definition of critical structures and margins

The structures marked as "Required" in the table must be contoured and documented with the treatment plan. Structures marked as "Required when applicable" must be contoured and documented only when applicable.
Conventional RT (4-field box)
For a 4-field box treatment without 3D planning, contouring critical structures is not required. For 3D plans, critical structures and margins will be the same as for IMRT described below.

IMRT

Location	Specification
External (Required)	Normal tissues will be contoured on the CT simulation scan. The tissue within the skin surface and outside all other critical normal structures and the PTV should be contoured on every slice and designated as "External.
Bowel space (Required)	Bowel Space will be contoured beginning from the axial slice situated 1 cm superior to the superior-most slice containing PTV (if bowel is not present at this level, the bowel contour will start from its most superior extent), and will continue to its most inferior extent in the pelvis. The Bowel Space will include the outermost

	extent of the bowel loops plus any space within the abdominal cavity the bowel may occupy. Individual loops of bowel should not be contoured separately. Bowel Space will be outlined on each axial CT slice. Rectum should be contoured separately from bowel.
Rectum (Required)	The outer rectal wall will be contoured and filled in, treating the organ as a solid continuous structure, and will be defined from the level of the sigmoid flexure to the anus.
Bladder (Required)	The outer bladder wall will be contoured and filled in, treating the organ as a solid continuous structure.
Bone marrow (Required)	The outer bone contour will be delineated and filled in, treating the bone marrow as a solid continuous structure. The regions contoured will include the os coxae, L4 and L5 vertebral bodies, entire sacrum, acetabulae, and proximal femora. The caudal-most extent of the bone marrow contour should be at the level of the ischial tuberosities.
Active Bone Marrow (Required)	Active or functional BM will be a subset of the entire BM volume (delineated in Bone Marrow), as determined by ^{18}F-FDG-PET/CT. Active BM will be defined as the sub region of total BM with a standardized uptake value (SUV) greater than the mean value over the total BM volume. Automatic segmentation using commercially available software will be used to define the functional BM volume, which will be used as an avoidance structure for IMRT planning.
Femur (left and right, separately) (Required)	The outer contours of the left and the right femoral head will be delineated and filled in, treating each separately as its own solid continuous structure. Do not include the femoral neck.

Brachytherapy

Standard	**Specification**
Bladder (Required)	The outer bladder wall is contoured. Calculated at the center (in the superior-inferior plane on AP view) of a contrast-filled balloon of a Foley catheter and closest to the applicator system on a lateral view.
Rectum (Required)	The outer rectal wall is contoured from above the anal sphincter to the level of transition into the sigmoid.

5.7.5 Dose Prescription

Conventional RT

For Conventional RT, the prescription dose of 45 Gy at 1.8 Gy/fraction will be delivered to the isocenter which is defined as the intersection of the four beams. EBRT is preferably given once daily Monday-Friday, for 5 fractions per week. A three consecutive day parametrial boost may be optionally given in the sixth week.

IMRT

Standard	Dose (Gy)	Fraction size (# fractions)	Technique
PTV	45	1.8 (25)	Exactly 95% of PTV receives ≥ 45 Gy
PTV (for SIB)	47.6	1.7 (28)	Exactly 95% of PTV receives ≥ 47.6 Gy
PTV boost (for SIB)	54.0-59.4	1.93-2.12 (28)	Exactly 95% of PTV receives ≥ 54=58.4 Gy

Parametrial boost.

After the delivery of 45 Gy, at the discretion of the treating physician, a parametrial boost of 5.4 Gy at 1.8 Gy/fraction may be delivered to mid-plane given by AP/PA fields and the center of the unblocked portion of the field.

Lymph Node Boost

After the delivery of 45 Gy WPRT/EFRT +/- parametrial boost, a nodal boost may be delivered to any grossly positive lymph node (PET SUV > 2.5, LN > 15mm short axis diameter on CT/MRI, or histologically positive). Nodal boosts should be delivered to a final dose of 54-59.4 Gy in keeping with bowel tolerance at the discretion of the treating physician.

HDR Brachytherapy

In point-directed approach, the doses of 27.5 - 30 Gy and 35 - 40 Gy will be delivered to the point A for HDR. The HDR brachytherapy dose can be prescribed to a high-risk clinical target volume (CTV) as volume-directed approach, but point A dose must be documented.

Total EBRT (Gy)	# Fractions	HDR Point A dose/fraction (Gy)	Total HDR point A Dose (Gy)	Total Point A EQD2-Gy_{10}
45	4	7	28	83.9
45	5	5.5	27.5	79.8
45	5	6	30	84.3
47.6	4	7	28	86.1
47.6	5	5.5	27.5	81.9
47.6	5	6	30	86.4

HDR-Point A determined implant or volume directed approach

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In general, HDR insertions should start during the fourth week and be separated by a minimum of 48 hours and no more than 2 insertions should be performed per week. Iridium-192 is the preferred source for HDR brachytherapy. External beam radiation and brachytherapy may not be administered on the same day. Radiation therapy must be completed within 6 weeks of its initiation.

5.7.6 Treatment planning priorities and instructions

Critical structures and target priorities are listed in order of decreasing importance:

EBRT

1. Bowel
2. Bone marrow
3. Rectum
4. Bladder
5. Femurs

If max dose constraints are exceeded, the following solution can be entertained: For conventional RT with 3D planning, use the field in field technique to decrease hot spots and to reduce the bowel dose when MLCs are used.

Brachytherapy

1. Rectum
2. Bladder
3. Sigmoid

If dose constraints of critical structures are exceeded, the following solution can be entertained: For volume-directed brachytherapy, if the treatment planning system provides a manual optimization option, optimize the plan manually to reduce dose to the critical structures as long as D90 of CTV meets target volume constraints.

5.7.7 Dose Calculations

The primary data set for dose calculations is CT. In the case in which contrast is present during the treatment planning CT, the density of the contrast should be overridden to a representative background electron density. Heterogeneity corrections should be applied. The dose grid size should be ≤ 3 mm in all directions, which means that the CT slice thickness should be ≤ 3 mm.

For IMRT plans, patient specific QA is required. QA is performed by delivering the plan onto a phantom and measuring the dose using an ion chamber array or other 2D/3D device. Measured dose distribution will be compared to planned dose distribution using a Gamma criterion of 3% dose difference and 3 mm distance to agreement. The pass rate should be at least 90% measured

for the entire plan.

5.7.8 Daily treatment localization/Image-guided radiation therapy (IGRT)

Conventional RT (4-field box)
Skeletal imaging using an electronic portal imaging device (EPID) or film portal imaging should be performed at least weekly to verify setup accuracy. IGRT technique such as orthogonal kV or volumetric imaging such as Cone Beam CT (CBCT) can also be used for weekly setup verification.

IMRT
Daily IGRT is required for this protocol when the IMRT treatment technique is used. Any form of online imaging is acceptable, such as MV or kV planar imaging, MVCT or MV CBCT, kV CBCT, CT on rails, etc. The AAPM recommendations stated above for verifying coincidence of the imaging and treatment beam reference points must be adhered to for daily use of IGRT. At the time of simulation, it is recommended to place the isocenter along the patient's midline 1.5 cm caudal to the inferior border of the sacroiliac joint. In general, the CT or CBCT will be used for setup verification using bone landmarks only and not for soft tissue alignment. Small soft tissue shifts (≥3 mm) are acceptable. Otherwise, the treating physician may elect to postpone treatment or re-simulate.

5.7.9 Re-planning

Re-planning (such as to account for changes in tumor volume) is allowed. If re-planning is necessary, the new treatment plan should meet the same criteria as the initial plan, as if the new plan were delivered for the entire treatment course. The new treatment plan should be submitted for central review according to the same process as the initial plan.

6 DOSING DELAYS/DOSE MODIFICATIONS CISPLATIN/RADIATION

6.1 Prior to dosing with cisplatin any day, the following criteria must be met (please refer to Nivolumab requirements to dose as well if dosing on applicable day is for both drugs):

- ANC ≥ 1000/mcl
- Platelet count ≥ 50,000/mcl

*If patient experienced a ANC< 1,000 or a PLT count < 50,000 consider drawing CBC twice weekly (not required)

The following table will be used for dose adjustment:

Cisplatin dosing table

Starting dose all patients	Dose -1	Dose -2
40 mg/m2 (maximum 70mg/week BSA 1.75m2)	30 mg/m2 (maximum 60mg/week)	25mg/m2 (maximum 50mg/week)

*All dose reductions are permanent and each patient can only have 2 dose reductions before needing to come off study

For all patients undergoing chemoradiation, all non-hematological related toxicities must be $\leq$ grade 2 to continue with cisplatin, with the following notes:

- Hold chemoradiation for GI toxicities (including diarrhea, nausea, vomiting) $\geq$ grade 3, may resume only when $\leq$ grade 1

- Creatinine $\leq$ 2.0mg/dL
  If it is > 2.0mg/dL draw CrCl and consider renal ultrasound.
  If CrCl is $\geq$ 50 ml/min, continue therapy.
  If CrCl is $\leq$ 50 ml/min, hold treatment and check CrCl weekly.
  When the CrCl is $\geq$ 50 ml/min, or the serum creatinine $\leq$ 2.0 mg/dl, resume therapy at one dose level reduction.
  Persistence of CrCl $\leq$ 50 ml/min or serum creatinine $\geq$ 2.0 mg/dl for > two weeks patient's study therapy with Nivolumab will be stopped. However, patients will continue on definitive chemoradiation as standard of care, off protocol, as directed by their treating physician.

- Neurotoxicity (including neuropathy and paresthesia) $\leq$ grade 2
  If patient experiences a grade 3-4 neurotoxicity patient will be removed from study

Refer to section 7 for more information on supportive care

In situations when RT is not given (held for toxicity or other reasons (weather, machine is down, holiday), cisplatin and Nivolumab should not be given and should also be held.
If Nivolumab is held on a day Cisplatin is due and the patient meets criteria to receive Cisplatin and Radiation then every attempt should be made to administer Cisplatin and radiation, while holding Nivolumab.

Every attempt should be made for all patients to complete radiation therapy (even if cisplatin and nivolumab are held)

6.2 Radiation therapy:

Prior to Radiation administration a patient must be confirmed as having:

- ANC> 500/mcl
- Platelets > 50,000/mcl
- GI toxicities ≤ grade 2
- Bladder toxicities ≤ grade 2

Radiation therapy will not be interrupted for uncomplicated hematological toxicity. For purposes of this trial, complicated hematologic toxicity is defined as:

- Grade 4 neutropenia- hold radiation until neutropenia is grade 3 or less
  Grade 3-4 thrombocytopenia, hold radiation until thrombocytopenia is grade 2 or less

RT should be held until ANC > 500/mcl and platelets > 50,000/mcl. Radiation should then be restarted, even if cisplatin (and nivolumab) are held.

An uncomplicated hematological toxicity is any hematological toxicity that does not meet the above criteria.

Refer to section 7 for more information on supportive care

Other toxicities:

RT should be held for ≥ grade 3 GI toxicities (including diarrhea, nausea, vomiting).

Every attempt should be made for all patients to complete radiation therapy (even if cisplatin and nivolumab are held). Patient who require a hold of RT due to toxicity for 7 consecutive days or longer will be removed from protocol. See 5.7.1 for definition of deviations for RT delays.

In situations when RT is not given (held for toxicity or other reasons (weather, machine is down, holiday), cisplatin and Nivolumab should not be given and should also be held.

If Nivolumab is held on a day Cisplatin is due and the patient meets criteria to receive Cisplatin and Radiation then every attempt should be made to administer Cisplatin and radiation, while holding Nivolumab.

7 RESCUE MEDICATIONS AND SUPPORTIVE CARE

7.1 Supportive Care Guidelines

Subjects should receive appropriate supportive care measures as deemed necessary by the treating investigator. Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below.

Where appropriate, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary

as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment guidelines are recommended when the investigator determines the events to be related to nivolumab.

It may be necessary to perform conditional procedures such as bronchoscopy, endoscopy, or skin photography as part of evaluation of the event. These procedures should be performed at the discretion of the investigator and are not mandated by the protocol.

7.1.1. Diarrhea/Colitis

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

- For patients who are being treated with nivolumab **during** chemoradiation:
    - If diarrhea/colitis occurs **prior to** initiation of nivolumab or can be attributed to chemoradiation, then subjects should be advised to drink liberal quantities of clear fluids and will receive standard management for diarrhea with loperamide, low residue diet and Lomotil if needed. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
    - If diarrhea/colitis occurs **after** subject has received any administration of nivolumab, then it is critically important to evaluate the subject for immune-related diarrhea/ colitis. The diarrhea/colitis is likely to be immune-related if it has any of the following characteristics:
        - Bloody or mucous stools
        - Cramping occurs at a timepoint not typical for chemoRT (i.e., in first 2 weeks of treatment or after completion of external beam RT)
- If the event meets these criteria (immune mediated), then it should be treated as follows:
    - All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion.
    - For Grade 2 diarrhea/colitis that is felt to be possibly, probably, or likely related to nivolumab, administer oral corticosteroids consistent with Appendix D (GI Adverse Event Management Algorithm). Delay treatment as per

appendix D.

- For Grade 3 diarrhea/colitis that is felt to be possibly, probably, or likely related to nivolumab and that persists > 1 week, treat with 1-2 mg/kg/day methylprednisolone IV (or equivalent). Discontinue nivolumab permanently. If opportunistic infection suspected, begin antibiotics promptly. If warranted, consider lower endoscopy. If improves, continue steroids until grade 1 then taper over at least a month, pending symptoms. If symptoms persist up to 5 days later, add infliximab 5 mg/kg (if no contraindication).
- For Grade 4 diarrhea/colitis, treat with 1-2 mg/kg/day methylprednisolone IV (or equivalent). Discontinue nivolumab permanently. If opportunistic infection suspected, begin antibiotics promptly.

7.1.2. Nausea/Vomiting

Nausea and/or vomiting during the course of chemoradiation is expected and should be treated symptomatically by anti-emetic and anti-diarrheal medications, and dietary modifications. Every effort should be made to control diarrhea by dietary restriction and anti-peristaltic drugs.

- For Grade 1-2 nausea/vomiting with the onset of concomitant cisplatin and radiation therapy may be expected. Patients may receive the investigator's choice of drugs for the control of nausea and vomiting associated with the cisplatin administration. Intractable nausea and vomiting beyond the first few days after cisplatin chemotherapy should arouse suspicion of other causes such as bowel obstruction. Consider sending stool sample for Clostridia difficile toxin.

- For Grade 3-4 nausea/vomiting, subjects should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. IV antiemetics may be required, as indicated by institutional guidelines. Treatment with cisplatin and/or radiation therapy should be delayed until symptoms abate to <grade 3. In circumstances where cisplatin is delayed, nivolumab dose should be skipped and not made up.

- For patients who are delayed, every effort should be made to reinitiate chemoradiation within a week.

7.1.3. Suggested Management for Renal Adverse Effects

Increased frequency with dysuria may occur in some patients. This may be treated symptomatically with anti-spasmodics and increased fluid intake. Urinary tract infection should be ruled out if the symptoms persist.

Persistence of CrCl less than 50 ml/min or serum creatinine greater than 2.0 mg/dl for more than two weeks requires discontinuation of protocol treatment, see section 6.1. Selective renal tubular defects are sometimes observed. Hypocalcemia with hypomagnesemia and hypokalemia are common and potentially severe. Replacement of magnesium, calcium, and potassium are usually effective. Severe tubular defects, although rare, may require chronic replacement therapy. Diagnostic tests for alternative mechanisms of hypocalcemia (for example, GI or metabolic) are suggested.

RT related holds for $\geq$ 7 days will require removal from protocol treatment. If creatinine rises to greater than 2.0 mg/dl, obtain creatinine clearance (CrCl). Consider renal ultrasound. If CrCl is greater than or equal to 50 ml/min, continue therapy. If CrCl is less than 50 ml/min, hold treatment and check CrCl weekly. When the CrCl is greater than or equal to 50 ml/min, or the serum creatinine is less than 2.0 mg/dl, resume therapy at one dose level reduction.

7.1.4. Neurologic adverse effects

Neurotoxicity from cisplatin therapy is primarily seen as paresthesias, but may also result in hearing loss and/or vestibular symptoms due to toxicity to the eighth (VIII) cranial nerve. Cisplatin induced neurotoxicity may be related to cumulative dose and thus severe toxicity can be largely avoided by careful monitoring prior to each treatment.

Patients should be removed from study for Grade 3-4 neurotoxicity.

7.2 Criteria for Taking a Participant Off Protocol Therapy

Duration of therapy will depend on individual response, evidence of disease progression and tolerance. For patients receiving nivolumab during chemoradiation, treatment with nivolumab must be held if cisplatin is also held.

In the absence of treatment delays due to adverse event(s), treatment with nivolumab may continue as indicated in each cohort or until one of the following criteria applies:

- Disease progression
- Intercurrent illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Participant demonstrates non-compliance with treatment regimen and/or required study evaluations
- Participant decides to withdraw from the protocol therapy
- General or specific changes in the participant's condition render the participant unacceptable for further treatment in the judgment of the treating investigator
- Any required toxicity reason as noted in prior sections of the protocol requiring the

patient stop 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 nivolumab dosing

Participants will be removed from the protocol therapy when any of these criteria apply. The reason for removal from protocol therapy, and the date the participant was removed, must be documented in the case report form (CRF). Alternative care options will be discussed with the participant.

7.3 Duration of Follow Up

All Patients will be followed for three years from the end of study treatment. All patients who are removed for toxicity will be followed unless they withdraw consent for follow-up.

7.4 General Concomitant Medication and Supportive Care Guidelines

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 and documented source documents as concomitant medication.

Permitted Supportive/Ancillary Care and Concomitant Medications

- Analgesics
- Antibiotics
- Anticonvulsants
- Antiemetics
- Anticoagulants
- Antihistamines
- Corticosteroids +/- mineralocorticoid component
- Hydration
- Immunosuppressive agents – other
- Infliximab
- Mycophenolate mofetil
- Nutritional supplementation
- Interventional use of growth factors is allowed if deemed necessary by the Investigator but only to treat grade 4 neutropenia or febrile neutropenia only when radiation therapy is held**. G-CSF and GM-CSF are not allowed during radiation therapy.** Erythropoietin use is discouraged in accordance with ASCO guidelines.

Prohibited therapies

- Chronic systemic corticosteroids or other immunosuppressive agents for conditions other than for hypersensitivity or immune adverse effects associated with nivolumab

as specified in the protocol.
Patients in this study may use standard vaccines. Where possible, routine vaccination for influenza, pneumococcal pneumonia should be given prior to the start of therapy but may be administered during treatment when clinically indicated. Vaccination should be given when there is enough separation to distinguish any vaccine reactions from drug toxicity. NOTE: There is no experience using live attenuated vaccination during nivolumab therapy, so live vaccine should be used cautiously during treatment.
Concomitant systemic or local anti-cancer medications or treatments are prohibited.

- **G-CSF and GM-CSF are not allowed during radiation therapy.** Erythropoietin is discouraged in accordance with FDA guidelines.

8 ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of reported and/or potential AEs and the characteristics of an observed AE will determine whether the event requires expedited reporting **in addition** to routine reporting.

8.1 Expected Toxicities

Adverse Event List(s) for Nivolumab

Categorization of AEs Potentially Associated with Nivolumab

In order to characterize AEs of special clinical interest that are potentially associated with the use of nivolumab, the Sponsor identified select AEs based on the following 4 guiding principles:

- AEs that may differ in type, frequency, or severity from AEs caused by non-immunotherapies
- AEs that may require immunosuppression (e.g., corticosteroids) as part of their management
- AEs whose early recognition and management may mitigate severe toxicity
- AEs for which multiple event terms may be used to describe a single type of AE, thereby necessitating the pooling of terms for full characterization

Based on these guiding principles and taking into account the types of AEs already observed across studies of nivolumab monotherapy, endocrinopathies, diarrhea/colitis, hepatitis, pneumonitis, nephritis, and rash are currently considered to be select AEs. Multiple event terms that may describe each of these are grouped into endocrine, GI, hepatic, pulmonary, renal, and skin select AE categories, respectively. The list of AEs belonging to select AE categories may evolve as more safety information becomes available in the nivolumab program.

Hypersensitivity/infusion reactions were also analyzed along with the select AE categories because multiple AE terms may be used to describe these events, and therefore, pooling of terms provides a more complete characterization of the events. Hypersensitivity/infusion reactions do

not, otherwise, meet criteria to be considered select AEs.

Serious Adverse Events Reported from Clinical Trials with Nivolumab Monotherapy

As of June 2017, the following serious AEs have been reported in clinical studies in which nivolumab was given as monotherapy. The frequency of ADRs is defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); and very rare (< 1/10,000). For further information, including SAEs that are rarely associated, please reference the IB.

The following **common SAE** is associated: pneumonitis, diarrhea

The following **uncommon SAEs** by system organ class are associated:

- Endocrine: Adrenal insufficiency, Hypothyroidism
- Gastrointestinal: Abdominal pain, Colitis, Diarrhea, Nausea, Pancreatitis, Vomiting
- General and Administrative Site Conditions: Mucosal inflammation, Pyrexia
- Hepatobiliary: Abnormal hepatic function
- Immune system: Hypersensitivity
- Injury, Poisoning and Procedural Complications: Infusion-related reaction
- Metabolism and Nutrition: Dehydration, Hyperglycemia
- Neurologic: demyelinating polyneuropathy, myasthenic syndrome
- Renal and Urinary: Acute renal failure, Tubulointerstitial nephritis
- Respiratory, Thoracic and Mediastinal Disorders: Dyspnea, Hypoxia, Interstitial lung disease, Lung infiltration, Respiratory failure

Nonserious Adverse Events Reported from Clinical Trials with Nivolumab Monotherapy

As of June 2017, the following nonserious AEs have been reported in clinical studies in which nivolumab was given as monotherapy. The frequency of ADRs is defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1,000 to < 1/100); rare (≥ 1/10,000 to < 1/1,000); and very rare (< 1/10,000).

The following **very common** nonserious AEs are associated: Fatigue, Diarrhea
The following **common** nonserious AEs are associated: Arthralgia, Asthenia, Cough, Decreased appetite, Pyrexia, Rash, Nausea, Pruritus

A complete list of adverse events observed with nivolumab are detailed in the Investigator's Brochure (IB).

8.2 Adverse Event Characteristics

This study will utilize the descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 for grading all adverse events. All appropriate treatment areas should have access to a copy of the CTCAE version 4.03. A copy of the CTCAE version 4.03 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

An Adverse Event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and that does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of Nivolumab, cisplatin or radiation, whether or not considered related to Nivolumab, cisplatin or radiation. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of drug.

During clinical trials, adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more adverse events.)

Adverse events (AEs) will be recorded in the case report form for the duration of the trial, regardless of whether or not the event(s) are considered related to trial medication.

8.3 Definitions

An adverse event is any new, undesirable medical experience or change of an existing condition that occurs during or after treatment, whether or not considered product-related.

8.3.1 Attribution of the AE:

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

Suspected adverse reaction:
BrUOG, for the sponsor-investigator, is required to report in an IND safety report any suspected reaction to the study treatment that is both serious and unexpected.

As per 21 CFR 312.32 (a), the FDA has defined a suspected adverse reaction as any adverse event where there is reasonable possibility that the drug may have caused the adverse event. A reasonable possibility means there is evidence suggesting a causal relationship between the drug and the adverse event.

A suspected adverse reaction outlines the possibility of the causal relationship between the event and the drug, whereas an adverse reaction means the drug caused the event.

8.3.2 Serious Adverse Events (SAE)

An adverse event occurring at any dose that results in any of the following outcomes (CFR 312.32):

- death
- is life-threatening
- inpatient hospitalization or prolongation of existing hospitalization excluding those for study drug administration, transfusional support, disease staging/re-staging procedures, concomitant radiotherapy, thoracentesis / paracentesis, or placement of an indwelling catheter, unless associated with other serious events.
- persistent or significant disability or incapacity,
- congenital anomaly / birth defect.

The definition of serious adverse event (experience) also includes *important medical event*. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse. A new diagnosis of cancer during the course of treatment should be considered an important medical event.

Unexpected adverse event
An adverse event that is not mentioned in the Investigator's Brochure or package insert or the specificity or severity of which is not consistent with the investigator's brochure or package insert.

Life-threatening
Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred. It does not include a reaction that, had it occurred in a more severe form, might have caused death.

Events requiring reporting as an Important Medical Event:

- **Potential drug induced liver injury** (DILI) is also considered an important medical event.

Potential drug induced liver injury is defined as:

- ALT and/or AST elevation > 3 times upper limit of normal (ULN)
  AND
- Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase)
  AND
- No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing

chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Wherever possible, timely confirmation of initial liver related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

- Suspected transmission of an infectious agent (e.g., pathogenic or nonpathogenic) via the study drug is an SAE.
- Although pregnancy, overdose, and cancer (a second primary, excluding non-melanoma skin cancer) are not always serious by regulatory definition, these events must be handled as SAEs.
    - **Pregnancy:** see section for information
    - An **overdose** is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

NOTE: The following hospitalizations are **not considered SAEs**:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered "important medical event" or event life threatening)
- elective surgery, planned prior to signing consent and which would have been documented to BrUOG at time of registration (otherwise it will be a SAE)
- admissions as per protocol for a planned medical/surgical procedure per study
- routine health assessment requiring admission for baseline/trending of health status (ie, routine colonoscopy)
- medical/surgical admission for purpose other than remedying ill health state and was
- planned prior to entry into the study. Appropriate documentation is required in these cases and which would have been documented to BrUOG at time of registration admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (ie, lack of housing, economic inadequacy, care-giver respite, family circumstances, administrative)

8.4 Monitoring of Adverse Events and Period of Observation

Adverse events, both serious and non-serious, and deaths that occur during the patient's study participation will be recorded in the source documents.

8.5 BRUOG ADVERSE EVENT REPORTING REQUIREMENTS

Investigators are required by Federal Regulation to report adverse drug reactions. Questions regarding drugs as used in this study should be directed to the Brown University Oncology Research Group (BrUOG) Central Office, Phone: (401) 863-3000 Fax (401) 863-3820, which will in turn notify the Principal Investigator.

All adverse events and special reporting situations, whether serious or non-serious, related or

unrelated, will be reported from the time a signed and dated ICF is obtained until 30 days after the last treatment (Nivolumab, cisplatin, radiation, whichever is last), or until the subject withdraws consent from study participation (declines participation) or at the time patient becomes a screen failure, whichever occurs first.

8.6 Pregnancies

Pregnancies occurring while the subject is on study drug or within 30 days (+1 week) after the subject's last treatment (Nivolumab, cisplatin, radiation, whichever is last) are considered expedited reportable events. If the subject is on active treatment, the treatment is to be discontinued immediately. The pregnancy must be reported to the Brown University Oncology Research Group, by the site, immediately (within 24 hours of the site being made aware), via the site completed BMS pregnancy reporting Form **and** a 3500A MedWatch form (site to submit to BrUOG), and BrUOG will in turn report to BMS immediately (within 1 working day and once in receipt of the site submitted SAE forms). Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on treatment (Nivolumab, cisplatin, radiation), or within 30 days (+1 week) of the subject's last treatment (Nivolumab, cisplatin, radiation, whichever is last), are considered immediately reportable events. Treatment is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to BMS Drug Safety immediately by facsimile, email, or other appropriate method (to be done by BrUOG), using the required reporting forms (Forms to be completed by site and sent to BrUOG).

The Investigator will follow the subject until completion of the pregnancy, and must notify BMS (by informing BrUOG) of the outcome as specified below. The Investigator will provide this information as a follow-up to the initial report. If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting SAEs (i.e., report the event to BrUOG who will then report to BMS by facsimile or email within 1 working day of being made aware of the event via the sites formal submission of the SAE pregnancy forms).

The patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects to be related to the in utero exposure to the study drug should also be reported. In the case of a live "normal" birth, BMS should be advised as soon as the information is available (BrUOG will advise BMS once information is submitted to BrUOG).

8.7 Serious Adverse Event Reporting Procedures

All pregnancies or suspected pregnancies, including suspected fetal exposure or neonatal deaths must be reported to the Brown University Oncology Research Group immediately (within 24

hours of being made aware of the event). BrUOG will report all pregnancies to BMS within 1 working day, and once being made aware of the event once in receipt of the site submitted required reports. All other SAEs are to be announced via email to BrUOG within 24 hours of being made aware of the event and the site has 5 business days (from being made aware of the event) to send the written MedWatch 3500A report to BrUOG, who will then report the SAE to BMS product safety within 1 working day of being in receipt of the completed and signed Medwatch report (submitted to BrUOG from the site). Initial SAE information and all amendments or additions must be recorded on an SAE Form and faxed or emailed to BMS (to be done by BrUOG).

BMS Drug Safety Contact Information: (to be reported to by BrUOG)

BMS SAE EMAIL ADDRESS: Worldwide.Safety@BMS.com

A copy of the fax transmission or email confirmation of the SAE report to BMS should be attached to the SAE and retained with the study records at BrUOG.

The principal investigator (or his designee) has the obligation to report all serious adverse events to the Brown University Oncology Research Group's (BrUOG) office who in return will report to the FDA, BMS, and all sites participating in the trial. All SAE reports will be forwarded to BMS Product Safety by BrUOG. All events must be reported by the investigator utilizing the Form FDA 3500A (MedWatch Form). Sites must alert BrUOG to SAEs within 24 hours of being made aware of the event via phone or email, and the site will have 5 business days (from when site was made aware of the event) to submit formal signed report via the 3500A. BrUOG will then alert BMS within 1 business day of being in receipt of the signed Medwatch report. BrUOG will submit a SAE memo and Medwatch 3500A to the FDA within the reporting time frames.

The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report.

A final report to document discharge from hospital (or end of important medical event) is required.

All deaths during treatment or within 30 days following completion of active protocol treatment (Nivolumab, cisplatin, radiation, whichever is last) must be formally reported to BrUOG within 5 business days of being made aware of the event or as soon as the investigator is made aware of the event. If the death is thought to be related to the study treatment (Nivolumab, cisplatin, radiation), deaths must be reported to BrUOG within 24 hours of the investigator being made aware of the event.

All adverse events and special reporting situations, whether serious or non-serious, related or

unrelated, will be reported from the time a signed and dated ICF is obtained until 30 days after the last treatment (Nivolumab, cisplatin, radiation, whichever is last), or until the subject withdraws consent from study participation (declines participation) or at the time patient becomes a screen failure, whichever occurs first.
Every adverse event, serious or non-serious, must be assessed by the investigator with regard to whether it is considered immune-mediated.

Serious adverse events occurring more than 30 days (+1 week) after study discontinuation need only be reported if a relationship to the study treatment (Nivolumab, cisplatin, radiation) is suspected.

8.8 Types of Report: Guidelines for sites to report:

Telephone report: For SAE's contact the BrUOG office within 24 hours of learning of a SAE. For SAE notification: (initial and follow-up) contact BrUOG Central Office (401) 863-3000 (or via email), with 24 hour noticed prior to submitting a SAE report.

Written report: Send the signed Medwatch 3500A form (and BMS pregnancy reporting form for pregnancies if applicable) within 5 business days of being made aware of the event to the BrUOG Central Office by email. For Follow-up reports, please submit the signed Medwatch 3500A when new information has become available and the event can be closed out.

Brown University Oncology Research Group
Phone: (401) 863-3000, Fax: (401) 863-3820
Emails: BrUOG@brown.edu

All deaths during treatment or within 30 days following completion of active protocol treatment (Nivolumab, cisplatin, radiation, whichever is last) must be reported within 5 business days (from when site was made aware of the event) or as soon as the investigator is made aware of the event. If the death is thought to be related to the study treatment (Nivolumab, cisplatin, radiation), **deaths must be reported to BrUOG within 24 hours of the investigator being made aware of the event. SAEs post 30 days since last dose of drug (+1 week) that are thought to be possibly related to study treatment (**Nivolumab, cisplatin, radiation, whichever is last**) must be reported to BrUOG within the 5 business day time frame noted above.**

MedWatch 3500A Reporting Guidelines:
In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information within the Event Description (section 5) of the MedWatch 3500A form:

- Treatment regimen (dosing frequency, combination therapy): if related to treatment regimen add to section C suspect product, if not related to any, add to concomitant section noting Lot #
- Protocol description (and number, if assigned)
- **Description of event, severity, treatment, and outcome, if known**

- **Action taken with** Nivolumab, cisplatin, radiation **as a result of the SAE and expectedness (based on IB and consent)**
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to **each investigational** product (nivolumab) and suspect medication/treatment (cisplatin and radiation) and if event(s) is/are immune mediated
- Site to be clear to outline which events are being reports as serious
- Must be typed
- ****It is required that sites put the following numbers on the MedWatch form for tracking:**
    - **CA209-9LX**
    - **BrUOG 355**

A final report to document discharge from hospital (or resolution of important medical event) is required.

Follow-up information:
For any follow-up SAE report, submit a new MedWatch 3500A report; do not resubmit the initial report with any additions. The follow-up report must be submitted to BrUOG with subject identifiers (subject number, initials, and date of birth), protocol description and number (BrUOG 355 and CA209-9LX), suspect drug, a brief summary of previously reported SAE information, and any new information, including modification of prior events, causality, new serious events, discharge date, etc.
A final report documenting discharge date from the hospital is required.
The principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy.

8.9 BrUOG Responsibility Regarding Reporting:

The sponsor-investigator by way of BrUOG, the sponsor representative and central coordinating office, is required to promptly review all information relevant to the safety of the drug (21 CFR 312.32(b)).

Safety Reporting for IND Holders
In accordance with 21 CFR 212.32, Sponsor-Investigator of the study conducted under an IND must comply with following safety-reporting requirements:

The BrUOG Central Office will notify by fax all drug reaction reports to the FDA, the Principal Investigator, and the participating sites (who will in turn notify their local IRBs) as soon as possible but no later than 15 calendar days after initial receipt of the signed information, submitted to BrUOG by the site, as per regulatory requirements.

BrUOG, for the sponsor-investigator, is required to report in an IND safety report any suspected reaction to the study treatment that is both serious and unexpected (21 CFR 312.32 (c)(1)(i)). It is required that events that are suspected, serious and unexpected, be reported to the FDA via an

IND safety report.

BrUOG will fax reports to the FDA for IND Safety Reports: to the CDER DOP1 fax number at: (301)-796-9845

SAEs will be reported as an amendment to the IND (if applicable) within 15 days of sponsor notification. The FDA will all receive a simultaneous copy via facsimile of all adverse events filed with the FDA (which will be sent to the Medwatch fax line for IND exemption or to the division fax if there is an IND). A copy of the form will be kept by the BrUOG Central Office.

- "IND safety report" for 15-day reports
- "Follow-up IND safety report" for followup information
- "7-day IND safety report" for unexpected fatal or life threatening adverse reaction reports

Fax: 1-800-FDA-0178 (1-800-332-0178) For IND exempt study or for IND study the SAE will be sent to Center Drug Evaluation Division fax line that has responsibility for review of IND): CDER DOP1: (301)-796-9845

Mail: For IND studies BrUOG will send the SAE as an amendment to the IND as well

All SAEs that are serious and reasonably or probably related to the use of Nivolumab will be faxed to: BMS

BrUOG will alert BMS to an SAE within 1 business day of being in receipt of the complete signed site submitted documentation.

All written IND Safety Reports submitted to the FDA by the Sponsor-Investigator must also be faxed to BMS, as well as any pregnancy occurring in association with use of a BMS Product to:

BrUOG will send to: BMS SAE Email Address: Worldwide.Safety@BMS.com

BMS SAE Facsimile Number: +1 609-818-3804

8.10 IND Annual Reports, for IND study only

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to BMS as a supporter of this study

8. 11 Adverse event updates/IND safety reports

BMS shall notify the Brown University Oncology Research Group (BrUOG) via an IND Safety Report of the following information:

- Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected.

- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

BrUOG will then notify the sites who shall notify their IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

9 PHARMACEUTICAL INFORMATION

9.1 Nivolumab

9.1.1 Description

Nivolumab is an anti-PD-1Mab with a molecular weight of 146,221 daltons. 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.

Nivolumab Injection is a clear to opalescent, colorless to pale yellow liquid; light (few particulates may be present. The drug product is a sterile, non-pyrogenic, 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.

9.1.2 Form

Nivolumab Injection is a clear to opalescent, colorless to pale yellow liquid; light (few) particulates may be present. The drug product is a sterile, non-pyrogenic, 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.

Nivolumab is supplied by Bristol-Myers Squibb and distributed 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.

9.1.3 Storage and stability

Nivolumab Injection, 100 mg/10 mL (10 mg/mL) vials of nivolumab injection must be stored at 2ºC to 8ºC (36ºF to 46ºF) and protected from light and freezing.

Undiluted Nivolumab Injection and Diluted Nivolumab Injection in the IV Container

The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C, 36°F to 46°F) for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (20ºC to 25ºC, 68ºF to 77ºF) and room light. The maximum of 8 hours under room temperature and room light conditions includes the product administration period.

Shelf life
Unopened vial 2 years.
After opening:
From a microbiological point of view, once opened, the medicinal product should be infused or diluted and infused immediately.
After preparation of infusion
From a microbiological point of view, the product should be used immediately.

If not used immediately, chemical and physical in-use stability of OPDIVO has been demonstrated for 24 hours at 2ºC to 8ºC protected from light and a maximum of 8 hours at 20°C-25°C and room light (this 8-hour period of the total 24 hours should be inclusive of the product administration

9.1.4 Compatibility
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.

9.1.5 Handling
Qualified personnel, familiar with procedures that minimize undue exposure to themselves and the environment, should undertake the preparation, handling, and safe disposal of the chemotherapeutic agent in a self-contained and protective environment.

9.1.6 Availability
Nivolumab is an investigational agent and will be supplied free of charge from Bristol-Myers Squibb.

9.1.7 Preparation
Visually inspect the drug product solution for particulate matter and discoloration prior to administration. Discard if solution is cloudy, if there is pronounced discoloration (solution may have a pale-yellow color), or if there is foreign particulate matter other than a few translucent-to-white, amorphous particles.

*Note: Mix by **gently** inverting several times. **Do not** shake.*

Aseptically withdraw the required volume of nivolumab solution into a syringe, and dispense into an IV bag. If multiple vials are needed for a subject, it is important to use a separate sterile syringe and needle for each vial to prevent problems such as dulling of needle tip, stopper coring,

repeated friction of plunger against syringe barrel wall. **Do not** enter into each vial more than once. **Do not** administer study drug as an IV push or bolus injection

Add the appropriate volume of 0.9% Sodium Chloride Injection solution or 5% Dextrose Injection solution. *It is acceptable to add nivolumab solution from the vials into an appropriate pre-filled bag of diluent.*

> ***Note:* Nivolumab infusion concentration must be at or above the minimum allowable concentration of 0.35 mg/mL (see most up to date IB for reference)**
>
> *Note: It is not recommended that so-called "channel" or tube systems are used to transport prepared infusions of nivolumab.*

Attach the IV bag containing the nivolumab solution to the infusion set and filter.
At the end of the infusion period, flush the line with a sufficient quantity of approved diluents.
After nivolumab (BMS-936558-01) has been prepared for administration, the total storage time (combination of refrigeration and room temperature) is not to exceed 24 hours

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

9.1.8 Administration

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

Nivolumab will be given every two weeks at a dose of 240 mg to be administered as a 30 minute IV infusion. In maintenance the dose is 480mg to be administered as per the Investigator Brochure as a 30 minute IV infusion.

When the dose is fixed (eg, 240 mg, 360 mg, or 480 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 mL.

There are no premedications recommended for nivolumab on the first cycle. There will be no dose modifications allowed.

Subjects should be carefully monitored for infusion reactions during nivolumab administration. If an acute infusion reaction is noted, subjects should be managed according to the Protocol.

Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment.

Nivolumab Injection, 100 mg/10 mL (10 mg/mL)

Nivolumab injection is to be administered as an IV infusion through a 0.2-micron to 1.2-micron pore size, low-protein binding polyethersulfone membrane in-line filter at the protocol-specified doses and infusion time. It is not to be administered as an IV push or bolus injection. Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to protein concentrations as low as 0.35 mg/mL. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. No incompatibilities between nivolumab and polyvinyl chloride (PVC), non-PVC/non-DEHP (di(2-ethylhexyl) phthalate) IV components, or glass bottles have been observed.

9.1.9 Ordering

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

If concerns regarding the quality or appearance of the investigational product arise, do not dispense the investigational product, and contact BMS immediately.

Please allow for 5-7 business days for the shipment of drug.

Initial Orders

- Following submission and approval of the required regulatory documents, BrUOG will activate each site, which will allow a supply of nivolumab (when applicable) to be ordered by the investigational pharmacist via the BrUOG 355 drug order form.
- It is required that the box "request for initial drug supply" be checked, the investigator address be confirmed as correct (if pre-populated) or populated (if blank), and that the # of vials being requested be documented on the form.
- Once complete, email the form to the email addresses on the drug order form: distribution.allentown@thermofisher.com and Cc bruog@brown.edu.
- Nivolumab:
    - Nivolumab will be supplied in 100 mg vials.
    - The initial order should be limited to 20 vials. Allow 5 business days for shipment of drug from BMS receipt of the Drug Request Form. Drug is protocol specific, but not patient specific. All drug product will be shipped by courier in a temperature-controlled container. It is possible that sites may have more than one nivolumab clinical study ongoing at the same time. It is imperative that only drug product designated for this protocol number be used for this study.

- When drug is received, it is required that an email be sent to bruog@brown.edu to alert BrUOG the order was received.
- Take note that drug should be transferred to **+2°C/+8°C** storage immediately upon receipt
- Pharmacy supplies not provided by BMS: Empty IV bags/containers, approved diluents, In-line filters and infusion tubing

Re-Supply

- Drug re-supply request should be requested using the BrUOG 355 drug order form and allowing for 5-7 business days for drug shipment. Deliveries will be made Tuesday through Friday.
- When assessing need for resupply, institutions should keep in mind the number of vials used per treatment dose. Drug is not patient-specific. Be sure to check with your pharmacy regarding existing investigational stock to assure optimal use of drug on hand.
- It is required that the box "request for resupply" be checked, the investigator address be confirmed as correct (if pre-populated) or populated (if blank), and that the # of vials being requested be documented on the form.
- Once complete, email the form to the email addresses on the drug order form: distribution.allentown@thermofisher.com and Cc bruog@brown.edu.
- When drug is ordered it is required that an email be sent to bruog@brown.edu to alert BrUOG to the placed order.
- When drug is received, it is required that an email be sent to bruog@brown.edu to alert BrUOG the order was received.

Drug Excursions

- Drug excursions should be reported immediately to BMS on the form provided with the study-specific drug order form. Please cc bruog@brown.edu on all drug excursion emails

Questions on drug expiration, delayed shipments etc:

- Send an email to distribution.allentown@thermofisher.com and cc sashin.bhuta@bms.com, Rashmi.gadkari@bms.com, and bruog@brown.edu
- For questions on drug destruction please refer to 9.1.11 as this needs to be communicated directly with BrUOG only

9.1.10 Accountability

The investigator, or a responsible party designated by the investigator, should maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF) or another comparable drug accountability form. (See the NCI Investigator's Handbook for Procedures for Drug Accountability and Storage.)

9.1.11 Destruction and Return

At the end of the study, unused supplies of nivolumab will be destroyed according to institutional policies once BrUOG confirms and approves destruction. BrUOG will obtain approval to destroy

from BMS. Destruction will be documented in the Drug Accountability Record Form and the form will be routed to BrUOG.

Each participating hospital and pharmacy must submit, up front and throughout the trial, the most up to date drug destruction policy, to BrUOG.

Drug that is used (partially used vial for examples), can be destroyed in real-time as per the pharmacy destruction policy and do not need to be tracked on the accountability log.

Expired drug: Contact BrUOG to provide the number of expired vials and the current accountability logs. BrUOG will obtain approval to destroy drug and will communicate approval the pharmacy. BrUOG will then require submission of the drug accountability log, documenting the drug destruction of expired material.

10 BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

The aim of such studies will be to identify potentially predictive biomarkers of benefit for patients with cervical cancer treated with nivolumab and standard chemoradiation. Data from these investigations will be evaluated for associations with response, survival (OS, PFS) and/or safety (adverse event) data. Biomarkers analysis may include PD-L1 expression, and tumor mutation burden. We may explore the prognostic significance of Chitinase 3-like 1 (Chi3l1), which we have recently demonstrated to have prognostic significance following immune checkpoint inhibitors in lung cancer. It is anticipated that advances in the understanding of biomarkers for immune checkpoint inhibitors will be forthcoming over the next few years emphasizing the need for tissue storage for future collaborative studies.

Tissue:

Diagnostic:

For patients with diagnostic tissue at Rhode Island Hospital, The Miriam Hospital or Women and Infants Hospital, tissue should remain in the Pathology Department until correlative testing is imminent. At that time, all patient's tissue will be requested for sectioning (20 unstained slides of 4uM thickness) or a FFPE.

For patients with diagnostic tissue outside of the system (defined above): Tissue will be requested from patient's baseline diagnostic sample or most recent biopsy. Samples are to be labeled with study number (BrUOG 355), patient initials, patient study number and time point.

Formalin-fixed paraffin embedded (FFPE) tumor tissue block or at least 20 unstained slides (charged) of 4 uM thickness will be required to be sent to the Clinical Research Center (CRC) at Rhode Island Hospital.

Lifespan Clinical Research Center
1 Hoppin Street,

Coro West, Room 3.461,
Providence RI, 02903

For tissue from research only (optional) biopsy:
The research staff is to contact their respective pathology department point of contact (it is required to submit de-identified email chain with data to BrUOG), at least 24 hours prior to collection of a research only biopsy. Following the sites institutional policies & procedures, the specimen will be prepped, cassetted, processed, and embedded. The block will then be sectioned at 4µM, 20 sections and placed on charged slides. The tissue must be labeled with study number (BrUOG 355), patient initials, patient study number and time point. The tissue will then be sent for storage at the CRC for future testing.

Lifespan Clinical Research Center
1 Hoppin Street,
Coro West, Room 3.461,
Providence RI, 02903
LCRCLab@lifespan.org

11 STUDY CALENDAR

Baseline evaluations are to be conducted within 28 days prior to start of protocol therapy, unless otherwise specified. Scans and x-rays must be done ≤4 weeks (28 days) prior to the start of therapy.
Assessments must be performed within 3 days prior to each treatment dosing day. Study assessments (required to be completed and resulted prior to any drug administration) and agents should be administered within ± 3 days of the protocol-specified date, unless otherwise noted.
The day an assessment (PE, labs, scan etc) is completed is day 0 for counting for example labs drawn on Friday can be used for Monday dosing as this is within 3 days

	Baseline evaluations are to be conducted within 28 days prior to start of protocol therapy, unless otherwise specified below. Scans must be done <28 days prior to the start of therapy. Baseline labs are required within 14 days of registration. HCG is 7 days.					
Parameter	Pre-Study to be sent to BrUOG with results prior to registration	Weekly[aI] within 3 days prior to dosing day 1 each week.	Monthly[b] required within 3 days prior to day 1 of each cycle	Off study (post completion of whole cycle)j +1 week	30 days post last treatment (+1 week)j	Follow-up
Informed consent(within 30 days of day 1) *pts are to be re-consented if ICF will be outside 30 day window	X					
Diagnostic pathology	X- no time frame					
FNA	X- no time					

BrUOG 355: 7/8/17, 7/11/17, 7/20/17, 8/7/17, 8/8/17, 8/14/17, 8/16/17, 8/21/17, 8/22/17, 8/24/17, 8/28/17, 9/5/17, 9/6/17, 9/8/17, 9/11/17, 11/7/17, 11/8/17, 11/19/17 approved DD, 11/20/17, 12/12/17, 12/14/17, 1/29/18, 2/1/18, 2/6/18, 2/7/18,2/8/18, 2/9/18, 2/12/18, 2/13/18, 3/8/18 all reviews, 3/9/18, 3/13/18, 3/14/18, 3/15/18, 4/19/18, 4/23/18, 5/29/18, 6/5/18, Amendment # 1 7/9/18, Amendment # 2 12/12/18, Amendment #3, 4/6/2020, Amendment #4 5/11/2020

	frame k					
History & Physical	X	X	X	X	X	
Concurrent meds	X	X	X	X		
Toxicity Assessment	XD	X	X	X	X	
Vitals M	X	X	X	X		
Performance status	X	X	X	X		
Imaging evaluation(CT C/A/P preferred)	Xf			Xf	Xf	Xf
Tumor measurement	X			X		X
CBC (Including differential)	Xd	Xe	X	X		
Chemistries (CMP, CA/Mg/PO_4)	Xd	X	X	X		
Amylase and lipase	Xd	X	X	X		
Liver Function tests (AST, ALT, Alk Phos, LDH)	Xd	X	X	X		
EKG	X					
Pregnancy test	Xg	Xg	Xg			
Audiogram	Xh		Xh	Xh		
Thyroid Function Tests (TSH, Free T4, T3)	X		X	X		
Viral studies (CD4 count – only required for patients who are HIV positive to certify eligibility, see exclusion 3.2.2 for timeframes and requirements.; HBsAg, , HCV Ab, if positive HCV Ab then order HCV RNA testing)	X					
Tumor Biopsy	X[c]					
Radiation			X[N]			
Cystoscopy, proctoscopy, barium enema	X- optional but if done must submit					

CMP=Glucose, Calcium, Albumin, Total Protein, Sodium, Potassium, CO2, Chloride, BUN, Creatinine, ALP, ALT, AST, Bilirubin (total), amylase and lipase

a. Obtain during cycles 1 and 2 Nivolumab (all cohorts) and chemoradiation therapy. Amylase and Lipase are required within 3 days of dosing with Nivolumab, with cycles 1 and 2 and q 2 weeks during chemoradiation therapy.

b. Obtain for those patients receiving maintenance nivolumab treatment, prior to dosing each cycle

BrUOG 355: 7/8/17, 7/11/17, 7/20/17, 8/7/17, 8/8/17, 8/14/17, 8/16/17, 8/21/17, 8/22/17, 8/24/17, 8/28/17, 9/5/17, 9/6/17, 9/8/17, 9/11/17, 11/7/17, 11/8/17, 11/19/17 approved DD, 11/20/17, 12/12/17, 12/14/17, 1/29/18, 2/1/18, 2/6/18, 2/7/18,2/8/18, 2/9/18, 2/12/18, 2/13/18, 3/8/18 all reviews, 3/9/18, 3/13/18, 3/14/18, 3/15/18, 4/19/18, 4/23/18, 5/29/18, 6/5/18, Amendment # 1 7/9/18, Amendment # 2 12/12/18, Amendment #3, 4/6/2020, Amendment #4 5/11/2020

c. The first tumor biopsy may come from the diagnostic procedure where the diagnosis of cervical cancer was made. For patients who consent, a second biopsy should be attempted within 7 days after second dose of nivolumab in all patients, prior to chemoradiation.

d. Must be obtained within 14 days prior to initiation of protocol treatment

e. If grade 4 neutropenia is documented, monitor CBC twice weekly until resolved to ≤ grade 3

f. CT C/A/P is the preferred method of imaging. CT C/A/P must be obtained at the completion of chemoradiation (+ 14 days), 6 months later (+/- 14 days) and then q 6 months (+/- 14 days) for up to 3 years or until confirmation of PD. If an alternative imaging modality is used at baseline, the same imaging technique must be used throughout the study duration.

g. Serum pregnancy test (women of childbearing potential) required within 7 days prior to day 1, Also required every 4 weeks (+/- 1 week) while on-study. Cycle 1 day 1: required HCG for all women of child bearing potential within 24 hours (1 day) prior to dosing day 1 cycle 1 only and confirmation of negative HCG test required to be sent to BrUOG. Patients with a positive test are required to be taken off study prior to any dosing on study.

h. Required in all patients with a history of hearing loss. Must be obtained within 28 days prior to initiating protocol therapy. Repeat during treatment as clinically indicated.

I.If screening labs are performed greater than 14 days prior to Cycle 1 Day 1, labs must be repeated on Cycle 1 Day 1 and must meet eligibility criteria. The patient may not start on study treatment until Cycle 1 Day 1 labs meet eligibility criteria. If screening labs are performed within 14 days prior to Cycle 1 Day 1, and meet eligibility criteria, labs do not need to be repeated on Cycle 1 Day 1 unless the investigator believes they are likely to have changed significantly. History, AE & concomitant medication assessment, vitals and performance status can be used from screening for cycle 1 day 1 if they were within the 14 day screening period (14 days from day 1). A physical exam within 7 days prior to cycle 1 day 1 can be utilized.

j. Off-study evaluation to occur post completion of entire cycle. Follow-up visits or other contact are required in order to identify SAEs during the 30 days (+1 weeks) following the end of study treatment (Nivolumab, cisplatin or radiation), respectively. SAEs need to be reported after 30 days if the SAE is thought to be related to study treatment.

k. patients who have positive or suspicious para-aortic nodes on lymphangiography, CT scan, or ultrasound examinations will undergo a fine needle aspiration (FNA), extraperitoneal lymph node biopsy, or laparoscopic sampling

L. Survival and disease status will be collected approximately every 6 months (+/- 1 month) for 3 years. **DURING COVID 19, study follow-up may be done virtually if it is in the best interests for the patient and her safety. Virtual follow-up will be documented by the research team if performed.**

M. Vital signs include: Weight, height (baseline only required), Blood pressure, heart rate, temperature, and Pulse oximetry oxygen saturation

N Site to submit end of treatment Radiation Oncology note summarizing all treatment

12 MEASUREMENT OF EFFECT

12.1 Antitumor Effect – Solid Tumors

For the purposes of this study, participants should be re-evaluated for response at the completion of definitive chemoradiation (+ 14 days) and then six months later (+/- 14 days). Following this, all patients will be followed every 6 months (+/- 14 days) for up to three years. The same imaging modality should be used at each time point in this study. For purposes of this trial, imaging should consist of a CT Chest/Abdomen/Pelvis (CT/CAP).

Response and progression will be evaluated in this study using the new international criteria proposed by the 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.

Definitions

Evaluable for Target Disease response. Only those participants who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for target disease response. These participants will have their response classified according to the definitions stated below. (Note: Participants who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

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

Disease Parameters

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

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. NOTE: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all considered non-measurable.
Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same participant, 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, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion 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.

Methods for Evaluation of Disease

All measurements should be taken and recorded in metric notation using a ruler, calipers, or a digital measurement tool. 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 (inclusive of cervical masses and palpable lymph nodes) and ≥10 mm in diameter as assessed using calipers.
Conventional CT and MRI. This guideline has defined measurability of lesions on CT scan based on the assumption that CT thickness is 5mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size of a measurable lesion should be twice

the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

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, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

FDG-PET. While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

(a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
(b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
(c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

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

PET-CT. 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 and will not

be used on this trial.

Response Criteria
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 progressions).

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.

Evaluation of Non-Target Lesions

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

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

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

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

Although a clear progression of "non-target" lesions only 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).

Evaluation of New Lesions

The finding of a new lesion should be unequivocal (i.e. not due to difference in scanning technique, imaging modality, or findings thought to represent something other than tumor (for example, some 'new' bone lesions may be simply healing or flare of pre-existing lesions). However, a lesion identified on a follow-up scan in an anatomical location that was not scanned at baseline is considered new and will indicate PD. If a new lesion is equivocal (because of small size etc.), follow-up evaluation will clarify if it truly represents new disease and if PD is confirmed, progression should be declared using the date of the initial scan on which the lesion was discovered.

Evaluation of Best Overall Response

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

For Participants with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**	**Best Overall Response when Confirmation is Required***
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Participants with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration."* Every effort should be made to document the

objective progression even after discontinuation of treatment.

For Participants with Non-Measurable Disease (*i.e.*, Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD
* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised		

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, or death due to any cause. Participants without events reported are censored at the last disease evaluation).

Duration of overall complete response: 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, or death due to any cause. Participants without events reported are censored at the last disease evaluation.

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.

Progression-Free Survival

Overall Survival: Overall Survival (OS) is defined as the time from randomization (or registration) to death due to any cause, or censored at date last known alive.

Progression-Free Survival: Progression-Free Survival (PFS) is defined as the time from randomization (or registration) to the earlier of progression or death due to any cause. Participants alive without disease progression are censored at date of last disease evaluation.

Time to Progression: Time to Progression (TTP) is defined as the time from randomization (or registration) to progression, or censored at date of last disease evaluation for those without progression reported.

13 REGULATORY CONSIDERATIONS

This research study is sponsored by the Principal Investigator, Dr. Don Dizon, in collaboration with Brown University Oncology Research Group (BrUOG), which will serve as the central coordinating office for the study. This study is supported by BMS (the makers of Nivolumab).

13.1 Protection of Human Subjects

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

13.2 Compliance with the Protocol and Protocol Revisions:

The study must be conducted as described in this approved protocol.
All revisions to the protocol must be created by Brown University Oncology Research Group, and approved by BMS. The Investigator should not implement any deviation or change to the protocol without prior review and documented approval/favorable opinion from the IRB/IEC and BMS of an Amendment, except where necessary to eliminate an immediate hazard(s) to study patients.

Documentation of approval signed by the chairperson or designee of the IRB(s)/IEC(s) must be sent to Brown University Oncology Research Group, and BMS. If the revision is an Administrative Letter, Investigators must inform their IRB(s)/IEC(s).

The Investigator must ensure that patients or their legally acceptable representatives are clearly and fully informed about the purpose, potential risks and other critical issues regarding clinical trials in which they volunteer to participate. Preparation of the consent form is the responsibility of the Investigator and must include all elements required by CFR 21 Part 50.25 and the local IRB.

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

13.3 Protocol amendments or changes in study conduct:

Any change or addition (excluding administrative) to this protocol requires a written protocol amendment that must be created the Brown University Oncology Research Group, BMS and the investigator before implementation. Amendments significantly affecting the safety of subjects,

the scope of the investigation or the scientific quality of the study require additional approval by the IRB at each study center. A copy of the written approval of the IRB must be provided to Brown University Oncology Research Group, and BMS

- Examples of amendments requiring such approval
- Increases in drug dose or duration of exposure of subjects
- Significant changes in the study design (e.g. addition or deletion of a control group)
- Increases in the number of invasive procedures
- Addition or deletions of a test procedure required for monitoring of safety.

These requirements for approval should in no way prevent any immediate action from being taken by the investigator or by Brown University Oncology Research Group and BMS in the interests of preserving the safety of all patients included in the trial. If an immediate change to the protocol is felt to be necessary by the investigator and is implemented for safety reasons Brown University Oncology Research Group and BMS must be notified and the IRB at the center must be informed immediately.

14 DATA MONITORING / QUALITY ASSURANCE/ RECORD RETENTION

14.1 Good Clinical Practice:

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

14.2 Patient Confidentiality:

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

14.3 Protocol Compliance:

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Changes to the protocol will require approval from BMS and written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority (ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the

approval /favorable opinion of the IRB/IEC. The investigator will submit all protocol modifications to BMS and the regulatory authority (ies) in accordance with the governing regulations. Any departures from the protocol must be fully documented in the source documents.

14.4 On-site Audits:
Regulatory authorities, the IRB and/or BMS clinical quality assurance group may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

14.5 Drug Accountability:
Accountability for the drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site (if applicable), inventory at the site (if applicable), use by each patient, and return to BMS for disposal of the drug (if applicable and if approved by BMS) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers.

All material containing Nivolumab will be treated and disposed of as hazardous waste in accordance with governing regulations.

14.6 Premature Closure of the Study:
This study may be prematurely terminated, if in the opinion of the investigator or BMS, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or BMS by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the drug
- Should the study be closed prematurely, all study materials must be returned to BMS

14.7 Record Retention:
The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

The Brown University Oncology Research Group, as coordinator of this study, is responsible for ensuring proper conduct of the study with regard to protocol adherence and the validity of the data recorded on the case report forms. The Principal Investigator (Don Dizon, M.D.) and Brown University Oncology Research Group will monitor this study. The case report forms will be

monitored against the submitted documents for accuracy, completeness, adherence to the protocol and regulatory compliance.

U.S. FDA regulations (21CFR312.62[c] require all records and documents pertaining to the conduct of this study and the distribution of investigational drug, including CRFs, consents forms, laboratory test results and medication inventory records, must be retained by the Principal Investigator for 2 years after marketing application approval. If no application is filed, these records must be kept 2 years after the investigation is discontinued and the FDA and the applicable local health authorities are notified. BMS will notify the Principal Investigator if an application is filed.

15 DATA SAFETY AND MONITORING BOARDS

All trials initiated by the Brown University Oncology Research Group (BrUOG) are subject to oversight by the Data Safety Monitoring Board (DSMB). This board meets two times per year with any additional meetings scheduled when needed. The responsibilities are as follows:

- Familiarize themselves with the research protocol (s)
- The DSMB reviews trial performance information such as accrual information.
- Review interim analyses of outcome data and cumulative toxicity data summaries to determine whether the trial should continue as originally designed, should be changed, or should be terminated based on these data.
- The DSMB also determines whether and to whom outcome results should be released prior to the reporting of study results.
- All adverse events are reviewed by the committee, with assurances that these have been in fact sent for review to all pertinent IRBs.
- Review of reports of related studies to determine whether the monitored study needs to be changed or terminated.
- Review major proposed modifications to the study prior to their implementation (e.g., termination, dropping an arm based on toxicity results or other reported trial outcomes, increasing target sample size).
- Following each DSMB meeting, provide the study leadership with written information concerning findings for the trial as a whole related to cumulative toxicities observed and any relevant recommendations related to continuing, changing, or terminating the trial.

The study leadership will provide information on cumulative toxicities and relevant recommendations to the local principal investigators to be shared with their IRB's.

16 STATISTICAL CONSIDERATIONS

16.1 Study Design/Endpoints

The primary endpoint of this pilot study is to assess the acute toxicity of combining nivolumab with definitive chemoradiation. For the purposes of the study, acute toxicities will be those having onset during or within 30 days of completing treatment. For those receiving nivolumab as maintenance treatment, it will also include those events occurring during or within 30 days of

treatment completion.

16.1.1. Safety review

A safety review for each cohort will be conducted. For cohort 1, safety analysis will occur at the end of chemoradiation. For patients in cohort 2 (who receive nivolumab following chemoradiation), evaluation for safety will occur 4 weeks following initiation of maintenance nivolumab. For patients in cohort 3, safety analyses will occur at the end of chemoradiation and after maintenance therapy has completed.

Criteria that will determine safety will include:

- Grade 3 or higher adverse events that persists for 14 days or longer despite dose-holds and/or maximal medical support. This excludes uncomplicated neutropenia and any laboratory abnormalities deemed by the treating clinician as having no clinical significance
- Inability to complete chemoradiation within 8 weeks

The BrUOG overall PI, the Women & Infants' Hospital site PI (once study is activated), and the Medical Director of BrUOG will review safety data as described to make determinations of feasibility. Enrollment to cohort 2 will not be dependent on the safety review for cohort 1. However, the safety review will be completed for cohort 2, before enrollment begins in cohort 3.

If more than 25% of patients (more than 2 patients in cohort 1 or more than 1 patient in cohort 2) experience a grade 3 or higher adverse event that persists for 14 days or longer, despite dose-holds and/or maximal support, the treatment will be considered not feasible and the next cohort will not be opened.
If more than 25% of patients (more than 2 patients in cohort 1 or more than 1 patient in cohort 2) are unable to complete chemoradiation within 8 weeks, the treatment will be considered not feasible and the next cohort will not be opened.

16.2 Sample Size, Accrual Rate and Study Duration

For this feasibility study, the planned sample size is 24 patients (8 in cohorts 1 (1A and 1B)), 4 in cohort 2, and up to 12 in cohort 3 to enroll a maximum of 24 evaluable patients in the trial). The total sample size may need to be adjusted to allow for replacement of participants who withdraw prior to completion of the third week of chemoradiation, as these are the only reasons for replacement. It is anticipated that 4 patients will be enrolled per month for an approximate accrual period of 9 months. All patients who begin protocol therapy will be included in the evaluation of toxicity for 30 days post last treatment, unless patient withdraws from study.

16.3 Stratification Factors

For those treated with nivolumab during chemoradiation (Cohort 1) stratification will be guided by radiation field. Cohort 1A will consist of patients receiving whole pelvic RT, while Cohort 1B will consist of patients receiving extended field RT. No further stratification is anticipated for Cohorts 2 and 3. However, enrollment in Cohort 3 may be revised pending outcomes in Cohort

1.

16.4 Analysis of Primary Endpoints

Time-to-event endpoint of progression free survival at 3 years will be described using the method of Kaplan-Meier, and presented with 90% confidence intervals. Patients that are alive without disease progression at time of analysis are censored at the date of last disease evaluation. Acute Treatment-related toxicities that occur during and within six months of study treatment will be summarized by maximum grade and by term using CTCAE v4.0 and reported with 90% binomial exact confidence intervals. Acute toxicities will be used to determine the feasibility within each cohort.

16.5 Analysis of Secondary Endpoints

Recurrence patterns within three years of study entry will be described for each cohort, to determine whether there is a difference in patterns (locoregional versus distant).

Chronic treatment-related toxicities will be summarized by maximum grade, experienced beyond six months of completion of radiation therapy.

16.6 Reporting and Exclusions

Evaluation of Toxicity

All participants will be evaluable for toxicity from the time of their first treatment.

Evaluation of the Primary Efficacy Endpoint

All of the participants who met the eligibility criteria and who receive at least one dose of study drug will be included in the main intent-to-treat analysis of the response rate.

17 PUBLICATION PLAN

The results should be made public within 12 months of reaching the end of the study. The end of the study is the time point at which the last data items are to be reported, or after the outcome data are sufficiently mature for analysis, as defined in the section on Sample Size, Accrual Rate and Study Duration. If a report is planned to be published in a peer-reviewed journal, then that initial release may be an abstract that meets the requirements of the International Committee of Medical Journal Editors. A full report of the outcomes should be made public no later than 12 months after the end of the study.

18 REFERENCES

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APPENDIX A ELIGIBILITY CHECKLIST

BrUOG 355: A Pilot Feasibility study incorporating Nivolumab to tailored radiation therapy with concomitant cisplatin in the treatment of patients with cervical cancer

Inclusion criteria (UNLESS OTHERWISE SPECIFIED, ALL CRITERIA MUST BE FULFILLED WITHIN 28 days (labs are 14 days)OF ENROLLMENT):

_____(y/n) Age ≥ 18 years. Cervical cancer is rarely seen in women under 18 years.

_____(y/n) ECOG performance status ≤2 (Karnofsky ≥60%, see Appendix A)

_____(y/n) Patients with histologically confirmed advanced cervical cancer (any cell type): FIGO Clinical stages IB2, IIA, IIB, IIIA, IIIB, IVA.

_____(y/n) All patients must have tissue from the diagnostic biopsy submitted prior to enrollment for both pathologic confirmation of the diagnosis (if done outside of a BrUOG institution) and for specimen collection. Pathology must be reviewed by gynecological pathologist.NOTE: Patients with positive or negative pelvic and/or para-aortic lymph nodes by histologic confirmation or by radiological evaluation are eligible.

_____(y/n) Participants must have normal organ and marrow function as defined below:
- _____(y/n) absolute neutrophil count ≥1,500/mcL
- _____(y/n) platelets ≥100,000/mcL
- _____(y/n) total bilirubin within normal institutional limits
- _____(y/n) AST(SGOT)/ALT(SGPT) ≤2.5 × institutional upper limit of normal
- _____(y/n) creatinine Within normal institutional limits
- _____(y/n) hemoglobin ≥ 9.0g/dL

_____(y/n) Neuropathy (sensory and motor) ≤ CTCAE v4.0 grade 1

_____(y/n) Patients with ureteral obstruction should undergo stent or nephrostomy tube placement prior to study entry. Any side effects or complications associated with stent placement that, in the opinion of the treating investigator, puts the patient at increased risk for treatment-related toxicity, must be resolved completely prior to study enrollment.

_____(y/n) Patients of child-bearing potential must have a negative serum pregnancy test prior to study entry (within 7 days prior to initiation of study treatment) and be practicing an effective form of contraception during study treatment and for 24 months (2 years) thereafter.

_____(y/n) Women should not breast-feed while on this study

_____(y/n) Patients must not be receiving any other investigational agent

_____(y/n) Ability to understand and the willingness to sign a written informed consent document.

_____(y/n) All patients with a history of hearing loss are required to have an audiogram within 28 days prior to initiating protocol therapy. If patient does not have a history of hearing loss this must be documented by treating physician. Audiogram with results required to be submitted to BrUOG.

Exclusion:
_____(y/n) Participants with visceral metastases, including brain metastases.

_____(y/n) Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, hepatitis, active rheumatologic or collagen vascular disease, symptomatic congestive heart failure, unstable angina pectoris, clinically significant cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements. HIV disease not controlled on antiretroviral therapy are also excluded. See exclusion for hepatitis information.

_____(y/n) Patients who have received previous pelvic or abdominal radiation, cytotoxic chemotherapy, or previous therapy of any kind for this or any other malignancy.

_____(y/n) Patients who have circumstances that will not permit completion of this study or the required follow-up as per the treating physician

_____(y/n) Patients with a history of other invasive malignancies, with the exception of non-melanoma skin cancer are excluded if there is any evidence of other malignancy being present within the last three years (2 years for invasive breast cancer). However, patients with a malignancy that is non-likely to require treatment, as per the treating physician, in the next 2 years, such as a completely resected, early stage breast cancer, or other malignancies treated with curative intent are eligible. Patients are also excluded if their previous cancer treatment contraindicates this protocol therapy.

_____(y/n) Prior treatment with immunotherapy for any cancer, including immune checkpoint inhibitors or anti-CTLA4 agents

_____(y/n) Patients with renal abnormalities, such as pelvic kidney, horseshoe kidney, or renal transplantation, that would require modification of radiation fields as documented by treating physician

_____(y/n) Participants with an active, known or suspected autoimmune disease. Participants with type I diabetes mellitus, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia) not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.

_____(y/n) Participants with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 14 days of day 1 of treatment. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease

See section 3.3 in eligibility
It is required that all elements be submitted

Signed informed consent: The patient must be aware of the neoplastic nature of his/her disease and must willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side effects, risks, and discomforts.

The support documentation, per the requirements under the study parameters section of this study, as well as the consent form and this checklist, must be faxed to the BrUOG Central Office at the time of registration. Please check if "Enclosed", state reason when "Not Enclosed," or check if "Not Applicable."

1) Eligibility Form	Enclosed __Not Enclosed _____	Not Applicable __
2) Heme/Onc initial note	Enclosed __Not Enclosed _____	Not Applicable __
3) Pathology Report(s)	Enclosed __Not Enclosed _____	Not Applicable __
4) MRI/CT Report(s)	Enclosed __Not Enclosed _____	Not Applicable __
5) Lab Source Document	Enclosed __Not Enclosed _____	Not Applicable __
6) ICF signature page		
7) Other documentation		

It is required that each item from the schedule of evaluation be submitted to BrUOG along with confirmation via source to match each inclusion and confirm each exclusion criteria.

Most recent IRB approval date of protocol (whether this be the initial, latest amendment or CR):
_____

Date of treatment day 1 (Nivolumab):_____

Hospital where patient will be treated with Oncologist: _____

Name of treating physician: _____

Hospital/location where radiation will be administered:_____

Name of Radiation Oncologist:_____

Was tissue at diagnosis from outside hospital? _____(y/n)

If yes, document tissue was requested with date:_____
Confirm received and confirm by local gynecologic pathologist and pathology report of review of the outside sample with this registration: _____(y/n)

Your signature: _____

APPENDIX B: AGREEMENT TO PARTICIPATE IN A RESEARCH STUDY AND AUTHORIZATION FOR USE AND DISCLOSURE OF INFORMATION

BrUOG 355: A Pilot Feasibility study incorporating Nivolumab to tailored radiation therapy with concomitant cisplatin in the treatment of patients with cervical cancer

You are being asked to take part in a research study. All research studies carried out at <INSERT HOSPTIAL NAME> are covered by rules of the Federal government as well as rules of the State and <INSERT HOSPTIAL NAME>. Under these rules, the researcher will first explain the study, and then he or she will ask you to participate. You will be asked to sign this agreement that states that the study has been explained, that your questions have been answered, and that you agree to participate.

The researcher will explain the purpose of the study. He or she will explain how the study will be carried out and what you will be expected to do. The researcher will also explain the possible risks and possible benefits of being in the study. You should ask the researcher any questions you have about any of these things before you decide whether you wish to take part in the study. This process is called informed consent.

This form also explains the research study. Please read the form and talk to the researcher about any questions you may have. Then, if you decide to be in the study, please sign and date this form in front of the person who explained the study to you. You will be given a copy of this form to keep.

Nature and Purpose

Your doctors are participating in this research study sponsored by the Principal Investigator, Dr. Don Dizon, in collaboration with Brown University Oncology Research Group (BrUOG), which will serve as the central coordinating office for the study. Bristol-Myers Squibb, a pharmaceutical company, is financially supporting this research study by providing the study drug, Nivolumab, and funding for the study.

You are invited to take part in a clinical trial, a type of research study, because you have locally advanced cervical cancer that you have not previously received treatment for. Your doctor will explain standard options specific to your cancer type that are available outside of this clinical trial, but it may include standard available chemotherapy or other targeted treatment.

This research study is a Phase II clinical trial. Phase II clinical trials test the safety and effectiveness of the investigational drug in combination with radiation to learn whether the drug(s) works in treating a specific disease. "Investigational" means that the agent in this trial has not been approved for use in the treatment of this particular tumor type.

In this study, your doctors are studying three treatment arms, each using standard chemotherapy, with the drug cisplatin and radiation and the drug Nivolumab. Each treatment Arm will test the addition of Nivolumab at a different time point. This will be explained below. Your doctors will be comparing the arms to see if one is more effective and less toxic than the other. While some patients with locally advanced cervical cancer will be cured by standard treatment with cisplatin and radiation, in many patients, the cancer comes back after that treatment, and so we are hoping that the addition of nivolumab will make the standard treatment more effective. Nivolumab is believed to work by preventing the cancer from blocking the immune system from attacking it, which may help fight the cancer. We are unsure if the addition of adding nivolumab to standard treatment will improve the effectiveness of cisplatin and radiation, but this is being studied.

The FDA (the U.S. Food and Drug Administration) has not approved nivolumab for cervical cancer, but Nivolumab is approved for other cancers, such as advanced melanoma. The treatment of using the chemotherapy drug cisplatin and radiation is standard for the treatment of your disease. The primary objective of the study is to determine if nivolumab can be safely given in combination with cisplatin and pelvic radiation in patient with cervical cancer.

How Many People will take part in the Study?

It is expected that up to 24 people will take part in this research study.

Explanation of Procedures

What will happen if I take part in this research study?

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests, while on the study. They are part of regular cancer care.

- **A medical history,** which includes questions about your health, current medications, and any allergies.
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **An assessment of your tumor including the chest, abdomen and pelvis, by CT** (Computerized Tomography) scan
- **Blood tests.** about 4 teaspoons of blood will be taken to assess your organ function.
- **Pregnancy test (blood),** if you are a female of child-bearing potential will be performed both 7 days prior to the start of treatment and again within 1 day prior to the start of treatment.
- **Electrocardiogram (ECG)**, which measures the electrical activity of your heart
- **Audiogram,** a test to check your hearing may be done if you are found to have a history of hearing loss. This will be done as one of the drugs being used with radiation, cisplatin, has been known to cause hearing loss.

- **Cystoscopy (a test to examine the lining of your bladder), proctoscopy (a procedure to examine your anus, rectum and sigmoid colon) and barium enema (an X-ray to look for changes in your large intestine),** may all be done depending on the stage of your disease
- **Tissue**: A sample of your tumor from your initial diagnosis or the most recent biopsy procedure will be requested by your study doctor. Researchers at Rhode Island Hospital, will examine your tumor tissue to see how the study treatment may affect your cancer.

While on study:
There are three treatment groups in this study. Patients will be enrolled to one group at a time. Neither you nor your doctor may choose which Arm you are enrolled to or which treatment you get. Your doctor will tell you which Arm and treatment you have been assigned.

The first group of patients will only get nivolumab during their chemoradiation, the second group of patients will only get it for the 2 years after they complete the standard chemoradiation, the third group, assuming patients from the first 2 groups tolerated treatment well, will get the nivolumab both during chemoradiation and for the 2 years following it.

All patients in all treatment groups, will receive two doses of nivolumab prior to the start of chemotherapy and radiation.

Following the two doses of nivolumab, you have the option to consent for the collection of a second biopsy. Depending on the location of your cancer your doctor will choose what type of biopsy is best for you, such as a biopsy performed in clinic or a CT guided biopsy (a procedure using a very thin needle and syringe to withdraw tissue from a tumor with the help of a CT scan). This is not a required biopsy.

___ YES I consent to the second research biopsy

___ NO I do not want to have the second research biopsy

All patients will receive standard chemotherapy drug cisplatin with radiation. Cisplatin will be given by IV over about 1 hour once a week for 6 weeks beginning day 1 of radiation. Radiation will be given 5 days a week (preferably beginning on a Monday) for 6 weeks.

Arm 1: Will include about 8 patients.

A cycle is about 2 weeks long.

There will be 2 groups of patients in Arm 1: about 4 patients will receive external beam radiation and about 4 patients will receive a targeted radiation called intensity modulated radiotherapy (IMRT). The radiation field will be determined by your Radiation Oncologist depending on your disease.

Treatment in Arm 1 includes Nivolumab with standard chemotherapy (drug cisplatin) and radiation.
Nivolumab will be given once every 2 weeks into your vein (by intravenous infusion) beginning day 1 of radiation for 3 cycles (3 doses).

- **Pre-medications:** You may be pre-medicated with drugs to reduce the chance of having a reaction to the study treatment. If you tolerate the study treatment without a reaction, then pre-medications may be changed by your doctor**.**

Arm 2: Arm 2 will include about 4 patients. Enrollment to Arm 2 will open once all patients have been enrolled in Arm 1.

In the Arm 2, patients will receive standard chemotherapy (drug cisplatin) and radiation. The radiation field will be determined by your Radiation Oncologist depending on your disease.

Approximately 2-3 weeks post the completion of chemotherapy and radiation Nivolumab will be given once every 4 weeks into your vein (by intravenous infusion) for 2 years (about 24 doses).

- **Pre-medications:** You may be pre-medicated with drugs to reduce the chance of having a reaction to the study treatment. If you tolerate the study treatment without a reaction, then pre-medications may be changed by your doctor**.**

Arm 3: Once Arms 1 and 2 have been completed the study doctors will review the safety of the treatment and enrollment to Arm 3 will be opened. Arm 3 will enroll about 12 patients.

Treatment in Arm 3 includes Nivolumab with standard chemotherapy (drug cisplatin) and radiation. Nivolumab will be given once every 2 weeks (3 doses) into your vein (by intravenous infusion) beginning day 1 of radiation. The radiation field will be determined by your Radiation Oncologist depending on your disease.

Once chemotherapy and radiation ends, patients will then receive Nivolumab once every 4 weeks into your vein (by intravenous infusion) for 2 years (about 24 doses).

<u>All patients: Study Visit</u>: Weekly
This visit will involve the following:

- **Clinical Exams:** During this visit you will have a physical exam and you will be asked questions about your general health and specific questions about any problems that you might be having and any medications you may be taking.
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **Safety evaluation**

- **Blood tests (approximately 3 tablespoons)**,

All patients: Study visit: Monthly

- **Clinical Exams:** During this visit you will have a physical exam and you will be asked questions about your general health and specific questions about any problems that you might be having and any medications you may be taking.
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **Safety evaluation**
- **Blood tests (approximately 3 tablespoons)**, inclusive of a pregnancy test for women of child-bearing potential
- **Audiogram:** for patients with a history of hearing loss

All Arms: End of Treatment

This visit will involve the following:

- **Clinical Exams:** During this visit you will have a physical exam and you will be asked questions about your general health and specific questions about any problems that you might be having and any medications you may be taking.
- **Performance status**, which evaluates how you are able to carry on with your usual activities.
- **Safety evaluation**
- **Blood tests (approximately 3 tablespoons)**
- **An assessment of your tumor** CT scan (or other scan if determined to be more beneficial by your study doctor or your insurance) of your chest, abdomen and pelvis used to assess the response of your disease.
- **Audiogram:** for patients with a history of hearing loss
- At approximately 30 days after your final treatment, you will have another visit to assess any problems you may be having that may be related to your treatment

All Arms: Follow-up

After completion of treatment you will be seen by your doctor approximately every 6 months for 3 years. You will continue to be followed by a CT scan of the chest, abdomen and pelvis approximately every 6 months during follow-up. These scans will stop if your cancer progresses.

Can I stop being in the study?

Yes. You can decide to stop at any time. Tell your doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell your doctor if you are thinking about stopping so any risks from the

discontinuation of treatment can be evaluated. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.

Your doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

Costs for participating in this study

Some of the services you will receive are being performed only because you are participating in this research study. Examples of these 'research only' services include the drug Nivolumab. The drug will be will be provided by BMS, the makers of the drug, at no charge and will not be billed to you or your health insurance company. Also, the second optional biopsy, and its storage, which may be attempted post the first two doses of Nivolumab is a 'research only' service. Your insurance nor you will be charged for any costs associated with the research only biopsy.

Other services you will receive during this research study are considered "routine clinical services" that you would have received even if you were not in the research study.

These include all study doctor visits, blood tests, drugs used to reduce side effects, doctor visits, all blood tests, pregnancy tests, radiation, cisplatin, audiogram, the infusion of the study drug Nivolumab, disease related testing (such as a cystoscopy etc), CT scans, MRIs, PET scans and EKGs. Therefore, all of the services listed in this paragraph will be billed to your health insurance company, but you will be responsible for paying any deductibles, co-payments, or co-insurance that are a normal part of your health insurance plan. If you do not have health insurance or your insurance does not cover these services, you will be responsible for those costs.

Contact Information: If you have any questions regarding this study, you may contact your site's Principal Investigator, <INSERT NAME AND CONTACT>

Discomforts and Risks

There are risks to taking part in any research study. One risk is that you may get a study drug that does not help treat your disease or that makes your condition or disease worse. Another risk is that there may be side effects.

All cancer treatments can have side effects, which can range from mild and reversible to severe, long lasting and possibly life-threatening. There is a great deal of variability among side effects of different cancer treatments and between individuals. In a research study, all of the risks or side effects may not be known before you start the study. **You need to tell your doctor or a member of the study team immediately if you experience any side effects.**

Everyone in the research study will be watched carefully for side effects. You will be monitored during the administration of study drugs to keep track of your blood counts and organ function,

particularly your kidney and liver function. If you experience side effects, they may go away after you stop taking the study drug. Some side effects can be mild; but others can be long lasting and may never go away. Some may be life-threatening or fatal.

Since the effect of the study drug taken with other medications may not be known, it is important that you tell the research doctor about all prescription and non-prescription drugs, herbal preparations and nutritional supplements that you are taking or planning to take.

During the research study, you will be notified of newly discovered side effects or significant findings, which may affect your health or willingness to participate. You may be asked to sign a new consent form that shows that you have been informed of new information relating to this research study.
Taking part in this study may lead to time away from work.

Nivolumab is an immunotherapy drug. Nivolumab is an agent involved in the inhibition of "immune checkpoints," and may result in severe and possibly fatal immune-mediated side effects probably due to activation and growth of immune cells (T-cells). By stimulating the immune system, it is possible that the immune system could attack and damage normal organs and tissues. Immune-mediated side effects have been reported in patients receiving Nivolumab. In clinical trials, most side effects were reversible and managed by stopping Nivolumab temporarily, administration of corticosteroids and supportive care. While rare, immune mediated side effects may also occur after stopping Nivolumab. These are considered late onset immune mediated toxicities, which may begin even months after stopping treatment. Your doctor will closely monitor you after you stop treatment and provide supportive care as necessary. **There are also some side effects which may not yet be known. There is a small risk of death**

Nivolumab:
Frequent - Greater than 10% chance this will happen

- Diarrhea
- Nausea
- Fatigue
- Rash
- Itchiness

Occasional – Between 1 and 10% chance this will happen

- Thyroid gland abnormalities. May cause fatigue, weight gain, fluid retention, sensitivity to cold & mental apathy. Can be serious or life threatening.
- Elevated blood sugar
- Bowel inflammation. This could result in severe diarrhea and may require hospitalization for treatment. Severe and prolonged diarrhea can be life-threatening.
- Inflammation or ulceration of the mouth and lining of the digestive tract
- Vomiting

- Abdominal pain
- Constipation
- Dry mouth
- Fevers
- Swelling of the face, body, arms, or legs (edema).
- Abnormally high levels of enzymes produced by the liver meaning your liver is not functioning properly. Although this is usually mild and reversible, this can be serious or life threatening.
- Reaction to the drug infusion, including flushing, shortness of breath, dizziness, chest pain, or other symptoms.
- Infections
- Blood abnormalities, including low blood phosphate, magnesium, potassium, or sodium levels. These may require repletion or correction of abnormal blood test values.
- Blood test abnormalities, including increase in lipase or amylase, which may reflect inflammation of the pancreas.
- Decreased appetite
- Joint or muscle pain or stiffness
- Tingling, burning, or numbness in hands and feet
- Headache
- Dizziness
- Kidney failure which is when both of your kidneys fail and your body holds fluid which can be serious or life threatening. Your blood pressure rises and harmful wastes build up in your body. When this happens, you may need to be hospitalized or else be placed in dialysis.
- Shortness of breath
- Cough
- Loss of color (pigment) from areas of skin
- Skin reactions, including hives, redness, and dry skin. Rarely, a skin reaction may be severe and result in extensive skin blistering (Stevens Johnson syndrome). This can be a life-threatening event.
- Hair thinning or loss
- Elevated blood pressure
- Inflammation of the lungs which can cause shortness of breath and difficulty breathing. If severe, this can be life threatening.
- Muscle or joint pain

Rare – Less than 1% chance this will happen

- Changes in heart rhythm, resulting in a fast or irregular heartbeat. Certain types of irregular heartbeats can be serious or life-threatening.
- Adrenal gland abnormalities, which may cause you to feel weak.

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- Pituitary gland abnormalities, which may cause headaches, change in eyesight, increased thirst, and increased frequency passing urine.
- Diabetes. This is an elevated blood sugar that can occur when your body is not able to regulate blood sugar levels normally. Elevated blood sugar levels may be life-threatening and may require hospitalization for treatment.
- Inflammation of the eyes. This may result in decreased or blurry vision.
- Inflammation of the pancreas. This could become severe and cause nausea and vomiting, fever and rapid heart rate. This could require hospitalization and may be life threatening.
- Inflammation of the airways. This can result in cough or shortness of breath.
- Swollen lymph nodes
- Autoimmune disorders, including Guillain-Barre syndrome, which can be associated with progressive muscle weakness or paralysis.
- Inflammation or loss of the lining of the brain and spinal cord, which may cause neurological damage including confusion, hallucinations, difficulty walking or using arms
- Myasthenia gravis, when the body's immune system attacks muscle nerve cell receptors causing weakness in the muscles. This can be severe or life-threatening.
- Abnormal brain function due to brain inflammation (encephalitis), which can be potentially life-threatening or fatal.
- Inflammation of the blood vessels, which could cause possible bleeding and/or bruising.
- Cardiac issues, including the risk of heart inflammation, or myocarditis

Lung Inflammation (pneumonitis): It is possible that nivolumab may cause inflammation of the tissues of the lung. This adverse effect has been reported infrequently in patients treated with nivolumab. While many patients with x-ray or CT abnormalities have not developed any symptoms, some patients have developed mild to severe symptoms and in rare cases, death has occurred as a result of their lung inflammation. Signs and symptoms of lung inflammation may include difficulty breathing, pain or discomfort while breathing, chest pain, cough, shortness of breath, increased rate of breathing, fever, low blood oxygen levels, or fatigue.

Your study doctor and nurse will watch you closely for changes in your ability to breathe and for other signs or symptoms that might show you are developing this type of lung inflammation and will perform regular tests including physical exams, measurement of oxygen levels through non-invasive testing (i.e., pulse oximeter), blood tests, chest x-rays and/or CT scans.

Please inform your study doctor or nurse <u>AT ONCE</u> if you experience any of the following:

- Any new or increased shortness of breath;
- Any new or increased chest pain;
- Any new or increased pain/difficulty while breathing;
- Any new or increased cough or any significant change in your type of cough; for example any new or increased mucous or blood in your cough;

- Any change in the amount of oxygen you require;
- Any fever, fatigue, or other symptoms that occur at the same time as any changes to your breathing or other lung symptoms.

If you start to develop symptoms, your study doctor will ask you to return to the clinic for additional tests, which could include a physical exam, measurement of oxygen levels, blood tests, chest x-rays, and/or CT scans. You will be monitored very closely for changes in your overall lung symptoms, monitoring may require hospitalization. You may require specific treatment in order to control pneumonitis. You may also be seen by a special doctor called a pulmonologist, who has special training to be an expert in how your lungs work.

Prolonged treatment with medicines that suppress inflammation, sometimes needed to manage the side effects of nivolumab treatment, may lower your body's ability to fight off certain infections (i.e., opportunistic infections). These infections may require treatment with antibiotic or antifungal medications and may be fatal.

Reproductive Risks From nivolumab

Because the drug in this study can affect an unborn baby, you should not become pregnant while on this study.

If you are a woman of childbearing potential you must practice an effective method of birth control while receiving study treatment. For women of child-bearing potential, you should not attempt pregnancy while participating in this research study and for 2 years after.
Ask your study doctor for more information regarding preventing pregnancy during the study treatments.

You should not nurse your baby while on this study. If you are premenopausal, your periods are likely to stop temporarily and may stop permanently due to the study treatments, which may lead to symptoms of menopause, such as hot flashes, and the inability to become pregnant, which may be permanent. If you are concerned about this, ask your study doctor about options for preserving your reproductive choices, which may include referral to a specialist in this field.

By signing this document you are acknowledging that you understand and agree to the information presented in this Reproductive Risk section.

Risks from cisplatin

Risks and side effects related to cisplatin include those which are listed below.

Likely:
- Decreased white blood cell count, which may increase risk of infection
- Decreased red blood cell, also called anemia, which may cause tiredness, weakness, and

shortness of breath
- Decreased platelet counts, which may increase risk of bleeding
- Nausea
- Vomiting
- Decreased appetite
- Abnormal kidney function
- Hearing loss and/or ringing in ears

Less likely but serious:
- Numbness/tingling in hands and feet, difficulty walking
- Electrolyte imbalances (decreased calcium, magnesium)
- Vision problems
- Allergic reaction
- Abnormal liver function

Rare:
- Rash
- Hair loss
- Secondary leukemia
- Abnormal heart function
- Loss of appetite

Risks from Radiation Therapy

Risks and side effects related to radiation therapy include those which are listed below.

Likely:
- Tanning or reddening of the skin which is exposed to the radiation beam
- Burning or pain during urination or defecation
- Diarrhea
- Permanent pubic hair loss

Less likely but serious:
- Damage to the small or large intestine or rectum or ureter or bladder which may require medications, hospitalization for management, or rarely a surgical procedure to repair

Rare:
- Nerve damage which may cause numbness or weakness in the legs

Other unknown side effects can occur with the combination of immunotherapy and standard chemoradiation, but you will be monitored for them.

Other risks:
Antiemetics (anti-nausea medications): Various medications used to prevent nausea and vomiting may cause drowsiness, dry mouth, diarrhea, constipation, headache, restlessness, agitation, anxiety, dizziness, involuntary tremors, skin rash, and possible allergic reaction. You will receive pre-medication to reduce the risk of infusion/injection reactions on your treatment days. Overall, the pre-medications you will be given are well tolerated.

Venipuncture (inserting a needle into a vein to obtain blood or give medication): May cause inflammation, pain, bruising, bleeding, or infection.

When you receive chemotherapy by vein, there is a slight risk that some of the drug may leak out around the needle at the injection site. A skin burn may result. Most skin burns are treatable and heal well.

In order to monitor the side effects, your physician will examine you frequently and obtain laboratory tests (blood tests, chest x-rays, or CT scans as needed) to determine the effects of your treatment and alter the drug dosages if necessary.

Risk of CT imaging: CT imaging uses x-rays. The radiation dose associated with this procedure is estimated to be a small fraction of the annual permissible dose to an x-ray technologist. There is no significant risk from this amount of radiation.

There may be other side effects that have not been reported. If you have any unusual symptoms, you should report them immediately to your doctor or nurse.

Benefits
We do not know if taking part in this study will help you. This study may help researchers learn information that could help people in the future.

Alternative Therapies

Taking part in this research study is voluntary. Instead of being in this research study, you have other options which may include the following:

- Receive standard treatment. Your doctor will discuss with you specific standard treatment options.
- Take part in another research study if there is one available.
- Receive no therapy specific to your cancer.
- Comfort care, also called palliative care. This type of care may help to reduce pain, tiredness, appetite problems and other problems caused by the cancer. It does not treat the cancer directly, but instead tries to treat the symptoms.

Please talk to the research doctor about your options before you decide whether you will take part in this research study.

Refusal/Withdrawal

It is up to you whether you want to be in the study. You are not required to enroll or participate. If you decide to participate, you can always change your mind and quit at any time. If you decide not to be in the study, or if you quit later, you will still be able to get the health care services you normally get. If you join, but later on the researcher or your doctor feels being in the study is no longer good for you, they may choose to take you out of the study before it is over. If new information becomes available that might change your mind about whether you want to stay in the study the researcher will share this information with you as soon as possible.

If you make the decision to withdraw from this study (stop taking study medication) for any reason, tell your doctor immediately. You will be asked to sign a form indicating whether you give your permission for your doctor and the research staff to continue to collect and submit follow-up information on your health status from your physicians and medical record. After signing the form, you still have the right to change your mind, at any time, regarding follow-up after withdrawal.

Medical Treatment/Payment in Case of Injury

A research injury is any physical or mental injury or illness caused by being in the study. If you are injured by a medical treatment or procedure you would have received even if you were not in the study that is not a research injury. To help avoid research injury and added medical expenses, it is very important to follow all study directions carefully. If you do experience a research injury, <INSERT HOSPITAL NAME> or the study doctor can arrange medical treatment for you. Such treatment will be paid for as described below.

Medical treatment will be available if you suffer a research related injury; however, you and/or your health insurance company will be charged for this treatment. The study will not pay for this medical treatment. Neither Dr. Don Dizon nor BrUOG, the coordinating center, have money set aside to reimburse you for medical bills from treatment of a research related injury or otherwise compensate you in the event of a study-related injury.

If you have insurance and have a research injury that is not covered by the study, it is possible that some or all of the cost of treating you could be billed to your insurer. If your health insurance will not cover such costs, it is possible you would have to pay out of pocket. In some cases, <INSERT HOSPITAL NAME> might be able to help you pay if you qualify for free care under <INSERT HOSPITAL NAME> policy. However, <INSERT HOSPITAL NAME> has no policy to cover payment for such things as lost wages, expenses other than medical care, or pain and suffering.

Rights and Complaints

Signing this form does not take away any of your lawful rights. If you have any complaints about this study, or would like more facts about the rules for research studies, or the rights of people

who take part in research studies you may contact <INSERT CONTACT NAME OF IRB>

Confidentiality

Your research records will be treated as private health care records and will be protected according to <INSERT HOSPITAL NAME> privacy practices and policies that are based on state and federal law. In particular, federal law requires us to get your permission to use or disclose (release your information to someone outside of <INSERT HOSPITAL NAME>) your health information for research purposes. If you sign this form you agree to be in this research study and you permit the use and disclosure of your health information for the purpose of conducting the research, providing treatment, collecting payment and running the business of the hospital. This permission has no expiration date. You may withdraw from the study at any time. However, if you do not want the researchers to use or disclose any further information in this study you must cancel permission in writing and may do so at any time. If you cancel your permission, you will stop taking part in the study and no new information will be collected about you. However, if you cancel your permission, it will not apply to actions already taken or information already collected about you by the hospital or the researchers before you canceled your permission.

Generally, the entire research record and any medical records held by the hospital may be used and released for research purposes. The following people or businesses/companies might use, release, or receive such information:

□ The researcher and their support staff;

□ The study sponsor and Principal Investigator Dr. Don Dizon and BrUOG, The Brown University Oncology Research Group and its representatives, including BMS the financial supporter of this trial and the maker of Nivolumab

□ Doctors, nurses, laboratories and others who provide services to you in connection with this study;

□ The company or section of the U.S. government that is paying for the study and others they hire to oversee, administer, or conduct the research;

□ The United States Food and Drug Administration, the Department of Health and Human Services, the Office of Inspector General, and the Office of Civil Rights;

□ People who volunteer to be patient advocates or research volunteer protectors;

□ Members of the hospital's administrative staff responsible for reviewing, approving and administering clinical trials and other healthcare or research activities.

There are times when the law might require or permit <INSERT HOSPITAL NAME> to release your health information without your permission. For example, <INSERT STATE> law requires researchers and health care workers to report abuse or neglect of children to the Department of Children, Youth and Families (DCYF) and to report abuse or neglect of people age 60 and older to the Department of Elderly Affairs.

All researchers and health care providers are required to protect the privacy of your health care

information. Other people and businesses/organizations that are not health care providers are not required by law to do that so it is possible they might re-release your information.
You have the right to refuse to sign this form and not participate in the research. Your refusal would have no effect on your treatment, charges billed to you, or benefits at any <INSERT HOSPITAL NAME> health care site. If you do not sign, you will not be able to enroll in the research study and will not receive treatment as a study participant.

If you decide to quit the study after signing this form (as described in Section 6) no new information will be collected about you unless you gave us permission to do so. However, the hospital or the researchers may continue to use information that was collected before you quit the study to complete analysis and reports of this research.

Additionally, a description of this clinical trial will be available on *http://www.ClinicalTrials.gov,* as required by U.S. law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time.
If after you have signed this form you have any questions relating to your rights, please contact <INSERT IRB CONATACT INFORMATION>
about your privacy rights see the <INSERT HOSPITAL NAME> which has or will be given to you.

Research authorization for use and disclosure of information.
The purpose of this section of the document is to provide you with some more information about how the information learned about you during the study will be used and shared.
We understand that your medical information is very personal and we will work hard to keep it private. If you sign this form you consent to participate in this research study and are giving us permission to use and share your personal health information in the ways described in this form.
Understandings and notifications

The main purpose of permitting the use and release of your information is to allow the research project to be conducted and to ensure that the information relating to that research is available to all parties who may need it for research purposes. Your information may also be used as necessary for your research-related treatment, to collect payment for your research-related treatment (when applicable), and to run the business operations of the hospital.

All health care providers are required to protect the privacy of your information. However, most persons or entities (i.e., businesses, organizations) that are not health care providers are not bound by law to protect the privacy of your information. You understand that if the person or entity that receives your information is not a health care provider bound to protect your privacy, such person or entity might re-release your health information.

You have the right to refuse to sign this form. If you do not sign this form, none of your health care outside the study, or the payment for your health care, or your health care benefits will be

affected. However, if you do not sign this form, you will not be able to enroll in the research study described in this form, and you will not receive treatment as a study participant.
If you sign this consent form, you may withdraw from the study at any time. However, if you do not want the researchers to use or disclose any further information in this study you must cancel permission in writing and may do so at any time. If you cancel your permission, you will stop taking part in the study and no new information will be collected about you. However, if you cancel your permission, it will not apply to actions already taken or information already collected about you by the hospital or the researchers before you canceled your permission. This information or action may be needed to complete analysis and reports of this research. This permission will never expire unless you cancel it. To cancel this permission, please write to Don Dizon, MD c/o the Medical Oncology Clinical Research Office at Rhode Island Hospital, 593 Eddy Street, APC Building Rm. 131, Providence, RI 02903.
If after you have signed this form you have any questions relating to your rights, please contact <INSERT IRB CONTACT>

Uses and releases covered by this authorization (permission)
Who will release, receive, and/or use your information? This form will allow the following person(s), class(es) of persons, and/or organization(s)* to release, use, and receive the information listed below in connection with this Study, or as required by law:
☒ Every research site for this study, including this hospital, and including each site's research staff and medical staff
☒ Health care providers who provide services to you in connection with this study
☒ Laboratories and other individuals and organizations that analyze your health information in connection with this study, in accordance with the study's protocol
☒ The following research sponsors and the people and companies that they use to oversee, administer, or conduct the research: The Principal Investigator and sponsor Don Dizon, MD, BrUOG, the group coordinating the study (or their advisers), and BMS, the makers of the drugs being used and the financial supporter of the trial
☒ The United States Food and Drug Administration, the Department of Health and Human Services, the Office of Inspector General, and the Office of Civil Rights
☒ The members and staff of the Institutional Review Board(s) or Ethics Committee(s) that approves this study
☒ Principal Investigator and other Investigators
☒ Study Coordinator
☒ Additional members of the Research Team
☐ The Patient Advocate or Research Volunteer Protector: _____
☒ Members of the hospital's administrative staff responsible for administering clinical trials and other research activities
☐ Contract Research Organization (A contract research organization is an independent organization that agrees to oversee and make possible, various aspects of the clinical research process for the research sponsor.)
☒ Data and Safety Monitoring Boards and others that monitor the conduct of the Study, for example a Clinical Events Committee

☐ The members and staff of the hospitals affiliated Privacy Board (if such a board is used)
☐ Others:
_____

* If, during the course of the research, one of the companies or institutions listed above merges with or is purchased by another company or institution, this permission to use or release protected health information in the research will extend to the new company or institution.

☒ The entire research record and any medical records held by the hospital may be used and released.
☐ The following information: _____

GINA STATEMENT
This study involves 'genetic testing' as defined by the Genetic Information Nondiscrimination Act of 2008 (GINA). GINA generally makes it illegal for health insurance companies, group health plans, and most employers to discriminate against you based on your genetic information. There are some limitations to GINA's protections (it does not apply to all insurers or employers, nor does it apply to all genetic information, such as information related to a genetic disease that you already have). In addition to GINA's protections regarding the ultimate use to which your genetic information is put, <INSERT HOSPITAL NAME>'s privacy policies generally protect the privacy of such information and restrict its release outside of <INSERT HOSPITAL NAME>, unless you specifically authorize its disclosure or unless disclosure without your authorization is permitted under applicable privacy laws.

Optional Participation in Specimen Banking (optional biopsy)
You are agreeing to participate in this research study by signing this form (the "Main Study") ***tissue*** samples will be collected from you, which will be referred to here as your 'Specimen.' In addition to being analyzed as part of the Main Study, your Specimen may be useful for future research purposes. Your signature on this consent form will document you to agree to this study are willing to allow your Specimen to be saved or 'banked' for use in future research studies. You give permission for your Specimen to be stored in a specimen bank indefinitely, until it is no longer usable. The Specimen may also be used to create a cell line, which would also be stored for an indefinite period of time. Along with the specimens, portions of your personal health information collected as part of the Main Study will also be stored. Your Specimen and personal health information may be stored and analyzed at Lifespan; or, they may be shared with researchers at other institutions or companies that may store them and use them for their own research. It is very unlikely that any future research performed using your Specimen would benefit you directly. However, the research may provide important medical knowledge that in the future could help other patients with your medical condition or other medical problems.

At this time, we do not know what future research studies may be done using your Specimen. Such research studies may include genetic tests that would analyze your DNA, RNA or other

gene products, like proteins and metabolites. These genetic tests may be done by Lifespan, or they may be done by other researchers with whom your Specimen and data have been shared. Because any genetic testing of your Specimen would be for research purposes, the results would have no clear implications for your health or medical condition, or that of your family members. Any testing results would not be made available to you or to any insurance company, your employer, your family, or any physician who treats you in the future.

There is a very remote possibility that your Specimen and some associated data may become part of a process or product that ultimately has commercial value. For instance, the Specimen could be used to establish a cell line (a group of cells that are able to reproduce, sometimes indefinitely) that could be patented and licensed. There are no plans to provide financial compensation to you should this occur.

If you decide at some time in the future that you no longer wish your stored Specimen to be used in future studies, you have the right to request that the Specimen be withdrawn from the specimen bank. However, withdrawal cannot be guaranteed and may be impossible. For example, it is possible that the Specimen might no longer be identifiable as belonging to you, or it may have been used up, or it may already have been shared with other institutions or companies for their own research. To request withdrawal of your Specimen, please write to: Don Dizon, MD 593 Eddy Street APC1 Providence, RI 02903.

If you are willing to allow your Specimen to be banked for future research purposes, please indicate your consent by signing below. Please note this refers to the optional biopsy.

_____ _____
Signature of study volunteer/authorized representative Date

SIGNATURE

I have read this informed consent and authorization form. ALL OF MY QUESTIONS HAVE BEEN ANSWERED, AND I WANT TO TAKE PART IN THIS RESEARCH STUDY.
By signing below, I give my permission to participate in this research study and for the described uses and releases of information. *I also confirm that I have been now or previously given a copy of the <INSERT HOSPITAL NAME> Privacy Notice*

This informed consent document expires on _____.
DO NOT sign this document after this expiration date

The Researcher is required to provide a copy of this consent to you.

_____ _____ _____
Signature of study volunteer/authorized representative Date and Time when signed*

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I was present during the consent PROCESS AND signing of this agreement by the study volunteer or authorized representative

_____ _____

Signature of witness (required if consent is presented orally or at the request of the IRB) *Date*

_____ _____

Signature of Translator Date

_____ _____ _____

Signature of researcher or designate *Date* *and* *Time when signed*

** If signed by agent other than study volunteer, please explain below.*

_____

APPENDIX C 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	20	Very sick, hospitalization indicated. Death not imminent.

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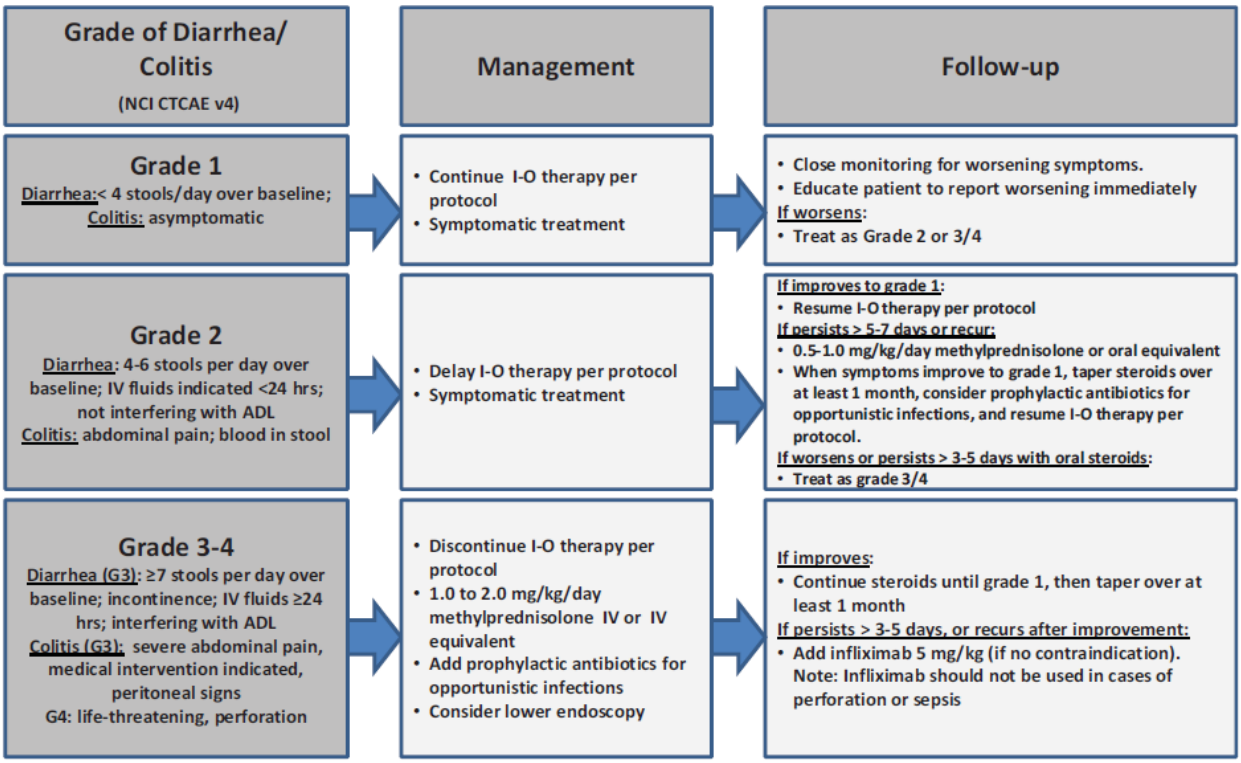
	self-care. Totally confined to bed or chair.	10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX D I-O AE ALGORITHMS

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.

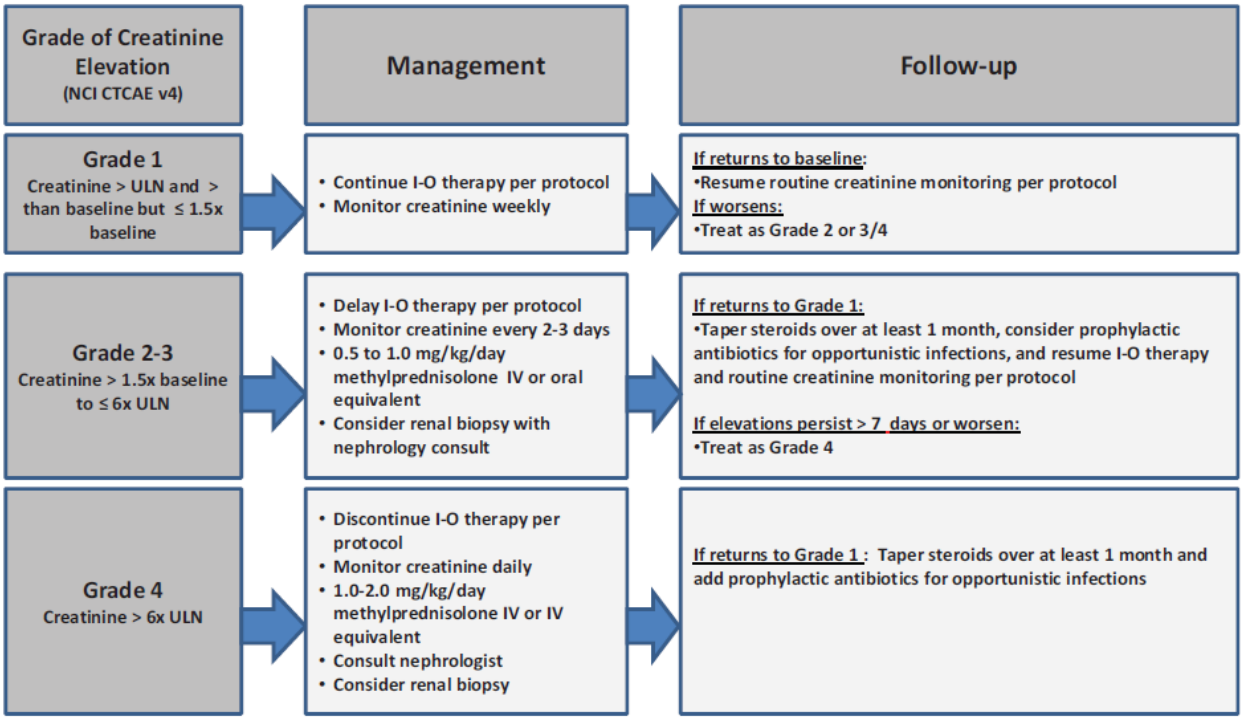


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

BrUOG 355: 7/8/17, 7/11/17, 7/20/17, 8/7/17, 8/8/17, 8/14/17, 8/16/17, 8/21/17, 8/22/17, 8/24/17, 8/28/17, 9/5/17, 9/6/17, 9/8/17, 9/11/17, 11/7/17, 11/8/17, 11/19/17 approved DD, 11/20/17, 12/12/17, 12/14/17, 1/29/18, 2/1/18, 2/6/18, 2/7/18,2/8/18, 2/9/18, 2/12/18, 2/13/18, 3/8/18 all reviews, 3/9/18, 3/13/18, 3/14/18, 3/15/18, 4/19/18, 4/23/18, 5/29/18, 6/5/18, Amendment # 1 7/9/18, Amendment # 2 12/12/18, Amendment #3, 4/6/2020, Amendment #4 5/11/2020

Renal Adverse Event Management Algorithm

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

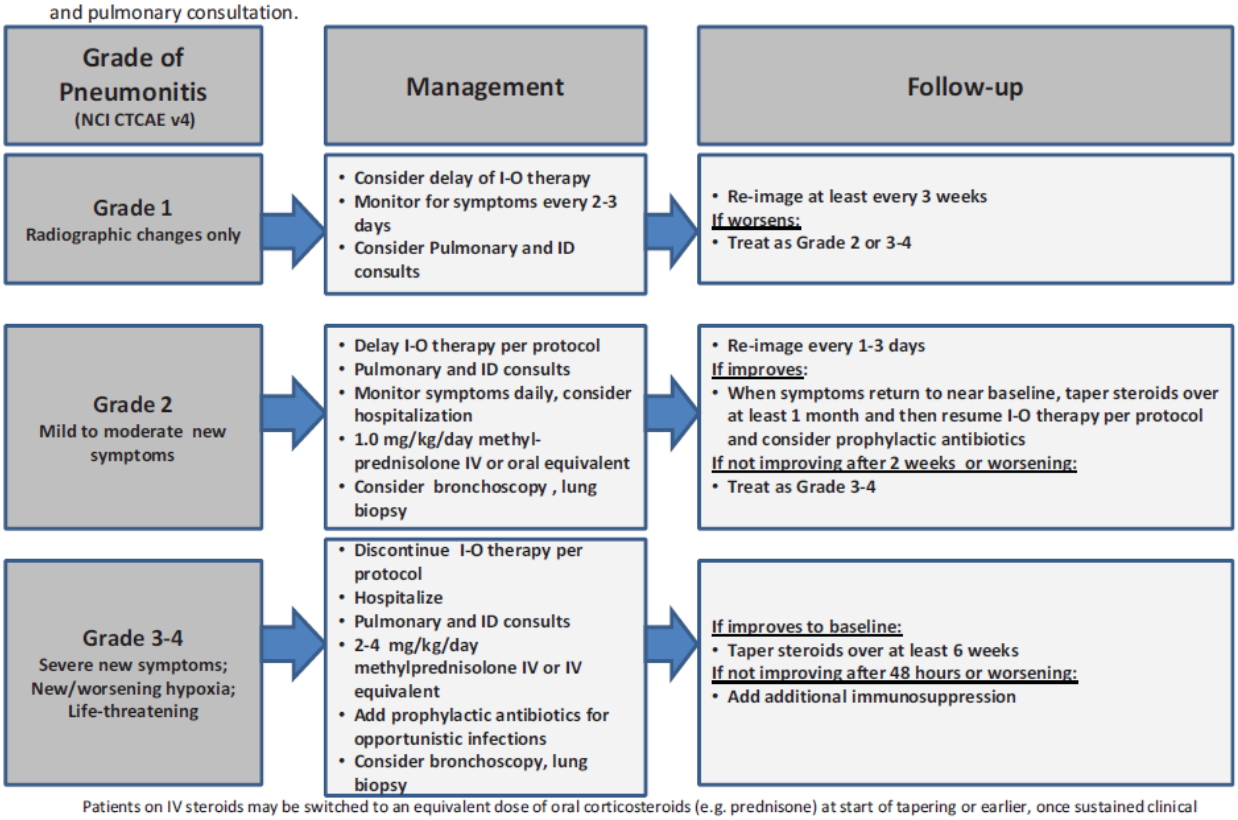


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

BrUOG 355: 7/8/17, 7/11/17, 7/20/17, 8/7/17, 8/8/17, 8/14/17, 8/16/17, 8/21/17, 8/22/17, 8/24/17, 8/28/17, 9/5/17, 9/6/17, 9/8/17, 9/11/17, 11/7/17, 11/8/17, 11/19/17 approved DD, 11/20/17, 12/12/17, 12/14/17, 1/29/18, 2/1/18, 2/6/18, 2/7/18,2/8/18, 2/9/18, 2/12/18, 2/13/18, 3/8/18 all reviews, 3/9/18, 3/13/18, 3/14/18, 3/15/18, 4/19/18, 4/23/18, 5/29/18, 6/5/18, Amendment # 1 7/9/18, Amendment # 2 12/12/18, Amendment #3, 4/6/2020, Amendment #4 5/11/2020

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.

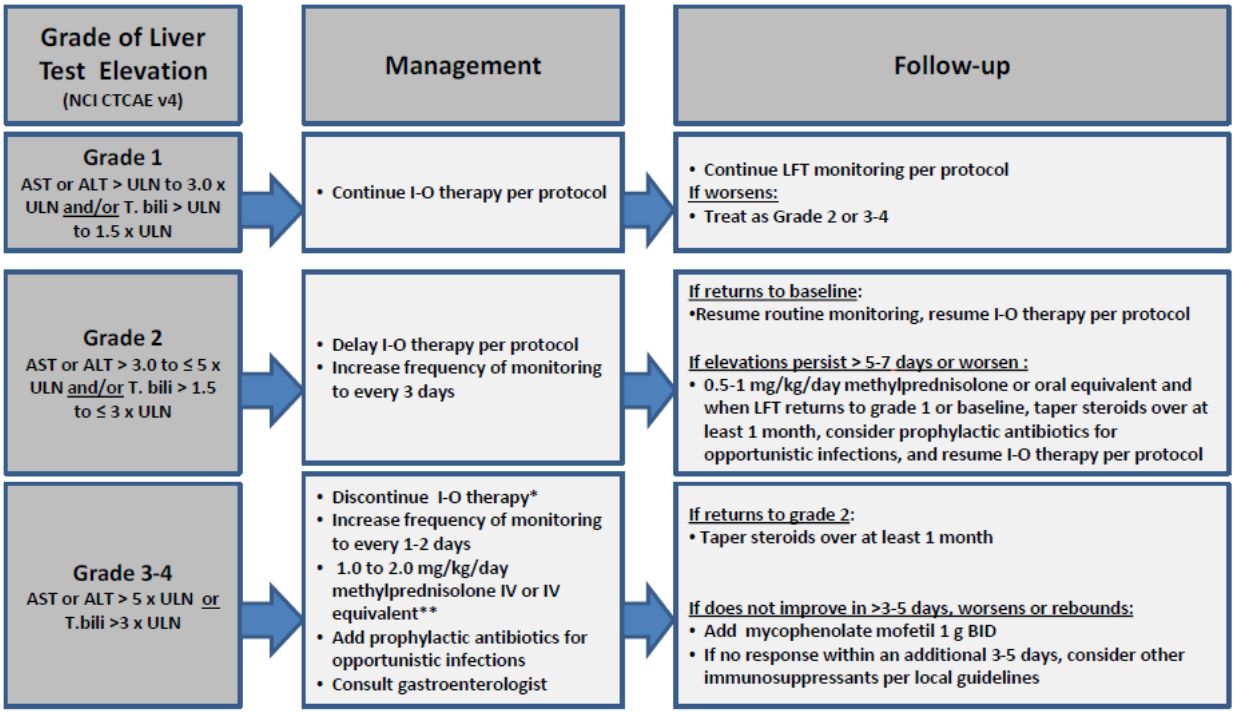


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

BrUOG 355: 7/8/17, 7/11/17, 7/20/17, 8/7/17, 8/8/17, 8/14/17, 8/16/17, 8/21/17, 8/22/17, 8/24/17, 8/28/17, 9/5/17, 9/6/17, 9/8/17, 9/11/17, 11/7/17, 11/8/17, 11/19/17 approved DD, 11/20/17, 12/12/17, 12/14/17, 1/29/18, 2/1/18, 2/6/18, 2/7/18,2/8/18, 2/9/18, 2/12/18, 2/13/18, 3/8/18 all reviews, 3/9/18, 3/13/18, 3/14/18, 3/15/18, 4/19/18, 4/23/18, 5/29/18, 6/5/18, Amendment # 1 7/9/18, Amendment # 2 12/12/18, Amendment #3, 4/6/2020, Amendment #4 5/11/2020

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.



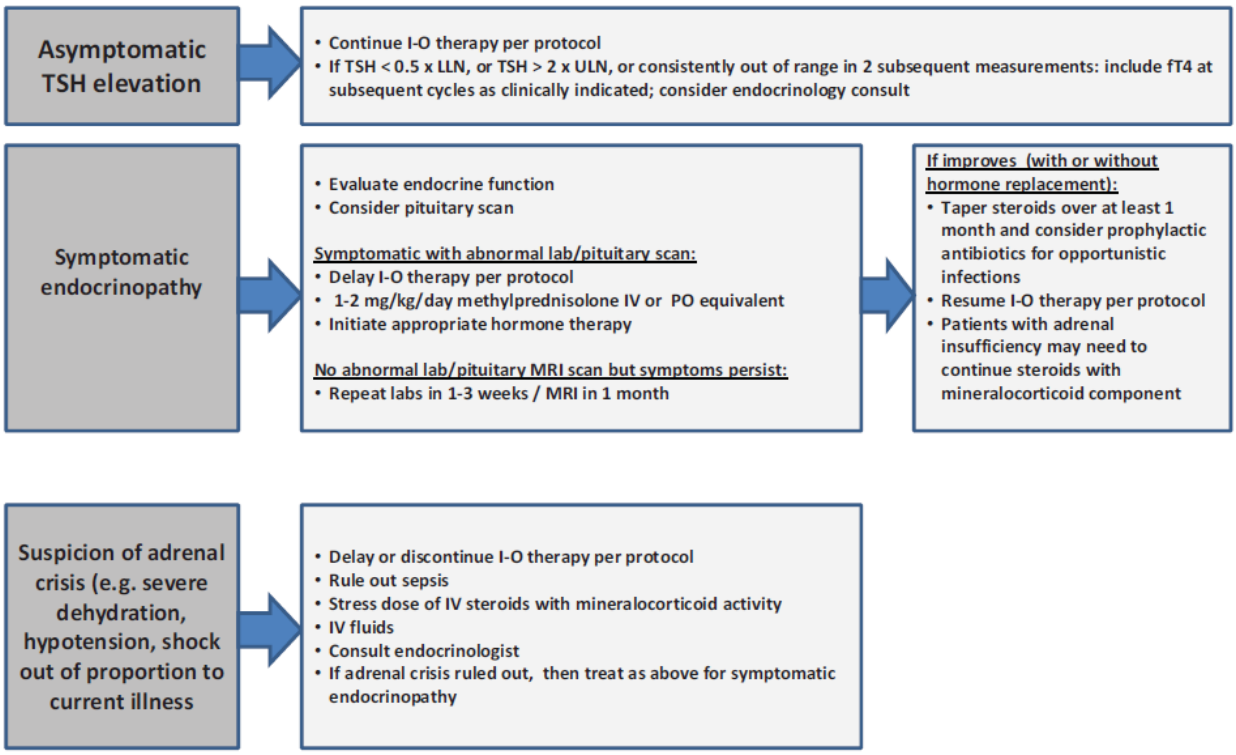
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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

Endocrinopathy Management Algorithm

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



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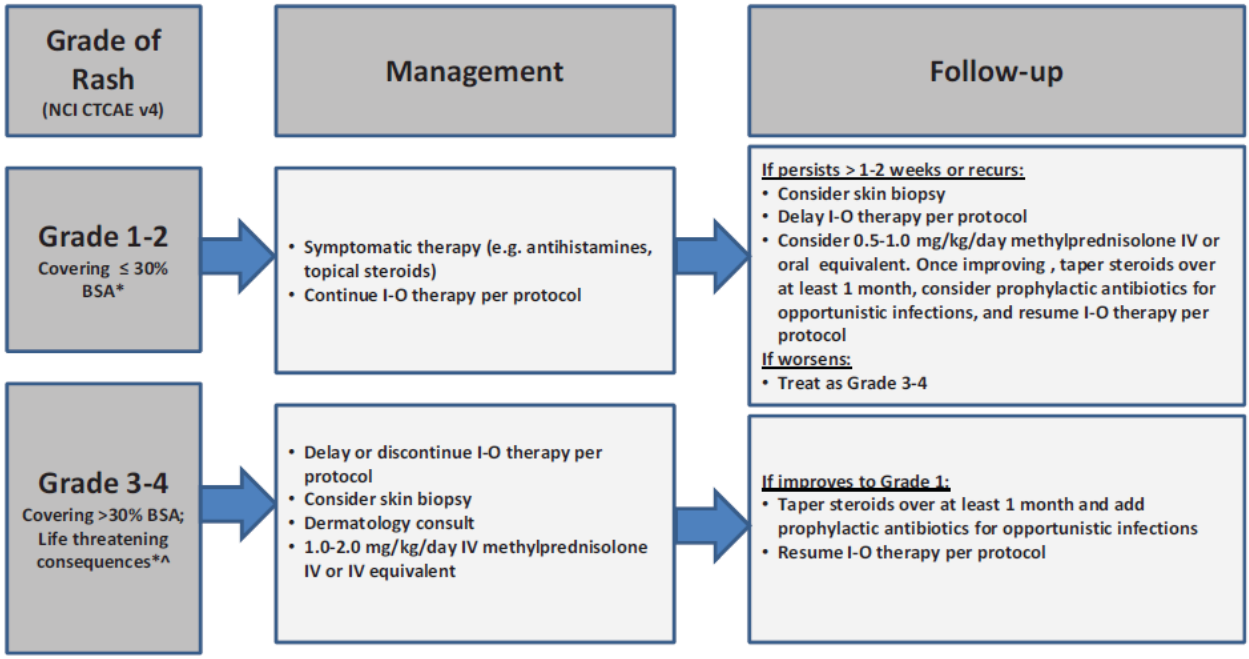
BrUOG 355: 7/8/17, 7/11/17, 7/20/17, 8/7/17, 8/8/17, 8/14/17, 8/16/17, 8/21/17, 8/22/17, 8/24/17, 8/28/17, 9/5/17, 9/6/17, 9/8/17, 9/11/17, 11/7/17, 11/8/17, 11/19/17 approved DD, 11/20/17, 12/12/17, 12/14/17, 1/29/18, 2/1/18, 2/6/18, 2/7/18,2/8/18, 2/9/18, 2/12/18, 2/13/18, 3/8/18 all reviews, 3/9/18, 3/13/18, 3/14/18, 3/15/18, 4/19/18, 4/23/18, 5/29/18, 6/5/18, Amendment # 1 7/9/18, Amendment # 2 12/12/18, Amendment #3, 4/6/2020, Amendment #4 5/11/2020

Skin Adverse Event Management Algorithm

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

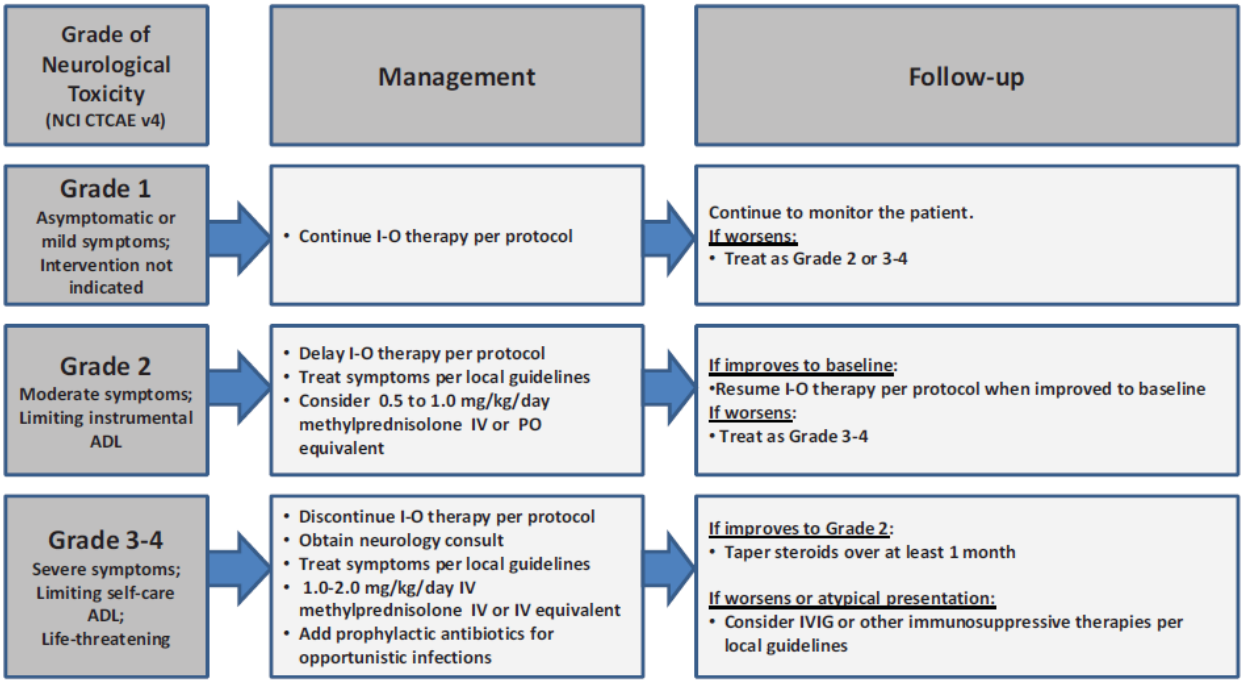


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.
*Refer to NCI CTCAE v4 for term-specific grading criteria.
^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

BrUOG 355: 7/8/17, 7/11/17, 7/20/17, 8/7/17, 8/8/17, 8/14/17, 8/16/17, 8/21/17, 8/22/17, 8/24/17, 8/28/17, 9/5/17, 9/6/17, 9/8/17, 9/11/17, 11/7/17, 11/8/17, 11/19/17 approved DD, 11/20/17, 12/12/17, 12/14/17, 1/29/18, 2/1/18, 2/6/18, 2/7/18,2/8/18, 2/9/18, 2/12/18, 2/13/18, 3/8/18 all reviews, 3/9/18, 3/13/18, 3/14/18, 3/15/18, 4/19/18, 4/23/18, 5/29/18, 6/5/18, Amendment # 1 7/9/18, Amendment # 2 12/12/18, Amendment #3, 4/6/2020, Amendment #4 5/11/2020

Neurological Adverse Event Management Algorithm

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



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BrUOG 355: 7/8/17, 7/11/17, 7/20/17, 8/7/17, 8/8/17, 8/14/17, 8/16/17, 8/21/17, 8/22/17, 8/24/17, 8/28/17, 9/5/17, 9/6/17, 9/8/17, 9/11/17, 11/7/17, 11/8/17, 11/19/17 approved DD, 11/20/17, 12/12/17, 12/14/17, 1/29/18, 2/1/18, 2/6/18, 2/7/18,2/8/18, 2/9/18, 2/12/18, 2/13/18, 3/8/18 all reviews, 3/9/18, 3/13/18, 3/14/18, 3/15/18, 4/19/18, 4/23/18, 5/29/18, 6/5/18, Amendment # 1 7/9/18, Amendment # 2 12/12/18, Amendment #3, 4/6/2020, Amendment #4 5/11/2020