ECOG-ACRIN
cancer research group
Reshaping the future of patient care

February 17, 2020

Martha Kruhm, MS RAC
Head, Protocol and Information Office
Quality Assurance Section
CTEP, DCT, NCI
6130 Executive Blvd, EPN Room 7000
Bethesda, MD 20892

Dear Ms. Kruhm:

Enclosed is Addendum #5 to EA5161, *Randomized Phase II Clinical Trial of Cisplatin/Carboplatin and Etoposide (CE) Alone or in Combination with Nivolumab as Frontline Therapy for Extensive Stage Small Cell Lung Cancer (ED-SCLC)*

This addendum is in response to a nivolumab rapid request for amendment from Dr. Jeffrey Moscow dated January 28, 2021.

No updates to the case report forms in Medidata Rave are planned as a result of this amendment.

Please replace your current copy of the protocol and Informed Consent document with these updated versions. We recommend that each institution maintain a file containing the original protocol, Informed Consent, and all subsequent revisions/versions.

IRB Review Requirements:

A) Full IRB review of this addendum is **recommended**, however, ECOG-ACRIN will accept the method of review determined by the standard operating procedures for the IRB of record for this protocol.

Sites using the CIRB as their IRB of record: The protocol and/or informed consent form changes have been approved by the CIRB and must be activated within 30 days of the CIRB posting of this notice.

Sites not using the NCI CIRB: Per CTMB Guidelines, the protocol updates and/or informed consent changes must be approved by local IRBs within 90 days of distribution of this notice. If your local IRB has different SOPs, they must be available at future E-A audit.

The following revisions to EA5161 protocol have been made in this addendum:

	Section	Change
1.	Cover Page	Updated Version Date and added Addendum #5.
2.	Section 5.3	Updated CAEPR to Version 2.4, December 2, 2020.

28 State Street, Suite 1100, Boston, MA 02109 p: 857.504.2900 f: 617. 589.0914 ecog-acrin.org

The following revisions to EA5161 Informed Consent Document have been made in this addendum:

	Section	Change
1.	Cover Page	Updated Version Date.
2.	"What possible risks can I expect from taking part in this study?"	Updated Risk List for nivolumab to version 2.4, December, 2020.

If you have any questions regarding this addendum, please contact Jack Fraulini at jfraulini@ecog-acrin.org or 857-504-2900.

We request review and approval of this addendum to EA5161 so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

Pamela Cogliano

Senior Director, Protocol Development

ECOG-ACRIN cancer research group
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EA5161

Randomized Phase II Clinical Trial of Cisplatin/Carboplatin and Etoposide (CE) Alone or in Combination with Nivolumab as Frontline Therapy for Extensive Stage Small Cell Lung Cancer (ED-SCLC)

STUDY CHAIR: Ticiana Leal, MD
STUDY CO-CHAIR: Afshin Dowlati, MD
STUDY STATISTICIAN: Suzanne Dahlberg, PhD
THORACIC COMMITTEE CHAIR: Suresh Ramalingam, MD
LABORATORY CO-CHAIR Afshin Dowlati, MD

Version Date: February 17, 2021

STUDY PARTICIPANTS

ALLIANCE / Alliance for Clinical Trials in Oncology

NRG / NRG Oncology

SWOG / SWOG

US Only

AMENDMENTS

Addendum #1
Addendum #2
Addendum #3
Addendum #4
Addendum #5

Agents	IND#	NSC#	Supply
Nivolumab		748726	NCI
Cisplatin		119875	Commercial
Carboplatin		241240	Commercial
Etoposide		141540	Commercial

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STUDY CHAIR

Ticiana Leal, MD
University of Wisconsin Hospital and Clinics
1111 Highland Ave, WIMR 3037
Madison, WI 53705
Phone: 608-263-9063
Fax: 608-531-2737
Email: tbleal@medicine.wisc.edu

STUDY CO-CHAIR

Afshin Dowlati, MD
University Hospitals Seidman Cancer Center
11100 Euclid Avenue
Cleveland, OH 44106
Phone: 216-844-5181
Fax: 216-844-5234
Email: afshin.dowlati@case.edu

STUDY CHAIR LIAISON (SCL)

Kasey Schneider, RN
Thoracic Oncology Program Manager
University of Wisconsin Hospital and Clinics
600 Highland Ave
Madison, WI 53792
Phone: 608-262-3078
Fax: 608-531-2737
Email: lunggroup@uwcarbone.wisc.edu

Rev. Add3

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**Submit study data**
Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal: Regulatory Submission Portal (Sign in at www.ctsu.org, and select the Regulatory Submission sub-tab under the Regulatory tab.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at 1-866-651-2878 to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com.	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For clinical questions (i.e., patient eligibility or treatment-related) Contact the Study PI of the Coordinating Group.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
The CTSU Web site is located at https://www.ctsu.org		

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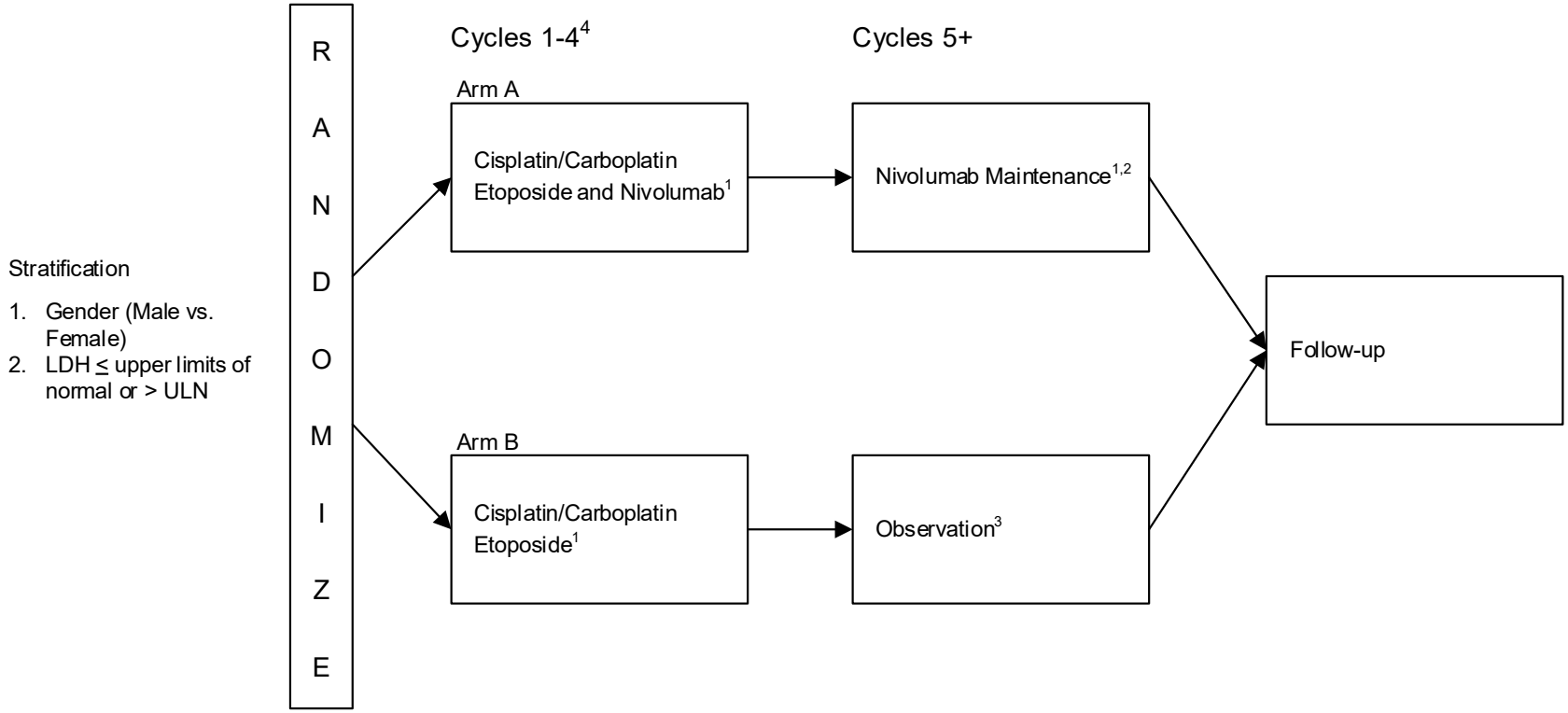
Schema



Cycle = 3 weeks during cycles 1-4 (21 days)
Cycle = 6 weeks during maintenance cycle 5+
Accrual goal = 150 patients

1. Refer to Section 5.1 for specific doses.
2. Until progressive disease, unacceptable toxicity, patient desire to discontinue study treatment, or up to 2 years (or 50 doses) maximum.
3. Until disease progression or non-protocol treatment regimen is initiated.
4. All patients will proceed to maintenance or observation after 4 cycles of chemotherapy.

1. Introduction

1.1 Small Cell Lung Cancer (SCLC)

Approximately 65% of all cases of SCLC in the US are diagnosed at the extensive stage of the disease. There is at present no curative treatment for this stage of the disease. The management approach of systemic chemotherapy using a platinum-etoposide doublet is the most common regimen in the North American patient population. This regimen achieves a response rate of 50-70%, a median survival of 9-11 months and median 5-year survival rate of less than 5%[1-4]. There has been no significant therapeutic improvement in clinical outcome for patients with extensive stage SCLC in the last 2 decades, making it one of the most fatal cancers. While SCLC remains very sensitive to frontline platinum-based doublet chemotherapy with response rate of up to 70%, the majority of the patients will relapse and die of their disease. Previous strategies to improve the outcome of the disease with the use of high intensity chemotherapy led to an improvement in the response rate, which did not translate into survival benefit due to the heightened toxicities of intensive chemotherapy[5-7].The incorporation of novel immunotherapy agents with excellent safety profile and limited additive toxicity in combination with standard chemotherapy agents as a strategy for improved efficacy has a great potential for improved clinical outcome in this disease.

1.2 PD-1 inhibition

The programmed death-1 (PD-1) receptor serves as an immunologic checkpoint, limiting bystander tissue damage and preventing the development of autoimmunity during inflammatory responses. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes.[8] 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.

PD-1, a 55-kDa type 1 transmembrane protein, is a member of the CD28 family of T-cell co-stimulatory receptors that include Ig super family member CD28, CTLA-4, inducible co-stimulator (ICOS), and B and T lymphocyte attenuator (BTLA) (Investigator Brochure, version 16, 2017). PD-1 is transiently but highly expressed on activated T cells functioning to limit immune effectors at the site of activation. Chronic stimulation may prevent the re-methylation of the PD-1 gene leading to continuous expression and characterizes a state of “exhausted” T cells that lose function and proliferative capacity while enhancing a suppressive tumor microenvironment. PD-1 may act together with other T-cell modulating molecules, including CTLA-4, TIM-3, lymphocyte-activation gene 3 (LAG-3) as well as indoleamine-pyrrole 2,3-dioxygenase 1 (IDO-1), cytokines, and transforming growth factor beta (TGF-beta).

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

PD-1 knockout mice develop strain-specific lupus-like glomerulonephritis (C57BL/6) and cardiomyopathy (BALB/c). In transplantable tumor models that expressed PD-1 and LAG-3 on tumor-infiltrating $CD4^+$ and $CD8^+$ T cells dual anti-LAG-3/anti-PD-1 antibody treatment cured most mice of established tumors that were largely resistant to single antibody treatment.[9] Despite minimal immunopathologic sequelae in PD-1 and LAG-3 single knockout mice, dual knockout mice abrogated self-tolerance with resultant autoimmune infiltrates in multiple organs, leading to eventual lethality.

PD-L1 expression is found on a number of tumors, and is associated with poor prognosis based on overall survival (OS) in many tumors, including melanoma,[10] renal,[11] esophageal,[12] gastric,[13] ovarian,[14] pancreatic,[15] lung,[16] and other cancers (Investigator Brochure, version 16, 2017).

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In summary, the PD-1/PD-L1 pathway plays a critical role in tumor immune evasion and therefore represents an attractive target for therapeutic intervention.

1.2.1 Nivolumab

Nivolumab (BMS-936558, MDX-1106, and ONO-4538) is a fully human monoclonal immunoglobulin G4 (IgG4) antibody (HuMAb) that is specific for human programmed death-1 (PD-1, cluster of differentiation 279 [CD279]) cell surface membrane receptor (Investigator Brochure, version 16, 2017). PD-1 is a negative regulatory molecule that is expressed transiently following T-cell activation and on chronically stimulated T cells characterized by an "exhausted" phenotype.[8] Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. Nivolumab is approved for use in multiple countries including the United States (US, Dec-2014), the European Union (EU, Jun-2015), and Japan (Jul-2014).

1.2.1.1 Nonclinical Studies of Nivolumab

Nivolumab has been shown to bind specifically to the human PD-1 receptor and not to related members of the CD28 family.[17] Nivolumab inhibits the interaction of PD-1 with its ligands, PD-L1 and PD-L2, resulting in enhanced T-cell proliferation and interferon-gamma (IFN-γ) release in vitro.[18] Nivolumab binds with high affinity to activated human T-cells expressing cell surface PD-1 and to cynomolgus monkey PD-1.[17] In a mixed lymphocyte reaction (MLR), nivolumab promoted a reproducible concentration-dependent enhancement of IFN-γ release.[17]

In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, nivolumab was well tolerated at doses up to 50 mg/kg, administered weekly for 5 weeks, and at doses up to 50 mg/kg, administered twice weekly for 27 doses. While nivolumab alone was well tolerated in cynomolgus monkeys, combination studies have highlighted the potential for enhanced toxicity when combined with other immunostimulatory agents, such as ipilumumab (Investigator Brochure, version 16, 2017).

In addition, an enhanced pre- and postnatal development (ePPND) study in pregnant cynomolgus monkeys with nivolumab was conducted. Administration of nivolumab at up to 50 mg/kg 2QW was well tolerated by pregnant monkeys; however, nivolumab was determined to be a selective developmental toxicant when administered from the period of organogenesis to parturition at ≥ 10 mg/kg (area under the concentration-time curve [AUC] from time zero to 168 hours [AUC (0-168 h)] 117,000 μg•h/mL). Specifically, increased developmental mortality (including late gestational fetal losses and extreme prematurity with associated neonatal mortality) was noted in the absence of overt maternal toxicity. There were no nivolumab-related changes in surviving infants tested throughout the 6-month postnatal period. Although the cause of these pregnancy failures was undetermined, nivolumab-related effects on pregnancy maintenance are consistent with the established role of PD-L1 in maintaining fetomaternal tolerance in mice.[19]

1.2.1.2 Clinical Development of Nivolumab

The pharmacokinetics (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.

Clinical activity of nivolumab has been observed in patients with melanoma, NSCLC, SCLC, head and neck cancer, RCC, urothelial cancer, and cHL. In addition, the combination of nivolumab and ipilimumab (anti-cytotoxic T lymphocyte associated antigen-4 [anti-CTLA-4]) in a phase 1/2 trial showed markedly enhanced clinical activity with an acceptable safety profile in melanoma [20-22] and NSCLC patients.[23]

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Nivolumab monotherapy is now 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. In addition, nivolumab has been approved for use in combination with ipilimumab for unresectable melanoma in multiple countries, including the US and EU.

Nivolumab is being investigated both as monotherapy and in combination with chemotherapy, targeted therapies, and other immunotherapies.

1.2.1.3 Pharmacokinetics (PK)

The PK of nivolumab was studied in subjects over a dose range of 0.1 to 10 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. The

geometric mean (% CV%) clearance (CL) was 9.5 mL/h (49.7%), geometric mean volume of distribution at steady state (Vss) was 8.0 L (30.4%), and geometric mean elimination half-life (t1/2) was 26.7 days (101%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 3-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. Additionally, nivolumab has a low potential for drug-drug interactions. The clearance of nivolumab increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1. A PPK analysis suggested no difference in CL of nivolumab based on age, gender, race, solid tumor type, baseline tumor size, and hepatic impairment.

Although ECOG status, baseline glomerular filtration rate (GFR), albumin, body weight, and mild hepatic impairment had an effect on nivolumab CL, the effect was not clinically meaningful. PPK analysis suggest that nivolumab CL in subjects with cHL was approximately 32% lower relative to subjects with NSCLC; however, the lower CL in cHL subjects was not considered to be clinically relevant as nivolumab exposure was not a significant predictor for safety risks for these patients. When nivolumab is administered in combination with ipilimumab, the CL of nivolumab was increased by 24%, whereas there was no effect on the clearance of ipilimumab. Additionally, PPK and exposure response analyses have been performed to support use of 240 mg Q2W dosing in addition to the 3 mg/kg Q2W regimen. A flat dose of nivolumab 240 mg Q2W was selected since it is identical to a dose of 3 mg/kg for subjects weighing 80 kg, the observed median body weight in nivolumab-treated cancer patients. Using a PPK model, the overall distributions of nivolumab exposures (Cavgss, Cminss, Cmaxss, and Cmin1) are comparable after treatment with either 3 mg/kg or 240 mg nivolumab. (Investigator Brochure, version 16, 2017).

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1.2.1.4 Clinical Efficacy

In early clinical trials, nivolumab monotherapy demonstrated clinical activity in multiple tumor types, including melanoma, renal cell carcinoma, and NSCLC.[24] In a multicenter phase I trial enrolling NSCLC, melanoma, renal cell carcinoma, castration-resistant prostate cancer, and colorectal cancer, radiographic response rate in advanced, previously treated NSCLC was 18% (14 of 76 patients).[25] In some cases, these responses were prolonged. For 8 of the 14 responding cases, responses

lasted ≥ 24 weeks; in 2 cases, responses lasted more than one year. In 7% of cases, stable disease lasted ≥ 24 weeks.

Response rates varied according to treatment dose, histology, and biomarkers. In the 1.0 mg/kg cohort, response rate was 6%. In the 3.0 mg/kg arm, response rate was 27%. In the 10.0 mg/kg arm, response rate was 20%. For squamous cases, response rate was 17% (9/54) [22% at the 3.0 mg/kg level], compared to 18% (13/74) [26% at the 3.0 mg/kg level] in non- squamous cases. For tumors negative for PD-L1 by immunohistochemistry, there were no radiographic responses (0/17). For PD-L1-positive tumors, response rate was 36% (9/25; P=0.006).[26]

While treatment in this study was overall well tolerated, there were instances of immune- related adverse events. The most common treatment-related adverse events included fatigue, rash, diarrhea, pruritus, decreased appetite, and nausea. Apparent immune-related adverse events included pneumonitis, vitiligo, colitis, hepatitis, hypophysitis, and thyroiditis. In total, grade 3 or 4 treatment-related adverse events occurred in 14% of patients. Pneumonitis occurred in 3% of patients (1% grade 3-4). There were 3 deaths attributed to pneumonitis (2 NSCLC, 1 colorectal cancer). In many cases, early pneumonitis was reversible with stopping treatment, initiating glucocorticoids, or both.

Nivolumab has also been given in combination with platinum doublet chemotherapy for advanced NSCLC. In a phase I trial dose de-escalation trial, 43 patients were treated with nivolumab plus either gemcitabine-cisplatin, pemetrexed-cisplatin, or carboplatin-paclitaxel.[27] No dose-limiting toxicities (DLTs) were observed with any combination when nivolumab was administered 10 mg/kg every 3 weeks. Grade 3 pneumonitis developed in 3 patients (7%). Other apparent immune-related grade 3-4 toxicities included rash, nephritis, and colitis.

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More recently, two phase 3 clinical trials (Checkmate 057[28] and Checkmate 017[29]) comparing nivolumab to single-agent docetaxel chemotherapy in previously treated advanced NSCLC have been conducted. Both trials have demonstrated improved overall survival with nivolumab compared to docetaxel.

The Checkmate 057 trial enrolled patients with non-squamous NSCLC; the trial met its primary endpoint of improving OS. In the unselected population, for patients receiving nivolumab (N=287), median overall survival (OS) was 12.2 months compared with 9.4 months for docetaxel (N=268) (HR 0.73, 96% CI 0.59-0.89, p=0.002). Fewer grade 3 to 5 adverse events were reported for nivolumab

(10%) when compared with docetaxel (54%). Clinical benefit was particularly evident for patients whose tumors had PD-L1 staining of 1% or more, with OS of 17.2 to 19.4 months compared with 8- 9 months for docetaxel (HR 0.59). Conversely, there did not appear to be a benefit for nivolumab over docetaxel in the PDL1-negative population (HR 0.9).[29] Treatment-related select adverse events observed included infusion-related reactions (3%; no grade 3-4), rash (9%; < 1% grade 3-4), pneumonitis (3%; 1% grade 3-4), ALT/AST increased (3%; < 1% grade 3-4), diarrhea (8%; 1% grade 3-4), and hypothyroidism (7%; no grade 3-4).

Checkmate 017 enrolled patients with squamous NSCLC and also met its primary endpoint of improving OS.[28] Patients were randomized to nivolumab (3 mg/kg IV over 60 minutes every 2 weeks) (n=135) versus standard of care docetaxel (75 mg/m^2 IV every 3 weeks) (n=137). In a prespecified interim analysis, compared to docetaxel, nivolumab resulted in a 41% reduction in the risk of death (HR 0.59; 95% CI 0.44-0.79; P<0.001). Median OS was 9.2 months in the nivolumab arm (95% CI, 7.3-13.3 months) and 6 months in the docetaxel arm (95% CI, 5.1-7.3 months). Notably, the trial included patients regardless of tumor PD-L1 status. In the nivolumab arm, the most common adverse reactions (reported in ≥ 20% of patients) were fatigue (50%), dyspnea (38%), musculoskeletal pain (36%), decreased appetite (35%), cough (32%), nausea (29%), and constipation (24%). Serious adverse events occurred in 59% of patients receiving nivolumab. The most frequent serious adverse events reported in ≥ 2% of patients were dyspnea, pneumonia, chronic obstructive pulmonary disease exacerbation, pneumonitis, hypercalcemia, pleural effusion, hemoptysis, and pain. Pneumonitis occurred in 7 patients (6%). There were five grade 3 cases, and two grade 2 cases. All patients discontinued nivolumab and experienced complete resolution following high-dose corticosteroids. Median time to onset of pneumonitis was 3.3 months (range 1.4- 13.5 months). Overall, nivolumab was discontinued due to adverse events in 27% of patients, and 29% of patients receiving nivolumab had a drug delay for an adverse event. With at least 10 months of minimum follow up for all patients, the confirmed objective response rate (ORR), the study's primary endpoint, was 15% (95% CI, 9-22%), of which all were partial responses. Median time to onset of response was 3.3 months (range 1.7-8.8 months) after treatment initiation. Among responders, 67% had ongoing responses with durability of response ranging from 1.9+ to 11.5+ months. Among this cohort, 59% had durable responses of ≥ 6 months.

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 (Investigator Brochure, version 16, 2017).

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. The most advanced combination under development is nivolumab in combination with ipilimumab, which is approved in subjects with unresectable or metastatic melanoma, and being studied in multiple tumor types. Results to date suggest that the safety profile of nivolumab in combination with ipilimumab is consistent with the mechanisms of action of nivolumab and ipilimumab. The nature of the AEs is similar to that observed with either agent used as monotherapy; however, both frequency and severity of most AEs are increased with the combination.

1.2.1.5 Biomarker studies

The clinical use of monoclonal antibodies to T-cell inhibitory receptors has provided transformative information on the nature of the immune system and cancer. An emerging picture suggests that endogenous immune responses can mediate effective tumor regression and/or improved survival even in patients with large volume tumors resistant to other forms of therapy. It is not yet clear what factors determine responses and which components of the immune system are needed for this to occur. It seems likely that both memory helper and effector T cells would be needed to sustain long-term responses. Understanding the relationships of the tumor, cellular infiltrate, and immunologic milieu surrounding each tumor is key.

The effect of tumor PD-L1 expression on treatment response to anti-PD-1 targeted immunotherapy is a key focus of ongoing investigation. The observation that tumor PD-L1 expression may be prognostic in general lung cancer populations—but not among cases treated with

radiation or chemotherapy, further suggests that baseline assessment of this biomarker may not adequately define the target population most likely to benefit. Nevertheless, these results cannot be extrapolated to this clinical trial due to important clinical and biologic differences between populations and treatment paradigms.

In Checkmate 032, PD-L1 expression was assessable in 148 (69%) of 216 patient specimens, of which 39 (27%) were provided as fresh biopsies and 109 (74%) were archived specimens. 25 (17%) had 1% or greater PD-L1 expression, and seven (5%) had 5% or greater PD-L1 expression. In a pre-planned exploratory analysis of the nivolumab 3 mg/kg, nivolumab 1 mg/kg plus ipilimumab 3 mg/kg, and nivolumab 3 mg/kg plus ipilimumab 1 mg/kg cohorts, tumor responses occurred in patients irrespective of PD-L1 expression.[30]

For these reasons, this trial does not restrict enrollment to PD-L1-positive SCLC. To investigate the association between this biomarker and clinical outcomes, we will correlate baseline tumor PD-L1 expression with clinical outcomes in this trial.

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Tumor mutational burden (TMB) is emerging as an independent biomarker predictive of responses with immunotherapy. In Checkmate 032, patients with high TMB, determined by whole exome sequencing, had higher response rates, progression-free survival and overall survival compared to patients with low/medium TMB. However, optimization of TMB cutoffs and assay to use are still investigational in SCLC[56]

1.3 Immunotherapy in SCLC

Increasing evidence suggests that immune responses against SCLC cells make immunotherapy a viable approach. Preclinical data have shown that certain chemotherapeutic regimens may augment the immunotherapeutic response in lung cancer. In the M109 mouse model of lung cancer, treatment of animals with an anti-CTLA-4 monoclonal antibody in combination with chemotherapy such as gemcitabine, etoposide, and ixabepilone, revealed synergistic anti-tumor effects. Furthermore, after combination treatment with CTLA-4 blockade and chemotherapy, animals rejected a subsequent rechallenge, suggesting the development of a protective immune response in this model.[31,32] This may suggest that chemotherapy may improve the effect of CTLA-4 blockade.

Early studies have shown promising efficacy of immune checkpoint therapy in the second-line setting in SCLC after prior platinum-based chemotherapy. In CheckMate 032, 216 patients were enrolled and treated with nivolumab on a variety of different schedules. Responses and stable disease were seen in all treatment cohorts. A 10% response rate was seen in patients receiving nivolumab at 3 mg/kg, 23% response rate was noted in patients receiving nivolumab at 1 mg/kg plus ipilimumab at 3 mg/kg, followed by nivolumab at 3 mg/kg maintenance and 19% response rate in patients receiving nivolumab 3

mg/kg plus ipilimumab 1 mg/kg.[30] In a post-hoc analysis in patients treated with a platinum agent as a first-line treatment, objective responses were achieved in patients with both platinum- sensitive and platinum-resistant disease. Median overall survival was 4·4 months in the nivolumab 3 mg/kg cohort, 7·7 months in the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg cohort, and 6·0 months in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg cohort. 1-year overall survival was 33% for the nivolumab 3 mg/kg cohort, 43% for the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg cohort, and 35% for the nivolumab 3 mg/g plus ipilimumab 1 mg/kg cohort. Grade 3 or 4 treatment-related adverse events occurred in 13 (13%) patients in the nivolumab 3 mg/kg cohort, 18 (30%) in the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg cohort, and ten (19%) in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg cohort; the most commonly reported grade 3 or 4 treatment-related adverse events were increased lipase (none *vs* 5 [8%] *vs* none) and diarrhea (none *vs* 3 [5%] *vs* 1 [2%]). No patients in the nivolumab 1 mg/kg plus ipilimumab 1 mg/kg cohort had a grade 3 or 4 treatment-related adverse event. Six (6%) patients in the nivolumab 3 mg/kg group, seven (11%) in the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg group, and four (7%) in the nivolumab 3 mg/kg plus ipilimumab 1 mg/kg group discontinued treatment due to treatment-related adverse events. Two patients who received nivolumab 1 mg/kg plus ipilimumab 3 mg/kg died from treatment-related adverse events (myasthenia gravis and worsening of renal failure), and one patient who received nivolumab 3 mg/kg plus ipilimumab 1 mg/kg died from treatment-related pneumonitis. Two patients had grade 2 limbic encephalitis: one in the nivolumab 3 mg/kg cohort (reported as not treatment-related by investigator) and one in the nivolumab 1 mg/kg plus ipilimumab 3 mg/kg cohort (reported as treatment-related by investigator); both events resolved with immunosuppressive treatment. One patient in the nivolumab 3 mg/kg cohort had grade 4 limbic encephalitis (reported as treatment- related by investigator) that did not resolve with intravenous immunoglobulin and corticosteroid treatment. Treatment-related pneumonitis occurred in eight patients and resolved in six of eight patients with treatment. The outcome was unknown for one patient, and one patient died. In summary, these findings showed that nivolumab and nivolumab in combination with ipilimumab provide clinically meaningful activity with durable responses and with manageable safety profile, but both frequency and severity of most AEs are increased with the combination. These promising results led the National Comprehensive Cancer Network® to add both nivolumab monotherapy and nivolumab plus ipilimumab as potential treatment options in second-line SCLC while awaiting the results of ongoing confirmatory trials with these and other immune checkpoint inhibitors.[33,34]

Additionally, ipilimumab has been studied in combination with chemotherapy in the first-line setting.[35,36] In the phase 2 setting, ipilimumab in combination with paclitaxel and carboplatin was investigated in patients with ED-SCLC. One hundred thirty patients with treatment-naive ED-SCLC were randomized to 1 of 3 treatment arms: 1) concurrent ipilimumab (ipilimumab plus chemotherapy for 4 cycles followed by 2 cycles of chemotherapy plus placebo), 2) phased ipilimumab (chemotherapy plus placebo for 2 cycles followed by chemotherapy plus ipilimumab for 4 cycles), or 3) chemotherapy plus placebo. In the patients who received phased ipilimumab, an improvement was observed in progression-free survival based on immune- related response criteria (HR 0.64; P=0.03), with a trend for improved overall survival (12.5 months vs 9.1 months). No improvement in PFS (HR=0.93; P=0.37) or OS (HR=0.75; P=0.13) occurred.

The common AEs seen during the study that are typically associated with paclitaxel/carboplatin, including alopecia, fatigue, nausea and peripheral neuropathy, were generally unaffected by the addition of ipilimumab. Consistent with previous experience from other studies, the most common irAEs involved skin (rash and pruritus) and gastrointestinal tract (diarrhea), and occurred more frequently in the ipilimumab-containing arms. Treatment-related AEs, irAEs and laboratory abnormalities were mostly grade 1/2. Overall rates of treatment-related grade 3/4 AEs appeared higher for ipilimumab-containing regimens compared with the control, as were the occurrence of alanine aminotransferase and aspartate aminotransferase elevations. Most grade 3/4 irAEs were managed by the protocol-specified treatment guidelines including close patient follow-up and the early administration of systemic corticosteroids. Overall, in this phase 2 trial, the combination of ipilimumab plus paclitaxel/carboplatin exhibited an acceptable safety profile in ED-SCLC patients.

In the largest randomized phase III study in patients with ED-SCLC, patients were randomly assigned at a ratio of 1:1 to receive etoposide and platinum (cisplatin or carboplatin) plus ipilimumab 10 mg/kg or placebo every 3 weeks for a total of four doses each in a phased induction schedule (chemotherapy in cycles one to four; ipilimumab or placebo beginning in cycle three up to cycle six), followed by ipilimumab or placebo maintenance every 12 weeks. Primary end point was overall survival (OS) among patients receiving at least one dose of blinded study therapy. Ipilimumab in combination with carboplatin and etoposide did not result in improvement in OS versus etoposide and platinum. Of note, no new or unexpected adverse events were observed[37], and a majority of grade 2 to 4 immune-related events resolved.[35] It is unclear why ipilimumab did not confer additional benefit over etoposide and platinum. One possible explanation is that without corresponding T-cell activation in the tumor microenvironment, ipilimumab monotherapy, which stimulates peripheral T-cell activation, may not be effective in mounting a sufficiently strong antitumor response in ED-SCLC.

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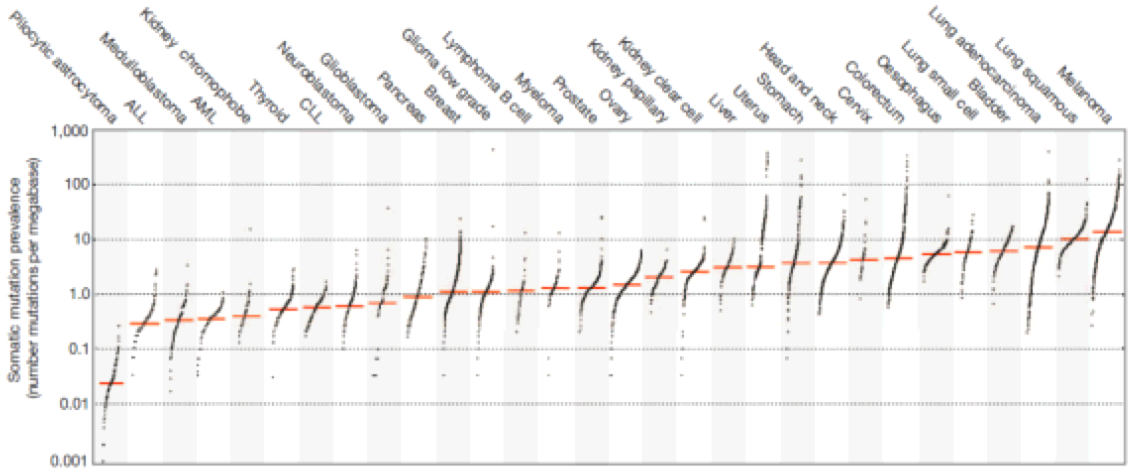
1.4 Rationale for the combination

Increasing evidence suggests that the antitumor activity of chemotherapy is mediated not only though cytotoxic effects, but also through immunological effects, including reducing T-regulatory cell activity and enhancing cross-presentation of tumor antigens.[38-40] It has also been hypothesized that decreasing tumor burden through chemotherapy decreases the immunosuppressive properties of tumor and creates an environment better suited for T-cell activation.[41]

In addition, in the vast majority of patients, the development of SCLC is associated with tobacco exposure.[42,43] This combined with frequent *TP53* mutation (>75-90% pf SCLCs),[44,45] results in an aggressive, highly complex disease at the molecular level with a large number of mutations present in each tumor.[46] A number of studies have suggested that tumor mutational burden is associated with benefit from immunotherapy.[47,48] Presumably, increased mutational burden results in increased tumor antigenicity, thereby priming the tumor for immune attack. As shown in Figure 1 below, SCLC carries one of the highest mutational burdens of any malignancy. In this figure, each dot represents a sample, the red horizontal lines represent median numbers of mutations, and the vertical axis (log scale) shows the number of mutations per megabase.

Figure 1. Mutational burden by malignancy



Given the rapid progression and high tumor burden associated with SCLC, combining chemotherapy with nivolumab is the favored approach. This will allow time required for an immune response to translate into clinical antitumor activity.

The proposed study has the potential to advance the management strategy in SCLC if it results in improved clinical outcome. A positive outcome in this phase II evaluation will provide a strong rationale to conduct a large definitive phase III trial of this novel combination in SCLC.

Hypothesis: We hypothesize that the combination of nivolumab with platinum-etoposide chemotherapy will result in improved progression-free survival in patients with extensive-stage SCLC without concomitant increased toxicity.

1.5 Correlatives Background

The need for biomarkers for identification of a suitable patient population for this type of therapy is now pressing.[49]

1.5.1 Optional Blood Collection for Blood Biomarkers

Circulating tumor DNA quantification and sequencing: We will collect peripheral blood at baseline, and cycle 2 day 1. Circulating tumor DNA will be assessed using Guardant 360 platform that will inform on allelic frequency of mutations, mutational burden and specific targeted exome sequencing and amplification of relevant cancer related genes.

Immunoregulatory proteins such as soluble PD-L1, IL-10, IL-6, IL-8, MIP-1 alpha, MCP-1, TNF-alpha, ICAM-1, IL-1ra, MMP-3, AAT, CRP, vWF, RANTES, TIMP-1, TNFR2, IP-10, MCP-2, MIG, IL-2 using multiplex immunoassay will be performed.

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Additional biomarkers will be considered depending on evolving science in SCLC.

2. Objectives

2.1 Primary Endpoints

2.1.1 To evaluate the progression-free survival (PFS) of patients with ED-SCLC treated with cisplatin/carboplatin and etoposide (CE) or CE with nivolumab (CEN) as front-line treatment.

2.2 Secondary Endpoints

2.2.1 To estimate overall survival of patients with ED-SCLC treated with cisplatin/carboplatin and etoposide (CE) or CE with nivolumab (CEN) as front-line treatment.

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2.2.2 To assess best overall response rate after treatment with CE with or without nivolumab as first line treatment

2.2.3 To evaluate the toxicity profile of Nivolumab with CE

2.3 Exploratory objectives

2.3.1 To evaluate immune biomarkers and biomarkers correlatives

2.3.2 To evaluate serial circulating tumor DNA and explore whether clinical outcome is associated with fluctuations in DNA levels following the administration of therapy.

3. Selection of Patients

Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: CTEP Policy does not allow for the issuance of waivers to any protocol specified criteria (http://ctep.cancer.gov/protocolDevelopment/policies_deviations.htm). Therefore, all eligibility criteria listed in Section 3 must be met, without exception. The registration of individuals who do not meet all criteria listed in Section 3 can result in the participant being censored from the analysis of the study, and the citation of a major protocol violation during an audit. All questions regarding clarification of eligibility criteria must be directed to the Group's Executive Officer (EA.ExecOfficer@jimmy.harvard.edu) or the Group's Regulatory Officer (EA.RegOfficer@jimmy.harvard.edu).

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

3.1 Eligibility Criteria

_____ 3.1.1 Age ≥ 18 years

_____ 3.1.2 Patients must have histologically or cytologically confirmed extensive stage small cell lung cancer and must be a candidate for systemic therapy

NOTE: The extensive disease SCLC classification for this protocol includes all patients with disease sites not defined as limited stage. Limited stage disease category includes patients with disease restricted to one hemithorax with regional lymph node metastases, including hilar, ipsilateral and contralateral mediastinal, and/or ipsilateral supraclavicular nodes. Extensive disease patients are defined as those patients with extrathoracic metastatic disease, malignant pleural effusion, bilateral or contralateral supraclavicular adenopathy. Patients with locally recurrent SCLC who are not eligible for curative intent chemoradiation are eligible.

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Rev. Add4 _____ 3.1.3 Patients must have measurable disease based on RECIST 1.1 (see Section 6.1.2)

_____ 3.1.4 ECOG performance status 0 or 1 (see Appendix V)

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_____ 3.1.5 Patients must have acceptable organ and marrow function as defined below (these must be obtained ≤ 7 days prior to protocol registration)

_____ Absolute neutrophil count ≥ 1,500/mm^3

ANC:_____ Date of Test:_____

_____ Platelets ≥ 100,000/mm^3

Platelet:_____ Date of Test:_____

_____ Leukocytes ≥ 3000/mm^3

Leukocytes:_____ Date of Test:_____

_____ Hemoglobin ≥ 9 g/dL

Hemoglobin: _____Date of Test:_____

_____ Total bilirubin ≤ 1.5 X institutional upper limit of normal (ULN) (except subjects with Gilbert Syndrome, who must have total bilirubin < 3 mg/dL)

Bilirubin:_____ Date of Test:_____

_____ AST (SGOT) and ALT (SGPT) ≤ 3 X institutional upper limit of normal (ULN) (≤ 5 X ULN if LFT elevations due to known liver metastases)

ALT:_____ Institutional ULN:_____

Date of Test:_____

AST:_____Institutional ULN:_____

Date of Test:_____

_____ Serum creatinine ≤ 1.5 x ULN or calculated creatinine clearance > 50 mL/min (using the Cockcroft-Gault formula)

Serum creatinine _____Date of Test:_____

or

Creatinine clearance:_____ Date of Test:_____

_____ 3.1.6 Patients are eligible if CNS metastases are adequately treated and neurological symptoms have returned to baseline or are controlled for at least 2 weeks prior to enrollment. In addition, subjects must be either off corticosteroids, or on a stable or decreasing dose of ≤ 10 mg daily prednisone (or equivalent). Patients with untreated CNS metastases are eligible if they are not symptomatic and the lesions are less than 1 cm in size.

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_____ 3.1.7 Patients cannot have had prior chemotherapy or biologic therapy for extensive stage small cell lung cancer for front line treatment. Patients receiving prior whole brain radiation cannot register within 7 days after completion of radiation and must have resolved adverse events attributed to radiation to ≤ grade 1. A 1-week washout is permitted for palliative radiation (≤ 2 weeks of radiotherapy) to non-CNS disease.

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_____ 3.1.8 Patients who have received prior chemoradiation treatment with chemotherapy regimen including cisplatin or carboplatin/etoposide for

limited-stage SCLC are eligible if treated with curative intent at least 6 months since last treatment from diagnosis of extensive-stage SCLC.

_____ 3.1.9 Patients may not be receiving any other investigational agents while on study.

_____ 3.1.10 Patients must not have history of allergic reactions attributed to compounds of similar chemical or biologic composition to nivolumab or other agents used in the study.

Rev. Add4 _____ 3.1.11 Women must not be pregnant or breast-feeding. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with the agents used in this study, breastfeeding must be discontinued or the subject is not eligible for the study.

Rev. Add1 All females of childbearing potential must have a blood test or urine study, with a minimum sensitivity 50mIU/L or equivalent units of HCG, within 14 days prior to registration to rule out pregnancy. A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e. has had menses at any time in the preceding 24 consecutive months).

Female of childbearing potential? _____ (Yes or No)

Date of blood test or urine study: _____

Rev. Add4 _____ 3.1.12 Women of childbearing potential (WOCBP) and males who are sexually active with WOCBP must use accepted and effective method(s) of contraception or abstain from sexual intercourse for at least one week prior to the start of treatment, and continue for 5 months after the last dose of protocol treatment for women of childbearing potential and 7 months after the last dose of protocol treatment for males who are sexually active with WOCBP.

_____ 3.1.13 No prior or current invasive malignancy (except non-melanomatous skin cancer, localized bladder and prostate cancer) unless disease free for a minimum of 2 years (for example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible);

_____ 3.1.14 No prior systemic treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways;

_____ 3.1.15 Patient must not have leptomeningeal disease

_____ 3.1.16 No patients with an active, known or suspected autoimmune disease and neuromuscular paraneoplastic syndromes including but not limited to myasthenia gravis, Lambert-Eaton myasthenic syndrome, limbic encephalitis, myositis, Guillain-Barré. Subjects 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.

_____ 3.1.17 No patients with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications within 7 days of randomization. Inhaled or topical steroids, and adrenal replacement steroid doses > 10 mg daily prednisone equivalent, are permitted in the absence of active autoimmune disease.

_____ 3.1.18 No patients with interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity

_____ 3.1.19 Patients must NOT have uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, uncontrolled cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

_____ 3.1.20 HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with Nivolumab. In addition, these patients are at increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

_____ 3.1.21 Any positive test for hepatitis B virus or hepatitis C virus indicating acute or chronic infection, patients are excluded.

Rev. Add4 _____ 3.1.22 Patients are ineligible if they received a live, attenuated vaccine within 4 weeks before randomization

_____ 3.1.23 No history of severe hypersensitivity reaction to any monoclonal antibody or allergy to study drug components;

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

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4. Registration and Randomization Procedures

CTEP Investigator Registration Procedures

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

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

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

- Added to a site roster
- Assigned the treating, credit, consenting, or drug shipment (IVR only) tasks in OPEN
- Act as the site-protocol PI on the IRB approval

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

CTSU Registration Procedures

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

IRB Approval:

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

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

- Compliance with all protocol specific requirements.

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

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

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

Downloading Site Registration Documents:

Site registration forms may be downloaded from the EA5161 protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Either enter the protocol # in the search field at the top of the protocol tree, or
- Click on the By Lead Organization folder to expand
- Click on the ECOG-ACRIN link to expand, then select trial protocol EA5161
- Click LPO Documents, select the Site Registration documents link, and download and complete the forms provided.

Requirements For *EA5161* Site Registration:

- IRB approval (For sites not participating via the NCI CIRB; local IRB documentation and IRB-signed CTSU IRB Certification Form, Protocol of Human Subjects Assurance Identification/IRB Declaration of Exception Form, or combination is accepted)

Submitting Regulatory Documents

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

Regulatory Submission Portal: www.ctsu.org (members' area) → Regulatory Tab →Regulatory Submission

When applicable original documents should be mailed to:

CTSU Regulatory Office
1818 Market Street, Suite 3000
Philadelphia, PA 19103

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

Required Protocol Specific Regulatory Documents

1. Copy of IRB Informed Consent Document.

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

2. A. CTSU IRB Certification Form.
   Or
   B. Signed HHS OMB No. 0990-0263 (replaces Form 310).
   Or
   C. IRB Approval Letter

   NOTE: The above submissions must include the following details:

   - Indicate all sites approved for the protocol under an assurance number.
   - OHRP assurance number of reviewing IRB
   - Full protocol title and number
   - Version Date
   - Type of review (full board vs. expedited)
   - Date of review.
   - Signature of IRB official

Checking Your Site's Registration Status:

You can verify your site registration status on the members' section of the CTSU website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

NOTE: The status given only reflects compliance with IRB documentation and institutional compliance with protocol-specific requirements outlined by the Lead Network. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with the NCI or their affiliated networks.

Patient Enrollment

Patients must not start protocol treatment prior to registration.

Treatment should start within seven working days after registration.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at https://ctepcore.nci.nih.gov/iam) and a 'Registrar' role on either the LPO or participating organization roster. Registrars must hold a minimum of an AP registration type.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the

patient in the Rave Database. OPEN can be accessed at https://open.ctsu.org or from the OPEN tab on the CTSU members' side of the website at https://www.ctsu.org. To assign an IVR or NPIVR as the treating, crediting, consenting, drug shipment (IVR only), or investigator receiving a transfer in OPEN, the IVR or NPIVR must list on their Form FDA 1572 in RCR the IRB number used on the site's IRB approval.

Prior to accessing OPEN, site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes, including verifying availability of tumor tissue as per eligibility criteria.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

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

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

4.1 Protocol Number

4.2 Investigator Identification

- Institution and affiliate name
- Investigator's name

4.3 Patient Identification

- Patient's initials (first and last)
- Patient's Hospital ID and/or Social Security number
- Patient demographics
  - Gender
  - Birth date (mm/yyyy)
  - Race
  - Ethnicity
  - Nine-digit ZIP code
  - Method of payment
  - Country of residence

4.4 Eligibility Verification

Patients must meet all of the eligibility requirements listed in Section 3.

4.5 Stratification Factors

4.5.1 Gender (Male vs. Female)

4.5.2 LDH (≤ upper limits of normal vs. > ULN)

4.6 Additional Requirements

4.6.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

4.6.2 Pathological materials are to be submitted for future undefined laboratory research studies per patient consent as outlined in Section 10.

4.6.3 Peripheral blood specimens are to be submitted for defined laboratory research studies per patient consent as outlined in Section 10.

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4.6.4 Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS). To access Rave via iMedidata, the site user must have an active CTEP-IAM account (check at < https://ctepcore.nci.nih.gov/iam >) and the appropriate Rave role (Rave CRA, Read-Only, CRA, Lab Admin, SLA, or Site Investigator) on either the LPO or participating organization roster at the enrolling site. To the hold Rave CRA role or CRA Lab Admin role, the user must hold a minimum of an AP registration type. To hold the Rave Site Investigator role, the individual must be registered as an NPIVR or IVR. Associates can hold read-only roles in Rave.

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

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

4.7 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the EA5161 Forms Completion Guidelines.

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5. Treatment Plan

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5.1 Agent Administration

Treatment will be administered on an outpatient basis unless local institutional standard practice requires inpatient administration. No therapies (investigational or commercial agents) other than those described below may be administered with the intent to treat the patient's malignancy. Reported adverse events and potential risks for nivolumab, cisplatin or carboplatin, and etoposide are described in Sections 5.3 and 8. Appropriate dose modifications are described in Section 5.4. BSA should be recalculated if ≥ 10% weight loss.

Cycle Length (Cycles 1-4) = 3 weeks (21 days)

Maintenance Cycle Length (Cycles 5+) = 6 weeks (42 days)

NOTE: All treatment visits must occur +/- 3 days from the scheduled date unless otherwise noted. If scheduled dosing and study assessments are precluded because of a holiday, weekend, or other event, then dosing may be postponed to the soonest following date, with subsequent dosing continuing on a 21-day schedule during Cycles 1-4 or every 2 weeks during maintenance nivolumab. If treatment was postponed for fewer than 3 days, the patient can resume the original schedule.

Arm A Description (Nivolumab arm) Cycles 1-4* **					
Agent	**Pre-medications**; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Nivolumab ****		360 mg IV over 30 minutes	IV	Day 1	21 days (3 weeks)
Carboplatin*	Dexamethasone 5-HT3 antagonist Aprepitant or Fosaprepitant	AUC 5 or 6 IV over 30 to 60 minutes	IV	Day 1 after nivolumab infusion is completed	
Cisplatin*	Dexamethasone 5-HT3 antagonist Aprepitant or Fosaprepitant	75mg/m2 IV over 60 to 120 minutes	IV	Day 1 after nivolumab infusion is completed	
Etoposide	Dexamethasone 5-HT3 antagonist	100 mg/m2 IV over 60 to 120 minutes	IV	Days 1, 2, 3 after platinum infusion is completed	

Nivolumab is given first, followed by carboplatin/cisplatin, then etoposide.

* The decision to administer cisplatin or carboplatin is at the discretion of the treating physician. If the choice is made to administer carboplatin, starting dose of AUC 5 or 6 is at the discretion of the treating physician.

** Cisplatin or carboplatin and etoposide (CE) will be administered with standard of care pre-medications and pre/post hydration every 3 weeks.

*** A maximum of 4 cycles of platinum and etoposide will be given.

Rev. Add1

**** After 4 cycles of combination therapy in the investigational arm (Arm A), nivolumab only will be continued as maintenance therapy, **administered at 240 mg IV over 30 minutes every 2 weeks** until progressive disease, unacceptable toxicity, patient desire to discontinue study therapy or up to 2 years (or 50 doses) maximum.

Arm B Description (Standard arm) – Cycles 1-4* **					
Agent	**Pre-medications**; Precautions**	**Dose**	**Route**	**Schedule**	**Cycle Length**
Carboplatin*	Dexamethasone 5-HT3 antagonist Aprepitant or Fosaprepitant	AUC 5 or 6 IV over 30 to 60 minutes	IV	Day 1	21 days (3 weeks)
Cisplatin*	Dexamethasone 5-HT3 antagonist Aprepitant or Fosaprepitant	75mg/m2 IV over 60 to 120 minutes	IV	Day 1	
Etoposide	Dexamethasone 5-HT3 antagonist	100 mg/m2 IV over 60 to 120 minutes	IV	Days 1, 2, 3 after platinum infusion is completed	

Carboplatin/Cisplatin is given first, followed by etoposide.

* The decision to administer cisplatin or carboplatin is at the discretion of the treating physician. If the choice is made to administer carboplatin, starting dose of AUC 5 or 6 is at the discretion of the treating physician.

** Cisplatin or carboplatin and etoposide (CE) will be administered with standard of care pre-medications and pre/post hydration every 3 weeks.

*** A maximum of 4 cycles of platinum and etoposide will be given then the patient will proceed to observation until disease progression or non-protocol treatment regimen is initiated.

Rev. Add3

5.1.1 Radiation Therapy

Patients with good clinical response (i.e. stable or response) after 4 cycles of first line chemotherapy can receive prophylactic cranial radiation (PCI) or whole brain radiation (if patient initially had asymptomatic untreated brain metastatic disease that has not progressed) as per local standard of care. In the investigational arm, nivolumab will not be administered during 1 week before and after brain radiation treatment.

Thoracic radiation with the intent to eliminate residual disease (i.e. consolidation thoracic radiation) is not allowed following completion of 4 cycles of first-line chemotherapy. Palliative radiation is allowed in non-measurable sites of disease. A 1-week washout is permitted for palliative radiation (≤ 2 weeks of radiotherapy) to non-CNS disease.

Rev. Add1
Rev. Add4

5.2 Adverse Event Reporting Requirements

All toxicity grades described in this protocol and all reportable adverse events on this protocol will be graded using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

5.2.1 Purpose

Adverse event (AE) data collection and reporting, which are a required part of every clinical trial, are done so investigators and regulatory agencies can detect and analyze adverse events and risk situations to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

5.2.2 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of an agent in humans, whether or not considered agent related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is *clearly NOT related* to treatment.
Unlikely	The AE is *doubtfully related* to treatment.
Possible	The AE *may be related* to treatment.
Probable	The AE is *likely related* to treatment.
Definite	The AE is *clearly related* to treatment.

- **CAEPR (Comprehensive Adverse Events and Potential Risks List):** An NCI generated list of reported and/or potential AEs associated with an agent currently under an NCI IND. Information contained in the CAEPR is compiled from the Investigator's Brochure, the Package Insert, as well as company safety reports.
- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Expectedness:** Expected events are those that have been previously identified as resulting from administration of the agent. An adverse event is considered unexpected, for expedited reporting purposes, when either the type of event or the severity of the event is NOT listed in the protocol or drug package insert.
- **Hospitalization (or prolongation of hospitalization):** For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.
- **Life Threatening Adverse Event:** Any AE that places the subject at immediate risk of death from the AE as it occurred.

- **Serious Adverse Event (SAE):** Any adverse event occurring at any dose that results in **ANY** of the following outcomes:
  - Death
  - A life-threatening adverse event
  - Inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours).
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
  - A congenital anomaly/birth defect.
  - Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgement, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.
- **SPEER (Specific Protocol Exceptions to Expedited Reporting):** A subset of AEs within the CAEPR that contains a list of events that are protocol specific exceptions to expedited reporting. If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ONLY be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event

5.2.3 Mechanisms for Adverse Event Reporting

Routine reporting: Adverse events are reported in a routine manner at scheduled times during a trial using the Medidata Rave clinical data management system. Please refer to section 4 of the protocol for more information on how to access the Medidata Rave system and the EA5161 forms packet for instructions on where and when adverse events are to be reported routinely.

Expedited reporting: In addition to routine reporting, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care. The remainder of this section provides information and instructions regarding expedited adverse event reporting.

Rev. Add4

5.2.4 Expedited Adverse Event Reporting Procedure

Adverse events requiring expedited reporting will use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov.

For this study, all adverse events requiring expedited reporting must initially be reported PROMPTLY upon learning of the event on the Adverse Event Form in the appropriate Treatment Cycle folder in Medidata Rave, even if the reporting cycle has not ended yet. Once the adverse event is entered into Rave, the Rules Engine on the Expedited Reporting Evaluation Form will confirm whether or not the adverse event requires expedited reporting. The CTEP-AERS report must then be initiated directly

from the Expedited Reporting Evaluation Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. Once the event is reported in CTEP-AERS, ECOG-ACRIN, the NCI, and all appropriate regulatory agencies will be notified of the event in an expeditious manner.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (857-504-2900) – For Arm A and B
- the NCI (301-897-7497) – For Arm A
- the FDA (1-800-FDA-1088) – For Arm B

For this study, an electronic CTEP-AERS report MUST be initiated via Medidata Rave and submitted immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the NCI (301-897-7404) – For Arm A and FDA (1-800-332-0178) – For Arm B in the same timeframe.

CTEP Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.2.5 Determination of Reporting Requirements

Many factors determine the reporting requirements of each individual protocol, and which events are reportable in an expeditious manner, including:

- the phase (0, 1, 2, or 3) of the trial
- whether the patient has received an investigational or commercial agent or both
- the seriousness of the event
- the Common Terminology Criteria for Adverse Events (CTCAE) grade
- whether or not hospitalization or prolongation of hospitalization was associated with the event
- when the adverse event occurred (within 30 days of the last administration of investigational agent vs. ≥ 30 days after the last administration of investigational agent)
- the relationship to the study treatment (attribution)
- the expectedness of the adverse event

Using these factors, the instructions and tables in the following sections have been customized for protocol EA5161 and outline the specific expedited adverse event reporting requirements for study EA5161.

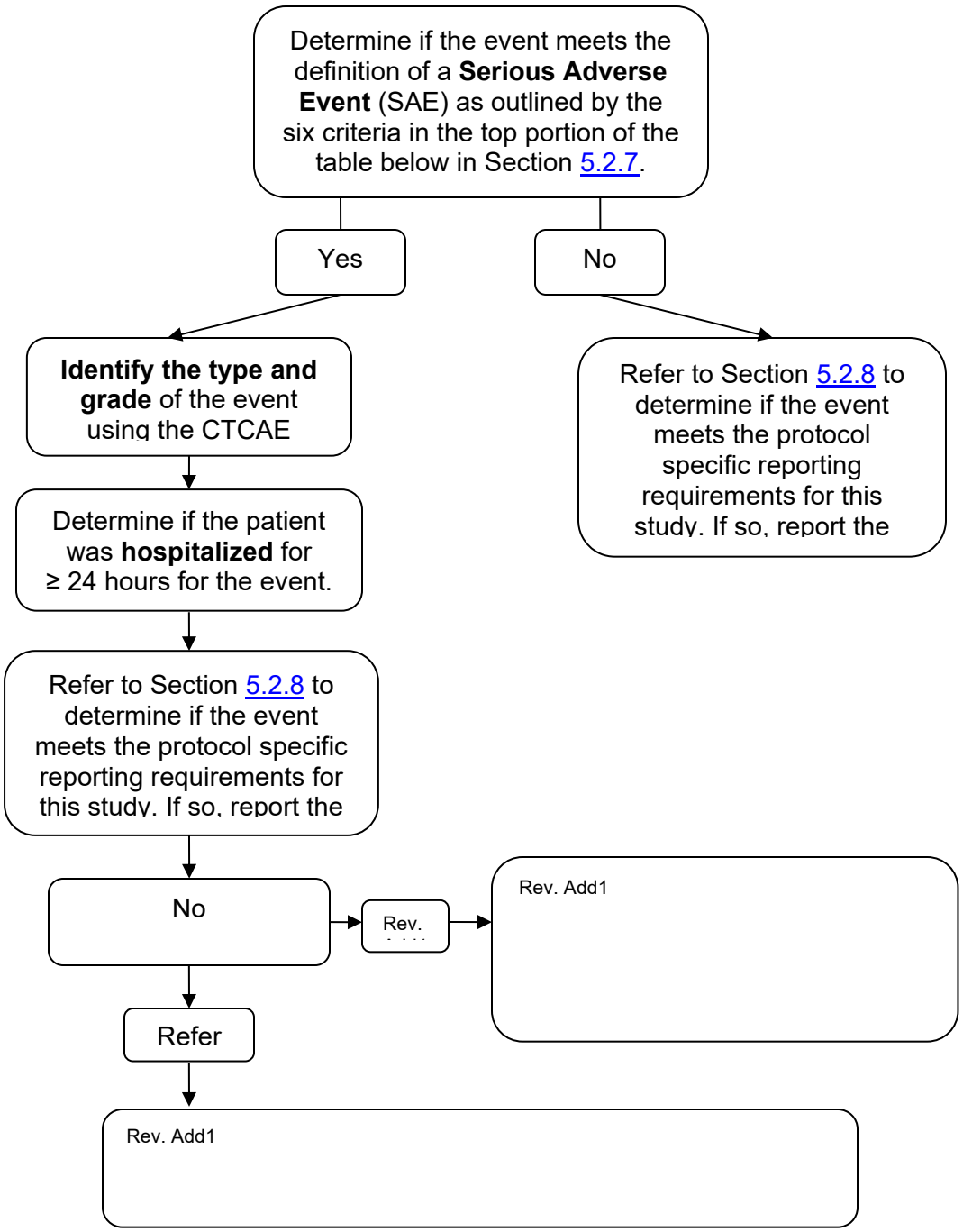
5.2.6 Steps to determine if an adverse event is to be reported in an expedited manner – Arm A

Rev. Add4

5.2.6.1 Guidelines for adverse events **OCCURRING WHILE ON PROTOCOL TREATMENT AND WITHIN 30 DAYS** of the last administration of the investigational agent(s).

NOTE: **For this study, all adverse events requiring expedited reporting must initially be reported PROMPTLY upon learning of the event on the Adverse Event Form in the appropriate Treatment Cycle folder in Medidata Rave, even if the reporting cycle has not ended yet.** Once the adverse event is entered into Rave, the Rules Engine on the Expedited Reporting Evaluation Form will confirm whether or not the adverse event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Expedited Reporting Evaluation Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. We encourage all sites to confirm the Rules Engine assessment with the charts below.

Rev. Add2


Determine if the event meets the definition of a **Serious Adverse Event** (SAE) as outlined by the six criteria in the top portion of the table below in Section 5.2.7.
Yes
No
Identify the type and grade of the event using the CTCAE
Refer to Section 5.2.8 to determine if the event meets the protocol specific reporting requirements for this study. If so, report the
Determine if the patient was **hospitalized** for ≥ 24 hours for the event.
Refer to Section 5.2.8 to determine if the event meets the protocol specific reporting requirements for this study. If so, report the
No
Rev.
Rev. Add1
Refer
Rev. Add1

Rev. Add4

5.2.6.2 Guidelines for adverse events **OCCURRING GREATER THAN 30 DAYS** after the last administration of the investigational agent(s).

NOTE: **For this study, all adverse events requiring expedited reporting must initially be reported PROMPTLY upon learning of the event on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave, even if the reporting cycle/period has not ended yet.** Once the adverse event is entered into Rave, the Rules Engine on the Expedited Reporting Evaluation Form will confirm whether or not the adverse event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Expedited Reporting Evaluation Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. We encourage all sites to confirm the Rules Engine assessment with the requirements outlined below.

If the adverse event meets the definition of a **Serious Adverse Event (SAE)** as outlined by the six criteria in the top portion of the table below in Section 5.2.7, AND has an attribution of possible, probably or definite, the following events require reporting as follows:

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

- All Grade 4 and Grade 5 AEs

NOTE: Any death occurring greater than 30 days after the last dose of investigational agent with an attribution of possible, probable or definite must be reported in CTEP-AERS accessed via Medidata Rave even if the patient is off study.

Expedited 10 calendar day reports for:

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

5.2.7 Expedited Reporting Requirements for Arm A on protocol EA5161

Investigational Agents: Nivolumab

Commercial Agents: Cisplatin, Carboplatin, Etoposide

When an investigational agent(s) is used in combination with a commercial agent(s), the combination is considered to be investigational and expedited reporting of adverse events follow the guidelines for investigational agents.

Late Phase 2 and Phase 3 Studies

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND *within 30 Days of the Last Administration of the Investigational Agent/Intervention.*[1]

NOTE: Footnote 1 instructs how to report serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention.

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

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

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

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

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

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

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

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" – The AE must initially be reported in CTEP-AERS accessed via Medidata Rave within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

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

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

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

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

Rev. Add4

5.2.8 Additional instructions, requirements and exceptions for protocol EA5161

Additional Instructions

- For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events in CTEP-AERS accessed via Medidata Rave, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.
- **Reporting a death on study:** A death occurring while on study or within 30 days of the last dose of treatment requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

  NOTE: A death due to progressive disease should be reported as a Grade 5 "Disease progression" under the System Organ Class (SOC) "General disorder and administration site conditions". Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted

EA5161 specific expedited reporting requirements:

- **Infusion Reactions:** Any grade 3 and higher infusion reaction must be reported in CTEP-AERS accessed via Medidata Rave according to the timeframes outlined in the AE table in Section 5.2.7.
- **Pregnancies:** Pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test, regardless of age or disease state) occurring while the female patient is on nivolumab, or within 28 days of the female patient's last dose of nivolumab, are considered immediately reportable events. The pregnancy, suspected pregnancy, or positive/ inconclusive pregnancy test must be reported in CTEP-AERS accessed via Medidata Rave within 24 hours of the Investigator's knowledge. Please refer to Appendix VI for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

EA5161 specific expedited reporting exceptions:

For study arm A, the adverse events listed below **do not** require expedited reporting:

- If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ONLY be reported

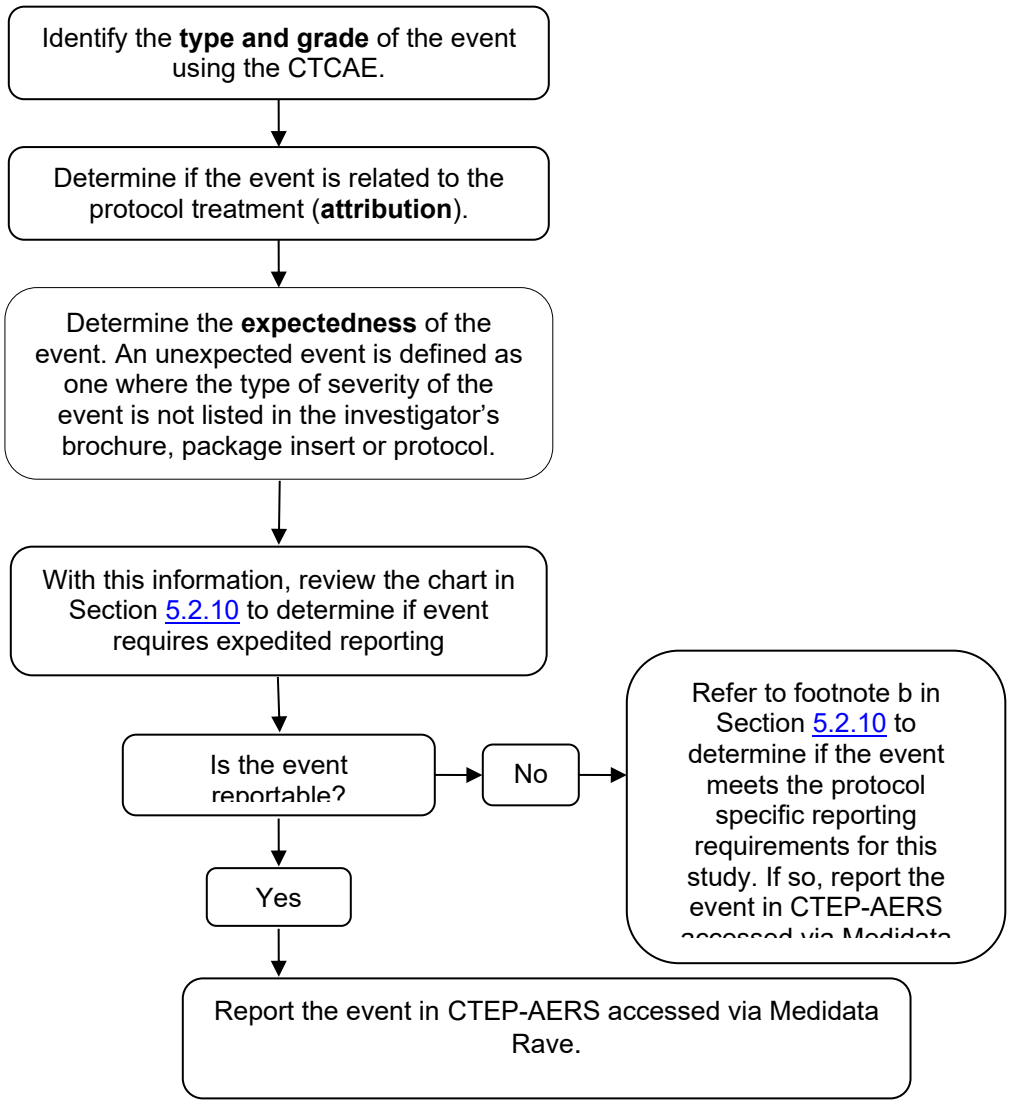
expeditiously if the grade being reported exceeds the grade listed in the parentheses next to the event

Rev. Add4

5.2.9 Steps to determine if an event is to be reported in an expedited manner – Arm B

NOTE: **For this study, all adverse events requiring expedited reporting must initially be reported PROMPTLY upon learning of the event on the Adverse Event Form in the appropriate Treatment Cycle folder in Medidata Rave, even if the reporting cycle/period has not ended yet**. Once the adverse event is entered into Rave, the Rules Engine on the Expedited Reporting Evaluation Form will confirm whether or not the adverse event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Expedited Reporting Evaluation Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. We encourage all sites to confirm the Rules Engine assessment with the charts below.

Rev. Add2


Identify the **type and grade** of the event using the CTCAE.
Determine if the event is related to the protocol treatment (**attribution**).
Determine the **expectedness** of the event. An unexpected event is defined as one where the type of severity of the event is not listed in the investigator's brochure, package insert or protocol.
With this information, review the chart in Section 5.2.10 to determine if event requires expedited reporting
Is the event reportable?
No
Refer to footnote b in Section 5.2.10 to determine if the event meets the protocol specific reporting requirements for this study. If so, report the event in CTEP-AERS accessed via Medidata
Yes
Report the event in CTEP-AERS accessed via Medidata Rave.

5.2.10 Expedited Reporting Requirements for Arm B on protocol EA5161

Commercial Agents: Cisplatin, Carboplatin, Etoposide

Expedited reporting requirements for adverse events experienced by patients on arm(s) with commercial agents only – Arm B

Attribution	Grade 4		Grade 5[a]		ECOG-ACRIN and Protocol-Specific Requirements
	Unexpected	Expected	Unexpected	Expected	
Unrelated or Unlikely			7 calendar days	7 calendar days	See footnote (b) for special requirements.
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	

7 Calendar Days: Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.

a A death occurring while on study or within 30 days of the last dose of treatment requires both routine and expedited reporting, regardless of causality. Attribution to treatment or other cause must be provided.

NOTE: A death due to progressive disease should be reported as a Grade 5 "Disease progression" under the System Organ Class (SOC) "General disorder and administration site conditions". Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

NOTE: Any death that occurs > 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the treatment must be reported within 7 calendar days of learning of the event.

b Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:

Serious Events: Any event following treatment that results in *persistent or significant disabilities/incapacities, congenital anomalies, or birth defects* must be reported in CTEP-AERS accessed via Medidata Rave within 7 calendar days of learning of the event. For instructions on how to specifically report these events, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case-by-case basis.

5.2.11 Other recipients of adverse event reports and supplemental data

DCTD/NCI, as the IND sponsor, is responsible for submitting all expedited AE reports for Arm A to the Food and Drug Administration.

DCTD/NCI will notify ECOG-ACRIN/pharmaceutical collaborator(s) of all AEs reported to the FDA. Any additional written AE information requested by DCTD/NCI or ECOG-ACRIN MUST be submitted to BOTH the DCTD/NCI and ECOG-ACRIN.

Adverse events determined to require expedited reporting must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

Rev. Add4

5.2.12 Second Primary Cancer Reporting Requirements

All cases of second primary cancers, including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS), that occur following treatment on NCI-sponsored trials must be reported to ECOG-ACRIN using Medidata Rave

- **A <u>second malignancy</u> is a cancer that is UNRELATED to any prior anti-cancer treatment (including the treatment on this protocol). Second malignancies require ONLY routine reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave confirming the diagnosis.
  3. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave.
- **A <u>secondary malignancy</u> is a cancer CAUSED BY any prior anti-cancer treatment (including the treatment on this protocol). Secondary malignancies require both routine and expedited reporting as follows:**
  1. Complete a Second Primary Form in Medidata Rave within 14 days.
  2. For this study: Report the diagnosis expeditiously by initially reporting it PROMPTLY upon learning of the secondary malignancy in the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle of Post Registration folder in Medidata Rave. Once the adverse event is entered into Rave, the Rules Engine on the Expedited Reporting Evaluation Form will confirm whether or not the adverse event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Expedited Reporting Evaluation Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website.

     Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, or c.) treatment related secondary malignancy
  3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
  4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: The ECOG-ACRIN Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the ECOG-ACRIN Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the ECOG-ACRIN Second Primary Form.

Rev. Add2

5.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Nivolumab (NSC 748726)

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

NOTE: If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ONLY be reported expeditiously if the grade being reported exceeds the grade listed in the parentheses next to the event. Since some arms on this protocol use multiple investigational agents, if an AE is listed on multiple SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.4, December 2, 2020[1]

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

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Colitis[3]		
		Colonic perforation[3]	
	Diarrhea		***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
		Enterocolitis	
		Gastritis	
		Mucositis oral	
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[4]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Injection site reaction		***Injection site reaction (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (immune-mediated hepatitis)	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[3]	
		Autoimmune disorder[3]	
		Cytokine release syndrome[5]	
		Immune system disorders - Other (GVHD in the setting of allotransplant)[3,6]	
		Immune system disorders - Other (sarcoidosis)[3]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[7]		
INVESTIGATIONS			
	Alanine aminotransferase increased[3]		***Alanine aminotransferase increased[3] (Gr 3)***
	Aspartate aminotransferase increased[3]		***Aspartate aminotransferase increased[3] (Gr 3)***
	Blood bilirubin increased[3]		***Blood bilirubin increased[3] (Gr 2)***
	CD4 lymphocytes decreased		***CD4 lymphocyte decreased (Gr 4)***
	Creatinine increased		
	Lipase increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		
	Platelet count decreased		
	Serum amylase increased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Hyperglycemia	***Hyperglycemia (Gr 2)***
		Metabolism and nutrition disorders - Other (diabetes mellitus with ketoacidosis)[3]	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
		Musculoskeletal and connective tissue disorder - Other (polymyositis)	
		Myositis	
		Rhabdomyolysis	
NERVOUS SYSTEM DISORDERS			
		Encephalopathy[3]	
		Facial nerve disorder[3]	
		Guillain-Barre syndrome[3]	
		Myasthenia gravis[3]	
		Nervous system disorders - Other (demyelination myasthenic syndrome)	
		Nervous system disorders - Other (encephalitis)[3]	
		Nervous system disorders - Other (meningoencephalitis)	
		Nervous system disorders - Other (meningoradiculitis)[3]	
		Nervous system disorders - Other (myasthenic syndrome)	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
		Reversible posterior leukoencephalopathy syndrome[3]	
RENAL AND URINARY DISORDERS			
		Acute kidney injury[3]	
		Renal and urinary disorders - Other (immune-mediated nephritis)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pleural effusion[3]		
	Pneumonitis[3]		
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)[3]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme[3]	
	Pruritus[3]		***Pruritus[3] (Gr 2)***
	Rash maculo-papular[3]		***Rash maculo-papular[3] (Gr 2)***

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Skin and subcutaneous tissue disorders - Other (bullous pemphigoid)	
	Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome)[3]		
	Skin hypopigmentation[3]		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	

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

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

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

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

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

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

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

Adverse events reported on Nivolumab trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Nivolumab caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Leukocytosis

CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Heart failure; Ventricular arrhythmia

EAR AND LABYRINTH DISORDERS - Vestibular disorder

EYE DISORDERS - Eye disorders - Other (iridocyclitis); Optic nerve disorder; Periorbital edema

GASTROINTESTINAL DISORDERS - Constipation; Duodenal ulcer; Flatulence; Gastrointestinal disorders - Other (mouth sores); Vomiting

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Pain

HEPATOBILIARY DISORDERS - Bile duct stenosis

IMMUNE SYSTEM DISORDERS - Anaphylaxis; Immune system disorders - Other (autoimmune thrombotic microangiopathy); Immune system disorders - Other (limbic encephalitis)

INFECTIONS AND INFESTATIONS - Bronchial infection; Lung infection; Sepsis; Upper respiratory infection

INVESTIGATIONS - Blood lactate dehydrogenase increased; GGT increased; Investigations - Other (protein total decreased); Lymphocyte count increased; Weight loss

METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Hypophosphatemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Musculoskeletal and connective tissue disorder - Other (musculoskeletal pain); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Myalgia; Pain in extremity

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Histiocytic necrotizing lymphadenitis)

NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Intracranial hemorrhage

PSYCHIATRIC DISORDERS - Insomnia

RENAL AND URINARY DISORDERS - Hematuria; Renal and urinary disorders - Other (tubulointerstitial nephritis)

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchospasm; Cough; Dyspnea; Hypoxia

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Pain of skin; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (rosacea)

VASCULAR DISORDERS - Flushing; Hypertension; Hypotension; Vasculitis

NOTE: Nivolumab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

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5.4 Dose Modifications

Dose modifications for platinum and etoposide are permitted for toxicity according to the prescribing information. Dose modification guidelines are provided below.

In order to ensure accurate determination of the duration of adverse events, patients must be evaluated at least once weekly (intervals should not be longer than every 7 days) while awaiting resolution of any adverse event whose duration may necessitate dose modification.

5.4.1 Cisplatin/Carboplatin and Etoposide Supportive Care

NOTE: Dose reductions for all events are permanent and should be for all subsequent cycles. Patients may receive a maximum of two chemotherapy dose reductions. If a third chemotherapy dose reduction is required, the patient should discontinue chemotherapy protocol treatment. If different percentages of dose reductions for a specific drug are required because of two different types of toxicities, the greater percentage dose reduction should be undertaken.

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5.4.1.1 Hematologic Toxicity

Neutropenia and/or Thrombocytopenia

Granulocyte or platelet counts for Day 1: Based on counts within 3 days of the start of each cycle, give the following:

Granulocytes/mm^3		Platelets / mm^3	Cisplatin/carboplatin and etoposide
ANC ≥ 1,500	and	PLT ≥ 100,000	100%
ANC < 1,500	and/or	PLT < 100,000	Hold dose*

* Hold cisplatin/carboplatin and etoposide; repeat counts at least once weekly and reinstitute therapy at 100% when granulocytes ≥ 1,500/mm^3 and platelets ≥ 100,000/mm^3 if recovery within 7 days.

If cisplatin administered, reinstitute at 75% of the original dose if more than 7 days. If carboplatin administered, reinstitute carboplatin AUC with decrease by one dose level (i.e. starting dose of AUC 6 dose reduction 1= AUC 5), if more than 7 days.

If counts do not reach these levels within 3 weeks of the next scheduled treatment, discontinue chemotherapy protocol therapy.

Neutropenia or Febrile Neutropenia

For nadir neutropenia in the absence of fever or with fever that is successfully treated by oral antibiotics, there will be no dose adjustment. Filgrastim, sargramostim, or pegfilgrastim are allowed (for the next cycle of chemotherapy). Growth factors may be used in

accordance with American Society of Clinical Oncology (ASCO) and NCCN guidelines.

For treatment delays (hold both chemotherapy and nivolumab) due to chemotherapy toxicities of more than 7 days, both chemotherapy drugs, cisplatin and etoposide, should be dose reduced by 25%. If carboplatin administered, reinstitute carboplatin AUC with decrease by one dose level (i.e. starting dose of AUC 6 dose reduction 1= AUC 5), if more than 7 days.

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For neutropenic fever (ANC <1000/mm3 with a single temperature of >38.3 degrees C (101 degrees F) or a sustained temperature of ≥ 38 degrees C (100.4 degrees F) for more than one hour) requiring intravenous antibiotics, the doses of all chemotherapy drugs should be reduced by 25% for the next cycle. If carboplatin administered, reinstitute carboplatin AUC with decrease by one dose level (i.e. starting dose of AUC 6 dose reduction 1= AUC 5), if more than 7 days. If counts do not recover within 3 weeks, discontinue chemotherapy protocol therapy.

Thrombocytopenia

For grade 4 nadir platelet count decrease (platelets < 25,000 mm^3), the dose of all chemotherapy drugs should be reduced by 25% from the previous dose for the next cycle. If carboplatin administered, reinstitute carboplatin AUC with decrease by one dose level (i.e. starting dose of AUC 6 dose reduction 1= AUC 5), if more than 7 days. If counts do not recover within 3 weeks, discontinue chemotherapy protocol therapy.

Anemia

No dose reductions will be made for anemia. Patients should be supported per the treating physician's discretion. The use of blood transfusions for anemia will be allowed as indicated. The use of growth factors for anemia is not permitted during cycle 1 for patients and may be use for cycle 2 (please refer to supportive care guidelines in Section 5.5).

5.4.1.2 Gastrointestinal Toxicity, Nausea and Vomiting

All patients should receive antiemetics* to prevent nausea and vomiting. Specific antiemetic therapy is left to the discretion of the treating physician (steroids and 5-HT3 antagonists should be used). If vomiting is severe, consider hospital admission and/or use of aprepitant if possible. Do not modify chemotherapy doses, until anti-emetics have been maximally optimized.

*Aprepitant, when given once daily for 14 days as a 100 mg capsule with an oral contraceptive containing 35 mcg

of ethinyl estradiol and 1 mg of norethindrone, decreased the AUC of ethinyl estradiol by 43% and decreased the AUC of norethindrone by 8%. Women of childbearing potential using pregnancy contraception that includes ethinyl estradiol should not receive Aprepitant for the treatment of nausea/delayed emesis. Patients may change to a different method of contraception if they wish to use Aprepitant.

5.4.1.3 Hepatic toxicity

This table only lists Etoposide dose modifications.

Bilirubin	Etoposide*
≤ 1.5 x ULN	100%
>1.5 – 3.0 x ULN	50%
> 3.0 x ULN - ≤ 5.0 x ULN	30%
> 5 x ULN	Hold**

* Please note that the % dose administered is based on the original starting dose of etoposide (100mg/m^2).

** For bilirubin greater than 5 X ULN it is recommended not to use etoposide for that cycle but this is at the discretion of the treating physician. If holding, repeat labs on a weekly basis for up to 3 weeks until total bilirubin is ≤ 5 x ULN. The cisplatin and nivolumab doses should also be held if etoposide is held so that all drugs are kept on the same schedule. If bilirubin improves within 3 weeks to ≤ 5 x ULN, then resume treatment and use reduced dose per table above. If bilirubin does not improve to ≤ 5 x ULN within 3 weeks, discontinue all protocol therapy.

A clinically relevant overlap in toxicity may arise between the immune-related hepatic toxicity attributed to nivolumab and hepatic toxicity attributed to etoposide. The management of hepatic toxicity should be guided by clinical judgment and an assessment of the most likely causative etiology, with special consideration given to the potential for immune-mediated hepatic toxicity. Nivolumab administration should be delayed for toxicities as indicated in the management algorithms (Appendix III) that in the opinion of the treating physician are related to nivolumab. Please refer to Section 5.4.2.2.

5.4.1.4 Nephrotoxicity (based on measured or calculated creatinine clearance)

Creatinine Clearance (ml/min)	Cisplatin*
≥ 60	100%
59 – 50	67%
< 50	0**

* Please note that the % dose administered is based on the original starting dose of cisplatin (75mg/m2).

**Only patients randomized to Arm A will receive Nivolumab. If serum creatinine clearance is < 50 ml/min on day 1 of the next cycle, delay the start of that cycle for up to 2 weeks (check creatinine at least weekly). If CrCl decrease persists beyond 2 weeks, skip cisplatin for that cycle and proceed with etoposide and nivolumab. NOTE: The etoposide and nivolumab doses will be held if cisplatin is held until a decision is made to skip cisplatin for the current cycle so that all drugs are kept on the same schedule. If the serum creatinine returns to ≥ 50 ml/min within 3 weeks of original hold, cisplatin may be reinstituted at 67% of the full dose during the next cycle (permanent dose reduction). A more aggressive hydration regimen (as tolerated by patient clinical state) should be instituted as well with all subsequent doses of cisplatin. If CrCl does not recover to ≥ 50 ml/min after 3 weeks, remove patient from all protocol therapy.

5.4.1.5 Hypomagnesemia

Hypomagnesemia is not an indication for stopping therapy. Oral or parenteral magnesium supplementation is indicated for serum magnesium levels < 1.5 mEq/L.

5.4.1.6 Nervous System Disorder (Neurologic Toxicity)

Grade	Cisplatin*
0-1	100%
2	75%**
3	0***

* Please note that the % dose administered is based on the original starting dose of cisplatin (75mg/m2).

** Patients with a grade 2 nervous system disorder (neurotoxicity) should hold all protocol treatment until recovery to grade 1 or less, then administer 75% dose. If grade 2 nervous system disorder (neurotoxicity) recurs with 75%, drug will be given at 50% upon resolution of nervous system disorder (neurotoxicity) to grade 1 or less. If grade 2 nervous system disorder (neurotoxicity) persists for 3 weeks, remove the patient from all protocol therapy.

*** Discontinue all protocol therapy for nervous system disorder (neurotoxicity) ≥ grade 3.

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5.4.1.7 Allergic Reactions

Discontinue infusion that has led to allergic reaction promptly if ≥ grade 3 anaphylaxis develops.

Suggested Management of Allergic Reaction:

In case of mild allergic symptoms (e.g., Grade 1 – systemic intervention not indicated; Grade 2 – oral intervention indicated), symptomatic treatment may be given (e.g., oral antihistamine or topical corticosteroids).

Patient experiencing significant allergic reaction should be managed according to local institutional standards. A combination of corticosteroids, antihistamines, nebulized

respiratory therapy with beta (2) agonists and isotonic fluid support should be employed as appropriate based on patient's clinical condition.

For Grade 3 or Grade 4 symptoms: (Grade 3: bronchospasm; hospitalization indicated for clinical sequelae; intravenous intervention indicated; Grade 4: life-threatening consequences; urgent intervention indicated):

Immediately discontinue infusion that has led to Grade 3 or Grade 4 allergic reaction. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration, 0.3 mg of a 1:1,000 solution for intramuscular administration, or 0.1 to 0.25 mg of a 1:10,000 solution slowly for IV administration, and/or diphenhydramine 50 mg (oral or IV) with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the Investigator is comfortable that the symptoms will not recur. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery from symptoms.

For Grade 3 or Grade 4 allergic reaction attributed to IV etoposide, it is acceptable to switch to oral etoposide, if clinically appropriate.

5.4.1.8 Ototoxicity

Remove patient from therapy for grade ≥ 3 ear and labyrinth disorder (ototoxicity).

5.4.1.9 Grade 3 or 4 Non-Hematologic Toxicity

If patient develops grade 3 or 4 non-hematologic toxicity attributed to protocol therapy but not detailed above [excluding the following: anorexia, fatigue and fever without grade 3 or 4 neutrophil count decrease (neutropenia)] hold all therapy. Therapy can be restarted if the toxicity has resolved to < grade 1 by the time of the next treatment. Doses of all chemotherapy should then be reduced by 25% (of the dose received during the previous cycle). If carboplatin administered, reinstitute carboplatin AUC with decrease by one dose level (i.e. starting dose of AUC 6 dose reduction 1= AUC 5). If chemotherapy is held for more than 3 weeks, remove the patient from all protocol therapy.

A clinically relevant overlap in toxicity may arise between the immune-related dermatologic and cardiac toxicities attributed to nivolumab and dermatologic and cardiac toxicities attributed to etoposide. The management of overlapping toxicities should be guided by clinical judgment and an assessment of the most likely causative etiology, with special consideration given to the potential

for immune-mediated toxicities. Nivolumab administration should be delayed for toxicities as indicated in the management algorithms (Appendix III) that in the opinion of the treating physician are related to nivolumab. Please refer to Section 5.4.2.2.

5.4.2 Nivolumab

There are no nivolumab dose modifications. Depending on toxicities, nivolumab will either be given at full dose, withheld, or discontinued.

NOTE: Nivolumab treatment may only be held for a maximum of 12 weeks for nivolumab-specific toxicity, otherwise the patient should be removed from all protocol therapy.

Grading of AEs is based on the NCI CTCAE.

If a patient discontinued nivolumab due to nivolumab-specific toxicities, chemotherapy may continue, if appropriate. Patient should be followed for assessment of the toxicities until the AEs resolve or are deemed irreversible.

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5.4.2.1 Management Algorithms for Nivolumab

Immuno-oncology (I-O) agents are associated with adverse events that can differ in severity and duration than adverse events caused by other therapeutic classes. Nivolumab is considered an immuno-oncology agent in this protocol. Management algorithms have been developed to assist investigators in assessing and managing the following groups of adverse events: Gastrointestinal, Renal, Pulmonary, Hepatic, Endocrinopathies, Skin, and Neurological. See Appendix III for the treatment algorithms.

Early recognition and intervention are recommended according to the management algorithms found in Appendix III. In addition, the Investigator Brochure (IB, version 16, 2017) includes ophthalmologic evaluations for any visual symptoms in order to evaluate for nivolumab related uveitis. Investigators should follow the algorithms in Appendix III for immune- related events.

NOTE: The algorithms are essential guides for AE management, but the guidance provided in these algorithms should not replace the investigator's medical judgment but should complement it.

For patients expected who require more than 4 weeks of corticosteroids or other immunosuppressants to manage an adverse event, consider the following recommendations: Antimicrobial/antifungal prophylaxis per institutional guidelines to prevent opportunistic infections such as Pneumocystis jiroveci and fungal infections.

Early consultation with an infectious disease specialist should be considered. Depending on the presentation, consultation with a pulmonologist for bronchoscopy or a gastroenterologist for endoscopy may also be appropriate.

In patients who develop recurrent adverse events in the setting of ongoing or prior immunosuppressant use, an opportunistic infection should be considered in the differential diagnosis.

Additional details on the safety of nivolumab, including results from clinical studies, are available in the IB (IB, version 16, 2017).

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

In places that there are differences from the algorithms regarding protocol directed drug modifications, please follow the protocol specific guidelines in this section.

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

ALL OTHER EVENTS	**Management/Next Dose for Nivolumab**
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1 OR baseline (exceptions as noted below)
Grade 3	Off protocol therapy (exceptions as noted below)
Grade 4	Off protocol therapy
Recommended management: As clinically indicated	

- Any grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment should go off protocol treatment
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued study drug dosing should go off protocol treatment.
- Any grade 3 or 4 drug-related laboratory abnormality (i.e. amylase, lipase) or electrolyte abnormality, that can be managed with electrolyte replacement,

hormone replacement, insulin or that does not require treatment does not require discontinuation.

Skin Rash and Oral Lesions	**Management/Next Dose for Nivolumab**
≤ Grade 1	No change in dose *
Grade 2	Hold* until Grade ≤ 1 or resolved. Resume at same dose level.
Grade 3	Hold* until ≤ Grade 1. Resume at same level at investigator discretion
Grade 4	Off protocol therapy
*Patients with purpuric or bullous lesions must be evaluated for vasculitis, Steven-Johnson syndrome, TEN, and autoimmune bullous disease including oral lesions of bullous pemphigus/pemphigoid. Pruritus may occur with or without skin rash and should be treated symptomatically if there is no associated liver or GI toxicity. Note skin rash typically occurs early and may be followed by additional events particularly during steroids tapering.	
Recommended management: AE management guidelines	

Liver Function AST, ALT, Bilirubin	**Management/Next Dose for Nivolumab**
≤ Grade 1	No change in dose
Grade 2	Hold until WNL or baseline. Resume at same dose level.
Grade 3	Off protocol therapy
Grade 4	Off protocol therapy
Continued treatment with active immune mediated hepatitis may exacerbate ongoing inflammation. Holding drug to evaluate LFT changes and early treatment are recommended. LFT changes may occur during steroid taper from other events and may occur together with other GI events including cholecystitis/pancreatitis.	
Recommended management: see Hepatic AE management algorithm	

Diarrhea/ Colitis	**Management/Next Dose for Nivolumab**
≤ Grade 1	No change in dose
Grade 2	Hold until baseline. No change in dose
Grade 3	Off protocol therapy.
Grade 4	Off protocol therapy
See GI AE Algorithm for management of symptomatic colitis. Patients with grade 2 symptoms but normal colonoscopy and biopsies may be retreated after resolution. Evaluation for all patients for additional causes includes *C. diff*, acute and self-limited infectious and foodborne illness, ischemic bowel, diverticulitis, and IBD.	
Recommended management: see GI AE management Algorithm	

Pneumonitis	**Management/Next Dose for Nivolumab**
≤ Grade 1	No change in dose
Grade 2	Hold dose pending evaluation. Resume no change in dose after pulmonary and/or ID consultation as needed.
Recurrent Grade 2 or Grade 3	Hold dose pending evaluation. Off protocol therapy.

Pneumonitis	Management/Next Dose for Nivolumab
Grade 4	Off protocol therapy
Distinguishing inflammatory pneumonitis is often a diagnosis of exclusion for patients who do not respond to antibiotics and have no causal organism identified including influenza. Most patients with respiratory failure or hypoxia will be treated with steroids. Bronchoscopy may be required and analysis of lavage fluid for lymphocytic predominance may be helpful. Patients with new lung nodules should be evaluated for sarcoid like granuloma. Please consider recommending seasonal influenza killed vaccine for all patients.	
Recommended management: See Pulmonary Adverse Event Management Algorithm	

Neurologic events	Management/Next Dose for Nivolumab
≤ Grade 1	No change in dose.
Grade 2	Hold dose pending evaluation and observation. Hold until ≤ Grade 1. Off protocol therapy per investigator discretion. Resume at same dose level for peripheral isolated n. VII (Bell's palsy).
Grade 3	Off protocol therapy
Grade 4	Off protocol therapy
Patients with any CNS events including aseptic meningitis, encephalitis, symptomatic hypophysitis, or myopathy, peripheral demyelinating neuropathy, cranial neuropathy (other than peripheral n. VII), Guillain-Barre Syndrome, myasthenia gravis should be off study.	
Recommended management: See Neurologic Adverse Event Management Algorithm	

Renal	Management/Next Dose for Nivolumab
≤ Grade 1	No change in dose
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Off protocol therapy.
Grade 4	Off protocol therapy.
Recommended management: See Renal Adverse Event Management Algorithm	

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5.4.2.2 Treatment of Nivolumab-Related Infusion Reactions

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

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

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

Remain at bedside and monitor subject until recovery from symptoms

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

If clinically appropriate, infusion rate may be slowed or interrupted and restarted at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely.

The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent, oral) and/or acetaminophen 325 to 1000 mg at least 30 minutes before additional nivolumab administrations, slowing infusion rate as above.

For Grade 2 symptoms: (Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs), and no further nivolumab administration should be considered at that visit.

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent, oral) and/or acetaminophen 325 to 1000 mg; remain at bedside and monitor patient until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If it is deemed clinically appropriate to restart, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely. If symptoms recur, re administer diphenhydramine 50 mg (oral or IV), and remain at bedside and monitor the patient until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF).

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

For Grade 3 or Grade 4 symptoms: (Severe reaction),

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

Grade 4 symptoms: (life-threatening consequences; urgent intervention indicated).

Nivolumab will be permanently discontinued

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

Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor patient until recovery from symptoms.

In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or topical or oral corticosteroids). Additional treatment prior to next dose as per guidelines above.

Please note that late occurring events including isolated fever and fatigue may represent the presentation of systemic inflammation. Please evaluate accordingly.

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5.5 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study. Supportive care (including IVF hydration) is not considered non-protocol therapy

The clinical tolerance of the patients, the overall tumor response, and the medical judgment of the investigator will determine if it is in the patient's best interest to continue or discontinue treatment. If treatment is discontinued due to any toxicity, the patient must be followed to monitor duration of toxicity, response and time to progression (even if non-protocol therapy is initiated). Suggested supportive care medications may be substituted at the discretion of the investigator based on drug availability.

Hyperalimentation may be used, but details must be clearly outlined on treatment forms.

Concomitant aminoglycoside antibiotic use should be avoided during cisplatin therapy until patient has fully recovered (i.e., at least 4 weeks from last dose of cisplatin).

The use of bisphosphonates or denosumab is allowed for patients with bone metastasis or hypercalcemia.

Systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalent) or other immunosuppressive medications are prohibited. Topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption) and adrenal replacement steroid doses > 10 mg daily prednisone are permitted. A brief (less than 3 weeks) course of corticosteroids for prophylaxis (eg, contrast dye allergy) or for treatment of non-autoimmune

conditions (eg, delayed-type hypersensitivity reaction caused by a contact allergen) or prevention of nausea/vomiting is permitted.

The use of erythropoiesis-stimulating agents (ESAs) is allowed if clinically indicated based on the recommendations by the American Society of Clinical Oncology (2010). For patients undergoing myelosuppressive chemotherapy who have a hemoglobin (Hb) level less than 10 g/dL, the ASCO Guideline Update Committee recommends that clinicians discuss potential harms (e.g., thromboembolism, shorter survival) and benefits (e.g., decreased transfusions) of ESAs and compare these with potential harms (e.g., serious infections, immune-mediated adverse reactions) and benefits (e.g. rapid Hb improvement) of RBC transfusions. If used, ESAs should be administered at the lowest dose possible and should increase Hb to the lowest concentration possible to avoid transfusions. Available evidence does not identify Hb levels of 10 g/dL either as thresholds for initiating treatment or as targets for ESA therapy. Starting doses and dose modifications after response or nonresponse should follow US Food and Drug Administration– approved labeling. ESAs should be discontinued after 6 to 8 weeks in nonresponders. ESAs should be avoided in patients with cancer not receiving concurrent chemotherapy, except for those with lower risk myelodysplastic syndromes.

G-CSF and pegylated G-CSF should be used in accordance with American Society of Clinical Oncology (ASCO) and NCCN guidelines. G-CSF and pegylated G-CSF may be used during all treatment cycles for patients for cycle 2 and beyond as indicated. These agents (G-CSF and pegylated G- CSF) may be used at the discretion of the investigator after neutropenia is documented, or prophylactically to reduce the chance of febrile neutropenia at all other times during the study. Growth factor use or dose reduction is only mandated, however, in the setting of prior febrile neutropenia.

The ASCO guidelines state, “even if febrile neutropenia has not occurred, the use of CSFs may be considered if prolonged neutropenia is causing excessive dose reduction or delay in chemotherapy. However, in the absence of clinical data supporting the maintenance of chemotherapy dose intensity, physicians should consider chemotherapy dose reduction as an alternative to the use of CSFs. There are inadequate data to know whether patients with neutropenia but no fever will benefit clinically from the initiation of a CSF at the time neutropenia is diagnosed; intervention with a CSF in afebrile neutropenic patients is not recommended. For the majority of patients with febrile neutropenia, the available data does not support the routine initiation of CSFs as adjuncts to antibiotic therapy. However, certain febrile neutropenic patients may have prognostic factors that are predictive of clinical deterioration, such as pneumonia, hypotension, multiorgan dysfunction (sepsis syndrome), or fungal infection. The use of CSFs together with antibiotics may be reasonable in such high risk patients, even though the benefits of administration under these circumstances have not been definitively proved (ASCO, 2013).”

Diarrhea may occur on either arm. Appropriate supportive measures including Imodium and/or Lomotil should be implemented immediately to prevent dehydration.

Hydration guidelines may be modified at the discretion of the treating physician provided adequate pre and post cisplatin hydration is achieved and renal function remains adequate. One suggested regimen consists of administering cisplatin in

250 cc to 1000 cc of IV fluids following adequate hydration and the establishment of adequate urinary output. It is suggested the pre-cisplatin hydration consist of NS at 500 cc/hr x 1 liter and post-cisplatin hydration consist of 1/2 NS + 10 meq KCl/liter + 1 gram magnesium sulfate/liter + 25 grams mannitol/liter at 500 cc/hr for at least one hour, followed by additional hydration at the discretion of the investigator.

Antiemetic therapy is critical for proper administration of cisplatin/carboplatin. The specific antiemetic regimen is at the discretion of the treating physician, provided adequate control is achieved. However, on the day of cisplatin therapy the investigator should use a steroid medication, a 5HT3 antagonist and NK1 antagonist such as fosaprepitant or aprepitant since cisplatin is highly emetogenic. One such regimen consists of 10 mg of dexamethasone and a high dose of a 5HT3 antagonist (such as 2 mg oral of 10 mcg/kg IV granisetron or 24 mg ondansetron or equivalent) and continuing with 4 days or dexamethasone or equivalent steroid and 4 days of scheduled anti- emetic such as a 5HT3 antagonist. If this regimen is ineffective, consideration of the long-acting 5HT3 antagonist palonosetron should be considered at the discretion of the investigator.

NOTE: Aprepitant should be used with caution in patients receiving concomitant medicinal products, including chemotherapy agents that are primarily metabolized through CYP3A4. Inhibition of CYP3A4 by aprepitant could result in elevated plasma concentrations of these concomitant medicinal products. The effect of aprepitant on the pharmacokinetics of orally administered CYP3A4 substrates is expected to be greater than the effect of aprepitant on the pharmacokinetics of intravenously administered CYP3A4 substrates.

Dexamethasone dose should be reduced by 50% when administered with aprepitant.

Patients are ineligible if administration of a live, attenuated vaccine within 4 weeks before randomization.

5.6 Duration of Therapy

Treatment may continue for up to 4 cycles of chemotherapy (CE) as described in Section 5.1. In the investigational arm (Arm A), nivolumab in combination with chemotherapy (CE) will be given for up to 4 cycles, followed by maintenance nivolumab for up to a total of 2 years (or 50 doses) of treatment with nivolumab as described in Section 5.1. Treatment may continue until one of the following criteria applies:

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Patients will receive protocol therapy unless:

- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the EA5161 Forms Packet.
- Patient withdraws consent.
- Patient experiences unacceptable toxicity.
- Non-protocol therapies are administered.
- Disease progression as defined in Section 6.

5.7 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression, even if non-protocol therapy is initiated, and for survival for 5 years from the date of registration.

6. Measurement of Effect

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6.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response every 6 weeks. All patients will be evaluated for response every 6 weeks for the first 6 months on study, every 8 weeks until 1 year on study, and then every 12 weeks after 1 year on study.

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

The following general principles must be followed:

1. To assess objective response, it is necessary to estimate the overall tumor burden at baseline to which subsequent measurements will be compared. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than four weeks before registration.
2. Measurable disease is defined by the presence of at least one measurable lesion.
3. All measurements should be recorded in metric notation by use of a ruler or calipers.
4. The same method of assessment and the same technique must be used to characterize each identified lesion at baseline and during follow-up.

6.1.1 Definitions

Evaluable for Objective Response

Only those patients 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 response. These patients will have their response classified according to the definitions stated below.

NOTE: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.

Evaluable Non-Target Disease Response

Patients 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 lesion assessment. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

6.1.2 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, as ≥ 10 mm with CT scan, or ≥ 10 mm

with calipers by clinical exam. All tumor measurements must be recorded in millimeters.

NOTE: Previously irradiated lesions can only be considered as measurable disease if disease progression has been unequivocally documented at that site since radiation.

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. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable. Non-measurable also includes lesions that are < 20 mm by chest x-ray.

NOTE: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

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 of the 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 or absence of unequivocal progression of each should be noted throughout follow-up.

6.1.3 Methods for Evaluation of Disease

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

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

Clinical Lesions

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

Chest X-ray

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

Conventional CT and MRI

This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

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 must 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.

PET-CT

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

Ultrasound

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

Endoscopy, Laparoscopy

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

Tumor Markers

Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [JNCI 96:487-488, 2004; J Clin Oncol 17, 3461-3467, 1999; J Clin Oncol 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [JNCI 92:1534-1535, 2000].

Cytology, Histology

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

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

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.

6.1.4 Response Criteria

6.1.4.1 Evaluation of Target Lesions

Complete Response (CR)

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

Partial Response (PR)

At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD)

At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm.

NOTE: The appearance of one or more new lesions is also considered progression, See Section 6.1.4.3.

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. (Note: a change of 20% or more that does not increase the sum of the diameters by 5 mm or more is coded as stable disease)

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 6 weeks.

6.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR)

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

Non-CR/Non-PD

Persistence of one or more non-target lesion(s.

Progressive Disease (PD)

Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions (see Section 6.1.4.3). Unequivocal progression should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

When the patient also has measurable disease, there must be an overall level of substantial worsening in non-target disease such that, even in the presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest “increase” in the size of one or more non-target lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target disease in the face of SD or PR of target disease will therefore be extremely rare.

When the patient only has non-measurable disease, the increase in overall disease burden should be comparable in magnitude to the increase that would be required to

declare PD for measurable disease: i.e., an increase in tumor burden from “trace” to “large”, an increase in nodal disease from “localized” to “widespread”, or an increase sufficient to require a change in therapy.

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).

6.1.4.3 Evaluation of New Lesions

The appearance of new lesions constitutes Progressive Disease (PD).

A growing lymph node that did not meet the criteria for reporting as a measurable or non-measurable lymph node at baseline should only be reported as a new lesion (and therefore progressive disease) if it:

a) increases in size to ≥ 15 mm in the short axis, or

b) there is new pathological confirmation that it is disease (regardless of size).

new effusion or ascites that appears during treatment should only be reported as a new lesion (and therefore progressive disease) if it has cytological confirmation of malignancy.

6.1.4.4 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence or non-protocol therapy (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.

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

Target Lesions	Non-Target Lesions	New Lesions*	Best Overall Response	Remarks
CR	CR	No	CR	
CR	Non-CR/Non-PD***	No	PR	
CR	Not evaluated	No	PR	
PR	Non-PD***/not evaluated	No	PR	
SD	Non-PD***/not evaluated	No	SD	Documented at least once ≥ 6 wks. from study entry
PD	Any	Yes or No	PD	
Any	PD**	Yes or No	PD***	No prior SD, PR or CR
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.

** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

*** PD in non-target lesions should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase. Please refer to the Evaluation of Non-Target Lesions – Progressive Disease section for further explanation.

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

6.1.4.5 Duration of Response

Duration of Overall Response

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

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

Duration of Stable Disease

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

To be assigned a status of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval of 6 weeks.

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7. Study Parameters

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7.1 Therapeutic Parameters

1. Pre- study screening CT scans and MRIs used to assess all measurable or non-measurable sites of disease must be done within 4 weeks prior to randomization/registration.
2. Pre-study screening CBC (with differential and platelet count) and chemistries as outlined in Section 3.1 should be done ≤ 1 week before randomization/registration. All other pre-study screening labs should be done within 2 weeks prior to randomization/registration. Screening assessments performed ≤ 72 hours before Cycle 1, Day 1 are not required to be repeated for Cycle 1, Day 1.
3. Please see Section 5.1 for more information on treatment administration parameters.

Therapeutic parameters	Pre-study screening	Cycle 1 Day 1	Cycle 2 Day 1	Cycle 3 Day 1	Cycle 4 Day 1	Maintenance Nivolumab Cycle 5+ Day 1, 15, 29	Observation (Arm B)[11]	Post Treatment/ Observation [12] to 5 years from study entry
Full Medical History	X							
Interval History[1]		X	X	X	X	X	X	X
Vital signs including weight[1]	X	X	X	X	X	X	X	X
Performance status[1]	X	X	X	X	X	X	X	X
CBC with Differential[2]	X	X	X	X	X	X	X[11]	
Serum chemistry[2]	X	X	X	X	X	X	X[11]	
TSH, reflex free T3, reflex free T4[3]	X	X		X		X[3]		
Amylase[4]		X						
Lipase[4]		X						
HIV, HBV, HCV serology[5]	X							
Pregnancy Test[6]	X							
EKG[7]	X							
Urinalysis[8]	X	X	X	X	X	X[8]		
CT chest[9]	X			X		X	X	X
CT abdomen[9]	X			X		X	X	X
CT pelvis[9]	X			X		X	X	X
MRI brain[10]	X							

1. At subsequent visits, symptom-directed history and physical examinations including vital signs, weight and performance status should be performed. Symptom-directed history, physical exam and performance status may be performed up to 72 hours prior to each cycle.
2. CBCs (with differential and platelet count) which includes WBC, ANC, Platelets, Hgb, and Hct, and chemistry to include Albumin, alkaline phosphatase, total bilirubin, carbon dioxide, BUN, calcium, chloride, creatinine, glucose, LDH, phosphorus, potassium, total protein, SGOT [AST], SGPT [ALT], sodium, required for protocol therapy must be done ≤ 72 hours prior to treatment administration. Magnesium is only required for patients receiving cisplatin on day 1 of each cycle that cisplatin is administered. For cycle 1 day 1, need not be repeated if the screening labs were done within 72 hours of treatment administration.
3. TSH, reflex free T3 and reflex free T4 will be done at screening as clinically indicated. For the Nivolumab Arm only, these tests will also be done on C1D1, C3D1, C5D1, and every 8 weeks during the maintenance phase. Thyroid labs collected at screening do not need to be repeated at C1D1 if done within 72 hours of treatment administration.
4. Amylase, lipase will be required for patients receiving nivolumab on C1D1 and when clinically indicated.
5. All patients will be tested for HIV, hepatitis B and hepatitis C at screening, if clinically indicated.
6. Blood or Urine pregnancy test (women of childbearing potential). All women of childbearing potential must have a negative pregnancy test (sensitivity of at least 50 mIU/mL). The pregnancy test must be performed within 14 days prior to registration.
7. All patients will have an EKG at screening, if clinically indicated. Patients randomized to the Nivolumab Arm will have troponin as clinically indicated. Further cardiac evaluation is recommended including troponin, EKG, echocardiogram, and cardiology consult when clinically indicated.
8. Urinalysis will be required at screening for all patients and on day 1 of every cycle on the Nivolumab Arm. It does not need to be performed on days 15 or 29 for Cycle 5+.
9. Screening assessments will include CT chest and abdomen. CT pelvis should be performed as clinically indicated. On study and follow-up assessments will include a CT chest and abdomen at each time point, and CT pelvis as clinically indicated. For both Arm A and Arm B, all patients will be evaluated for response while on study using radiographic evaluations with tumor measurements every 6 weeks (+/- 7 days) for the first 6 months on study, every 8 weeks (+/- 7 days) until 1 year on study, and then every 12 weeks (+/- 7 days) after 1 year on study until the patient discontinues protocol treatment (Arm A) or the end of observation (Arm B) and enters follow-up (see footnote 12 for follow-up schedule). Documentation (radiologic) must be provided for patients removed from study for progressive disease. For all patients on Arm A and Arm B, CT scans will be done until disease progression.
10. Head CT allowed, if patient cannot tolerate MRI. Brain imaging will be done at screening and then as clinically indicated.
11. For Arm B patients on observation, symptom-directed history and physical examinations including vital signs, weight and performance status should be performed every 6 weeks (+/- 7 days) for the first 6 months on study, then every 8 weeks (+/- 7 days) until 1 year on study; and every 12 weeks (+/- 7 days) after 1 year on study, alongside the radiologic evaluations. Labs (CBC w/diff, serum chemistries) are done as clinically indicated. CT scans will be done until disease progression
12. Follow-up after patient discontinues protocol treatment (Arm A) or the end of observation (Arm B): every 3 months for patients < 2 years from registration, every 6 months if patient is 2-3 years from registration, and yearly until 5 years from registration. Patients in the observation phase on Arm B may be seen more frequently per schedule of CT scans as per footnote 9. All patients, including those who discontinue protocol therapy early, will be followed for response until progression, even if non-protocol therapy is initiated, and for survival for 5 years from the date of registration. For all patients during follow-up, symptom-directed history and physical examinations including vital signs, weight and performance status should be performed until progression. Follow-up for survival after progression may occur via phone calls.

7.2 Biological Sample Submissions

Specimens are to be submitted as outlined in Section 10.

All specimens must be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS).

Biological Materials	Prior to Start of Treatment	Cycle Two (2), Day One (1)	Submit to:
Submit from patients who answer 'Yes' to 'I agree to have my samples collected and I agree that my samples and related information may be used for the laboratory studies.'			
Peripheral Blood (two 10mL Streck Cell-Free DNA tubes)	X	X	CBPF
Submit from patients who answer 'Yes' to 'I agree to provide additional samples for research.'			
Tumor Tissue Biopsy	X		CBPF

[1.] Kits are being provided for the collection and shipment of the peripheral blood specimens. See Appendix VII for instructions. Kit orders will on average be delivered within three (3) business days from the time the order is placed.

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8. Drug Formulation and Procurement

This information has been prepared by the ECOG-ACRIN Pharmacy and Nursing Committees.

Availability

NCI Supplied Nivolumab – General Information

Drug Ordering: Bristol-Myers Squibb is supplying Nivolumab, through the Division of Cancer Treatment and Diagnosis, NCI, for this protocol. Maintenance of NCI drug accountability records is required. Nivolumab (NSC #748726 and IND#)] may be requested by eligible participating Investigators (or their authorized designees) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

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

NOTE: Under no circumstances can commercially supplied nivolumab be used or substituted for the NCI-supplied nivolumab.

NOTE: In general, sites may order an initial 5 vials of Nivolumab when a subject is being screened for enrollment onto the study.

Drug Returns: All unused drug supplies must be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when a patient permanently discontinues protocol treatment, expired vials recalled by the PMB), investigators must return the study drug to the PMB using the NCI Return Agent Form available from the link below, or by calling the PMB at 240-276-6575.

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

Useful Links and Contacts

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

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

Investigator Brochure Availability

The current version of the IB for Nivolumab will be accessible to site investigators and research staff through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registrations status. Questions about IB access may be directed to the PMB IB coordinator via email.

8.1 Nivolumab (NSC 748726)

8.1.1 Other Names

BMS-936558, MDX1106, Opdivo™

8.1.2 Classification

Anti-PD-1MAb

8.1.3 Mode of Action

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

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8.1.4 Description

Nivolumab Injection is a clear to opalescent, colorless to pale yellow liquid; light (few) particulates may be present. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated in sodium citrate dihydrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid), polysorbate 80 (Tween® 80), and water for injection. Dilute solutions of hydrochloric acid and/or sodium hydroxide may be used for pH adjustment (pH 5.5-6.5).

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8.1.5 Storage and Stability

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

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

Shelf-life surveillance of the intact vials is ongoing.

If not used immediately, the infusion solution may be stored up to 24 hours in a refrigerator at 2°-8°C (36°-46°F) and a maximum of 8hours of the total 24 hours can be at room temperature (20°-25°C, 68°-77°F) and room light. The maximum 8-hour period under room temperature and room light conditions includes the product administration period.

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

8.1.6 Dose Specifics

Refer to Section 5.1 for specific dosing of nivolumab

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8.1.7 Preparation

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

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8.1.8 Route of Administration

Intravenous infusion over 30 minutes. Do not administer as an IV push or bolus injection. See Section 5.1

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8.1.9 Availability

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

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

Nivolumab is supplied as 100 mg vials (10 mg/mL) with a 0.7mL overfill, in 10 mL type I flint glass vials, with fluoropolymer film-laminated rubber stoppers and aluminum seals.

8.1.10 Side Effects

See Section 5.3

8.1.11 Nursing/Patient Implications

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.

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Administer through a 0.2 micron to 1.2 micron pore size, low-protein binding (polyethersulfone membrane) in-line filter. Do not co-administer other drugs through the same intravenous line. The infusion line should be flushed as per institution guidelines after completion of the infusion to ensure the entire dose was administered.

8.1.12 References

Nivolumab IB, Version 16, 23-JUN-2017

8.2 Cisplatin

8.2.1 Other Names

Cisdiaminedichloroplatinum, Cis-diaminedichloroplatinum (II), diaminedichloroplatinum, cis-platinum, platinum, Platinol, Platinol-AQ, DDP, CDDP, DACP, NSC 119875.

8.2.2 Classification

Cytotoxic chemotherapy, alkylating agent

8.2.3 Mode of Action

Inhibits DNA synthesis by forming inter- and intra-strand crosslinks. Other possible mechanism include chelation of DNA and binding to cell membranes thereby stimulating immune mechanisms.

8.2.4 Storage and Stability

Intact vials of cisplatin are stored at room temperature. Protect unopened container from light. Refer to the cisplatin package insert for stability of the infusion solution after prepared. Due to the risk of precipitation, cisplatin solutions should **not** be refrigerated.

8.2.5 Dose Specifics

Refer to Section 5.1 for specific cisplatin dosing.

8.2.6 Preparation

Cisplatin to be mixed per institutional standard.

8.2.7 Route of Administration

Intravenous

8.2.8 Incompatibilities

Amsacrine, cefepime, gallium nitrate, mesna, piperacillin, sodium bicarbonate, thiotepa. Cisplatin may react with aluminum which is found in some syringe needles or IV sets, forming a black precipitate.

Compatibilities:

Admixture: Amphotericin-B, aztreonam, carmustine, cefazolin, cephalothin, droperidol, etoposide, floxuridine, hydroxyzine, ifosphamide, leucovorin, magnesium sulfate, mannitol, potassium chloride. Y-site: Allopurinol, bleomycin chlorpromazine, cimetidine,

cyclophosphamide, dexamethasone, diphenhydramine, doxapram, doxorubicin, famotidine, filgrastim, fludarabine, fluorouracil, furosemide, ganciclovir, heparin, hydromorphone, lorazepam, melphalan, methotrexate, methylprednisolone, metoclopramide, mitomycin, morphine, ondansetron, paclitaxel, prochlorperazine, ranitidine, sargramostim, vinblastine, vincristine, vinorelbine.

Consult your pharmacist regarding specific concentrations.

8.2.9 Availability

Commercially available as a 1 mg/mL solution in 50, 100, and 200 mg vials.

8.2.10 Side Effects

Please refer to the package insert for a comprehensive list of adverse events.

8.2.11 Nursing/Patient Implications

8.2.11.1 Monitor CBC, platelet count, BUN and creatinine prior to drug administration.

8.2.11.2 Monitor for signs of ototoxicity or neurotoxicity.

8.2.11.3 Symptom management of expected nausea and vomiting. Ondansetron (or other 5HT3 antagonist) and dexamethasone will be given daily prior to chemotherapy administration. Additional antiemetics may be provided per physician discretion.

If the treating physician chooses to use Aprepitant, when given once daily for 14 days as a 100 mg capsule with an oral contraceptive containing 35 mcg of ethinyl estradiol and 1 mg of norethindrone, this decreased the AUC of ethinyl estradiol by 43% and decreased the AUC of norethindrone by 8%. Women of childbearing potential using pregnancy contraception that includes ethinyl estradiol should not receive Aprepitant for the treatment of nausea/delayed emesis. Patients may change to a different method of contraception if they wish to use Aprepitant.

8.2.11.4 Pre- and post-treatment hydration may be administered per institutional standards.

8.2.11.5 Diuretics may be ordered as needed per physician discretion.

8.2.11.6 Use of granulocyte colony stimulating factors are permitted.

8.2.11.7 Observe for signs of allergic reaction.

8.2.12 References

1. Alberts DS. Carboplatin versus cisplatin in ovarian cancer. Semin Oncol 1995;22 (5 Suppl 12):88-90.

2. Bonomi P. Platinum/etoposide therapy in non-small cell lung cancer. Oncology 1992;49 (Suppl 1):43-50.
3. Dabholkar M, Reed E. Cisplatin. Cancer Chemother Biol Response Modifiers 1993;14:86-97.
4. Fram RJ. Cisplatin and platinum analogues: recent advances. Curr Opin Oncol 1992;4:1073-9.
5. Garrow GC, Johnson, DH. Treatment of "good risk" metastatic testicular cancer. Semin Oncol 1992;19:159-65.
6. Markman M. Current status of intraperitoneal therapy for ovarian cancer. Curr Opinion Obstet Gynecol 1993;5:99-104.
7. Ozols RF, et al. Advanced ovarian cancer. Dose intensity. Ann Oncol 1993; (4 Suppl 4):49-56.
8. Saxman S. Salvage therapy in recurrent testicular cancer. Semin Oncol 1992;19:143-7.
9. Wheeler RH, Spencer S. Cisplatin plus radiation therapy. J Infusional Chemother 1995;5:61-6.

8.3 Carboplatin

8.3.1 Other Names

Paraplatin®

8.3.2 Classification

Carboplatin (carboplatin injection) (platinum, diammine[1,1-cyclobutanedicarboxylato(2-)-O,O']-, (SP-4-2)) is a platinum coordination compound, used as an anti-neoplastic agent. It is a second-generation tetravalent organic platinum compound. It is a crystalline powder with the molecular formula of C6H12N2O4Pt and a molecular weight of 371.25. It is soluble in water at a rate of approximately 14 mg/mL, and the pH of a 1% solution is 5 to 7. It is virtually insoluble in ethanol, acetone, and dimethylacetamide.

8.3.3 Mode of Action

Like cisplatin, carboplatin binds to DNA, thereby inhibiting DNA synthesis, in a cell cycle nonspecific manner. Carboplatin must first undergo activation to produce antineoplastic activity. Bidentate carboxylate ligands of carboplatin are displaced by water forming (aquation) positively charged platinum complexes, which bind to nucleophilic sites in DNA, such as the O-6 position on guanine. Carboplatin produces predominantly interstrand DNA crosslinks rather than DNA-protein crosslinks. Intrastrand crosslinks result from the formation of adducts between the activated platinum complexes of the drug and the N-7 atom (not exclusively) atom on guanine to produce 1,2 intrastrand links between adjacent guanine molecules, between neighboring guanine and adenosine molecules, or between neighboring guanine molecules. Interstrand cross-linking within the DNA helix also occurs. Platinum adducts may inhibit DNA replication, transcription and ultimately cell division.

8.3.4 Storage and Stability

Store intact vials at room temperature at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light. Further dilution to a concentration as low as 0.5 mg/mL is stable at room temperature (25°C) for 8 hours in NS or D_5W. Stability has also been demonstrated for dilutions in D_5W in PVC bags at room temperature for 9 days; however, the manufacturer recommends use within 8 hours due to lack of preservative. Multidose vials are stable for up to 14 days after opening when stored at 25°C (77°F) following multiple needle entries.

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8.3.5 Dose Specifics

See Section 5.1 for specific carboplatin dosing.

Calvert Formula for Carboplatin (AUC) Dosing

Total dose (mg) = target AUC (in mg x mL/minute) x [*GFR (in mL/minute) + 25]

For the purposes of this protocol, the GFR is considered to be equivalent to the creatinine clearance.

Glomerular Filtration Rate (GFR)* Estimation: Calculated creatinine clearance of ≥ 50 cc/min using the Cockcroft-Gault formula:

$$\text{Males:} \quad \frac{(140 - \text{Age in years}) \times \text{Actual Body Weight in kg}}{72 \times \text{Serum Creatinine (mg/dL)}}$$

Females: Estimated creatinine clearance for males x 0.85

With the Calvert formula, the total (final) dose of carboplatin is calculated in mg, not mg/m^2.

The minimum serum creatinine value used will be 0.7 mg/dL and a CrCl cap will be 125 mL/min.

Questions about this calculation should be directed to the principal investigator.

8.3.6 Preparation

Manufacturer's labeling states solution can be further diluted to concentrations as low as 0.5 mg/mL in NS or D_5W; however, most clinicians generally dilute dose in either 100 mL or 250 mL of NS or D_5W. Concentrations used for desensitization vary based on protocol. Hazardous agent; use appropriate precautions for handling and disposal. Needles or IV administration sets that contain aluminum should not be used in the preparation or administration of carboplatin; aluminum can react with carboplatin resulting in precipitate formation and loss of potency.

8.3.7 Route of Administration

Intravenous

8.3.8 Incompatibilities

Amphoterecin B chloesteryl sulfate complex. Aluminum reacts with carboplatin causing precipitate formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that

may come in contact with the drug must NOT be used for the preparation or administration of carboplatin.

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8.3.9 Availability

Carboplatin (Bristol-Myers Oncology Division) is commercially available as a 10 mg/mL solution in 50, 150, 450, and 600 mg vials.

8.3.10 Side Effects

Please refer to the package insert for a comprehensive list of adverse events.

8.3.11 Nursing/Patient Implications

8.3.11.1 Monitor CBC and platelet count; nadir occurs at approximately day 21 with recovery by day 28-30.

8.3.11.2 Premedicate with antiemetics—evaluate effectiveness. Ondansetron (or other 5HT3 antagonist) and dexamethasone are required.

8.3.11.3 Monitor fluid status—maintain adequate hydration. Pre- and post-treatment hydration may be administered per institutional standards.

8.3.11.4 Assess skin/mucous membranes.

8.3.11.5 Assess for signs of peripheral neuropathy—coordination, sensory loss.

8.3.12 References

1. Calvert AH, et al. Carboplatin dosage: Prospective evaluation of a simple formula based on renal function. J Clin Oncol 1989; 7:1748-1756.
2. Woloschuk DMM, Pruemer JM, Cluxton RJ. Carboplatin: A new cisplatin analog. Drug Intell Clin Pharm 1988; 22:843-849.
3. Christian MC. Carboplatin. In: Principles and Practice of Oncology, PPO Updates 1989; 3(11):1-16.

8.4 Etoposide

8.4.1 Other Names

VP-16, VePesid, VP-16-213, EPEG, epipodophyllotoxin, NSC # 141540.

8.4.2 Classification

Cytotoxic chemotherapy, podophyllotoxin derivative.

8.4.3 Mode of Action

Etoposide inhibits the enzyme topoisomerase II, nucleoside transport and incorporation, and causes DNA breakage.

8.4.4 Storage and Stability

The vials should be stored at room temperature. Following dilution in 0.9% sodium chloride or 5% dextrose to concentrations of 0.2-0.4

mg/mL the drug is chemically stable for 96 and 24 hours at room temperature respectively. Bristol-Myers in-house data indicate that etoposide may be stable in 5% dextrose or normal saline for 24 hours (0.6 mg/mL), 4 hours (1 mg/mL), and 2 hours (2 mg/mL).

8.4.5 Dose Specifics

Refer to Section 5.1 for specific etoposide dosing.

8.4.6 Preparation

Etoposide to be prepared per institutional standard.

8.4.7 Route of Administration

Intravenous

8.4.8 Incompatibilities

Please refer to the etoposide prescribing information for more detailed information regarding incompatibilities.

8.4.9 Availability

Commercially available

Etoposide is commercially available as a 20 mg/mL solution in 100 mg, 500 mg and 1 gm vials.

8.4.10 Side Effects

Please refer to the package insert for a comprehensive list of adverse events.

8.4.11 Nursing/Patient Implications

8.4.11.1 Monitor CBC and platelet count prior to drug administration.

8.4.11.2 Advise patient of possible alopecia. Instruct how to obtain wig, hairpiece, etc.

8.4.11.3 Observe for possible phlebitis at injection site or burning pain with infusion.

8.4.11.4 Monitor for rare anaphylactoid reaction.

8.4.11.5 Administer antiemetics as indicated.

8.4.12 References

1. van Maanen JMS, *et al.* Mechanism of action of antitumor drug etoposide: A review. J Natl Cancer Instit 1988; 80:1526-1533.
2. Stewart CF, Hampton EM. Stability of cisplatin and etoposide in intravenous admixtures. Am J Hosp Pharm 1989; 46:1400-1404.
3. Seargeant LE, *et al. In vitro* stability and compatibility of daunorubicin, cytarabine and etoposide. Cancer Treat Rep 1987; 71:1189-1192.
4. Fleming RA, *et al.* Etoposide: An update. Clin Pharm 1989; 8:274-293.

5. O'Dwyer PJ, *et al.* Etoposide, current status of an active anticancer drug. N Engl J Med 1985; 312:692-7

9. Statistical Considerations

9.1 Study Design and Objectives

This is a randomized phase II clinical trial comparing etoposide combined with a choice of platinum-based therapy (carboplatin or cisplatin; CE) with or without nivolumab (CEN) in patients with previously untreated extensive stage SCLC.

The primary objective of the trial is to determine whether combination therapy including nivolumab extends progression-free survival (PFS) for this patient population. Secondary objectives include estimation of overall survival, best objective response, and toxicity with first line therapy. Correlative endpoints include evaluation of PD-L1 expression in archival tumor tissues and other serum biomarkers in relation to clinical outcome.

9.2 Study Endpoints

PFS is defined as the time from randomization to documented disease progression or death from any cause, whichever occurs first. Patients who have not experienced an event of interest by the time of analysis will be censored at the date they are last known to be alive and progression-free. Overall survival is defined as the time from randomization to death from any cause, and patients who are thought to be alive at the time of final analysis will be censored at the last date of contact. Best objective response will be evaluated via RECIST1.1 criteria. Toxicity will be determined using the CTCAE criteria. IHC positivity is defined as positive membrane staining in more than 1% of viable tumor cells among a minimum of 100 evaluable tumor cells.

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9.3 Statistical Analysis Plan

The primary and some secondary analyses will include all eligible and treated patients. Exception to this include: analysis of toxicity data, which will include all patients who received study drug regardless of eligibility, and analyses of response, which will include eligible and treated patients with measurable disease. Time-to-event data, such as PFS and OS, will be estimated using the Kaplan-Meier method, and Cox proportional hazards models will be used to estimate the treatment hazard ratios. The primary comparison of PFS will use a logrank test stratified on the randomization stratification factors with a one-sided type I error rate of 10%. Other comparisons of groups will be made using the log rank test and Cox modeling. Categorical data, such as response rates (CR+PR) and toxicity, will be compared using Fisher's exact tests with a one-sided type I error rate of 10%; multivariable logistic regression modeling will be used to adjust for the effect of any covariates that are associated with these categorical outcomes. Continuous outcomes will be analyzed using Wilcoxon rank sum test, and multivariable linear regression models may be used to adjust for multiple associations with outcome.

Modeling procedures will implement backward selection; variables significant at the 0.10 level in the univariate setting will be chosen for inclusion in an initial full model, and at each step the least significant variable will be removed from the model. Only those covariates with $p<0.05$ will remain in any final models, unless there are factors identified by the study team as crucial to model interpretation.

Point estimates of all endpoints will be accompanied by the corresponding 95% confidence intervals; however, 80% confidence intervals will also be provided for

the primary endpoint (PFS) hazard ratio. In the event that there are missing data, no imputation of the missing data will be conducted. We will assume that data are missing at random and will conduct all analyses as originally planned because we do not anticipate an excess of missing data.

Subset analyses are planned for all stratification factors and all known prognostic factors, such as performance status, age, sites of metastases, gender, etc. Subset analyses of all variables, including correlatives, are considered to be exploratory in nature.

9.4 Sample Size Considerations

The primary comparison will include all eligible and treated patients, of whom 135 will be accrued and randomized equally, for a total accrual of 67 patients per arm. After adjusting for an ineligibility rate of 10%, the total required sample size for randomization is 150 patients. Using an overall one-sided 0.10 level log rank test, this study will have 88% power to detect a 37.5% reduction in the PFS hazard rate of 0.139 to 0.087 based on the estimated accrual and follow-up period. Assuming an exponential survival, this corresponds to a 60% improvement in the median PFS of 5 months on CE to 8 months on CE plus nivolumab. The number of PFS events needed to achieve this power is 113 events under the alternative hypothesis.

Correlative Study Statistical Considerations:

Tumor DNA levels obtained from the serial collection of cfDNA samples will be examined to explore whether clinical outcome is associated with fluctuations in DNA levels following the administration of therapy. Plasma will be collected from 30 patients on each arm of the study at baseline and cycle 2 day 1.

A variety of statistical techniques will be employed for the analyses of cfDNA. The rate of change at a particular time point may be compared to baseline measures of cfDNA and that measure will be analyzed for association with subject demographics and/or disease characteristics using the Kruskal Wallis test. Landmark analyses of PFS and OS in which the landmark time is defined by the cfDNA measurements at a particular time point, may be used as well. Presence or absence of mutations in plasma will be analyzed for association with other variables using Fisher's exact test. To account for the repeated measures of plasma over time, we may potentially use these data as time varying covariates in multivariable Cox models to study their impact on outcomes like PFS and OS. Models would be adjusted for known prognostic factors and treatment arm; we will also fit a marker by treatment interaction, though it is difficult to power for an interaction test in this setting. If we are to dichotomize patients according to the median change in plasma levels from baseline to a second timepoint such as end of chemotherapy, with at least 60 patients in the analysis we would have 85% power to detect a difference in induction response rates of 40% among those with low plasma response and 80% among those with high plasma response while testing with a one-sided 0.025 level Fisher's exact test.

9.5 Projected Accrual

As reflected by previous ECOG SCLC studies, it is estimated that patient accrual will be approximately 9 patients per month. It is estimated that the accrual goal

will be reached within approximately 15 months with a follow up period of approximately 10 months, for total study duration of 25 months.

9.6 Randomization Scheme

Randomization to treatment will be determined using permuted blocks within strata with dynamic balancing on main ECOG-ACRIN institutions plus affiliates. The randomization will be stratified by gender (Male vs. Female) and LDH (WNL vs. > upper limit of normal).

9.7 Monitoring Plan

9.7.1 Interim Analysis: Efficacy

This study will also be monitored for futility and one interim analysis at roughly 50% information is planned. At that time, if the point estimate of the PFS hazard ratio is consistent with detriment (HR > 1.0), then the data monitoring committee may consider terminating the study early for overall lack of treatment difference.

9.7.2

Interim analyses of toxicity are performed twice yearly for all ECOG-ACRIN studies. Reports of these analyses are sent to the ECOG-ACRIN Principal Investigator or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required, as described in Section 5.2.

9.8 Gender and Ethnicity

Based on previous data from ***E2511*** the anticipated accrual in subgroups defined by gender and race is:

PLANNED ENROLLMENT REPORT					
Racial Categories	**Ethnic Categories**				**Total**
	Not Hispanic or Latino		**Hispanic or Latino**		
	Female	**Male**	**Female**	**Male**	
American Indian/ Alaska Native	0	0	0	0	0
Asian	0	2	0	0	2
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	0	4	0	0	4
White	74	70	0	0	144
More Than One Race	0	0	0	0	0
Total	74	76	0	0	150

The accrual targets in individual cells are not large enough for definitive subgroup analyses. Therefore, overall accrual to the study will not be extended to meet individual subgroup accrual targets.

10. Specimen Submissions

Peripheral blood specimens are to be submitted per patient consent for defined laboratory research studies described in Section 11.

Tumor tissue specimens are to be submitted per patient consent for future undefined research studies.

All specimens must be clearly labeled with the ECOG-ACRIN protocol number (EA5161), the patient's initials and ECOG-ACRIN patient sequence number, the collection date, and specimen type

It is required that all specimens submitted on this trial be entered and tracked via the ECOG-ACRIN Sample Tracking System (STS) (Section 10.3). An STS shipping manifest form is to be included with every submission.

10.1 Submissions to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBFP)

If you have any questions concerning tumor tissue and peripheral blood submissions please contact the ECOG-ACRIN CBPF at (844) 744-2420 or eacbpf@mdanderson.org

10.1.1 Pathological Material Submissions

Submit from patients who answer "Yes" to "I agree to provide additional samples for research."

Representative tumor tissue specimens from the pretreatment diagnostic biopsy are to be submitted for undefined research studies (per patient consent) within one (1) month of randomization.

Submitting pathologist and clinical research associate may refer to Appendix I which outlines the Pathology Submission Guidelines.

The tumor tissue specimens are to be labeled with the institution's assigned pathology ID# as well as the information above.

10.1.1.1 Required Materials

Forms: Must be submitted with all pathology submissions.

STS generated shipping manifest form

Copy of the institutional pathology report

Immunological study reports, if available

Tumor Tissue Submission:

Formalin-fixed paraffin-embedded (FFPE) tumor tissue block

NOTE: If blocks are unavailable for submission, cores and slides are to be submitted. All cores and slides must be adequately labeled, with slides numbered sequentially in the order cut. Alternative submission requirements:

- One (1) H&E slide

- Twenty (20) 5 µm unstained, uncharged, air-dried plus slides from the thickest part of the tumor
- One (1) or more core punches (minimum of 4mm diameter). If core punch tool is unavailable, request core punch kit from the ECOG-ACRIN CBPF (844) 744-2420. Adequately label every slide and core submitted.

If these criteria cannot be met, please contact the ECOG-ACRIN CBPF (eacbpf@mdanderson.org) to obtain alternative submission requirements.

10.1.2 Peripheral Blood Submissions

Submit from patients who answer 'Yes' to 'I agree to have my samples collected and I agree that my samples and related information may be used for the laboratory studies.'

Kits for the collection and shipment of the peripheral blood specimens are ordered online from Cenetron Central Laboratories. Instructions are provided in Appendix VII. Questions regarding kits can be directed to projectmanagement@cenetron.com or call the Cenetron Clinical Trials Group at (512) 439-2000. Kits must be ordered after the patient has been randomized to the trial and will generally arrive within three (3) business days from when the order was placed.

10.1.2.1 Specimen Preparation Guidelines

Peripheral blood specimens are to be collected at the following time points:

- Prior to Start of Treatment
- Cyce Two (2), Day One (1)

Streck Cell-Free DNA Tubes

- Draw two (2) 10mL Streck Cell-Free DNA BCT tubes of whole blood at each time point. Fill each tube completely.
- Ensure at least 10mL of blood is drawn. Avoid low volume to minimize agitation during shipping.
- Immediately after collection, gently invert tube 180 degrees and back 10 times to ensure adequate mixing.
    - Maintain blood at room temperature (6°C to 37°C) until shipping. **Do Not** place tubes in refrigerator.

10.1.3 Shipping Procedures

Pathology materials are to be shipped at ambient temperature within one (1) month following randomization.

Peripheral blood specimens are to be shipped at ambient temperature Monday-Thursday via overnight courier.

Friday shipments are ill advised, similarly shipping before holidays is often problematic. The laboratory is closed Saturday, Sunday, and holidays.

Ship using the CBPF's FedEx account using the FedEx online ship manager

Ship to:

ECOG-ACRIN Central Biorepository and Pathology Facility
MD Anderson Cancer Center
Department of Pathology, Unit 085
Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3598
1515 Holcombe Boulevard
Houston, TX 77030
Phone: Toll Free (844) 744-2420 (713-745-4440 Local or International Sites)
Fax: (713) 563-6506
Email: eacbpf@mdanderson.org

Access to the FedEx shipping account for shipments to the ECOG-ACRIN CBPF at MD Anderson Cancer Center can only be obtained by logging onto fedex.com with an account issued by the ECOG-ACRIN CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. If your institution needs to have an account created, please contact the ECOG-ACRIN CBPF by email at eacbpf@mdanderson.org

An STS shipping manifest form must be generated and shipped with all specimen submissions.

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10.2 Use of Specimens in Research

See Section 11 for the description of the laboratory research studies to be performed.

Specimens (tumor tissue and blood leftover after the laboratory research studies) from patients who consented to allow their specimens to be used for future undefined ECOG-ACRIN approved research studies will be retained in an ECOG-ACRIN designated central repository.

For this trial, specimens will be retained at the ECOG-ACRIN Central Biorepository and Pathology Facility.

Specimens submitted will be processed to maximize their utility for current and future research projects. Tissue processing may include, but not limited to, extraction of DNA and RNA and construction of tissue microarrays (TMAs). DNA, RNA, serum, and plasma (if appropriate) will be isolated from the submitted peripheral blood specimens.

Any residual blocks will be available for purposes of individual patient management on specific written request.

If future use is denied or withdrawn by the patient, the specimens will be removed from consideration for use in any future research study. Pathology materials may be retained for documentation purposes or returned to the institution. All other specimens will be destroyed per guidelines of the respective repository.

10.3 ECOG-ACRIN Sample Tracking System

It is **required** that all specimens submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the specimens required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst

Important: Please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html

Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest form should be shipped with all specimen submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu

Study Specific Notes

Generic Specimen Submission Form (#2981v3) will be required only if STS is unavailable at time of specimen submission. Notify the laboratory of the shipment by faxing a copy of the completed form to the laboratory.

Retroactively enter all specimen collection and shipping information when STS is available.

10.4 Sample Inventory Submission Guidelines

Inventories of all specimens submitted will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of specimens forwarded and utilized for the approved laboratory research studies will be submitted by the investigating laboratories to the ECOG-ACRIN Operations Office - Boston on a monthly basis in an electronic format defined by the ECOG-ACRIN Operations Office - Boston.

11. Laboratory Research Studies

Results of these studies are for the purposes of the trial only and will not be returned to the institution or reported to the patient.

11.1 Circulating Tumor DNA Qualification and Sequencing

Rev. Add1

We will collect peripheral blood at baseline and cycle two, day one. Circulating tumor DNA will be measured quantitatively and total exonic mutation burden will be assessed with whole exome sequencing using the Guardant360 platform that will inform on allelic frequency of mutations, mutational burden, and specific targeted exome sequencing and amplification of relevant caner related genes. Baseline nonsynonymous mutation burden, neo-antigen burden and DNA repair pathway mutations will be correlated with response to immunotherapy.

11.2 Lab Data Transfer Guidelines

The data collected on the above mentioned laboratory research studies will be submitted electronically using a secured data transfer to the ECOG-ACRIN Operations Office - Boston by the investigating laboratories on a quarterly basis or per joint agreement between ECOG-ACRIN and the Investigator.

Rev. Add1

12. Electronic Data Capture

Please refer to the EA5161 Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave.

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP website.

(http://ctep.cancer.gov/reporting/cdus.html).

13. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed.

Rev. Add1

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Randomized Phase II Clinical Trial of Cisplatin/Carboplatin and Etoposide (CE) alone or in Combination with Nivolumab as Frontline Therapy for Extensive Stage Small Cell Lung Cancer (ED-SCLC)

Appendix I

Pathology Submission Guidelines

The following items are included in Appendix I:

1. Guidelines for Submission of Pathology Materials (instructional sheet for Clinical Research Associates [CRAs])
2. Instructional memo to submitting pathologists
3. ECOG-ACRIN Generic Specimen Submission Form (#2981)

Guidelines for Submission of Pathology Materials

The following pathology materials are to be submitted within one (1) month of randomization:

1. Pathology Submissions:
   - Formalin-fixed paraffin-embedded (FFPE) tumor tissue block from the pretreatment diagnostic biopsy

   NOTE: If blocks are unavailable for submission, cores and slides are to be submitted. All cores and slides must be adequately labeled, with slides numbered sequentially in the order cut. Alternative submission requirements:
   - One (1) H&E slide
   - Twenty (20) 5 µm unstained, uncharged air-dried plus slides from the thickest part of the tumor
   - One (1) or more core punches (minimum of 4mm diameter). If core punch tool is unavailable, request core punch kit from the ECOG-ACRIN CBPF (844) 744-2420

   If these criteria cannot be met, please contact the ECOG-ACRIN CBPF (eacbpf@mdanderson.org) to obtain alternative submission requirements.
2. Forms and Reports:

   NOTE: Adequate patient identifying information must be included with every submission. It is strongly recommended that full patient names be provided. The information will be used only to identify patient materials, and will help to expedite any required communications with the institution (including pathologists).

   The following items are to be included with the pathology materials:
   - Institutional Pathology Report
   - ECOG-ACRIN Generic Specimen Submission Form (#2981) [if STS is unavailable]
   - Sample Tracking System (STS) Shipping Manifest Form
   - Immunological study reports, if available
3. Mail pathology materials to:

   ECOG-ACRIN Central Biorepository and Pathology Facility
   MD Anderson Cancer Center
   Department of Pathology, Unit 085
   Tissue Qualification Laboratory for ECOG-ACRIN, Room G1.3598
   1515 Holcombe Boulevard
   Houston, TX 77030
   Phone: Toll Free (844) 744-2420 (713-745-4440 Local or International Sites)
   Fax: (713) 563-6506
   Email: eacbpf@mdanderson.org

   If you have any questions concerning the above instructions or if you anticipate any problems in meeting the pathology material submission deadline of one month, contact the Pathology Coordinator at the ECOG-ACRIN Central Biorepository and Pathology Facility by telephone: (844) 744-2420 or email: eacbpf@mdanderson.org

Robert L. Comis, MD, and Mitchell D. Schnall, MD, PhD
Group Co-Chairs

MEMORANDUM

TO: _____
(Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair
ECOG-ACRIN Laboratory Science and Pathology Committee

DATE: _____

Rev. Add1

SUBJECT: **Submission of Pathology Materials for EA5161:** Randomized Phase II Clinical Trial of Cisplatin/Carboplatin and Etoposide (CE) alone or in Combination with Nivolumab as Frontline Therapy for Extensive Stage Small Cell Lung Cancer (ED-SCLC)

The patient named on the attached request has been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for future undefined laboratory research studies.

Keep a copy of the submission for your records and return any relevant completed forms, the surgical pathology report(s), the slides and/or blocks and any other required material to the Clinical Research Associate (CRA). The CRA will forward all required pathology materials to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF).

Pathology materials submitted for this study will be retained at the ECOG-ACRIN Central Repository for future research studies per patient consent. Paraffin blocks will be returned upon request for purposes of patient management.

If you have any questions regarding this request, please contact the ECOG-ACRIN Central Biorepository and Pathology Facility at (1-844-744-2420 (713-745-4440 Local or International Sites) or email: eacbpf@mdanderson.org

The ECOG-ACRIN CRA at your institution is:

Name:_____

Address: _____

Phone: _____

Thank you.

ECOG-ACRIN Generic Specimen Submission Form

Form No. 2981v3

Institution Instructions: This form is to be completed and submitted with **all specimens** ONLY if the Sample Tracking System (STS) is not available. **Use one form per patient, per time- point.** All specimens shipped to the laboratory must be listed on this form. Enter all dates as MM/DD/YY. Keep a copy for your files. Retroactively log all specimens into STS once the system is available. **Contact the receiving lab to inform them of shipments that will be sent with this form.**

Protocol Number _____ **Patient ID** _____ **Patient Initials** Last _____ First _____

Date Shipped _____ **Courier** _____ **Courier Tracking Number** _____

Shipped To (Laboratory Name) _____ **Date CRA will log into STS** _____

FORMS AND REPORTS: Include all forms and reports as directed per protocol, e.g., pathology, cytogenetics, flow cytometry, patient consult, etc.

Required fields for all samples				**Additional fields for tissue submissions**				**Completed by Receiving Lab**
Protocol Specified Timepoint:								
Sample Type (fluid or fresh tissue, include collection tube type)	**Quantity**	**Collection Date and Time 24 HR**		**Surgical or Sample ID**	**Anatomic Site**	**Disease Status** (e.g., primary, mets, normal)	**Stain or Fixative**	**Lab ID**

Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required.					
Leukemia/Myeloma Studies:	**Diagnosis**	**Intended Treatment Trial**	**Peripheral WBC Count (x1000)**	**Peripheral Blasts %**	**Lymphocytes %**
Study Drug Information:	**Therapy Drug Name**	**Date Drug Administered**	**Start Time 24 HR**	**Stop Time 24HR**	
Caloric Intake:	**Date of Last Caloric Intake**		**Time of Last Caloric Intake 24HR**		

CRA Name _____ **CRA Phone** _____ **CRA Email** _____

Comments

9/12/14

Randomized Phase II Clinical Trial of Cisplatin/Carboplatin and Etoposide (CE) alone or in Combination with Nivolumab as Frontline Therapy for Extensive Stage Small Cell Lung Cancer (ED-SCLC)

Appendix II

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we hope to improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and ECOG-ACRIN, we thank you again for being an important part of this study.

Sincerely,

[PHYSICIAN NAME]

Randomized Phase II Clinical Trial of Cisplatin/Carboplatin and Etoposide (CE) alone or in Combination with Nivolumab as Frontline Therapy for Extensive Stage Small Cell Lung Cancer (ED-SCLC)

Appendix III

Nivolumab (BMS-936558) TOXICITY MANAGEMENT ALGORITHMS

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with Study Chair/Medical Oncologist. The guidance applies to all immune-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

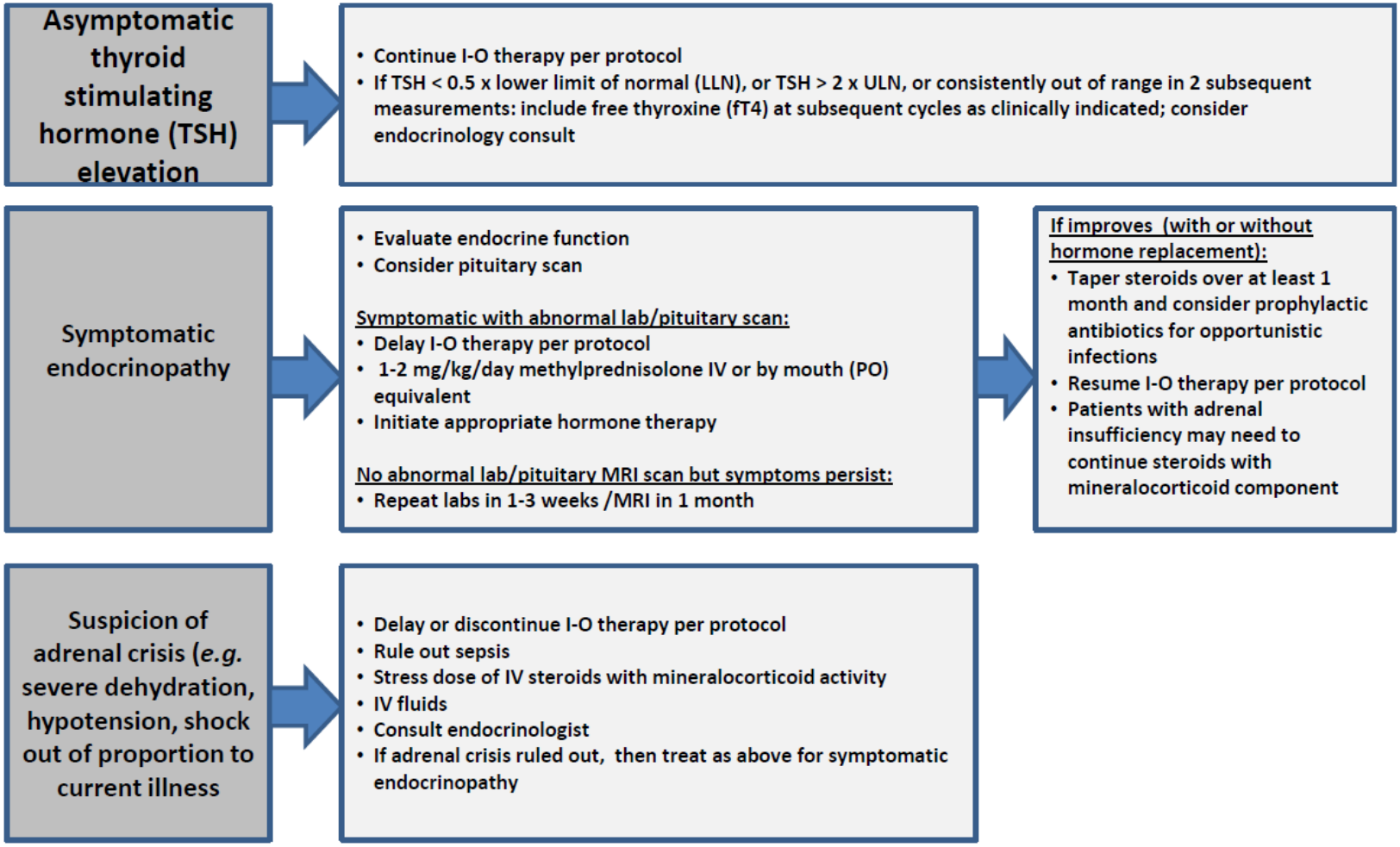
Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

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

Endocrinopathy Management Algorithm

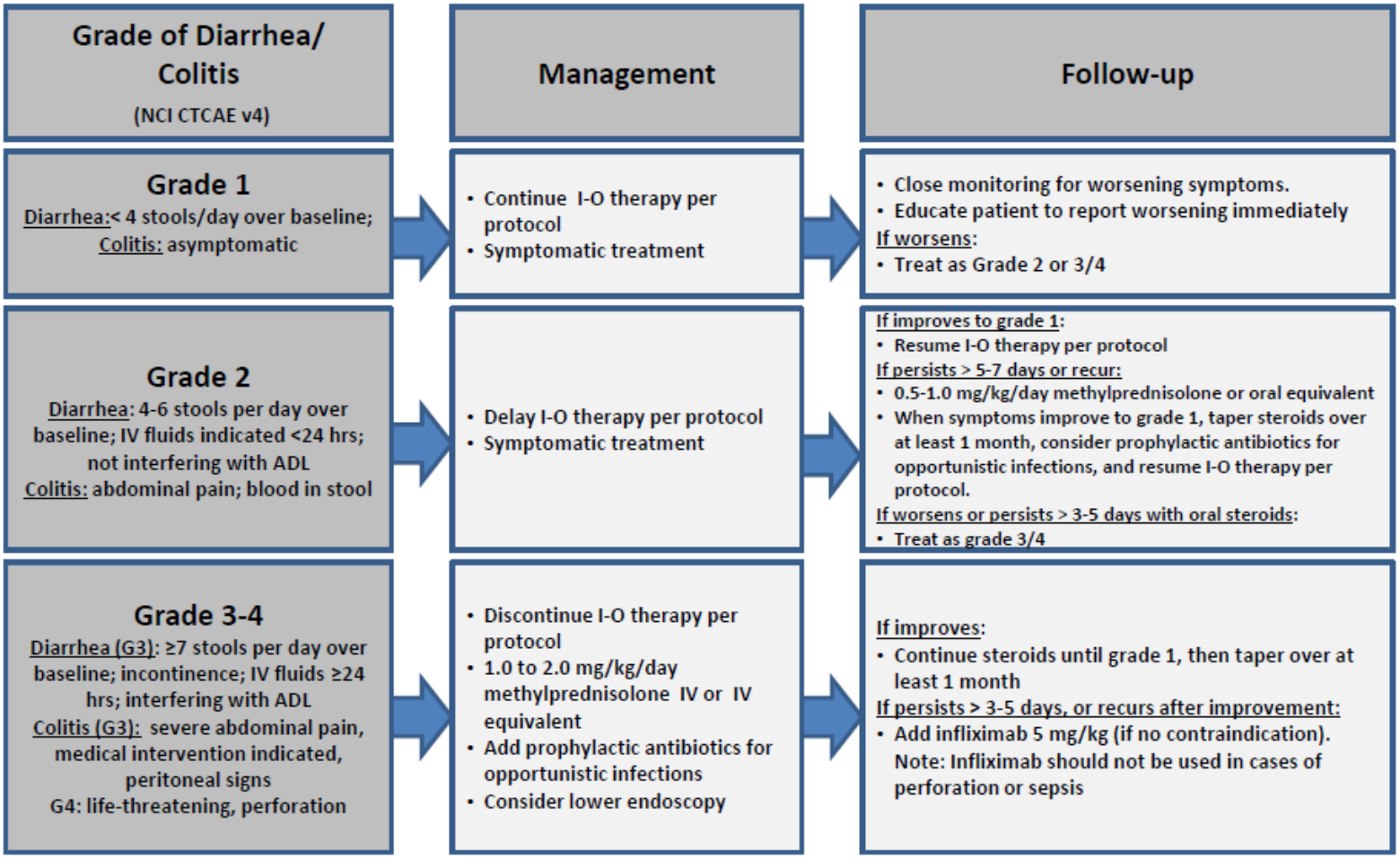
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue immuno-oncology (I-O) therapy.
Consider visual field testing, endocrinology consultation, and imaging.



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

GI Adverse Event Management Algorithm

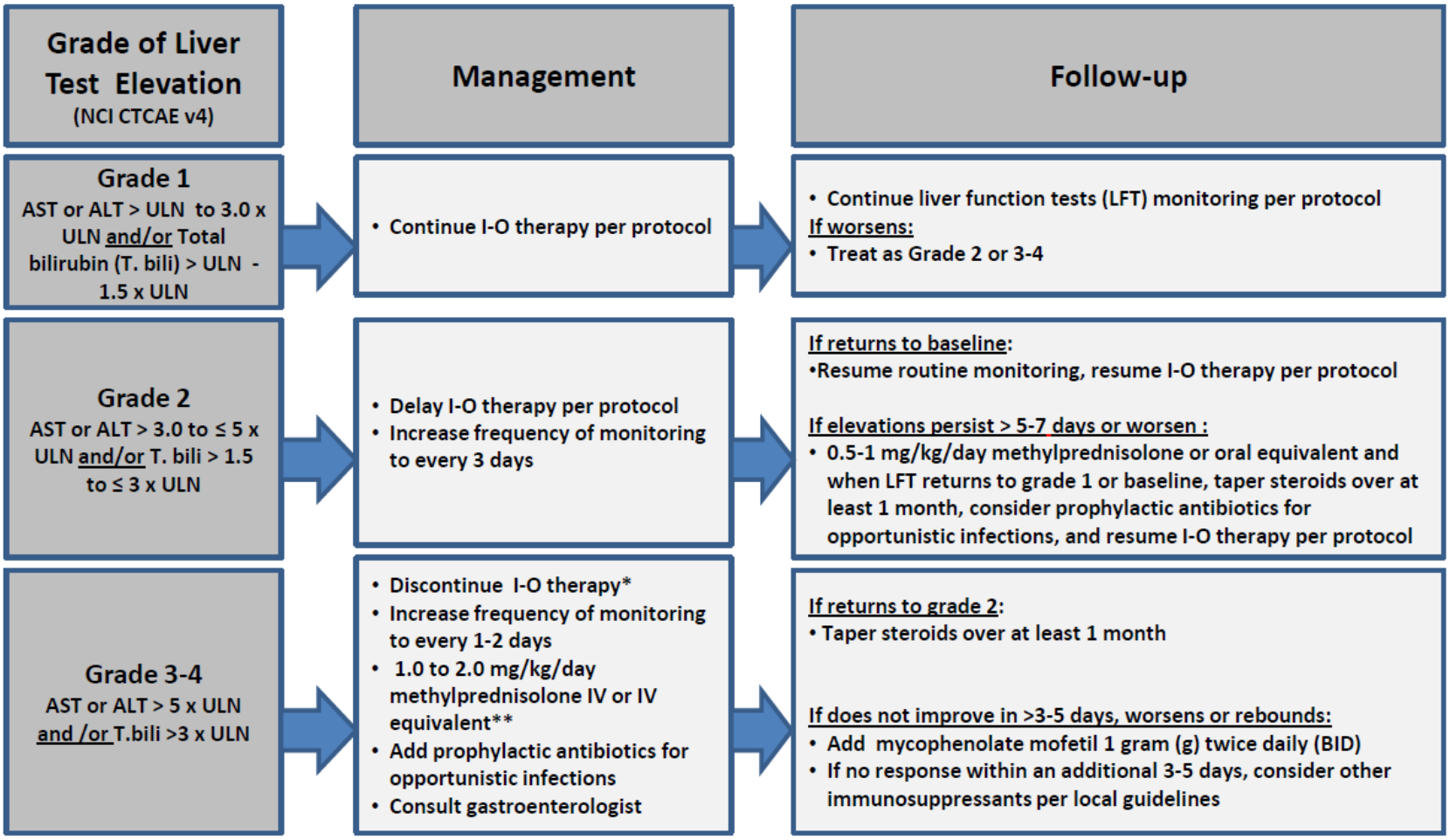
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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

Hepatic Adverse Event Management Algorithm

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



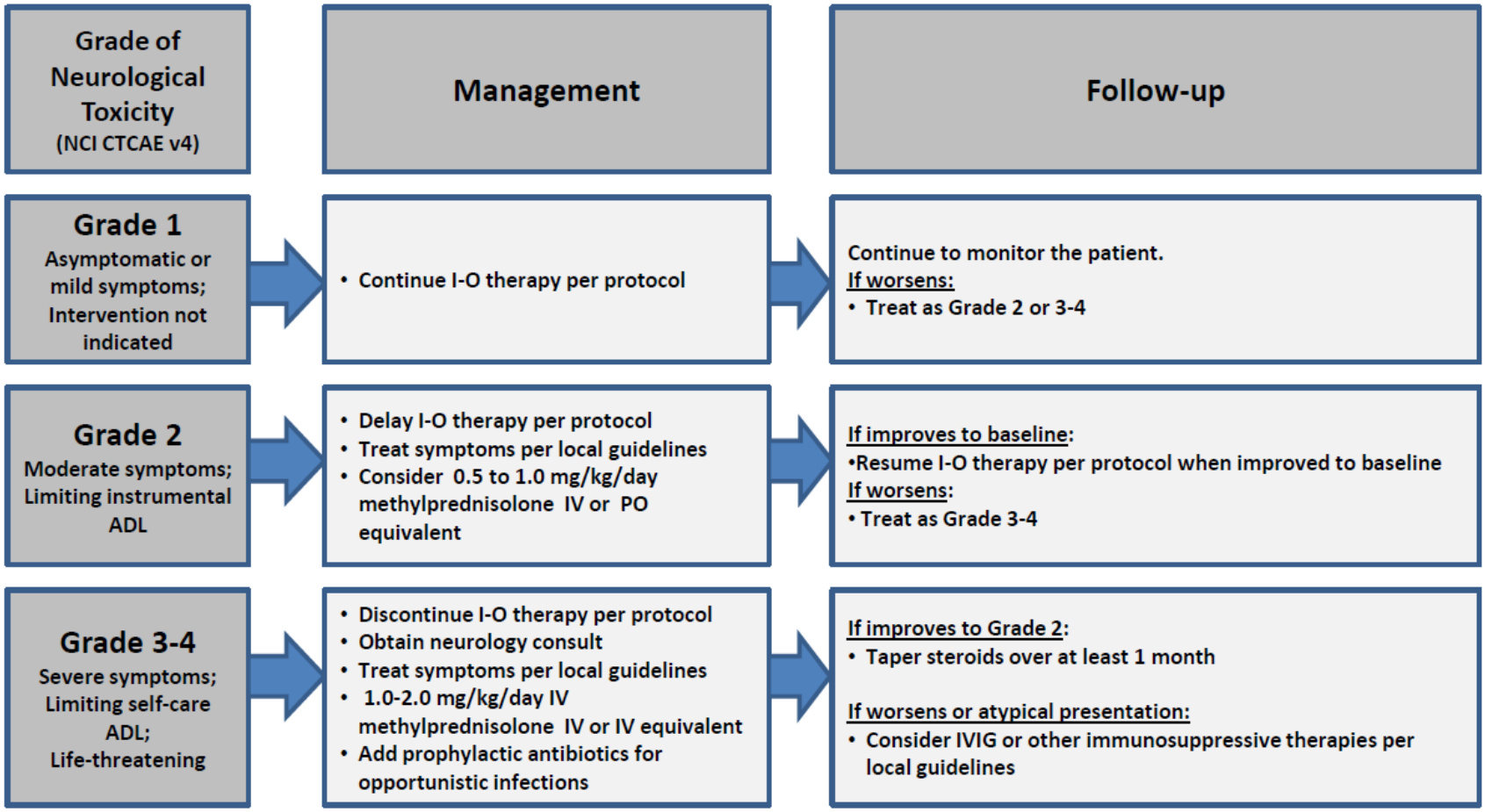
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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

Neurological Adverse Event Management Algorithm

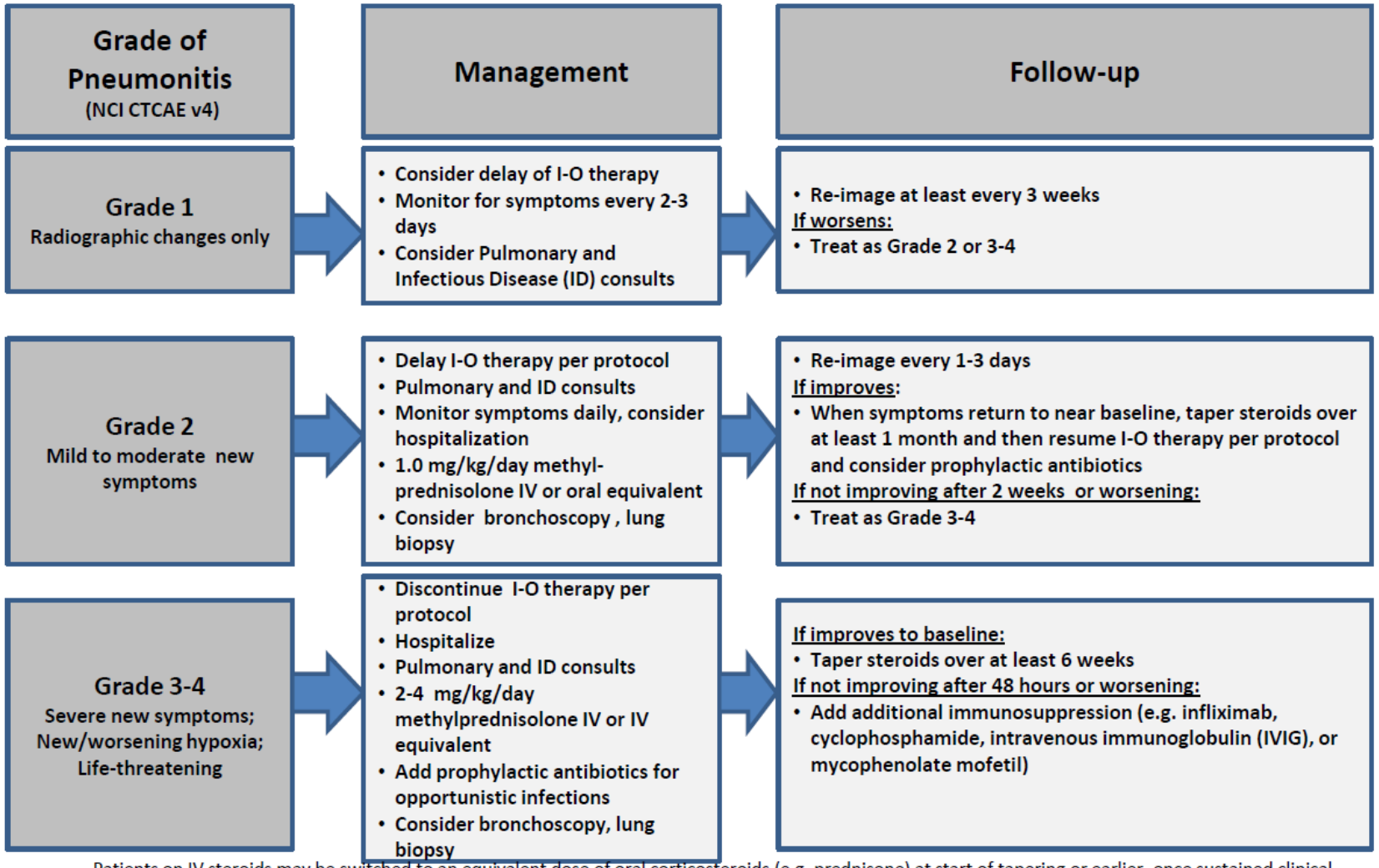
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

Pulmonary Adverse Event Management Algorithm

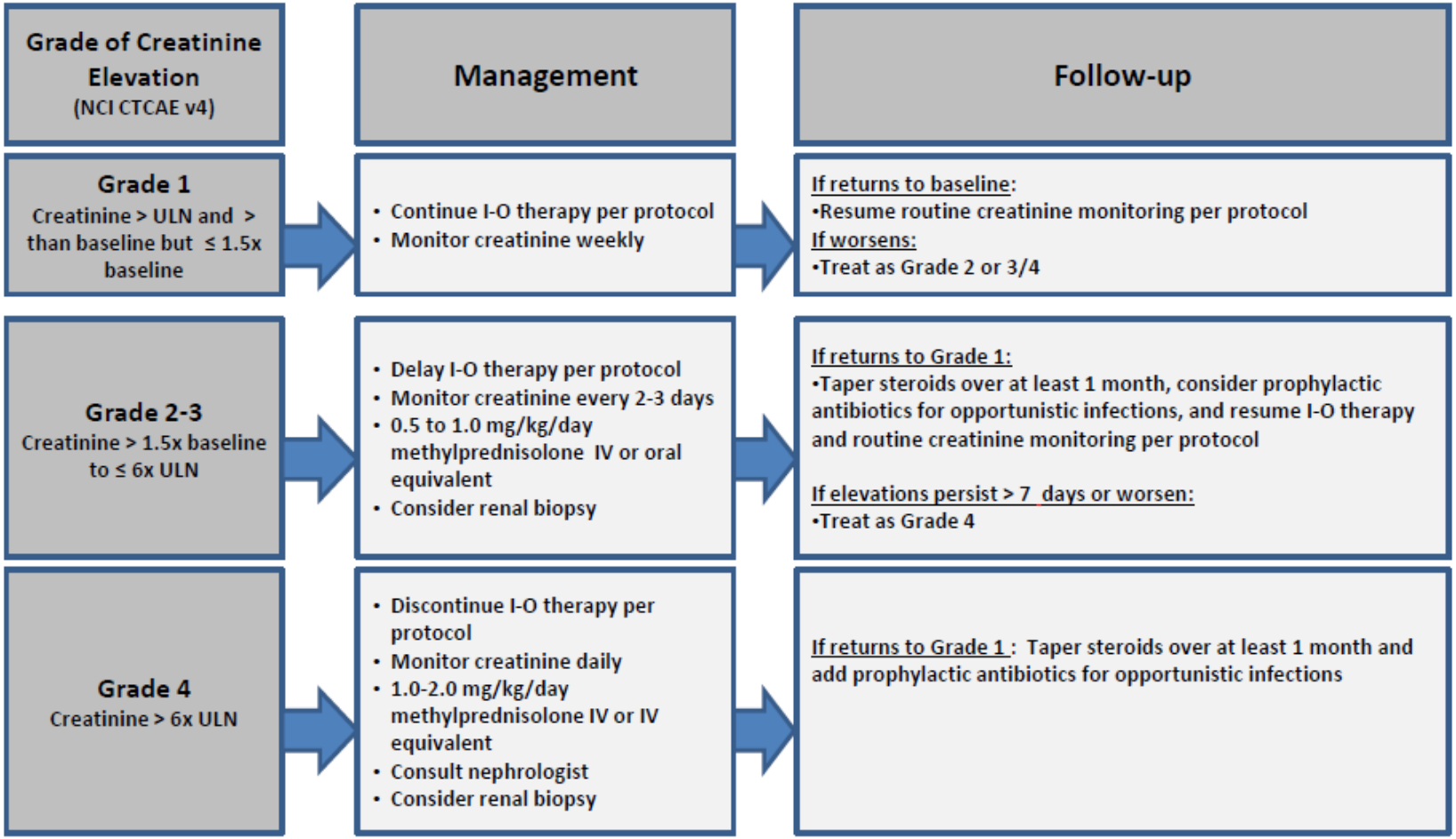
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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

Renal Adverse Event Management Algorithm

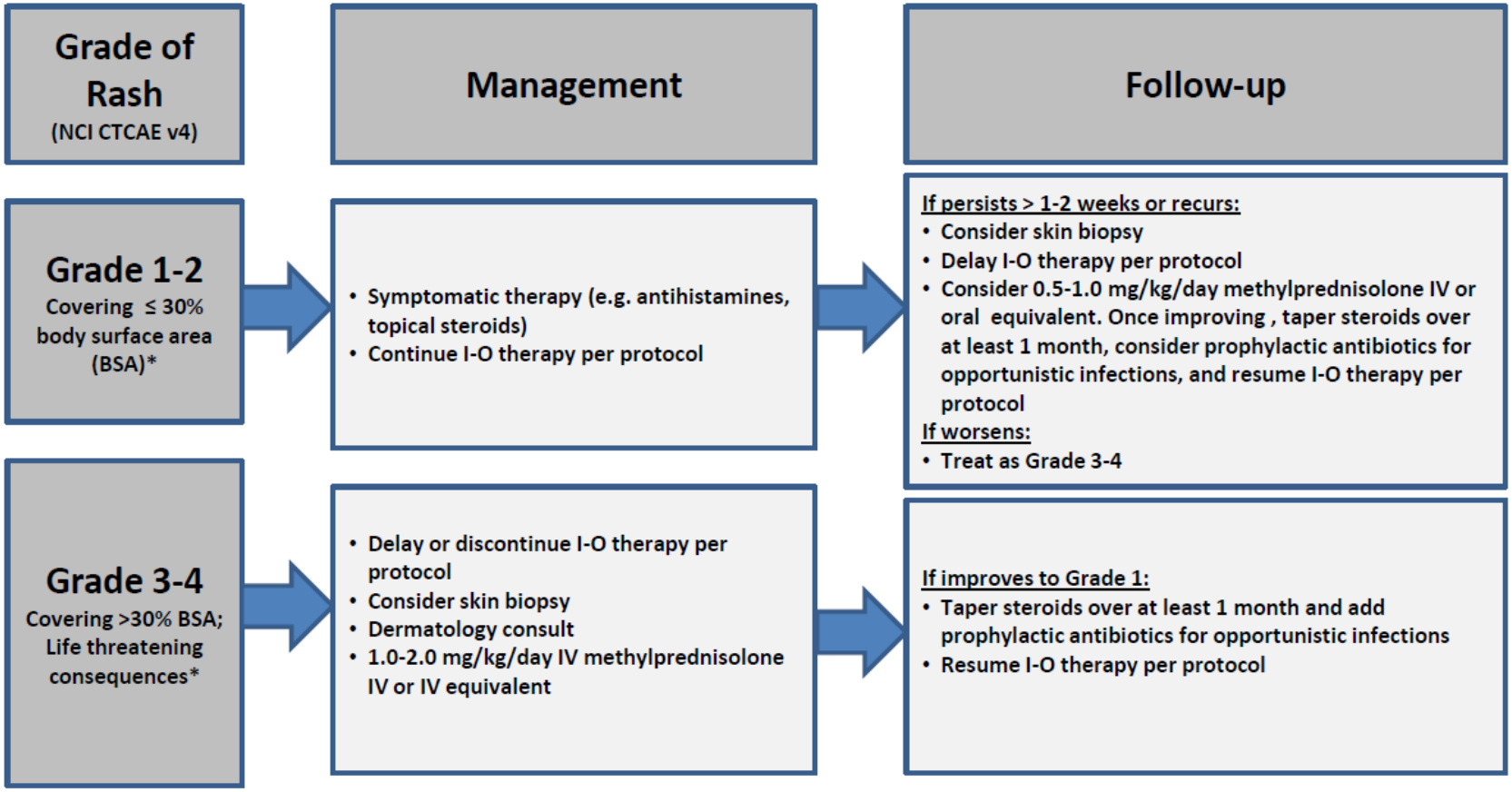
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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

Skin Adverse Event Management Algorithm

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



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

Randomized Phase II Clinical Trial of Cisplatin/Carboplatin and Etoposide (CE) alone or in Combination with Nivolumab as Frontline Therapy for Extensive Stage Small Cell Lung Cancer (ED-SCLC)

Appendix IV

CRADA/CTA

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

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements , the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data."):
    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.
5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.
6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   ncicteppubs@mail.nih.gov

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

Randomized Phase II Clinical Trial of Cisplatin/Carboplatin and Etoposide (CE) alone or in Combination with Nivolumab as Frontline Therapy for Extensive Stage Small Cell Lung Cancer (ED-SCLC)

Appendix V

ECOG Performance Status

PS 0	Fully active, able to carry on all pre-disease performance without restriction
PS 1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature e.g., light house work, office work.
PS 2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
PS 3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
PS 4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.

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Rev. Add1
Rev. Add2
Rev. Add4

Appendix VI

Instructions for Reporting Pregnancies on a Clinical Trial

What needs to be reported?

All pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test regardless of age or disease state) of a female patient while she is on nivolumab, or within 28 days of the female patient's last dose of nivolumab must be reported in an expeditious manner. The outcome of the pregnancy and neonatal status must also be reported.

How should the pregnancy be reported?

For this study, a pregnancy, suspected pregnancy (including a positive or inconclusive pregnancy test) must be initially reported on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave. Once the adverse event is entered into Rave, the Rules Engine on the Expedited Reporting Evaluation Form will confirm whether or not the adverse event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Expedited Reporting Evaluation Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website

When does a pregnancy, suspected pregnancy or positive/inconclusive pregnancy test need to be reported?

An initial report must be done within 24 hours of the Investigator's learning of the event, followed by a complete expedited CTEP-AERs report within 5 calendar days of the initial 24-hour report.

What other information do I need in order to complete the CTEP-AERs report for a pregnancy?

- The pregnancy (fetal exposure) must be reported as a Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions"
- The pregnancy must be reported within the timeframe specified in the Adverse Event Reporting section of the protocol for a grade 3 event.
- The start date of the pregnancy should be reported as the calculated date of conception.
- The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERs report.

What else do I need to know when a pregnancy occurs to a patient?

- The Investigator must follow the female patient until completion of the pregnancy and must report the outcome of the pregnancy and neonatal status in CTEP-AERs accessed via Medidata Rave.
- The decision on whether an individual female patient can continue protocol treatment will be made by the site physician in collaboration with the study chair and ECOG-ACRIN Operations Office – Boston. Please contact the ECOG-ACRIN Operations Office – Boston to ask for a conference call to be set up with the appropriate individuals.

- *It is recommended the female subject be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.*

How should the outcome of a pregnancy be reported?

The outcome of a pregnancy should be reported as an *amendment* to the initial CTEP-AERs report if the outcome occurs on the same cycle of treatment as the pregnancy itself. However, if the outcome of the pregnancy occurred on a subsequent cycle, a *new* CTEP-AERs report should be initiated reporting the outcome of the pregnancy.

What constitutes an abnormal outcome?

An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. For assistance in recording the grade or category of these events, please contact the CTEP AEMD Help Desk at 301-897-7497 or aemd@tech-res.com, for it will need to be discussed on a case by case basis.

Reporting a Pregnancy Loss

A pregnancy loss is defined in CTCAE as "*A death in utero.*"

For this study, it must initially be reported on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave. Once the adverse event is entered into Rave, the Rules Engine on the Expedited Reporting Evaluation Form will confirm whether or not the adverse event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Expedited Reporting Evaluation Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. The pregnancy loss must be reported as a Grade 4 "*Pregnancy loss"* under the System Organ Class (SOC) "*Pregnancy, puerperium and perinatal conditions"*.

A fetal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERs recognizes this event as a patient's death.

Reporting a Neonatal Death

A neonatal death is defined in CTCAE as "*A newborn death occurring during the first 28 days after birth*" that is felt by the investigator to be at least possibly due to the investigational agent/intervention. However, for this protocol, any neonatal death that occurs within 28 days of birth, without regard to causality, AND any infant death after 28 days that is suspected of being related to the *in utero* exposure to nivolumab must be initially reported on the Adverse Event Form or Late Adverse Event Form in the appropriate Treatment Cycle or Post Registration folder in Medidata Rave. Once the event is entered into Rave, the Rules engine on the Expedited Reporting Evaluation Form will confirm whether or not the event requires expedited reporting. The CTEP-AERS report must then be initiated directly from the Expedited Reporting Evaluation Form in Medidata Rave. Do not initiate the CTEP-AERS report via the CTEP-AERS website. The neonatal death must be reported as a Grade 4 "*Death neonatal"* under the System Organ Class (SOC) "General disorder and administration site conditions".

A neonatal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERs recognizes this event as a patient's death.

Additional Required Forms:

When submitting CTEP-AERs reports for pregnancy, pregnancy loss, or neonatal loss, the **CTEP *'Pregnancy Information Form'*** must be completed and faxed along with any

additional medical information to CTEP (301-897-7404). This form is available on CTEP's website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf)

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Appendix VII

EA5161 Collection and Shipping Kit Order Instructions

Specimen Collection/Shipping Kits are being provided by CENETRON CENTRAL LABORATORIES and are to be ordered ONLINE.

Starter kits are not available. Kit requests are to be made AFTER patient randomization.

Questions regarding kits can be directed to projectmanagement@cenetron.com or call the Cenetron Clinical Trials Group at (512) 439-2000.

Ordering Process:

- At time of patient randomization, provide the contact for kit ordering in OPEN
- Following randomization of the patient to the trial, go to the website www.cenetron.com and click on the 'Order Kits' button at the top right. It is recommended that kits be ordered same day as patient randomization.
- The order form is not study specific and can be used for any study. Complete the online form as follows:
  - Sponsor (REQUIRED): ECOG-ACRIN
  - Contact Name (REQUIRED): Name of the institution kit contact. Should match the name of the individual provided in OPEN as the kit contact
  - Protocol Number (REQUIRED): EA5161
  - Phone Number (REQUIRED): Phone number of the kit contact. Please ensure that this is a number that can be reached from an external caller
  - Site Number (REQUIRED): Institution NCI Site ID
  - FAX Number: Fax number of the kit contact
  - Investigator: Last name of the kit contact is adequate
  - Email (REQUIRED): Email of the institution kit contact. Must be entered twice to confirm
  - Date Supplies Needed (REQUIRED): Add three (3) business days or more to order date. (E.g. if ordering on 2/5/2016, indicate 2/10/2016 to accommodate the weekend. Reminder that holidays must also be considered in this timeline)
  - KIT NAME (REQUIRED): EA5161 Collection Kit
  - Quantity: 1
  - Comments: Provide EA5161 Patient Case ID# and full shipping address
    - 'Patient Case ID =' #####
    - *'Ship Kit to'* name of the individual to whom the kit is being shipped. (May be different than the kit contact provided above)
    - Full street address, town, state and zip code
  - Answer the security question

Please complete this form correctly, including the valid ECOG-ACRIN patient case number and complete shipping address. If information is missing the kit processing will be delayed.