For Protocol Amendment 1 to: **NRG-HN007**, An Open-Label, Phase III Study of Platinum-Gemcitabine With or Without Nivolumab in the First-Line Treatment of Recurrent or Metastatic Nasopharyngeal Carcinoma

NCI/Local Protocol #: NRG-HN007

NCI Protocol Version Date: February 16, 2021

Request for Rapid Amendment (RRA) for studies using nivolumab:

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| 7.3 | In response to a CTEP Request for Rapid Amendment (RRA) for studies using nivolumab, the CAEPR for nivolumab (Version 2.4, December 2, 2020) was revised as follows:<br><br>• The SPEER grades have been updated.<br>• Added New Risk:<br>  • Less Likely: CD4 lymphocytes decreased<br>  • Rare: Enterocolitis; Eye disorders - Other (Vogt-Koyanagi-Harada); Hepatobiliary disorders - Other (immune-mediated hepatitis); Renal and urinary disorders - Other (immune-mediated nephritis)<br>• Modified Specific Protocol Exceptions to Expedited Reporting (SPEER) reporting requirements:<br>  • Added: CD4 lymphocytes decreased<br>• Provided Further Clarification:<br>  • Immune system disorders - Other (sarcoid granuloma) is now reported as Immune system disorders - Other (sarcoidosis). |

Other changes:

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|---|---|
| Global | • The protocol version date was updated in the document footer.<br>• Formatting and typographical errors were corrected as needed. |
| Cover page | • Contact information for the Quality of Life Co-Chair was updated.<br>• This amendment was added to the Document History table. |
| 3.1.11 | *"Arm 2"* was corrected to *"Arm 1"*. |
| 3.1.12 | The weblink was updated. |
| 4.1 | • *"Urine analysis"* was revised to *"Urinalysis (to include protein)"* for clarification.<br>• In footnote number 3, *"free"* was added before *"T4"* and *"T3"* for clarification. |
| 5.1.5 | The infusion time was corrected from 60 to 30 minutes to align with section 9.2 as referenced in NRG's December 02, 2020 broadcasted study memo. |
| 5.2.2 | *"5.4.2"* was inadvertently referenced in the 3rd bullet and was removed. |
| 7.5.2 | The first paragraph under "Additional Protocol-Specific Instructions or Exceptions to Expedited Reporting Requirements" was removed as this text was inadvertently added. |
| 8.1<br>8.3.1 | These sections were updated per current CTSU logistics. |
| 10.1.3<br>10.3.1 | These sections were updated per NRG Biobank logistics and to clarify ctDNA collection for Asian sites. |

**NRG ONCOLOGY**

**NRG-HN007**
***(ClinicalTrials.gov NCT #04458909)***

# AN OPEN-LABEL, PHASE III STUDY OF PLATINUM-GEMCITABINE WITH OR WITHOUT NIVOLUMAB IN THE FIRST-LINE TREATMENT OF RECURRENT OR METASTATIC NASOPHARYNGEAL CARCINOMA

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology; ECOG-ACRIN Medical Group; and SWOG.

**Coordinating Center:**
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**The following NCTN Group Study Champion has been added to this trial:**

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**Protocol Agent**

| Agent | Supply | NSC # | IND # | IND Sponsor |
|---|---|---|---|---|
| Nivolumab | CTEP/PMB | 748726 | | DCTD, NCI |
| Carboplatin | Commercial | 241240 | | |
| Cisplatin | Commercial | 119875 | | |
| Gemcitabine | Commercial | 613327 | | |

**Participating Sites**

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

**Document History**

| | Version Date |
|---|---|
| **Amendment 1** | **February 16, 2021** |
| Initial | August 31, 2020 |

**NRG ONCOLOGY**

**NRG-HN007**

**AN OPEN-LABEL, PHASE III STUDY OF PLATINUM-GEMCITABINE WITH OR WITHOUT NIVOLUMAB IN THE FIRST-LINE TREATMENT OF RECURRENT OR METASTATIC NASOPHARYNGEAL CARCINOMA**

<table>
<tr><td colspan="3">CONTACT INFORMATION</td></tr>
<tr><td>For regulatory requirements:</td><td>For patient enrollments:</td><td>For data submission:</td></tr>
<tr><td>Regulatory documentation must be submitted to the CTSU via the Regulatory Submission Portal. Regulatory Submission Portal: (Sign in at www.ctsu.org, and select Regulatory > Regulatory Submission.)<br><br>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.<br><br>Contact the CTSU Regulatory Help Desk at 1-866-651-2878 for regulatory assistance.</td><td>Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.<br><br>Contact the CTSU Help Desk with any OPEN-related questions by phone or email : 1-888-823-5923, or ctsucontact@westat.com.</td><td>Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.</td></tr>
<tr><td colspan="3">The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific page located on the CTSU members' website (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 in with a CTEP-IAM username and password.</td></tr>
<tr><td colspan="3"><u>For clinical questions (i.e. patient eligibility or treatment-related)</u><br>Contact the Study Data Managers of the Lead Protocol Organization.</td></tr>
</table>

**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.

**TABLE OF CONTENTS**

**NRG-HN007**

**SCHEMA**

**STRATIFY**

- Disease (locoregional only vs. lung metastases vs. other distant metastases)
- Zubrod/ECOG performance status (0 vs. 1)
- Prior platinum-gemcitabine therapy (Yes vs. No)*

**RANDOMIZE** (1:1)

↓ ↓

| **Arm 1 (Experimental)**** | **Arm 2 (Control)**** |
|---|---|

| | |
|---|---|
| Platinum (Cisplatin or Carboplatin)<br>+<br>Gemcitabine<br>+<br>Nivolumab | Platinum (Cisplatin or Carboplatin)<br>+<br>Gemcitabine |

*See section 3.2.2 and 14.1 for more details.

**See Section 5 for systemic therapy treatment details.

# 1. OBJECTIVES

## 1.1 Primary Objective

To determine if adding nivolumab to platinum-gemcitabine as first-line treatment improves overall survival (OS) for patients with recurrent and/or metastatic nasopharyngeal carcinoma (NPC).

## 1.2 Secondary Objectives

1.2.1 To compare patterns of failure (local-regional relapse and distant metastasis) between treatment arms.

1.2.2 To determine if adding nivolumab to platinum-gemcitabine as first-line treatment improves the objective tumor response based on RECIST 1.1.

1.2.3 To determine if adding nivolumab to platinum-gemcitabine as first-line treatment improves progression free survival (PFS) for patients with recurrent and/or metastatic NPC.

1.2.4 To evaluate the toxicity based on CTCAE v5.0.

1.2.5 To characterize patient-reported symptomatic toxicities measured by PRO-CTCAE.

1.2.6 To assess quality of life (QOL), as measured by EORTC QLQ-C30, between the two arms (primary PRO).

1.2.7 To assess fatigue, as measured by Multidimensional Fatigue Inventory (MFI-20), between the two arms (secondary PRO).

1.2.8 To determine if a subset of patients based on an optimal cutoff point of PD-L1 CPS/TPS is more likely to benefit in terms of PFS from adding nivolumab to platinum-gemcitabine as first-line treatment.

## 1.3 Exploratory Objectives

1.3.1 To determine if a subset of patients based on an optimal cutoff point of PD-L1 CPS/TPS is more likely to benefit in terms of OS from adding nivolumab to platinum-gemcitabine as first-line treatment.

1.3.2 To determine changes in QOL as measured by EORTC QLQ-C30, and in fatigue as measured by MFI-20, between and within arms over time (exploratory PRO).

1.3.3 To collect blood and tissue specimens for future translational research.

# 2 BACKGROUND

## 2.1 Epidemiology and Natural History of Endemic Nasopharyngeal Carcinoma (NPC)

NPC is endemic to Southern China and Southeast Asia where 129,079 new cases and 72,987 NPC-related deaths were reported worldwide in 2018 (Globocan 2018). Approximately 5% to30% of patient presented with metastatic NPC at diagnosis, while 30% of patients will recur at distant sites (and less commonly at locoregional sites) despite radiotherapy (Chua 2016).

## 2.2 Current Standard of Care for Metastatic or Incurable Recurrent NPC

Platinum-based chemotherapy is the standard first-line therapy for the treatment of recurrent or metastatic NPC. Historic data from single-armed studies have reported the median OS of metastatic NPC to be 12 to 15 months following first-line chemotherapy (Lee 2015). Based on the phase III study by Zhang et al, which compared 6 cycles of cisplatin-gemcitabine (GC) with cisplatin-5-fluorouracil in the first-line treatment of metastatic NPC in 362

patients, GC was superior in terms of objective response rate (ORR) (64% vs 46%), median PFS (7.0 vs 5.6 months; hazard ratio, HR=0.55; 95% CI: 0.44-0.68; p<0.0001), and median OS (29.1 vs 20.9 months; HR=0.62; 95% CI: 0.45-0.84; p=0.0025) (Zhang 2016). However, most patients will progress within 5 to 7 months. A Canadian retrospective cohort containing patients with non-keratinizing and keratinizing NPC has shown that GC is active as well in the palliative setting (Ma 2002). A recent study by Zhang et al has shown that GC is effective as an induction regimen prior to radical chemoradiotherapy (CRT) for non-metastatic, locally advanced NPC (Zhang 2019). Therefore, in planning this study, one has to account for the probability that some patients who recur following CRT will have exposure to GC in the induction portion of their treatment.

### 2.3 Prognostic Factors in Metastatic NPC That Should Be Considered for Patient Stratification

There are several important prognostic factors in patients with metastatic NPC. These include (1) the site of metastasis – patients with metastases limited to the lung live longer than others; (2) the number of metastases – solitary versus multiple; and (3) synchronous or metachronous metastases (Chua 2016).

### 2.4 Preclinical Data on Targeting Immune-Checkpoint Signaling in NPC

NPC is often regarded as an "immune-hot" tumor with overexpression of the programmed death receptor ligand-1 (PD-L1) found in over 40% of NPC (Ma 2018). However, its prognostic significance remains inconsistent (Ma 2018; Fang 2014; Chan 2017). The principal investigators' collaborations have unraveled some characteristics of NPC, which may render it more susceptible to immune checkpoint inhibitors (Li 2017). For instance, the tumor mutational burden (TMB) of NPC is higher than previously described; also the expression of PD-L1 in immune cells and tumor cells is prevalent in NPC models and tumor samples which suggests that upregulation of PD-L1 is one of the immune-evading mechanisms of NPC. Other research has found that latent membrane protein (LMP)-1 can be up-regulated by PD-L1 in NPC cell lines (Fang 2014).

### 2.5 Clinical Data: The Development of Immunotherapy in Recurrent/Metastatic NPC

EBV is ubiquitous in endemic NPC. Strategies such as cytotoxic T-cell therapy directed against EBV infected cells and EBV vaccines have been evaluated in NPC (Chua 2016). However, clinical response was modest. Hsu et al reported a NPC expansion cohort of a phase 1 study of pembrolizumab in 27 patients with PD-L1 positive NPC (Hsu 2017), with ORR of 26.3% reported. In an NCI-sponsored study of 45 patients treated with nivolumab, the ORR was 20.5% and the 1-year OS rate was 59% (95% CI: 44.3-78.5%) (Ma 2018). Among the 41% of tumors expressing PD-L1, a higher proportion of responders was found in the group with higher PD-L1 expression – for PD-L1 expression at < 1%, ≥ 1% and ≥ 10%, the respective response rates to nivolumab were 13%, 29%, and 33% (non-statistical comparison). Two randomized studies comparing PD-1 inhibitors and chemotherapy in subsequent line in metastatic NPC have completed accrual (KEYNOTE-122 and NCT02605967).

## 2.6 Clinical Data on Combining PD-1 Inhibitor and Chemotherapy in NPC and Other Cancers

The positive result of the KEYNOTE-189 study has provided the scientific proof that addition of pembrolizumab can improve the efficacy of platinum-based chemotherapy (Gandhi 2018, Langer 2018). In the study by Gandhi et al, the 1-year OS was 69.2% in the pembrolizumab-chemotherapy group versus 49.4% in the placebo-chemotherapy group (HR=0.49; 95% CI: 0.38-0.64; $p<0.001$ for non-squamous lung cancer). With respect to nivolumab specifically, the safety of nivolumab with platinum-based chemotherapy has been evaluated in phase 1 studies of patients with solid cancers (Weiss 2017; Rizvi 2016). In the study by Rizvi et al (Checkmate 012), the combination of nivolumab (nivolumab at 10 mg/kg, D1), cisplatin (C, D1) gemcitabine (G, D1 & D8) on a 21-day cycle for 4 cycles, followed by nivolumab monotherapy every 3 weeks at the same dose as maintenance, was well tolerated in a cohort of 12 patients with advanced lung cancer. The incidence of treatment-related grade 3-4 toxicities reported in ≥ 10% of patients was 25% (any event) in patients who received GC+nivolumab, which was numerically lower than that reported with cisplatin-pemetrexed-nivolumab (47%, n = 15) or carboplatin-paclitaxel-nivolumab (73%, n = 15). In the GC+nivolumab arm, the most common grade 3-4 toxicities were anemia, pneumonitis, thrombocytopenia, and neutropenia (1 patient per toxicity). Other immune-related toxicities such as skin rash, diarrhea (no colitis), and thyroid function disturbances were only grade 1-2 in severity. Notably, there were no reports of renal failure or ALT/AST increase. Only 8% of patients (1 of 12 patients) in the GC+nivolumab arm discontinued study treatment due to treatment-related toxicities, the lowest rate compared with cisplatin-pemetrexed-nivolumab (33%). Importantly, Rivzi et al found that pharmacokinetic modeling suggested that nivolumab 5 mg/kg every 3 weeks results in sustained exposure between treatments, equivalent to nivolumab 3 mg/kg every 2 weeks. The authors concluded that the combination of nivolumab (5 mg/kg) and platinum doublet-chemotherapy at an every 3 week schedule should be the regimen for phase III evaluation.

Regarding the use of nivolumab at an every 3 week schedule (360 mg flat dose), the Checkmate 227 study is an ongoing 4-arm study comparing standard chemotherapy with nivolumab alone, nivolumab+ipilumab, or nivolumab+chemotherapy (Borghaei 2018). The nivolumab+chemotherapy arm uses a flat dose of nivolumab 360 mg every 3 weeks and platinum-doublet chemotherapy (choices included cisplatin or carboplatin, together with gemcitabine, pemetrexed, or paclitaxel). An interim report found that the nivolumab-chemotherapy arm (n = 177) improves PFS and is well tolerated (with only 13% discontinuation rate). Enrollment is ongoing.

Ueno et al recently published a phase I study of an every 2 week regimen of GC+nivolumab in patients with recurrent biliary cancer and found that the regimen is active with manageable toxicities (Ueno 2019). Gupta et al reported their interim experience with a 3-weekly schedule of cisplatin (70 mg/m$^2$ on D1), gemcitabine (1000 mg/m$^2$ on D1 & D8) and nivolumab (360 mg flat dose) IV on D8 every 21 days, in the neoadjuvant treatment of patients with muscle-invasive bladder cancer (Gupta 2019). Of the 12 (out of 41 planned total) patients treated to date, the combination has not resulted in any added toxicities or immune-related AEs.

Fang et al from China reported a phase I/II study of an IgG4 against PD-1, camrelizumab

(Hengrui Medicine Co., China) as monotherapy and in combination with GC in the treatment of recurrent/metastatic NPC (Fang 2018). The 1-yr PFS of 61% compares favorably with the historic PFS of 20% with GC alone in a similar setting (Zhang 2016).
Ma et al recently published a phase I trial of nivolumab at 240 mg every 2 weeks or 360 mg every 3 weeks flat dosing of nivolumab in patients with NPC (Ma 2019). Nivolumab monotherapy at 3 mg/kg and flat doses of 240 mg and 360 mg were well tolerated in this Chinese patient population, with PK profiles at 3 mg/kg being similar to those of patients treated in Korean patients, in which PK data were shown to be comparable to United States and Japanese populations treated in previous reports.

**2.7 Impact of KEYNOTE-048 on the Design of This Study**

Reported in late October 2018 and again in 2019 (Burtness 2018, Rischin 2019), this 3-arm trial compared pembrolizumab alone with pembrolizumab and platinum-5FU and the "EXTREME" regimen in recurrent head and neck squamous cancer (HNSC). Patients with tumors with a CPS ≥ 1% and ≥ 20% benefited more from having pembrolizumab alone or together with chemotherapy. We analyzed a cohort of 98 IO-naïve patients with NPC (unpublished data, Prof KW Lo). The percentage of tumors with CPS of ≥ 1% or ≥ 20% are 91.8% and 37.7%, while the percentages of TPS of ≥ 1% or ≥ 20% are 55.1% and 25.5%, respectively. A non-statistical trend favoring better RECIST response was observed in a nivolumab-treated cohort with a TPS or CPS ≥ 1% (Ma 2018). Therefore, we hypothesize that CPS or TPS may be useful in selecting patients for nivolumab-chemotherapy in NPC.

**2.8 Prognostic and Predictive Biomarkers in NPC**

Plasma EBV DNA as a prognostic biomarker for NPC: EBV infection is ubiquitous in non-keratinizing NPC and plasma EBV DNA can be detected in over 96% of NPC patients using real time PCR, a technique pioneered by the team led by Dennis Lo and Allen Chan at the Chinese University of Hong Kong. Plasma EBV DNA clearance during the early phase of treatment has been shown to correlate with survival in patients undergoing first-line chemotherapy for metastatic NPC (Wang 2010, Chua 2016). This marker has also been shown to closely reflect tumor burden. The role of this marker in patients undergoing combined chemotherapy and immune-checkpoint inhibitor in metastatic NPC warrants investigation.

Programmed death receptor ligand-1 as biomarker of response to immune-checkpoint inhibitors: PD-L1 expression in tumor has been evaluated extensively as a predictive biomarker of response to PD1/L1 inhibitor in different solid tumors. Different commercial companion diagnostic assays for PD-L1 are now available, each assay using a different method of scoring PD-L1 expression with different clinical cut-off values. The "Blueprint PD-L1 IHC Assay Comparison Project" revealed that the 22C3, 28-8, and SP263 PD-L1 assays are closely aligned on tumor cell staining whereas the SP142 assay showed consistently fewer tumor cells stained (Hirsch 2017). The PD-L1 CPS and TPS scoring system have been prospectively evaluated together with the 22C3 assay for selecting patients with lung, cervical, urothelial and non-NPC HNSC for PD1 inhibitor therapy. In KEYNOTE-048, over 800 patients with metastatic or recurrent HNSC were randomized to 1 of 3 arms: (1) pembrolizumab alone if the PD-L1 CPS was ≥ 20%; (2) EXTREME regimen (chemotherapy and cetuximab); or (3) pembrolizumab and chemotherapy. In this study, an

OS advantage was seen in patients with PD-L1 CPS "≥ 20%" (HR=0.61; 95% CI 0.45-0.83; p = 0.0007) or "≥ 1%" (HR=0.78; 95% CI: 0.64-0.96; p=0.0086) who received pembrolizumab alone compared with the EXTREME regimen (Burtness 2018). For patients randomized to the two chemotherapy-based arms, the subgroup analysis based on PD-L1 status has not been reported to date. There is no reported information about the clinical significance of CPS and TPS for NPC. In a single-arm phase II study of nivolumab in recurrent/metastatic NPC led by the principal investigator of this current study, there was a non-statistically higher proportion of responders among those with tumors expressing PD-L1 (22C3 assay) > 1% and > 10% (Ma 2018). But the study was underpowered to detect any survival difference. No other trials reported to date on PD-1 inhibitor in NPC have investigated the significance of PD-L1 expression using the 22C3 assay.

### 2.9 Quality of Life and Other Patient-Reported Outcomes in Patients with NPC Receiving Immunotherapy and Chemotherapy

Quality of life (QOL) is an important endpoint in phase III clinical trials to assess treatment effects from patients' perspectives. Findings from QOL or other patient-reported outcomes (PROs) can be used to inform and guide clinical practice changes suggested by the clinical trials. The effect of nivolumab combined with chemotherapy on QOL is unclear for patients with recurrent/metastatic NPC. Data from a phase III randomized trial for patients with recurrent/metastatic HNSC did show significant and clinically meaningful differences in favour of nivolumab for role functioning, social functioning, fatigue, dyspnoea, and appetite loss measured by the European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire–Core 30 (EORTC QLQ-C30, Harrington 2017). The beneficial effect of nivolumab on QOL was also demonstrated in phase III clinical trials for other cancers, such as advanced renal cell carcinoma (Cella 2019). Additionally, another PD-1 checkpoint inhibitor, pembrolizumab, has been shown to generate favourable results on QOL for patients with recurrent/metastatic HNSC (Cohen 2019) or with advanced non-small-cell lung cancer (Brahmer 2017).

Fatigue is among the most common and distressing side effects of cancer and its treatment; recent studies on immunotherapy have further shown that fatigue is one of the most prominent side effects of immune checkpoint inhibitors. The incidence rate of all-grade fatigue in patients receiving nivolumab ranged from 16% to 33% among various cancer diagnoses (Abdel-Rahman 2016). In patients with recurrent/metastatic NPC, a phase II single-arm trial showed that fatigue was the most common side effect of nivolumab, and was present in 22% of patients (Ma 2018). Similarly, fatigue was the second most common side effect for patients with recurrent/metastatic HNSC receiving pembrolizumab (Cohen 2019). Although the mechanisms of a high rate of fatigue among patients receiving immunotherapy are unclear, it is possible that other toxicities of immune checkpoint inhibitors may contribute to or present with nonspecific symptoms such as fatigue. These immunologic mediated toxicities from immunotherapy include pneumonitis and endocrinopathies (pituitary, hypothalamus, thyroid, and adrenal disease). Since the effects of nivolumab on patient-reported fatigue have not been well documented in patients with recurrent/metastatic NPC, further large studies are warranted.

# 3 ELIGIBILITY AND INELIGIBILITY CRITERIA

## 3.1 Inclusion Criteria (16-FEB-2021)

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

**3.1.1** Pathologically (histologically or cytologically) proven diagnosis of NPC that has recurred at locoregional and/or distant sites. For locoregional recurrence, the disease must not be amenable to potentially curative surgery or re-irradiation. The following histological types are accepted: (a) Keratinizing – squamous cell carcinoma; (b) Non-keratinizing – undifferentiated or poorly differentiated;

**3.1.2** Measurable disease by the RECIST 1.1 criteria. Lesion(s) that have been irradiated previously can be counted as measurable as long as radiological progression has been demonstrated prior to enrollment;

**3.1.3** Age ≥ 18;

**3.1.4** History/Physical examination by Medical Oncologist or Clinical Oncologist within 14 days prior to registration;

**3.1.5** Zubrod/ECOG Performance Status of 0-1 within 14 days prior to registration;

**3.1.6** Contrast enhanced MRI or CT of the nasopharynx and neck within 30 days prior to registration;

**3.1.7** Contrast enhanced CT scan of the chest, abdomen and pelvis within 30 days prior to registration;

**3.1.8** Adequate organ function within 14 days prior to registration defined as follows:

**Adequate Organ Function Laboratory Values**

| **Organ Function** | **Laboratory value** |
|---|---|
| **Hematological** | |
| Absolute neutrophil count (ANC) | ≥ 1500 cells/mm$^3$ |
| Platelets | ≥ 100,000 cells/mm$^3$ |
| Hemoglobin | ≥ 9.0 g/dL (Transfusion is accepted. Erythropoietin dependency not accepted.) |
| **Hepatic** | |
| Total bilirubin | ≤ 1.5 × ULN OR direct bilirubin ≤ ULN for patients with total bilirubin levels >1.5 × ULN. Patients with known Gilbert's syndrome are not excluded. |
| ALT (SGPT) | ≤ 2.5 × ULN (≤ 3 × ULN for patients with liver metastases) |
| **Renal** | |
| Serum creatinine<br>OR<br>Calculated creatinine clearance (CrCl) based on Cockcroft-Gault equation | ≤ 1.5× ULN<br>OR<br>≥ 30 mL/min for patients with serum creatinine levels > 1.5 × ULN. In this protocol, cisplatin or carboplatin may be used at the discretion of the investigator – |

| | |
|---|---|
| | except for patients with CrCl between 30-50 mL/min, for whom carboplatin should be used instead of cisplatin. |

Legend:

- ULN = upper limit of normal based on institutional standard
- ALT (SGPT) = alanine aminotransferase

**3.1.9** For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable and patients must be receiving anti-viral therapy at enrollment. Patients must agree to continue anti-viral therapy throughout the study period as directed by their treating physicians.

- Known positive test for hepatitis B virus surface antigen (HBsAg) indicating acute or chronic infection would make the patient ineligible unless the viral load becomes undetectable on anti-viral therapy.
- Patients who are immune to hepatitis B (anti-Hepatitis B surface antibody positive) are eligible (i.e., patients immunized against hepatitis B).
- In some centers, hepatitis B core antibody (anti-HBc) are done routinely before chemotherapy for some cancer patients. This is because patients who are HBsAg-negative but positive for anti-HBc should have undetectable HBV viral load at enrollment and receive prophylactic anti-viral therapy throughout the study (American Society of Clinical Oncology 2015 guideline, Hwang 2015). In this protocol anti-HBc should be performed based on institutional standards.

**3.1.10** Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load;

**Note**: Known positive test for hepatitis C virus ribonucleic acid (HCV RNA) indicating acute or chronic infection would make the patient ineligible unless the viral load becomes undetectable on suppressive therapy;

**3.1.11** For women of childbearing potential (WOCBP), negative serum or urine pregnancy test within 14 days prior to registration. For WOCBP randomized to Arm 1, an additional negative serum or urine pregnancy is required within 24 hours prior to starting nivolumab treatment.

- Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes.

**3.1.12** Women of childbearing potential (WOCBP) and men who are sexually active with WOCBP must be willing to use an adequate method of contraception (As a reference only for sites in the United States: https://www.cdc.gov/reproductivehealth/contraception/index.htm; for other sites, women must use an effective oral contraception and the male partner must use condom) during and after treatment (see Section 9.2);

**3.1.13** The patient or a legally authorized representative must provide written informed consent prior to study entry.

## 3.2 Exclusion Criteria

***Patients with any of the following conditions are NOT eligible for this study.***

**3.2.1** Diagnosed with another invasive malignancy (except non-melanomatous skin cancer) unless disease free for more than 3 years. Note: Patients with basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ (e.g. breast carcinoma, cervical cancer in situ) who have undergone potentially curative therapy are not excluded);

**3.2.2** Any prior systemic anti-cancer agents (including chemotherapy and investigational agents) for the purpose of treating locoregional and/or distant recurrence of NPC.

**3.2.3** Patients who have received neoadjuvant (induction) and/or adjuvant chemotherapy for primary NPC with chemotherapy (any drug regimens including those containing platinum and/or gemcitabine) at or within 6 months prior to registration are excluded (counting from the last day of the chemotherapy for the primary NPC, prior to enrolling into the current study). The following subgroups of patients are NOT excluded:

- Patients who have received neoadjuvant (induction) and/or adjuvant chemotherapy for primary (non-metastatic/non-recurrent) NPC more than 6 months prior to registration, counting from the last day of the chemoradiotherapy for the primary NPC, prior to enrolling into the current study.
- *For prior RT with radical intent:* Patients who have prior radiotherapy (RT) to the primary and locoregional disease (i.e. non-recurrent disease) with or without concurrent cisplatin or carboplatin monotherapy are not excluded as long as they have not received any neoadjuvant/adjuvant chemotherapy within 6 months prior to registration (counting from the last day of the chemotherapy), and that the last RT fraction (with radical intent) has been given more than 3 months prior to registration.
- *For RT with palliative intent*: Prior radiotherapy (RT) at or within 30 days prior to registration, this includes RT given with palliative intent (with or without concurrent cisplatin or carboplatin alone) to recurrent/ metastatic sites in patients with recurrent/metastatic NPC. The re-irradiated sites must not be the only sites of measurable recurrent disease;
- Prior chemotherapy for cancers other than NPC is allowed as long as the last course of chemotherapy was administered more than 3 years prior to registration and the patient has remained disease-free for more than 3 years;

**3.2.4** Prior therapy for any indication, with an anti-PD-1, anti-PD-L1, or anti-PD-L2 agent or with an agent directed to another stimulatory or co-inhibitory T-cell receptor (e.g. CTLA-4, OX-40, CD137);

**3.2.5** History of severe (grade 3-4) hypersensitivity reaction to any monoclonal antibody including nivolumab and/or any of its excipients;

**3.2.6** Severe, active co-morbidity defined as follows:

- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months.
- Myocardial infarction within the last 6 months.
- Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration.
- Chronic obstructive pulmonary disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days of registration.
- Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects.
- History of (non-infectious) pneumonitis that required steroids or has current pneumonitis requiring steroids and/or immunosuppressive therapy.
- History of active TB (Bacillus Tuberculosis, not known to be multi-drug resistant) as defined by the need to receive systemic treatment within the last 2 years or any known history of multi-drug resistant TB. Note: Patients who had a distant history of treated TB (not known to be multi-drug resistant) at 5 or more years from enrollment and have no current symptoms suggestive of active TB, are not excluded from this study. Note: Testing for prior exposure to TB is not required in this study since TB is endemic in parts of Asia.
- Prior solid organ transplant or bone marrow transplant.
- History of active primary immunodeficiency including, but not limited to acquired immune deficiency syndrome (AIDS) based upon current CDC definition; Note: HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatment involved in this protocol may be immunosuppressive.
- Condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone or equivalents) or other immunosuppressive medications within 14 days of registration. Inhaled or topical steroids and adrenal replacement doses < 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease. Steroid premedication for the prophylaxis of CT contrast-related allergies is allowed. The use of dexamethasone as an anti-emetic premedication prior to chemotherapy is also allowed.
- Active autoimmune disease requiring systemic treatment (i.e. disease modifying agents, corticosteroids, or immunosuppressive drugs) within the past 2 years. These include but are not limited to patients with a history of immune-related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as SLE, rheumatoid arthritis, connective tissue diseases, scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, hepatitis; and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome should be excluded because of the risk of recurrence or exacerbation of disease.

**Note**: Patients are permitted to enroll if they have vitiligo; type I diabetes mellitus; hypothyroidism, pituitary or adrenal insufficiency requiring only hormone replacement; psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger (precipitating event);

**3.2.7** Patients who are pregnant or breastfeeding and unwilling to discontinue breastfeeding.

**3.2.8** Known history of grade 3-4 allergic reaction and/or hepatic toxicity to cisplatin, carboplatin, or gemcitabine.

**NOTE:** For patients with known history of grade 3-4 renal toxicity to cisplatin or known history of clinically significant hearing loss (grade 2 or above) attributed to cisplatin, or other intolerances to cisplatin that are of clinical significance, carboplatin can be used in this study and therefore these patients are NOT excluded from enrollment.

**3.2.9** Known CNS metastases and/or carcinomatous meningitis. Patients with base of skull involvement by NPC are not excluded unless their disease is directly invading the brain parenchyma and is associated with clinical symptoms (headaches, nausea and vomiting, neurological abnormalities on physical examination) and/or cerebral edema on radiological imaging;

**3.2.10** Patients who have received a live vaccine within 30 days prior to the first dose of study treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., FluMist®) are live attenuated vaccines and are not allowed.

**3.2.11** History or current evidence of any condition, therapy, or laboratory abnormality that might confound the results of the study, interfere with the subject's participation for the full duration of the study, or is not in the best interest of the subject to participate, in the opinion of the treating investigator.

### 3.3 Inclusion of Women and Minorities

NIH policy requires that women and members of minority groups and their subpopulations be included in all NIH-supported biomedical and behavioral research projects involving NIH-defined clinical research unless a clear and compelling rationale and justification establishes to the satisfaction of the funding Institute & Center (IC) Director that inclusion is inappropriate with respect to the health of the subjects or the purpose of the research. Exclusion under other circumstances must be designated by the Director, NIH, upon the recommendation of an IC Director based on a compelling rationale and justification. Cost is not an acceptable reason for exclusion except when the study would duplicate data from other sources. Women of childbearing potential should not be routinely excluded from participation in clinical research. Please see http://grants.nih.gov/grants/funding/phs398/phs398.pdf.

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

## 4.1 Study Calendar for Treatment Arm 1 (Experimental): Chemotherapy & Nivolumab (See section 3.1 for details) (16-FEB-2021)

| | Prior to Registration | Prior to Treatment | Concurrent platinum, gemcitabine, and nivolumab (Q 21 days) | | | | | | Nivolumab Maintenance (Q 28 days)<br><br>Starts within 4 weeks (± 7 days) from end of last cycle of chemo | End of Treatment ± 30 Days | Follow-up from end of concurrent chemotherapy: q4 months for 2 yrs, q6 months for 3 yrs and then annually |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cyc 1 ± 3 Days | Cyc 2 ± 3 Days | Cyc 3 ± 3 Days | Cyc 4 ± 3 Days | Cyc 5 ± 3 Days | Cyc 6 ± 3 Days | Q 28 days (± 3 days) up to 24 cycles (2 years) | | |
| **Pathologically (histologically or cytologically) proven diagnosis of NPC** | X | | | | | | | | | | |
| **Physical examination by Medical Oncologist or Clinical Oncologist** [1] | Within 14 days | | X | X | X | X | X | X | X | X | X [7] |
| **Concomitant medication** | | X | | | | | | | | | |
| **Zubrod/ECOG Performance Status** | Within 14 days | | X | X | X | X | X | X | X | X | |
| **CBC + Diff** (including include ANC, platelets, Hgb) | Within 14 days | | D1+D8 | D1+D8 | D1+D8 | D1+D8 | D1+D8 | D1+D8 | D1 | | |
| **CMP** (total bilirubin, ALT (SGPT), serum creatinine, fasting glucose [2]**), calculated CrCl** | Within 14 days | | D1+D8 | D1+D8 | D1+D8 | D1+D8 | D1+D8 | D1+D8 | D1 | | |
| **Serum or urine pregnancy test for women of childbearing potential** | Within 14 days | Within 24 hours | | | | | | | | | |
| **Thyroid function tests, fasting glucose** [3] | | | X | | | X | | | X | | |
| **Urinalysis (to include protein)** | | X | | | | | | | D1 of Cyc 1 only | | |
| **HBsAg, Anti-HCV** [4] | X | | | | | | | | | | |
| **Contrast enhanced CT chest (include abdomen and pelvis if clinically indicated)** [5] | Within 30 days | | | | X | | | X | X | | |
| **Contrast enhanced CT or MRI NP+N** [5] | Within 30 days | | | | | | | | | | |
| **Adverse Events Evaluation** | | X | D1+D8 | D1+D8 | D1+D8 | D1+D8 | D1+D8 | D1+D8 | X | X | X [7] |

| | Prior to Registration | Prior to Treatment | Concurrent platinum, gemcitabine, and nivolumab (Q 21 days) | | | | | | Nivolumab Maintenance (Q 28 days)<br><br>Starts within 4 weeks (± 7 days) from end of last cycle of chemo | End of Treatment ± 30 Days | Follow-up from end of concurrent chemotherapy: q4 months for 2 yrs, q6 months for 3 yrs and then annually |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cyc 1 ± 3 Days | Cyc 2 ± 3 Days | Cyc 3 ± 3 Days | Cyc 4 ± 3 Days | Cyc 5 ± 3 Days | Cyc 6 ± 3 Days | Q 28 days (± 3 days) up to 24 cycles (2 years) | | |
| **PRO-CTCAE** [6] | | X | | | | | | X | X (Year 1, Year 2) | | |
| **QOL** [6]<br>▪ **EORTC QLQ-C30**<br>▪ **MFI-20** | | X | | | | | | X | X (Year 1, Year 2) | | |
| **Patient History form (patient reported): Optional** | | X | | | | | | | | | |
| **Specimen submissions for biobanking (Optional, but highly recommended -** See section 10.3 for details**):**<br>• **Archival or Newly Obtained Tissue**<br>• **ctDNA blood (for participating sites only)** | | X | | | | | | | | | |
| **Specimen submissions for biobanking (Optional, but highly recommended -** See section 10.3.1 for details**):**<br>**Plasma EBV DNA blood (for non-keratinizing NPC only)** | | X (Within 7 days of cycle 1, D1) | D8, D15 | D1, D8 | | | | | | | |

[1] For patients with evidence of CHF, MI, cardiomyopathy, or myositis, a cardiac evaluation including lab tests and cardiology consultations as clinically indicated including EKG, CPK, troponin, ECHO cardiogram.
[2] Fasting glucose needs to be performed within 14 days prior to starting treatment.
[3] Thyroid function test (TSH with reflex to free T4; free T3 if clinically indicated) and fasting glucose should be done at each new cycle of NIVOLUMAB for at least 6 months, and then at every 3 cycles of nivolumab thereafter until end of treatment (i.e., every 11-12 weeks).
[4] Patients who are HBsAg positive (or HbsAg-ve, but anti-HB core +ve) should have HBV DNA performed at registration to ensure that the level is undetectable to become eligible for the study. These patients should undergo HBV DNA monitoring according to institutional guideline/practice.
[5] Imaging: See Section 4.3 for details.
[6] This study uses Medidata Patient Cloud ePRO. Remember to register the patient to the Patient Cloud ePRO. For instructions on registering the patients, please refer to Appendix II. Baseline questionnaires will be completed on paper. Patients that consent to Medidata Patient Cloud ePRO will complete all questionnaires electronically using personal electronic device except baseline. The study-specific PRO-CTCAE items for this protocol can be found on the forms section of the CTSU protocol webpage and is titled "NRG-HN007 NCI PRO-CTCAE Item Library".
[7] Follow-up may coincide with the nivolumab cycle.

## 4.2 Study Calendar for Treatment Arm 2 (Control): Chemotherapy alone (See section 3.1 for details)

| | Prior to Registration | Prior to Treatment | Concurrent platinum, gemcitabine (Q 21 days) | | | | | | End of Treatment ± 30 Days | Follow-up from end of concurrent chemotherapy: q4 months for 2 yrs, q6 months for 3 yrs and then annually |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cyc 1 ± 3 Days | Cyc 2 ± 3 Days | Cyc 3 ± 3 Days | Cyc 4 ± 3 Days | Cyc 5 ± 3 Days | Cyc 6 ± 3 Days | | Until PD |
| **Pathologically (histologically or cytologically) proven diagnosis of NPC** | X | | | | | | | | | |
| **Physical examination by Medical Oncologist or Clinical Oncologist** [1] | Within 14 days | | X | X | X | X | X | X | X | X |
| **Concomitant medication** | | X | | | | | | | | |
| **Zubrod/ECOG Performance Status** | Within 14 days | | X | X | X | X | X | X | X | |
| **CBC + Diff** (including include ANC, platelets, Hgb) | Within 14 days | | D1+D8 | D1+D8 | D1+D8 | D1+D8 | D1+D8 | D1+D8 | X | |
| **CMP (**total bilirubin, ALT (SGPT), serum creatinine, fasting glucose [2]**), calculated CrCl** | Within 14 days | | D1+D8 | D1+D8 | D1+D8 | D1+D8 | D1+D8 | D1+D8 | X | |
| **Serum or urine pregnancy test for women of childbearing potential** | Within 14 days | | | | | | | | | |
| **HBsAg, Anti-HCV** [3] | X | | | | | | | | | |
| **Contrast enhanced CT chest (include abdomen and pelvis if clinically indicated)** [4] | Within 30 days | | | | X | | | X | | X [6] |
| **Contrast enhanced CT or MRI NP+N** [4] | Within 30 days | | | | | | | | | |
| **Adverse Events Evaluation** | | X | D1+D8 | D1+D8 | D1+D8 | D1+D8 | D1+D8 | D1+D8 | X | X |
| **PRO-CTCAE** [5] | | X | | | | | | X | | Year 1 & 2 |
| **QOL** [5]<br>**▪ EORTC QLQ-C30** | | X | | | | | | X | | Year 1 & 2 |

| | Prior to Registration | Prior to Treatment | Concurrent platinum, gemcitabine (Q 21 days) | | | | | | End of Treatment ± 30 Days | Follow-up from end of concurrent chemotherapy: q4 months for 2 yrs, q6 months for 3 yrs and then annually |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Cyc 1 ± 3 Days | Cyc 2 ± 3 Days | Cyc 3 ± 3 Days | Cyc 4 ± 3 Days | Cyc 5 ± 3 Days | Cyc 6 ± 3 Days | | Until PD |
| ▪ **MFI-20** | | | | | | | | | | |
| **Patient History form (patient reported)- optional** | | X | | | | | | | | |
| **Specimen submissions for biobanking (Optional, but highly recommended -** See section 10.3.1 for details**)**<br>• **Archival or Newly Obtained Tissue**<br>• **ctDNA blood (for participating sites only)** | | X | | | | | | | | |
| **Specimen submissions for biobanking (Optional, but highly recommended -** See section 10.3.1 for details**): Plasma EBV DNA blood (for non-keratinizing NPC only)** | | X (Within 7 days of cycle 1, D1) | D8, D15 | D1, D8 | | | | | | |

[1] For patients with evidence of CHF, MI, cardiomyopathy, or myositis, a cardiac evaluation including lab tests and cardiology consultations as clinically indicated including EKG, CPK, troponin, ECHO cardiogram.
[2] Fasting glucose needs to be performed within 14 days prior to starting treatment.
[3] Patients who are HBsAg positive (or HbsAg-ve, but anti-HB core +ve) should have HBV DNA performed at registration to ensure that the level is undetectable to become eligible for the study. These patients should undergo HBV DNA monitoring according to institutional guideline/practice.
[4] Imaging: See Section 4.3 for details.
[5] This study uses Medidata Patient Cloud ePRO. Remember to register the patient to the Patient Cloud ePRO. For instructions on registering the patients, please refer to Appendix II. Baseline questionnaires will be completed on paper. Patients that consent to Medidata Patient Cloud ePRO will complete all questionnaires electronically using personal electronic device except baseline. The study-specific PRO-CTCAE items for this protocol can be found on the forms section of the CTSU protocol webpage and is titled "NRG-HN007 NCI PRO-CTCAE Item Library".
[6] See section 4.4 for details.

### 4.3 Objective Tumor Response

The protocol will utilize RECIST, v1.1 for the purposes of evaluating response and progression (Eisenhauer 2009).

- **Progressive Disease (PD)** (per RECIST v1.1): At least a 20% increase in the sum of 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).
- **Second Primary Neoplasm:** Tumor reappearing within the initial and immediate adjoining anatomical region of the primary will be considered local recurrence. Multiple lung nodules/masses are considered distant metastases from the index cancer unless proven otherwise.
- **Local or Regional Relapse:** Relapse is defined as reappearance of tumor after complete response. If possible, relapse should be confirmed by biopsy.

In addition to formal evaluation of progressive disease by RECIST, v. 1.1, investigators will be asked at the time of first progression to report whether progressive disease was local, regional or distant. Sites of distant disease progression should be noted. This will accommodate analysis of patterns of failure.

### 4.4 Tumor Imaging During the Study

**Tumor imaging during concurrent chemotherapy phase:**

Post-treatment scan after cycle 3 +/- 7 days and after cycle 6 (+/-7 days). The result of the post-cycle 6 imaging must be available for assessing best response to chemotherapy (or concurrent chemotherapy-nivolumab) before starting the maintenance.

**Tumor imaging after concurrent chemotherapy phase (maintenance or observation phase):**

(a) **Arm 1 (experimental)**: Tumor imaging should be performed every 12 weeks (+/-7 days) during the nivolumab maintenance therapy. If the patient discontinues nivolumab then the imaging should continue until disease progression. The modality of tumor imaging could be decided at the physician's discretion based on local standards.

(b) **Arm 2 (Control)**: Tumor imaging is recommended within 6 months, and more frequently as clinically indicated such as every 12 weeks until disease progression. The modality of tumor imaging could be decided at the physician's discretion based on local standards.

More frequent imaging may be performed if clinically indicated.

**Tumor imaging after maintenance or observation phase:**

In patients who complete the maintenance (Arm 1) or observation (Arm 2) phase without documented disease progression, the imaging interval will be at the physician's discretion.

## 5. TREATMENT PLAN/REGIMEN DESCRIPTION

**Protocol treatment must begin within 14 days after randomization.**

### 5.1 Systemic Therapy - Summary (16-FEB-2021)

Trial treatment should begin within 14 days of randomization. The treatment to be used in this trial is outlined below in tables 5.1A and 5.1B.

Trial treatment should be administered on Day 1 of each 21 day cycle after all procedures/assessments have been completed as detailed on the Study Calendars in sections 4.2 and 4.3. Trial treatment may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons. For patients randomized to either treatment arms, carboplatin or cisplatin can be used at the investigator's discretion from cycle 1 onwards, except for patients with CrCl < 50 mL/min in whom carboplatin should be used instead of cisplatin – see section 5.1.1 Criteria for starting a new cycle of chemotherapy with or without nivolumab.

**Table 5.1A**

**Arm 1 (Experimental):** Nivolumab-gemcitabine-platinum for 6 cycles + Maintenance nivolumab monotherapy

| | Weeks (Cycle) | | | | | | |
|---|---|---|---|---|---|---|---|
| | **1-3** | **4-6** | **7-9** | **10-12** | **13-15** | **16-18** | **Maintenance Phase** |
| **Nivolumab** [a] Day 1 of each 21 day cycle | **X** | **X** | **X** | **X** | **X** | **X** | Nivolumab 480 mg Q 28 days until a maximum number of 24 cycles [c] |
| **Gemcitabine** Days 1 and 8 per 21 day cycle | **X** | **X** | **X** | **X** | **X** | **X** | |
| **Cisplatin/Carboplatin** [b] Day 1 of each 21 day cycle | **X** | **X** | **X** | **X** | **X** | **X** | |

[a] Nivolumab will be administered prior to chemotherapy when agents are delivered on the same day.

[b] Carboplatin or cisplatin can be used at the investigator's discretion from cycle 1 onwards, except for patients as noted in section 5.1.1.

[c] Nivolumab should be started 4 weeks (+/- 7 days) from the last cycle of chemotherapy (cycle 6). See section 5.1.1 Criteria for starting maintenance nivolumab.

**Table 5.1B**

**Arm 2 (Control):** Gemcitabine-platinum for 6 cycles

| | Weeks (Cycle) | | | | | |
|---|---|---|---|---|---|---|
| | **1-3** | **4-6** | **7-9** | **10-12** | **13-15** | **16-18** |
| **Gemcitabine** Days 1 and 8 per 21 day cycle | **X** | **X** | **X** | **X** | **X** | **X** |
| **Cisplatin/Carboplatin** [a] Day 1 of each 21 day cycle | **X** | **X** | **X** | **X** | **X** | **X** |

[a] Carboplatin or cisplatin can be used at the investigator's discretion from cycle 1 onwards, except for patients as noted in section 5.1.1.

### 5.1.1 Criteria for starting a new cycle of treatment:

Criteria for starting a new cycle (day 1) of chemotherapy with or without nivolumab:

- Zubrod/ECOG Performance status ≤ 1;
- CBC/differential and chemistries obtained on day 1 (+/- 2 days) of each new cycle of chemotherapy, with adequate bone marrow function defined as follows: Absolute Neutrophil Count (ANC) ≥ 1,500 cells/$mm^3$ and Platelets ≥ 100,000 cells/$mm^3$;
- Total bilirubin < Grade 2 (CTCAE, v5.0);
- ALT ≤ 2.5 × ULN (≤ 3 × ULN for patients with liver metastases)
- Serum creatinine < Grade 2 (CTCAE, v5.0). For patients on cisplatin, the calculated CrCl should be ≥ 50 mL/min (by Cockcroft-Gault formula) – switch to carboplatin is allowed during treatment with cisplatin – see section 6.2.1;
- All non-hematological AEs that are deemed related to the study drugs, and/or are clinically significant must be < Grade 3 (CTCAE, v5.0). Non-clinically significant AEs are those which are deemed unrelated to the study drugs, or biochemical abnormalities that are not worsening and are not accompanied by any clinical symptoms.

Criteria for starting a new cycle of maintenance nivolumab (for patients randomized to Arm 1):

Some patients may continue to benefit from treatment, maintaining or improving responses after progression including those treated with steroids.
Restarting applies only to grade 2 events and some grade 3 events (skin rash and thyroiditis).
For non-autoimmune or non-inflammatory events patients may resume treatment with study drug when the drug-related AE(s) resolve to Grade ≤ 1 or baseline value, with the following exceptions:

- Patients may resume treatment in the presence of Grade 2 fatigue
- Evaluation to exclude any additional immune mediated events endocrine, GI, and liver/pancreas function as clinically indicated must be made prior to restarting.
- Non-drug-related toxicity including hepatic, pulmonary toxicity, diarrhea, or colitis, must have resolved to baseline before treatment is resumed.

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

If treatment is delayed for > 6 weeks, (> 8 weeks for patients on a steroid taper), the patient must be permanently discontinued from study therapy, except as specified in Section 5.4 (Study withdrawal or discontinuation, duration of treatment, follow-up). It should be emphasized that if adverse event occurs which requires treatment with steroids, it is preferable to withhold nivolumab and start steroids earlier to obtain resolution with the possibility for restarting nivolumab, rather than just waiting for higher grade events.

### 5.1.2 Cisplatin

Administration Guidelines

Cisplatin infusion: 80 mg/m$^2$ intravenously over 30-60 minutes on day 1 of a 21 day cycle for 6 cycles. Infusion rate should not exceed 2 mg/min. See section 6.1 for dose modifications.

High-dose cisplatin is highly emetogenic and can cause both acute and delayed nausea (occurring > 24 hours after chemotherapy administration). Investigators should be prepared to use aggressive prophylactic antiemetics and hydration. Many institutions will have standard guidelines for the administration of cisplatin at the doses used in this study. **For purposes of this protocol, individual investigators may use their local guidelines for cisplatin administration.** The anti-emetic regimen is to be determined by the local investigator. The following represent some suggested anti-emetic regimens:

- All patients receiving cisplatin chemotherapy should be offered a combination of anti-emetics based on institutional standards. Examples of appropriate anti-emetic choices are provided.
    - Neurokinin 1 ($NK_1$) receptor antagonist
        - Aprepitant 125 mg PO on day of cisplatin and 80 mg PO on days 2 and 3, or
        - Fosaprepitant 150 mg IV on day of cisplatin
    - Serotonin (5-$HT_3$) receptor antagonist
        - Granisetron 1 mg IV on day of cisplatin, or
        - Ondansetron up to 16 mg IV on day of cisplatin, or
        - Palonosetron 0.25 mg IV on day of cisplatin
    - Steroid
        - Dexamethasone up to 20 mg IV on day of cisplatin
    - Olanzapine
        - 10 mg PO on day of cisplatin
- Dexamethasone (up to 8 mg PO daily) and olanzapine may be continued on days 2 to 4 of cisplatin administration to prevent delayed nausea.
- A 5-$HT_3$ receptor antagonist may also be used as needed for delayed nausea.
- *Cisplatin pre-hydration guidelines (for reference only, physician should follow institutional standard of care)*: 1 liter D5 ½ NS and 40 meq KCL/ liter x 1 liter prior to cisplatin. Mannitol 12.5 gm IV immediately prior to cisplatin.
- *Cisplatin post-hydration guidelines (for reference only, physician should follow institutional standard of care)*: Following the end of the cisplatin administration, an additional liter of ½ NS with 10 meq KCL/L, 8 meq MgSO4/L, and 25 g mannitol should be infused over 2 hours. On the second and third day following cisplatin, patient should be encouraged to take at least 2 liters of fluid per day orally. Patients unable to orally self-hydrate should be considered for additional IV hydration on these days with normal saline.

### 5.1.3 Carboplatin

Carboplatin should be dosed at AUC of 5 using the Calvert formula: dose (mg) = AUC (mg/mL - 1 min) x [GFR (mL/min) + 25 (mL/min)]. It should be infused in 250 to 500 mL of NS or 5% DW on day 1 over 30 to 60 minutes IV.

### 5.1.4 Gemcitabine

Gemcitabine infusion: 1000 mg/m$^2$ in 250 mL NS over 30 minutes on days 1 and 8 of a 21 day cycle. Note: The final concentration of the prepared drug should be in the range of 38 mg/mL to 0.1 mg/mL.

The preparation and administration of gemcitabine should follow local treatment guidelines. Pre-medication with steroids prior to IV infusion is permitted as per local standard of care.

### 5.1.5 Nivolumab

Nivolumab 360 mg fixed dose administered as a 30-minute IV infusion will be given every three weeks (± 3 days) when given concurrently with platinum-gemcitabine. Maintenance nivolumab will be given at 480 mg dose every 4 weeks as a 30-minute IV infusion (+/- 3 days).
Patients may be dosed no less than 18 days from the previous dose of drug. There will be no dose modifications allowed, although delayed doses are allowed to be made up.

**When nivolumab is to be given together with platinum-gemcitabine on the same day, the nivolumab should be given before giving the chemotherapy.**

During the nivolumab maintenance period, concomitant use of other systemic anti-cancer therapy is not allowed, and these include but not limited to maintenance chemotherapy, immunotherapy (including vaccines, cell therapy, antibodies) and any investigational therapy.

At disease progression (clinical and/or radiological), subsequent treatment will be decided at the physician's discretion. The type of systemic therapy to be given at disease progression will need to be recorded. For patients randomized to the control arm (Arm 2), the follow-up frequency is around 4 – 8 weeks at the discretion of the investigator to allow some flexibility.

## 5.2 General Concomitant Medication and Supportive Care Guidelines (16-FEB-2021)

**5.2.1** Permitted Supportive/Ancillary Care and Concomitant Medications

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

- Anticonvulsants
- Antiemetics
- Anticoagulants
- Antidiarrheals
- Analgesics
- Myeloid stimulating growth factors such as Pegfilgrastim or Filgrastim may be used
- Highly active antiretroviral therapy (HAART)

All treatments that the investigator considers necessary for a participant's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care.

*Herbal and Nutritional Supplement*

The concomitant use of herbal therapies is generally not recommended, as their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However the use of general nutritional foundation supplements will be allowed including: calcium with vitamin D

and/or minerals, Omega3s (fish oil), Vitamin B6, Vitamin B12, basic multivitamins , L-glutamine, or probiotics oral supplements will be permitted either at or below the recommended dosing by a healthcare provider. Herbal-based multivitamins are not allowed.

**5.2.2** Radiotherapy, surgery and local ablative therapy:

- External radiotherapy with palliative intent for the treatment of symptomatic bone metastases are permitted in this study. All study drugs must be withheld during radiotherapy and be resumed as soon as the patient has recovered from any acute toxicities (if any) of the radiotherapy. The maximum period of withholding study drugs is 8 weeks.
- External radiotherapy (e.g. SBRT), surgery and/or local ablative therapy (including but not limited to radiofrequency ablation, cryosurgery, percutaneous ethanol injection) for the treatment of any non-osseous metastases that are new or progressing on clinical and/or radiological assessment, are not permitted in this study. Such patients are considered to have progressive disease and will need to be taken off protocol treatment before undergoing any radiotherapy to such lesions. Such local therapies that are used at first disease progression will be recorded in the CRF.
- For patients on maintenance nivolumab who have developed oligoprogression in a single site of disease, but are otherwise stable, please refer to section on continuation of nivolumab beyond progression. The use of local therapy such as radiotherapy, surgery or local ablation are not permitted. If such local therapies are considered necessary for the patient's oncological care, the patient will need to be taken off protocol treatment.

**5.2.3** Prohibited Therapies

Participants are prohibited from receiving the following therapies during protocol treatment:

Anti-cancer systemic chemotherapy, biological therapy (including tyrosine kinase inhibitors, gene therapy, any immunotherapy such as but not limited to vaccines, cell-based therapy, any antibodies, CAR-T therapy) that not specified in this protocol are not permitted. In particular:

- For patients randomized to Arm 2, the use of chemotherapy or any systemic anti-cancer therapy(s) as listed above with a "maintenance" intent is NOT permitted. For such patients, if they experience disease progression, they will need to be taken off protocol treatment first before starting any other anti-cancer systemic therapies.
- Investigational agents other than nivolumab.
- Live vaccines within 30 days prior to the first dose of study treatment and while on treatment. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, varicella/zoster, yellow fever, rabies, BCG, and typhoid vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (eg, FluMist®) are live attenuated vaccines and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of clinical interest of suspected immunologic etiology. The use of physiologic doses of corticosteroids for patients with adrenal and/or pituitary insufficiency are permitted. Use of prophylactic corticosteroids to avoid allergic reactions (e.g. IV contrast dye) or for anti-

emetic premedication prior to chemotherapy is permitted. Intranasal steroid for the treatment of allergic rhinitis, and inhaled steroids for the treatment of stable asthma are permitted.

### 5.3 Participation in Other Trials

Patients are not to participate in other therapeutic trials that involve study interventions including systemic experimental agents including cytotoxic chemotherapy, herbal and/or alternative medicine, local ablative therapy, radiotherapy and surgery. However, non-interventional, observational studies are allowed (e.g. imaging trials, quality of life, blood-sampling, endoscopic biopsy of the primary nasopharyngeal tumor).

### 5.4 Duration of Therapy

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

- Any progression or recurrence of NPC, or any occurrence of another malignancy (diagnosed since enrollment) that requires active treatment,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable or intolerable adverse event(s), as described in Section 6 (see also specific nivolumab algorithms in the Investigator's Brochure)
- For patients receiving platinum-gemcitabine with or without nivolumab, and for patients on maintenance nivolumab: Any dosing interruption lasting > 8 weeks, with the following exceptions:
  (a) Dosing interruptions > 8 weeks that occur for non-drug-related reasons may be allowed if approved by the Study Chair or designate.
  (b) Dose interruptions > 8 weeks due to drug-related adverse events should result in permanent study therapy discontinuation, unless the study doctor thinks that it is in the patient's best interest to remain on the study treatment. The study doctor should consult the Study Chair or designate before continuing study treatment.
  (c) For patients with nivolumab-related immune toxicities that require systemic steroids, a maximum dose interruption of 8 weeks is allowed in order for the steroids to be weaned off completely. See section 6.3.

  **Note**: Tumor assessments should continue as per protocol even if dosing is interrupted.
- Patient or legally acceptable representative decides to withdraw consent for participation in the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Patient's repeated non-compliance with study procedures and/or requirement, which in the opinion of the investigator, result in an increased risk to the patient
- The patient has a confirmed positive serum pregnancy test.

## 6. TREATMENT MODIFICATIONS/MANAGEMENT

**NOTE:** PRO-CTCAE data should not be used for determining dose delays or dose modifications or any other protocol directed action.

## 6.1 Dose Modifications and Toxicity Management for Cisplatin-Gemcitabine

**Dose Modification levels for platinum-gemcitabine**

| Cisplatin Dose Levels During Cisplatin-Gemcitabine | | |
|---|---|---|
| Starting Dose | Dose Level -1 | Dose Level -2 |
| 80 mg/m$^2$ | 60 mg/m$^2$ | 45 mg/m$^2$ |

| Gemcitabine Dose Levels During Cisplatin-Gemcitabine | | |
|---|---|---|
| Starting Dose | Dose Level -1 | Dose Level -2 |
| 1000 mg/m$^2$ | 750 mg/m$^2$ | 500 mg/m$^2$ |

| Carboplatin Dose Levels During Carboplatin-Gemcitabine | | |
|---|---|---|
| Starting Dose | Dose Level -1 | Dose Level -2 |
| AUC = 5 | AUC = 4 | AUC = 3 |

### 6.1.1 Cisplatin Dose Modifications for Hematologic Adverse Events

Below are recommendations for cisplatin dose modifications. For purposes of this protocol, individual investigators may use their local institutional guidelines.

Chemotherapy should not be administered until blood count recovery (i.e., ANC is at least 1500 cells/mm$^3$ and the platelet count is at least 100,000 cells/mm$^3$ - see section 5.1.1 Criteria for starting a new cycle of chemotherapy with or without nivolumab. If these parameters are not met, then treatment should be delayed in weekly increments until they have recovered to this level, but no more than an 8 week delay is permitted.

Dose reductions for ANC and platelets based on counts at anticipated day of treatment, ONCE RECOVERY TO THE ABOVE LEVELS ARE ACHIEVED:

| For patients on cisplatin-gemcitabine with or without nivolumab | | | |
|---|---|---|---|
| **ANC at day of treatment (day 1 of each cycle)** | | **Platelets at day of treatment (day 1 of each cycle)** | **Cisplatin dose Reduction** |
| ≥ 1500 cells/mm$^3$ | and | ≥ 100,000 cells/mm$^3$ | None |
| < 1500 cells/mm$^3$ | or | < 100,000 cells/mm$^3$ | At count recovery, resume at one lower dose level of BOTH cisplatin and gemcitabine |

### 6.1.2 Cisplatin Dose Modifications for Cisplatin-Related Non-Hematologic Adverse Events

- In this study, cisplatin or carboplatin may be used at the discretion of the investigator, except for those patients with CrCl of < 50 mL/min in whom carboplatin should be used instead of cisplatin. The following treatment modification applies to patients who have been commenced on cisplatin in cycle 1 onwards.
- If any one or more of the following cisplatin-related adverse events occur during treatment, carboplatin may be used to substitute cisplatin at the investigator's discretion:

- Neurological Events Attributable to Cisplatin (i.e., peripheral neuropathy): Grade 2, decrease cisplatin by one dose level OR switch to carboplatin. For ≥ Grade 3, hold cisplatin and switch to carboplatin.
- Ototoxicity: Should patients develop any grade of ototoxicity, cisplatin should be substituted by carboplatin.
- Renal Adverse Events: Dose will be modified based on the calculated CrCl (Cockcroft-Gault formula) prior to each cisplatin dose. If the calculated CrCl is < 50 mL/min, cisplatin should be substituted by carboplatin and continued on carboplatin. For patients receiving concurrent nivolumab-cisplatin-gemcitabine, if the CrCl has stabilized after a dose interruption of a maximum of 3 weeks, AND the cause of the creatinine rise is considered unrelated to nivolumab, may substitute cisplatin with carboplatin in subsequent cycles.
- All Other Non-Hematologic and non-renal Adverse Events Attributable to Cisplatin: For all other non-hematologic adverse events in which toxicity is ≥ grade 2 (CTCAE v5.0), investigators are advised to evaluate and manage correctable issues promptly to prevent worsening of toxicity. Then switching to carboplatin is advised in subsequent cycles.
- Once a patient has been switched from cisplatin to carboplatin, he/her should stay on carboplatin for all subsequent cycles and not switched back to cisplatin.

**6.1.3** Dose Modification Guidelines for Gemcitabine Hematologic Drug-Related Events

For day 1 gemcitabine: please refer to "Criteria for starting a new cycle of chemotherapy" in section 5.1.1 and Table 5.1A: Trial Treatment. For dose modification on day 1 of gemcitabine:

| **Day 1 of each cycle: For patients on cisplatin-gemcitabine with or without nivolumab** | | | |
|---|---|---|---|
| **ANC at day 1 of each new cycle** | | **Platelets at day 1 of each new cycle** | **Gemcitabine dose Reduction** |
| ≥ 1500 cells/mm$^3$ | and | ≥ 100,000 cells/mm$^3$ | None |
| < 1500 cells/mm$^3$ | or | < 100,000 cells/mm$^3$ | At count recovery, resume at one lower dose level of BOTH cisplatin and gemcitabine |

| **Dose reduction for day 8 gemcitabine** | | | |
|---|---|---|---|
| **ANC (cells/mm$^3$)** | | **Platelets (cells/mm$^3$)** | **Gemcitabine Dose** |
| ≥ 1000 | and | ≥ 100,000 | 1000 mg/m$^2$ |
| 500-999 | or | 50,000 - 99,999 | 750 mg/m$^2$ |
| < 500 | or | < 50,000 | Hold |

**Note:** Day 1 of Gemcitabine may be delayed; however, held doses of gemcitabine on day 8 will be considered missed doses and will not be delayed or made up.

**6.1.4** Dose Modification Guidelines for Gemcitabine-specific Non-Hematologic Drug-Related Events

Withhold gemcitabine, then reduce dose to 500 mg/m$^2$ for other severe (Grade 3 or 4) non-hematologic toxicities until resolved to Grade 0-1. This applies to both day 1 and day 8 of each cycle.

- No dose modifications are recommended for alopecia, nausea, or vomiting.
- Permanently discontinue gemcitabine for the following:
  - Unexplained dyspnea or other evidence of severe pulmonary toxicity
  - Severe hepatic toxicity
  - Hemolytic-uremic syndrome
  - Capillary leak syndrome
  - Posterior reversible encephalopathy syndrome

For additional guidance regarding treatment modification of gemcitabine, please refer to the United States package insert (or local prescribing information) for dose modifications for hematologic and other non-hematologic toxicities

**6.1.5** All Other Non-Hematologic Adverse Events During cisplatin-gemcitabine

For grade 3 or 4 events, drugs should be held until resolution to grade 1 or less, then both drugs resumed at dose level -1. Gemcitabine doses on day 8 of each cycle will not be made up but merely skipped for grade 3 or greater AEs occurring between days 1 and 8. Chemotherapy should be stopped if greater than grade 2 AEs are not resolved to grade 1 within 3 weeks, and patient should proceed directly to next cycle of treatment. For specific AEs attributabed exclusively to one or the other agent (platinum or gemcitabine), dose reduction only for that agent is required.

### 6.2 Dose Modifications and Toxicity Management for Carboplatin

Chemotherapy should not be administered until blood count recovery - i.e. ANC is at least 1500 cells/mm$^3$ and the platelet count is at least 100,000/mm$^3$. If these parameters are not met, then treatment should be delayed in weekly increments until they have recovered to this level, but no more than an 8 week delay is permitted.

Dose reductions for ANC and platelets based on counts at anticipated day of treatment, ONCE RECOVERY TO THE ABOVE LEVELS ARE ACHIEVED:

**Table 6.2A**

**For patients on carboplatin-gemcitabine with or without nivolumab**

| **ANC at day 1 of each new cycle** | | **Platelets at day 1 of each new cycle** | **Carboplatin Dose Reduction** |
|---|---|---|---|
| ≥ 1500 cells/mm$^3$ | and | ≥ 100,000 cells/mm$^3$ | None |
| < 1500 cells/mm$^3$ | or | < 100,000 cells/mm$^3$ | At count recovery, resume at one lower dose level of BOTH carboplatin and gemcitabine |

### 6.3 Dose Modifications and Toxicity Management for Nivolumab-related Adverse Events

For suspected irAEs, ensure adequate evaluation to confirm etiology or exclude other causes. Additional procedures or tests such as bronchoscopy, endoscopy, skin biopsy may be included as part of the evaluation. Based on the severity of irAEs, withhold or permanently discontinue nivolumab and administer corticosteroids. Dose modification and toxicity management guidelines for irAEs associated with nivolumab are provided in section 6.3.1. Please refer to Appendix I for nivolumab toxicity management algorithms which include specific treatment guidelines. These guidelines are applicable to patients who are receiving nivolumab with chemotherapy and maintenance phase. These algorithms should be followed unless there are specific clinical circumstances for which the treating physician decides an alternative treatment approach is clinically appropriate. Dose reduction of nivolumab is not allowed in this study.

- Nivolumab dose interruption during concurrent phase: if the platinum and/or gemcitabine need to be withheld, nivolumab will also need to be withheld (i.e., the entire treatment cycle will be interrupted). However if only nivolumab needs to be withheld, platinum-gemcitabine can be continued as long as the patient does not need systemic steroids and/or potent immunosuppressive, and that it is safe to do so at the discretion of the investigator. If a patient needs systemic steroids for nivolumab-related AEs, the chemotherapy should be withheld until the nivolumab can be resumed and the steroids weaned off completely within 6 weeks from the date of dose interruption. If nivolumab cannot be resumed within 8 weeks, the patient should discontinue from study protocol treatment permanently.
- Any Grade 3 or 4 drug-related laboratory abnormality or electrolyte abnormality, that can be managed independently from underlying organ pathology with electrolyte replacement, hormone replacement, insulin or that does not require treatment **does not** require discontinuation. The exception is grade 3-4 pancreatitis complicated by diabetes mellitus – these patients need to discontinue protocol treatment permanently.
- Any AE, 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 discontinue nivolumab.

**Table 6.3A**

| **ALL NON-IMMUNOLOGIC EVENTS** | **Management/Next Dose for Nivolumab** |
|---|---|
| ≤ Grade 1 | Continue nivolumab. |
| Grade 2 | Hold until ≤ Grade 1 OR baseline (exceptions as noted below). If recurs at resumption, should discontinue nivolumab permanently. |
| Grade 3 | Hold* until ≤ Grade 1 OR baseline. Resume at investigator's discretion |
| Grade 4 | Discontinue nivolumab permanently. |
| *Not agent related, OR agent-related but non-immunologically mediated<br>Recommended management: As clinically indicated | |

| **ALL IMMUNOLOGIC EVENTS** | **Management/Next Dose for Nivolumab** |
|---|---|
| ≤ Grade 1 | Continue nivolumab. |
| Grade 2 | Hold until ≤ Grade 1 OR baseline (exceptions as noted below). If recurs at resumption, discontinue permanently. |
| Grade 3 | Hold until ≤ Grade 1 OR baseline and patient has been weaned off systemic steroid if it has been initiated (exceptions as noted below). Resume at investigator's discretion. Permanently discontinue for events with a high likelihood of morbidity or mortality with recurrent events. |
| Grade 4 | Discontinue nivolumab. |
| Recommended management: As clinically indicated | |

6.3.1 Guideline for Specific Nivolumab-Related Adverse Events

- Prior to starting corticosteroids or hormone replacement for any reason, appropriate endocrine testing including cortisol, Cortrosyn® adrenocorticotrophic hormone (ACTH), thyroid stimulating hormone (TSH), and thyroxine (T4) must be obtained to document baseline.
- Corticosteroid taper should be initiated upon AE improving to Grade 1 or less and continue to taper over at least 4 weeks.
- For situations where nivolumab has been withheld, nivolumab can be resumed after AE has been reduced to Grade 1 or 0 and corticosteroid has been tapered. Nivolumab should be permanently discontinued if AE does not resolve within 8 weeks of last dose of nivolumab, or corticosteroids cannot be weaned off within 8 weeks.
- For severe and life-threatening irAEs, IV corticosteroid should be initiated first followed by oral steroid. Other immunosuppressive treatment should be initiated if irAEs cannot be controlled by corticosteroids. Any patients receiving nivolumab who require additional immune suppressive treatment beyond systemic steroids should discontinue nivolumab. Any patient started on systemic corticosteroids empirically for suspected autoimmune toxicity, and is subsequently determined to be not requiring steroid treatment, may resume nivolumab after a 2-week observation period at the discretion of the PI or investigator.
- 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 discontinue nivolumab.

| **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 or has weaned off systemic steroids if it has been initiated. Resume at same level at investigator discretion |

| | |
|---|---|
| Grade 4 | Discontinue nivolumab. |
| *Patients with purpuric or bullous lesions must be evaluated for vasculitis, Steven-Johnson syndrome, toxic epidermal necrolysis (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 | Hold at investigator discretion until ULN or baseline. Resume at same dose level. |
| Grade 2 | Grade 2 (3x ULN to 5x ULN): Hold and resume at same dose level when return to grade 1 or baseline within 7 days without steroids. If systemic steroids are required, resume at same dose level when return to baseline or grade 1 and weaned off steroids. If grade 2 recurs, then discontinue permanently. |
| Grade 3-4 | Permanently discontinue nivolumab. |
| Continued treatment of active immune mediated hepatitis may exacerbate ongoing inflammation. Holding drug to evaluate liver function test (LFT) changes and early treatment are recommended. LFT changes may occur during steroid tapers from other events and may occur together with other GI events including cholecystitis/pancreatitis.<br>Please note: Grades for liver function follow ULN rather than multiples of baseline. | |
| Recommended management: see Hepatic AE management algorithm | |

| **Diarrhea/Colitis** | **Management/Next Dose for Nivolumab** |
|---|---|
| Grade 1 | Continue at same dose, use anti-diarrheal. |
| Grade 2-3 | Hold dose. Consult gastroenterologist. Resume at same dose level if resolved to grade 1 within 7 days without steroids and no evidence of colitis on endoscopy. If corticosteroids are needed, hold dose until resolution to baseline, and when steroids are weaned off within 8 weeks. If grade 2-3 diarrhea/colitis recurs at resumption, then discontinue from study treatment permanently. |
| Grade 4 | Permanently discontinue nivolumab. |
| See GI AE Algorithm for management of symptomatic colitis.<br>Patients with Grade 2 symptoms but normal colonoscopy and biopsies may be retreated with nivolumab after resolution. Patients who require systemic steroids and cannot be weaned off, should be taken off study treatment. | |
| Recommended management: see GI AE management Algorithm | |

| **Pancreatitis Amylase/Lipase** | **Management/Next Dose for Nivolumab** |
|---|---|
| ≤ Grade 1 | Continue nivolumab if asymptomatic at investigator discretion. |
| Grade 2 | Continue nivolumab if asymptomatic at investigator discretion. If symptomatic, resume nivolumab when resolved. |
| Grade 3 | Continue nivolumab if asymptomatic at investigator discretion. Patients should have imaging study when clinically indicated (grade 3 symptomatic pancreatitis) before resuming treatment. Patients who develop grade 3 symptomatic pancreatitis complicated by diabetes mellitus should discontinue nivolumab. |
| Grade 4 | Hold until grade 2. Resume at same dose level if asymptomatic. Patients who are symptomatic should have imaging study prior to resuming treatment and when clinically indicated. Patients who develop grade 4 symptomatic pancreatitis complicated with or without diabetes mellitus should be discontinue nivolumab. |
| Patients may develop symptomatic and radiologic evidence of pancreatitis as well as diabetes mellitus and diabetic ketoacidosis (DKA). Lipase elevation may occur during the period of steroid withdrawal and with other immune-mediated events or associated with colitis, hepatitis, and patients who have asymptomatic lipase elevation typically have self-limited course and may be retreated with nivolumab. For treatment management of symptomatic pancreatitis, please follow the Hepatic AE Management Algorithm. | |

| **Pneumonitis** | **Management/Next Dose for Nivolumab** |
|---|---|
| Grade 1 | Hold dose until resolution to baseline including baseline $pO_2$, then resume without change in dose. Consultation with respiratory team is advisable. |
| Grade 2 | Hold dose. Administer corticosteroids (initial dose of 1-2 mg/kg prednisone or equivalent) followed by taper. Consultation with respiratory team is advisable. Hold dose until resolution to baseline including baseline pO2, and when steroids are weaned off within 8 weeks, then resume without change in dose. If grade 2 pneumonitis recurs at resumption of nivolumab, discontinue nivolumab permanently. |
| Grade 3 or 4 | Permanently discontinue nivolumab. |
| Recommended management: See Pulmonary AE Management Algorithm | |

| **Other GI Nausea, Vomiting** | **Management/Next Dose for Nivolumab** |
|---|---|
| ≤ Grade 1 | Continue nivolumab. |
| Grade 2 | Hold pending evaluation for gastritis, duodenitis, and other immune AEs or other causes. Resume after resolution to ≤ Grade 1. |

| | |
|---|---|
| Grade 3 | Hold pending evaluation until ≤ Grade 1, then resume. If symptoms do not resolve within 7 days with symptomatic treatment, patients should discontinue nivolumab. |
| Grade 4 | Discontinue nivolumab. |
| Patients with Grade 2 or 3 N-V should be evaluated for upper GI inflammation and other immune related events. | |

| **Fatigue** | **Management/Next Dose for Nivolumab** |
|---|---|
| Grade 2 | Continue nivolumab. |
| Grade 3 | Hold until≤ Grade 2, then resume. |
| Fatigue is the most common AE associated with immune checkpoint therapy. Grade 2 or 3 fatigue should be evaluated for associated or underlying organ involvement including pituitary, thyroid, and hepatic, or muscle (CPK) inflammation. | |

| **Neurologic Events** | **Management/Next Dose for Nivolumab** |
|---|---|
| ≤ Grade 1 | Hold dose pending evaluation and observation. Resume when resolved to baseline. |
| Grade 2 | Hold dose pending evaluation and observation. Hold until ≤ Grade 1. Discontinue nivolumab if treatment with steroids is required. Resume at same dose level for peripheral isolated cranial nerve VII (Bell's palsy). |
| Grade 3 | Discontinue nivolumab. |
| Grade 4 | Discontinue nivolumab. |
| Patients with any CNS events including aseptic meningitis, encephalitis, or myopathy, peripheral demyelinating neuropathy, cranial neuropathy (other than peripheral n. VII), Gullain-Barre syndrome, and myasthenia gravis should discontinue nivolumab permanently. | |
| Recommended management: See Neurologic AE Management Algorithm | |

| **Hypophysitis Adrenal Insufficiency** | **Management/Next Dose for Nivolumab** |
|---|---|
| ≤ Grade 1 | *Hold pending evaluation for evidence of adrenal insufficiency or hypophysitis. Asymptomatic thyroid stimulating hormone (TSH) elevation may continue treatment while evaluating the need for thyroid replacement. |
| Grade 2 | Hold until patients are on a stable replacement hormone regimen. If treated with steroids, patients must be stable off steroids for 2 weeks. Then resume nivolumab. |
| Grade 3 | Hold until patients are on a stable replacement hormone |

| | |
|---|---|
| | regimen. If treated with steroids, patients must be stable off steroids for 2 weeks. Then resume nivolumab. |
| Grade 4 | Discontinue nivolumab. |
| Note all patients with symptomatic pituitary enlargement, exclusive of hormone deficiency, but including severe headache or enlarged pituitary on MRI should be considered Grade 3 events. Isolated thyroid or testosterone deficiency may be treated as Grade 2 if there are no other associated deficiencies and adrenal function is monitored.<br>Please evaluate pituitary function before beginning steroid therapy or replacement therapy of any kind. *Note patients with thyroiditis may be retreated on replacement therapy. Patients must be evaluated to rule out pituitary disease prior to initiating thyroid replacement. | |
| Recommended management: See Endocrine Management Algorithm | |

| **Hypothyroidism** | **Management/Next Dose for Nivolumab** |
|---|---|
| Grade 1 | Continue nivolumab. |
| Grade 2-3 | Continue nivolumab, initiate thyroid hormone replacement. |
| Grade 4 | Hold until patients are clinically stable and on a stable replacement hormone regimen, then resume nivolumab at same dose. The TSH level does not need to be normalized if the patient if clinically stable. |
| Recommended management: See Endocrine Management Algorithm | |

| **Hyperthyroidism** | **Management/Next Dose for Nivolumab** |
|---|---|
| Grade 1 | Continue nivolumab. |
| Grade 2 | Continue nivolumab at same dose, treat with non-selective beta-blockers (eg, propranolol) or thionamides as appropriate. |
| Grade 3-4 | Hold until patients are stable. Resume nivolumab or discontinue nivolumab permanently at the investigator's discretion. |
| Recommended management: See Endocrine Management Algorithm | |

| **Type 1 diabetes mellitus (T1DM) or Hyperglycemia** | **Management/Next Dose for Nivolumab** |
|---|---|
| Newly onset T1DM or Grade 3 or 4 hyperglycemia | Hold until patients are stabilized with medical therapy (e.g. insulin, or anti-hyperglycemic agents), then resume nivolumab. |
| Recommended management: See Endocrine Management Algorithm | |

| **Renal/nephritis** | **Management/Next Dose for Nivolumab** |
|---|---|
| Grade 1 | Monitor closely and continue therapy. |
| Grade 2 | Hold until ≤ Grade 1. Resume nivolumab. |
| Grade 3-4 | Discontinue nivolumab permanently. Administer systemic steroids. |
| Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever. | |

| **Infusion Reaction** | **Management/Next Dose for Nivolumab** |
|---|---|
| Grade 1 | 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.<br><br>The following prophylactic premedications are recommended for future infusions: diphenhydramine and/or paracetamol (or acetaminophen) at least 30 minutes before additional nivolumab administrations, slowing infusion rate as above. |
| Grade 2: Requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDs, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs | Stop the nivolumab infusion, give IV fluids, diphenhydramine (or equivalent) and/or paracetamol; Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve within 1 hour of stopping nivolumab; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely. If symptoms recur, re administer diphenhydramine 50 mg IV, and stop infusion.<br>Hold dose until resolved to baseline. The following prophylactic premedications are recommended for future |

| | |
|---|---|
| | infusions: diphenhydramine and acetaminophen (or paracetamol). If necessary, corticosteroids (up to 25 mg of IV hydrocortisone or equivalent) may be used. |
| Grade 3: 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)<br><br>Grade 4: Life-threatening; pressor or ventilatory support indicated | Nivolumab will be permanently discontinued. Immediately discontinue infusion of nivolumab. Give IV fluids, diphenhydramine (or equivalent) and/or paracetamol, bronchodilators, epinephrine and/or steroids if indicated. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. |
| 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. Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever. | |

| **Cardiac *** | **Management/Next Dose for Nivolumab Cardiac Toxicities** |
|---|---|
| Less than grade 2 | Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize without evidence of myocarditis may resume therapy. If labs worsen or symptoms develop then treat as below. |
| Grade ≥2 with suspected myocarditis | Hold dose.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone and immune suppression as clinically indicated. May resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely. |

| Cardiac * | Management/Next Dose for Nivolumab Cardiac Toxicities |
|---|---|
| Grade ≥2 with confirmed myocarditis | Discontinue nivolumab permanently. Consider high dose methylprednisolone. Add ATG or tacrolimus if no improvement. |
| **Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin*<br>***Patients with evidence of myositis without myocarditis may be treated according as "other event"*<br>Note: The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended. | |

## 7. ADVERSE EVENTS REPORTING REQUIREMENTS

### 7.1 Protocol Agents

Investigational Agent

The investigational agent administered in NRG-HN007, nivolumab, is being made available under an IND sponsored by CTEP.

Commercial Agent

The commercial agents in NRG-HN007 are cisplatin, carboplatin, and gemcitabine.

### 7.2 Adverse Events and Serious Adverse Events

**7.2.1** This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for CTEP-AERS (CTEP Adverse Event Reporting System) CAERs reporting of adverse events (AEs), located on the CTEP web site, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

PRO-CTCAE is not intended for expedited reporting, real time review, or safety reporting.

**7.2.2** Definition of an Adverse Event (AE)

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

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

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

Clinician graded CTCAE is the AE (adverse event) safety standard. PRO-CTCAE items are to complement CTCAE reporting. Patients will respond to PRO-CTCAE items but no protocol directed action will be taken. The specific PRO-CTCAE items for this protocol can be found on the forms section of the CTSU protocol webpage and is titled "NRG-HN007 NCI PRO-CTCAE Item Library. PRO-CTCAE is not intended for expedited reporting, real time review or safety reporting. PRO-CTCAE data are exploratory and not currently intended for use in data safety monitoring or adverse event stopping rules.

**NOTE:** PRO-CTCAE data should not be used for determining dose delays or dose modifications or any other protocol directed action.

## 7.3 Comprehensive Adverse Events and Potential Risks (CAEPR) List for CTEP Study Agent: Nivolumab (16-FEB-2021)

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

**Version 2.4, 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 | |

| 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%)** | |
| 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 | | |
| 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)*** |

| 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%)** | |
| | 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 | | |
| | | 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 | | | |

| 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%)** | |
| | Pleural effusion[3] | | |
| | Pneumonitis[3] | | |
| | | Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia)[3] | |
| SKIN AND SUBCUTANEOUS TISSUE DISORDERS | | | |
| | | Erythema multiforme[3] | |
| | Pruritus[3] | | ***Pruritus[3] (Gr 2)*** |
| | Rash maculo-papular[3] | | ***Rash maculo-papular[3] (Gr 2)*** |
| | | Skin and subcutaneous 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.

## 7.4 Adverse Events for Commercial Study Agents: Cisplatin, Carboplatin, and Gemcitabine

Refer to the package insert for detailed pharmacologic and safety information

### 7.4.1 Adverse Events and PRO-CTCAE

PRO-CTCAE

The PRO-CTCAE instrument will be used to assess patient reported toxicity outcomes.

PRO-CTCAE is a validated instrument developed by the National Cancer Institute to assess clinical trial toxicity outcomes by patient report; it complements information collected by

physician-reported CTCAE. PRO-CTCAE is available in English, Spanish, French (Canada), Chinese (simplified and traditional), and Korean for this study. Patients participating on the electronic patient-reported outcome (Medidata Patient Cloud ePRO) will only have the option to complete the English and Spanish language PRO-CTCAE. French or Chinese (simplified or traditional) language PRO-CTCAE is not currently available on the Medidata Patient Cloud ePRO. Collection time points are listed in Section 4.

Assessments will be collected as specified in the Section 4 assessment tables.

The patient-reported AEs that will be assessed using PRO-CTCAE are listed in the table below. These adverse events are considered expected and, if reported, should also be clinician graded using CTCAE v5.0.

| | **CTCAE v5.0** | **PRO-CTCAE Items With Attributes** |
|---|---|---|
| 1. | Dry mouth | Dry mouth (Severity) |
| 2. | Esophagitis<br>Dysphagia | Difficulty swallowing (Severity) |
| 3. | Voice alteration | Voice quality changes (Presence) |
| 4. | Mucositis oral | Mouth/throat sore (Severity) |
| 5. | Dysgeusia | Taste changes (Severity) |
| 6. | Abdominal pain | Abdominal pain (Severity) |
| 7. | Palpitations | Heart palpitations (Severity) |
| 8. | Rash acneiform<br>Rash maculo-papular | Rash (Presence) |
| 9. | Pruritus | Itching (Severity) |
| 10. | Peripheral sensory neuropathy | Numbness & tingling (Severity) |
| 11. | Blurred vision | Blurred vision (Severity) |
| 12. | Tinnitus | Ringing in ears (Severity) |
| 13. | Concentration impairment | Concentration (Severity) |
| 14. | Memory Impairment | Memory (Severity) |
| 15. | Headache | Headache (Severity) |
| 16. | Depression | Sad (Severity) |

## 7.5 Expedited Reporting of Adverse Events (16-FEB-2021)

All adverse events (AEs) are submitted for expedited reporting protocol-specific rules evaluation using the Medidata Rave data management system. All AEs will be evaluated by the Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) to determine whether expedited reporting is recommended based on a set of programmed expedited reporting rules. AEs identified as meeting the programmed expedited reporting requirements can then be submitted in CTEP-AERS. A deep link in Rave will take the user directly to CTEP-AERS where the expedited report may be completed and submitted via CTEP-AERS.

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the CTEP Adverse Event Reporting System, CTEP-

AERS, accessed via the link in RAVE. CTEP-AERS is also accessed via the CTEP website, **but all expedited reports must be initiated in RAVE:** https://eapps-ctep.nci.nih.gov/ctepaers/pages/task?rand=1390853489613.

Submitting a report via Rave-CTEP-AERS serves as notification to the NRG Biostatistical/Data Management Center and satisfies NRG requirements for expedited adverse event reporting.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to CTEP by telephone at 301-897-7497 and the NRG Oncology by phone at 1-215-574-3191. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

### 7.5.1 Expedited Reporting Methods

- Per CTEP NCI Guidelines for Adverse Events Reporting, a CTEP-AERS 24-hour notification must be submitted within 24 hours of learning of the adverse event.
- Supporting source documentation is requested by NRG as needed to complete adverse event review. Supporting source documentation should include the protocol number, patient ID number, and CTEP-AERS ticket number on each page; fax supporting documentation to CTEP at 301-897-7404 and contact NRG Oncology at 1-215-574-3191 for source documentation assistance.
- A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as "an action *not* recommended" must still be reported to fulfill NRG safety reporting obligations. Sites must bypass the "NOT recommended" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

### 7.5.2 Expedited Reporting Requirements for Adverse Events

**Arm 2: Any Phase Study Utilizing a Commercial Agent[1]**

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

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

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

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

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

| Attribution | Grade 4 | | Grade 5 | |
|---|---|---|---|---|
| | Unexpected | Expected | Unexpected | Expected |
| Unrelated<br>Unlikely | | | 10 day | 10 day |
| Possible<br>Probable<br>Definite | 24-h/5 day | | 24-h/5 day | 24-h/5 day |

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

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

- Unexpected Grade 4 and all Grade 5 AEs

## Late Phase 2 and Phase 3 Studies: Arm 1: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of Nivolumab[1, 2]

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

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

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

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

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

| Hospitalization | Grade 1 Timeframes | Grade 2 Timeframes | Grade 3 Timeframes | Grade 4 & 5 Timeframes |
|---|---|---|---|---|
| Resulting in Hospitalization ≥ 24 hrs | 10 Calendar Days | | | 24-Hour 5 Calendar Days |

| | | | |
|---|---|---|---|
| Not resulting in Hospitalization ≥ 24 hrs | Not required | 10 Calendar Days | |

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

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

- "24-Hour; 5 Calendar Days" - The AE must initially be submitted electronically 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 electronically 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

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

Effective Date: May 5, 2011

## Additional Protocol-Specific Instructions or Exceptions to Expedited Reporting Requirements

Clinician graded CTCAE is the AE safety standard. PRO-CTCAE items are to complement CTCAE reporting. Patients will respond to PRO-CTCAE items but no protocol directed action will be taken. The study-specific PRO-CTCAE items for this protocol can be found on the forms section of the CTSU protocol webpage and is titled "NRG-HN007 NCI PRO-CTCAE Item Library".

### 7.5.3 Reporting to the Site IRB/REB

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

### 7.5.4 Secondary Malignancy

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

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

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

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

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

### 7.6 Routine Reporting Requirements for Adverse Events

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.**

#### 7.6.1 Reporting PRO-CTCAE

Symptomatic Adverse Events reported by patients through PRO-CTCAE are not safety reporting and should also be clinician graded using CTCAE v5.0 and reported as routine AE data.

### 7.7 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 5 months or 7 months, respectively, after the last dose of nivolumab; or 6 months after the last dose of cisplatin; or 6 months or 3 months respectively, after the last dose of gemcitabine must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

## 8. REGISTRATION AND STUDY ENTRY PROCEDURES

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register and renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. In addition, persons with a registration type of Investigator (IVR), Non-Physician Investigator (NPIVR), or Associate Plus (AP) must complete their annual registration using CTEP's web-based Registration and Credential Repository (RCR) at https://ctepcore.nci.nih.gov/rcr.

RCR utilizes five person registration types.

- IVR — MD, DO, or international equivalent;

- NPIVR — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- AP — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

| Documentation Required | IVR | NPIVR | AP | A | AB |
|---|---|---|---|---|---|
| FDA Form 1572 | ✓ | ✓ | | | |
| Financial Disclosure Form | ✓ | ✓ | ✓ | | |
| NCI Biosketch (education, training, employment, license, and certification) | ✓ | ✓ | ✓ | | |
| 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 Cancer Trials Support Unit (CTSU) websites and applications. In addition, IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

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

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval) or consenting/treating/drug shipment investigator in OPEN or as the CI on the DTL must be rostered at the enrolling site with a participating organization. Additional information is located 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.

## 8.1 Cancer Trials Support Unit Registration Procedures (16-FEB-2021)

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

**IRB Approval**

For CTEP and Division of Cancer Prevention (DCP) studies open to the National Clinical

Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases after March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB). In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet for Local Context (SSW) to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria in order for the processing of the IRB/REB approval record to be completed:

- Holds an active CTEP status;
- Rostered at the site on the IRB/REB approval and on at least one participating roster;
- If using NCI CIRB, rostered on the NCI CIRB Signatory record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile; and
- Holds the appropriate CTEP registration type for the protocol.

**Additional Requirements for Protocol NRG-HN007 Site Registration**
Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO); and
- Compliance with all protocol-specific requirements (PSRs).
- Delegation Task Log (DTL) – see section 8.1.1 for instructions.

- IRB/REB approved consent (International and Canadian sites only: English and native language versions* English version must be submitted to NRG Regulatory (Regulatory-PHL@nrgoncology.org) for review prior to IRB/REB submission. International and Canadian Institutions must provide certification/verification of IRB/REB consent translation to NRG Oncology as described below).

*Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to the prohibitive costs involved NRG Oncology will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational letterhead/stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

Additional Requirements for sites in Canada

Prior to clinical trial commencement, sites in Canada must also complete and submit the following documents to CTSU via the Regulatory Submission Portal.

- Clinical Trial Site Information Form
- Qualified Investigator Undertaking Form
- Research Ethics Board Attestation Form
- Protocol Signature Page
- Investigator Brochure Signature Page
- List of Laboratories
- SIV/Training Confirmation of Completion Form – Research Associate (please refer to the activation memo for details)
- SIV/Training Confirmation of Completion Form – Qualified Investigator (please refer to the activation memo for details)

The following items are collected By NRG Oncology Regulatory on a yearly or biyearly basis:

- IRB/REB Membership Roster
- Laboratory Certificates and Normal Values
- CVs for Qualified Investigator and Sub-Investigators noted on the DTL

**Downloading Site Registration Documents:**

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted based on person and site roster assignment. To participate, the institution and its associated investigators and staff must be associated with the LPO or a Protocol Organization (PO) on the protocol. One way to search for a protocol is listed below.

- Log in to the CTSU members' website (https://www.ctsu.org) using your CTEP-IAM username and password;
- Click on *Protocols* in the upper left of the screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, then select *NRG Oncology* and protocol number *NRG-HN007.*
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

**Submitting Regulatory Documents:**

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the → Regulatory section and select → Regulatory Submission.

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

**Checking Site's Registration Status:**

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration;* and
- Enter the site's 5-character CTEP Institution Code and click on Go.
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

### 8.1.1 Delegation of Task Log (DTL)

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating

roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and include a Master Task List, which describes DTL task assignments, CI signature, and CTEP registration requirements.

## 8.2 Patient Enrollment

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

### 8.2.1 Oncology Patient Enrollment Network (OPEN)

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- A valid CTEP-IAM account;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- A Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. A DTL is required for the study, and the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

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

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- 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. You may print this confirmation for your records.

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

**8.3 Medidata Patient Cloud ePRO Registration** (16-FEB-2021)

This study includes the use of Medidata Patient Cloud ePRO (electronic patient-reported outcomes). After the patient is registered to the trial via OPEN, and if the patient is willing to participate in electronic data collection, the site staff will then complete a registration for the patient to the Patient Cloud ePRO through iMedidata. Note: Site staff must have already completed required eLearning for the Patient Cloud ePRO application to register a patient and information about the training is in the ePRO Appendix. The registration to the Patient Cloud ePRO will create a unique patient registration code that the site staff will provide to the patient. The patient (with assistance from the site staff) should be instructed to download the Patient Cloud ePRO app onto his/her own device (IOS, Android, phone or tablet) and use the unique patient registration code to create an account. Once the patient's account is set up, the patient will be able to complete the submission of patient reported outcomes electronically for the trial. There are multiple versions of the app available. The Patient Cloud App will be used on this study. Ensure that the patient downloads the correct version of the ePRO app. Note only 1 version of the app is active per protocol.

For sites providing a shared institutional device for use by multiple patients on site:

- The site staff should assist the patient with access and registration to the Patient Cloud ePRO app, and the patient can then complete the electronic data submission independently. Site staff may need to assist patients with logging on to the device at each visit.

**8.3.1** CRA Patient Registration Instructions for ePRO

Please visit the CTSU website for reference information.

i. The subject registration process starts in iMedidata. Begin by selecting the Patient Cloud ePRO Registration link for your study
ii. The patient management app will display, select your STUDY and SITE from the drop downs and click Launch.
iii. Now you can register your first patient. Create a subject ID and select a Country / Language from the drop down, (these are the only required data fields). The subject initials are optional, but are helpful in identifying which subject ID maps with which activation code. When finished, click Add.
iv. The subject added and will include the date the patient was added, the subject ID, subject initials, (if included) and a unique auto-generated activation code. The activation code is unique for each patient and linked to the subject ID, it is not interchangeable. In addition, there is a status section, which indicates if the patient has registered. When the patient has registered the status will change from "invited" to "registered".

Reminder- site staff must have already completed the Medidata Patient Cloud training in order to register study patients. Please visit the CTSU website for reference information.

## 9.0 DRUG INFORMATION

### 9.1 Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) 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 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.

**9.1.1** Starter supplies are not being provided. Patients must be registered prior to sites ordering study agents.

Refer to the Policy and Guidelines for Investigational Agent Ordering and the contact information below for order processing time and conditions. Normal order processing time is two business days. An express courier account number must be provided for next-day delivery.

**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 IAM account help:** ctepreghelp@ctep.nci.nih.gov
**PMB email:** PMBAfterHours@mail.nih.gov
**PMB phone and hours of service:** (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)
**IB Coordinator:** IBCoordinator@mail.nih.gov

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.

### 9.2 Investigational Study Agent: Nivolumab (NSC 748726)

To supplement the toxicity information contained in this document, investigators must obtain the current version of the investigator brochure for comprehensive pharmacologic and safety information.

The current version of the Investigator Brochure (IB) 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 registration status. Questions about IB access may be directed to the PMB IB Coordinator via email to ibcoordinator@mail.nih.gov or the IB Coordinator may be contacted at 240-276-6575.

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

**Other Names:** BMS-936558, MDX1106

**Classification:** Anti-PD-1MAb

**M.W.:** 146,221 Daltons

**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.

**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).

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

**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.

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

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

**Stability:** Shelf-life surveillance of the intact vials is ongoing.

The administration of undiluted and diluted solutions of Nivolumab must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored up to 24 hours in a refrigerator at 2°-8°C (36°-46°F) and a maximum of 8 hours of the total 24 hours can be at room temperature (up to 25°C, 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.

**Route of Administration:** Intravenous infusion over 30 minutes. Do not administer as an IV push or bolus injection.

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

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

**Patient Care Implications:** Women of childbearing potential (WOCBP) receiving nivolumab must continue contraception for a period of 5 months after the last dose of nivolumab. Men receiving nivolumab and who are sexually active with WOCBP must continue contraception for a period of 7 months after the last dose of nivolumab.

### 9.3 Commercial Agent: Cisplatin

Sites must refer to the package insert for detailed pharmacologic and safety information.

#### 9.3.1 Adverse Events

Please refer to the package insert.

**9.3.2** Availability/Supply

Please see Section 5.1 for administration instructions. Please refer to the current FDA-approved package insert provided with each drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.

**9.3.3** Patient Care Implications

Females of childbearing potential must use adequate contraception during treatment and for 6 months after the last dose of cisplatin chemotherapy. Male patients must who are sexually active with WOCBP must use highly effective contraception for a total of 6 months after last dose of cisplatin chemotherapy.

**9.4 Commercial Agent: Carboplatin**

Sites must refer to the package insert for detailed pharmacologic and safety information.

**9.4.1** Adverse Events

Please refer to the package insert.

**9.4.2** Availability/Supply

Please see Section 5.1 for administration instructions. Please refer to the current FDA-approved package insert provided with each drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.

**9.4.3** Patient Care Implications

Females of childbearing potential must use adequate contraception during treatment and for 6 months after the last dose of carboplatin chemotherapy. Male patients who are sexually active with WOCBP must use highly effective contraception for a total of 6 months after last dose of carboplatin chemotherapy.

**9.5 Commercial Agent: Gemcitabine**

Sites must refer to the package insert for detailed pharmacologic and safety information.

**9.5.1** Adverse Events

Please refer to the package insert.

**9.5.2** Availability/Supply

Please see Section 5.1 for administration instructions. Please refer to the current FDA-approved package insert provided with each drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.

**9.4.3** Patient Care Implications

Females of childbearing potential must use adequate contraception during treatment and for 6 months after the last dose of gemcitabine chemotherapy. Male patients who are sexually active with WOCBP must use highly effective contraception for a total of 3 months after last dose of gemcitabine chemotherapy.

## 10. PATHOLOGY/BIOSPECIMEN

### 10.1 Optional Tumor Tissue Collection and Correlative Studies Blood Sampling (16-FEB-2021)

Patients must be offered the opportunity to consent to optional specimen collection (highly recommended). If the patient consents to participate, the site is required to submit the patient's specimens as specified per protocol. Sites are not permitted to delete the specimen component from the protocol or from the sample consent.

See detailed specimen collection/processing/shipping instructions on the protocol-specific website, www.ctsu.org.

This study will include collection of biospecimens for future analyses. An amendment for any correlative science studies to be performed on biological samples will be submitted to CTEP, NCI for review and approval according to NCTN guidelines or via the Navigator portal after the trial has been reported. Amendments to the protocol and/or proposals for use of banked tissue or blood samples will include the appropriate background, experimental plans with assay details, and a detailed statistical section. Samples for testing will not be released for testing until the appropriate NCI approvals have been obtained.

#### 10.1.1 Tumor tissue collection for PD-L1 Status

*Background*: PD-L1 expression in tumor has been evaluated extensively as a predictive biomarker of response to PD1/L1 inhibitor in different solid tumors. Different commercial companion diagnostic assays for PD-L1 are now available, each assay using a different method of scoring PD-L1 expression with different clinical cut-off values. The "Blueprint PD-L1 IHC Assay Comparison Project" revealed that the 22C3, 28-8, and SP263 PD-L1 assays are closely aligned on tumor cell staining whereas the SP142 assay showed consistently fewer tumor cells stained (Hirsch 2017). The PD-L1 CPS and TPS scoring system have been prospectively evaluated together with the 22C3 assay for selecting patients with lung, cervical, urothelial and non-NPC HNSC for PD1 inhibitor therapy. In the KEYNOTE-048, over 800 patients with metastatic or recurrent HNSC were randomized 3 arms: (1) pembrolizumab alone if the PD-L1 CPS was ≥ 20%; (2) EXTREME regimen (chemotherapy and cetuximab); (3) or pembrolizumab and chemotherapy. In this study, an OS advantage was seen in patients with PD-L1 CPS "≥ 20%" (HR=0.61; 95% CI: 0.45-0.83; p=0.0007) or "≥ 1%" (HR=0.78; 95% CI: 0.64-0.96; p=0.0086) who received pembrolizumab alone compared with the EXTREME regimen (Burtness 2018). For patients randomized to the two chemotherapy-based arms, the subgroup analysis based on PD-L1 status has not been reported to date. There is no reported information about the clinical significance of CPS and TPS for NPC. In the single arm phase II study of nivolumab in recurrent/metastatic NPC led by the principal investigator of this NCI proposal, there was a non-statistically higher proportion of responders among those with tumors expressing PD-L1 (22C3 assay) > 1% and > 10% (Ma 2018). But the study was underpowered to detect any survival difference. No other trials reported to date on PD-1 inhibitor in NPC have investigated the significance of PD-L1 expression using the 22C3 assay.

*Rationale and study plan*: This study plans to use programmed death receptor ligand-1 (PD-L1) expression in NPC as an integrated biomarker. PD-L1 expression will be

recorded according to the Tumor Proportion Score (TPS) and the Combined Positive Score (CPS). The biomarker will be used in to examine the association with overall survival and progression-free survival in this study. PD-L1 analysis will be performed on archived or fresh tumor biopsies (collected at baseline) toward the end of enrollment. PD-L1 expression will not be used as an eligibility criterion or used for treatment assignment. This study hypothesizes that the use of PD-L1 expression based on the TPS or CPS may be useful in identifying those patients who are more likely to benefit from treatment with PD-1 inhibitor in combination with chemotherapy. This study will explore a range of CPS and TPS scores.

*Tissue collection*: All subjects who consent should submit either a newly obtained core or excisional biopsy or archival tissue (FNA not adequate for both archival and new tissue samples). Submission of formalin-fixed paraffin embedded tumor tissue sample blocks is preferred. United States and Canadian sites will send their FFPE samples to the NRGBB-SF. For Asian and Australian sites, FFPE samples will be sent at the end of the study to a laboratory affiliated with the Chinese University of Hong Kong (CUHK) for the characterization of PD-L1 status. The PD-L1 status will be determined at the end of the study, and will not be used to stratify patients prior to randomization.

- Detailed instructions for tissue collection, processing, and shipment are provided in section 10.3.
- If the subject signs the consent for future research, any leftover samples that would ordinarily be discarded at the end of the main study will be retained for Future Biomedical Research future research.

**10.1.2** For patients with non-keratinizing NPC: Plasma Epstein-Barr virus DNA

- Rationale: We hypothesize that plasma EBV DNA half-life during the first 6 weeks of treatment may be associated with subsequent response in patients with non-keratinizing NPC.
- Collection time points: A total of five sampling time points will be used: 5 mL of EDTA blood sample (5 mL tube x 1) will be taken at baseline (within 7 days prior to starting the first dose of study drug), and then at: cycle 1 day 8 +/-3 days, day 15 +/-3 days; cycle 2 day 1 +/- 3 days and day 8 +/- 3 days.
- Detailed instructions for blood sample collection, processing, and shipment are provided in section 10.3.
- All samples from patients who consent are to be submitted for central testing.
- If the subject signs the Future Biomedical Research consent, any leftover samples that would ordinarily be discarded at the end of the main study will be retained for Future Biomedical Research.

**10.1.3** For participating sites in Asia only: Circulating Tumor DNA (ctDNA) Analysis

*Background:* The team at the Chinese University of Hong Kong led by Dennis Lo and Allen Chan has pioneered the real-time PCR technique for detecting plasma EBV DNA. Lately, they have developed a second-generation and more accurate way of detecting plasma EBV DNA (Lam 2018). Furthermore, they have developed a new ctDNA analysis technique called 'Orientation-aware plasma DNA fragmentation analysis' (Sun 2019)

which may inform the tissue of origin of the ctDNA for various types of cancers. The group is able to perform whole genome-wide profiling of copy number aberrations and point mutations in the plasma of cancer patients using massively parallel sequencing (Chan 2013).

*Blood sample collection:* Collection of blood sample for ctDNA is optional and patients who are enrolled into the study must give separate consent. This sample collection is only applicable to selected NRG Oncology sites which are interested in participating. The clinical significance of the alteration in ctDNA, including point mutations, copy number aberrations and the changes in the tissue contribution, has not been evaluated prospectively in NPC patients undergoing chemotherapy +/- nivolumab. In this study, we plan to collect a single baseline sample of blood from patients who consent for research into the alterations in ctDNA. The decision of whether Streck or EDTA tubes will be made following discussion between the study team and the participating site. If EDTA tubes are used: Twenty (20) mL of EDTA blood (for those sites which can process the samples within 6 hours of collection as outlined in section 10.3) will be collected into special tubes for ctDNA analysis at baseline.

Detailed instructions for blood sample collection, processing, and shipment are provided in section 10.3.

## 10.2 Tissue Selection for Integrated Marker Testing

### 10.2.1 Testing requirements and reporting

- Testing will be performed in a molecular diagnostics service laboratory at the Department of Anatomical and Cellular Pathology, Prince of Wales Hospital, the Chinese University of Hong Kong. This laboratory is accredited by the National Testing Authority of Australia (NATA). The performance of the 22C3 (DAKO) assay has been well characterized as it is a FDA approved assay. Additionally, the pathologists at the department have published a comparison of technical performance of 4 different PD-L1 assays in over 700 lung cancer specimens from Chinese patients (Chan 2018). For Mainland China sites: Samples will be shipped to and analysed at a designated laboratory affiliated with the Chinese University of Hong Kong within Mainland China, in batches towards the end of the study.
- PD-L1 assay will be performed towards the end of study enrolment.

### 10.2.2 Method of testing

- Immunohistochemistry (IHC) using the FDA-approved Dako PD-L1 IHC 22C3 pharmDx platform (Agilent, Santa Clara, USA) will be used to analyse PD-L1 expression in formalin fixed paraffin embedded (FFPE) tissues.
- IHC will be performed as previously described (Ma 2018). In brief, all specimens will be fixed in 10% buffered formalin and sectioned at a thickness of 4 μm. Paraffin-embedded sections will be deparaffinized by dissolving the paraffin in xylene and then rehydration with a gradient of ethanol and water. The EnVision Detection Systems Peroxidases/DAB (DAKO) will be used according to manufacturer's instructions. Two experienced pathologists who are blinded to the patient's clinical information will score the PD-L1 IHC independently using the CPS and TPS according to the DAKO's manufacturer's

manual.

- Specimen requirements (tissue/tumor requirements): Corresponding FFPE Block must be from the same block as the H&E slide that is being submitted.
- Invalid test results: When testing cannot be performed within the validated parameters of a test, the result is an "invalid" result. An "invalid" result will be reported when inadequate tumor amount, poor quality of the sections, and wrong tumor type/specimen were found. Firstly, a new specimen will be requested for the test.

**10.2.3** Location of testing

Molecular Diagnostic Laboratory, Department of Anatomical & Cellular Pathology, The Chinese University of Hong Kong; Location: 5/F, Sir YK Pao Centre for Cancer, Prince of Wales Hospital, Shatin, N.T., Hong Kong SAR, China; Contact person: Kwok Wai Lo, Email: kwlo@cuhk.edu.hk, Tel: 852-35052178 or Chit Chow, Email: chit@cuhk.edu.hk, Tel: 853-35051141.

**10.2.4** Tissue Submission for testing

See Biospecimen Submission tables in section 10.3 below.

**10.3 Biospecimen Submission Tables** (16-FEB-2021)

**10.3.1** Optional Specimen Submissions

See detailed specimen collection/processing/shipping instructions on the protocol-specific website.

**Specimen Collection for Biobanking for Potential Future Research (US and Canada Sites) (to be offered to all patients)**

**Forms**: ST Form

**Kits:** Frozen Specimen kits can be requested from the NRGBB-SF at NRGBB@ucsf.edu. Allow 5-10 business days for kits. Sites must have IRB approval before requesting kits.

**Shipping:** One prepaid return label provided for each case for batch shipping all frozen biospecimens only. Batch shipments can be made once sites have collected the post treatment samples or with other cases. Shipping Days: Frozen specimens should be shipped on dry ice by priority overnight Monday-Wednesday for US Sites, or Monday-Tuesday for Canadian sites.

**Processing:** Instructions for processing and shipping are included with the protocol pathology and correlatives documents included on the CTSU website, www.ctsu.org.

**Ship all specimens to:**
Attn: NRG Oncology Biospecimen Bank – San Francisco
UCSF – Dept of Radiation Oncology
2340 Sutter Street - Room S341
San Francisco, CA 94115

For questions, please contact the San Francisco Bank at:

| Email: NRGBB@ucsf.edu<br>415-476-7864/Fax 415-476-5271 | | | |
|---|---|---|---|
| **Specimen Type** | **Collection Time Points** | **Collection Information and Requirements/Instructions for Site** | **Shipping** |
| H&E slide(s) of primary or recurrent/metastatic tumor | Baseline pre-treatment | H&E slide can be duplicate cut H&E slide, does not have to be diagnostic slide. H&E must come from same block being submitted.<br><br>*Note: Unstained slides are not allowed.* | Ship ambient to NRG BB-SF |
| FFPE block of primary tumor or recurrent/ metastatic (same as H&E) | Baseline pre-treatment | Corresponding FFPE block (paraffin-embedded) from the same block as the H&E slide that is being submitted.<br><br>Sites unable to submit blocks should instead submit one to two 3 mm punches from the block. | Ship ambient to NRG BB-SF (use cold packs during warm weather) |
| Plasma for EBV DNA analysis | • Baseline pre-treatment (within 7 days prior to chemotherapy)<br>• Cycle 1: day 8 +/- 3 days<br>• Cycle 1: day 15 +/-3 days<br>• Cycle 2: day 1 +/- 3 days<br>• Cycle 2: day 8 +/- 3 days | <u>The following method is preferred. Sites with any queries should check with study team first:</u><br><br>5 mL of EDTA blood would be collected for each time point. Blood samples would need to be processed within 6 hours after the sample collection.<br><br>The whole blood sample is centrifuged at 3,000 g for 10 minutes. The supernatant would be harvested carefully without disturbing the blood cells into 2 mL Eppendorf tubes.<br><br>The harvested supernatant would be re-centrifuged at 30,000 g for 10 minutes at 4ºC | The harvested plasma samples can be batch shipped to the NRG BB-SF on dry ice. |

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| | | to remove all remaining cells. *NOTE:* For sites unable to spin in Eppendorf tubes at 30,000 g, they can spin a second time at 16,000 g in one 15 mL tube instead. The spinning can also be carried out without refrigeration if the room temperature is below 25ºC.<br><br>The plasma is harvested into one to two 2.5 mL cryovials and stored frozen at -80ºC. | |
| Whole Blood: One 5-10 mL EDTA tube | Baseline pre-treatment<br><br>*Note: If site missed this collection, they may collect at any other time but must note this on the ST form when submitting* | Collect blood, mix and aliquot 1-1.5 mL of whole blood per vial into three 2 mL cryovials.<br><br>Place into biohazard bag and immediately freeze tubes upright at -70 to -90ºC.<br><br>Samples should be frozen and stored at -80$^0$C until ready to batch ship. | Batch ship on Dry Ice by overnight courier to NRG BB-SF. |

**Specimen Collection for Biobanking for Potential Future Research (International: Asia and Australian Sites)**
**(to be offered to all patients)**

**Processing:** Instructions for processing and shipping are included with the protocol documents included on the CTSU website, www.ctsu.org.

**Ship all specimens to:**
Prof Kwok Wai Lo or Dr. Chit Chow
5/F, Sir YK Pao Centre for Cancer,
Prince of Wales Hospital,
Shatin, N.T.,
Hong Kong SAR, China

For questions, please contact Kwok Wai Lo at:
Email: kwlo@cuhk.edu.hk

Tel: 852-35052178

For Mainland China sites: Samples will be shipped to a designated laboratory affiliated with the Chinese University of Hong Kong in batches towards the end of the study.

For Plasma EBV DNA and ctDNA:
To Prof. Allen K.C. Chan
Rm 401, 4/F, Li Ka Shing Medical Sciences Building, Prince of Wales Hospital, Shatin, N.T. Hong Kong SAR.
Email: allen@cuhk.edu.hk or brigette@clo.cuhk.edu.hk

| **Specimen Type** | **Collection Time Points** | **Collection Information and Requirements/Instructions for Site** | **Shipping** |
|---|---|---|---|
| H&E slide(s) of primary or recurrent/ metastatic tumor | Baseline pre-treatment | H&E slide can be duplicate cut H&E slide, does not have to be diagnostic slide. H&E must come from same block being submitted. | Ship ambient to Kwok Wai Lo / Chit Chow, Hong Kong |
| FFPE block of primary or recurrent/ metastatic tumor (same as H&E) | Baseline pre-treatment | Corresponding FFPE block (paraffin-embedded) from the same block as the H&E slide that is being submitted.<br><br>Sites unable to submit blocks should instead submit one to two 3 mm punches from the block. | Ship ambient to Kwok Wai Lo / Chit Chow, Hong Kong |
| Plasma for EBV DNA analysis | • Baseline pre-treatment (within 7 days prior to chemotherapy)<br>• Cycle 1: day 8 +/- 3 days<br>• Cycle 1: day 15 +/- 3 days<br>• Cycle 2: day 1 +/- 3 days<br>• Cycle 2: day 8 +/- 3 days | The following method is preferred. Sites with any queries should check with study team first:<br><br>5 mL of EDTA blood would be collected for each time point.<br><br>Blood samples would need to be processed within 6 hours after the sample collection.<br><br>The whole blood sample is centrifuged at 3,000 g for 10 minutes. The supernatant would be harvested carefully without disturbing the blood | The harvested plasma samples will be sent to Prof Allen Chan's laboratory responsible for the plasma EBV DNA analysis in dry ice.<br><br>The samples will be sent in batches. |

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| | | cells into 2 mL Eppendorf tubes.<br><br>The harvested supernatant would be re-centrifuged at 30,000 g for 10 minutes at 4ºC to remove all remaining cells. *NOTE*: For sites unable to spin in Eppendorf tubes at 30,000 g, they can spin a second time at 16,000 g in one 15 mL tube instead. The spinning can also be carried out without refrigeration if the room temperature is below 25ºC.<br><br>The plasma is harvested into one to two 2.5 mL cryovials and stored frozen at -80ºC. | |
| Plasma for ctDNA analysis **(for participating sites in Asia only)** | Baseline pre-treatment | The site will need to discuss with the study team regarding whether to use EDTA or Streck tubes.<br><br>If EDTA tubes are used:<br>20 mL of EDTA blood would be collected for each time point.<br><br>Blood samples would need to be processed within 6 hours after the sample collection.<br><br>The whole blood sample is centrifuged at 3,000 g for 10 minutes. The supernatant would be harvested carefully without disturbing the blood cells into 2 mL Eppendorf tubes.*<br><br>The harvested supernatant | Plasma samples will be sent in dry ice to Prof Allen Chan's laboratory for the plasma ctDNA analysis.<br><br>Whole Blood samples in Streck tubes need to kept at room temperature and shipped to Prof Allen Chan's laboratory within 7 days.<br><br>The samples will be sent in batches. |

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| | | would be recentrifuged at 30,000 g for 10 minutes at 4ºC to remove all remaining cells. *NOTE*: For sites unable to spin in Eppendorf tubes at 30,000 g, they can spin a second time at 16,000 g in one 15 mL tube instead. The spinning can also be carried out without refrigeration if the room temperature is below 25ºC.<br><br>The plasma would be harvested into five 2 mL cyrovials and stored frozen at -80ºC.<br><br>*For sites that cannot perform the above method of sample processing, Streck tubes can be used for sample collection. | |
| Whole Blood: One 5-10 mL EDTA tube | Baseline pre-treatment<br><br>*Note: If site missed this collection, they may collect at any other time but must note this on the ST form when submitting* | Collect blood, mix and aliquot 1-1.5 mL of whole blood per vial into three 2 mL cryovials.<br><br>Place into biohazard bag and immediately freeze tubes upright at -70 to -90ºC.<br><br>Samples should be frozen and stored at -80$^0$C until ready to batch ship. | |

## 11. SPECIAL STUDIES (NON-TISSUE)

All participating centers will be required to participate in the patient-reported outcome and quality of life assessments.

### 11.1 Description of QOL/PRO Instruments

*EORTC QLQ-C30*

The EORTC QLQ-C30 Version 3.0 is a well-established, 30-item self-reporting questionnaire developed to assess overall QOL of patients with cancer. The EORTC QLQ-C30 is grouped into five functional subscales (role, physical, cognitive, emotional and social functioning), three multi-item symptom scales (fatigue, pain, and nausea and vomiting), individual questions concerning common symptoms in cancer patients, and two questions assessing overall QOL. The subscales and symptom measures range in score from 0 to 100; a high scale score represents

better functioning or higher symptom burden (symptom scales will be reversed to facilitate presentation). The EORTC QLQ-C30 has been used in clinical trials using nivolumab for patients with recurrent/metastatic HNSC (Ferris 2016, Harrington 2017) and using the EORTC QLQ-C30 in this trial will provide a reliable comparison among trials. The time for administration is about 7-10 minutes. Clinical meaningful changes in the EORTC QLQ-C30 will be defined as a 10-point difference (Osoba 1998).

NRG Oncology has obtained permission to use the EORTC QLQ-C30 for this study in English, Spanish, French (Canada), Chinese (Mandarin), and Korean.

*MFI-20*
Fatigue will be measured by using the Multidimensional Fatigue Inventory (MFI)-20. MFI is a 20-item self-report instrument with five dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity (Smets 1995). Each dimension includes four items on a 1- to 5-point scale. The total score is the sum of the 20 items or the sum of the 5 dimensions, and ranged from 20 to 100 with a higher score representing more fatigue. The MFI-20 has well-established validity and reliability ($\alpha$=0.84) in use with patients with cancer and is available in English, Spanish, French (Canada), Chinese (Hong Kong), traditional Chinese (Chuang 2018, Chung 2014), and Korean (Yoon 2020). The MFI-20 can be completed in 5-10 minutes. A total score of $\geq$ 43.5 indicates moderate-to-severe fatigue, and a total score of $\geq$ 52.5 suggests severe fatigue (Andic 2019).

## 11.2 Administration of Patient-Completed Questionnaires

### 11.2.1 Time Points for Administration:

All questionnaires will be completed as specified in the Study Assessment Calendars in section 4.0.

### 11.2.2 Administration Instructions

Questionnaires are to be administered per section 4.0. For patient opting out of ePRO, the PRO forms should be administered during an office visit if at all possible, preferably while the patient is waiting to be seen. Once the questionnaires are completed by the patient, the staff member should review it to ensure that no items were unintentionally left blank. When absolutely necessary, it may also be administered by mail or phone. The completed forms will be data entered in Medidata Rave.

Patients who never initiate NRG-HN007 study therapy or who experience disease progression should continue participating in the PRO study. If a patient does not come in to clinic, the questionnaires will either be mailed to the patient or the research assistant will call the patient to complete the forms. If the patient does not return the forms within two weeks the patient will be called and either another set will be sent or the patient will complete the questionnaires over the phone with the research assistant.

If a patient declines to complete a scheduled PRO forms or if the questionnaire is not completed for any other reason (and cannot be completed by phone or mail), the QOL coversheet must be completed in Rave. For patients who agree to use ePRO for PRO collection please refer to Appendix II.

Patients who speak and understand English or Spanish will have the option to complete the PROs using ePRO (see Appendix II for more details).

## 12. MODALITY REVIEWS

### 12.1 Medical Oncology Modality Quality Assurance Reviews

The Medical Oncology Co-Chair or NRG Oncology Headquarters approved designee(s) will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data. The scoring mechanism is: **1) Per Protocol, 2) Variation Acceptable, 3) Deviation Unacceptable, and 4) Not Evaluable**.

The Medical Oncology Co-Chair or designee will perform a Quality Assurance Review after NRG Headquarters has received complete data for each case enrolled. The reviews will be ongoing.

## 13. DATA AND RECORDS

### 13.1 Data Management/Collection

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments. Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.
- Rave role requirements:
    - Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
    - Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
    - Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in Regulatory Support System (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 staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password, and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff 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. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name

in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section 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.

### 13.2 Summary of Data Submission

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See Sections 7.5 and 7.6 for information about expedited and routine reporting.

Summary of All Data Submission: Refer to the CTSU website.

### 13.3 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, and timeliness reports. Review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff that are rostered to a site and have access to the CTSU website. Staff that have Rave study access can access the Rave study data using a direct link on the DQP.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

Note: Some Rave protocols may not have delinquent form details or reports specified on the DQP. A protocol must have the Calendar functionality implemented in Rave by the Lead Protocol Organization for delinquent form details and reports to be available on the DQP. Site staff should contact the LPO Data Manager for their protocol regarding questions about Rave Calendaring functionality.

### 13.4 Rave-CTEP-AERS integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) Integration enables evaluation of post-baseline Adverse Events (AE) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

All AEs that occur after baseline are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment or reporting period and used to collect AEs that start during the period or persist from the previous reporting period. The CRA will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Events form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form.

In the rare occurrence that Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: Protocols > Documents> Education and Promotion; and
- Expedited Safety Reporting Rules Evaluation user guide: Resources > CTSU Operations Information> User Guides & Help Topics.

NCI requirements for SAE reporting are available on the CTEP website:

- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is

available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf.

### 13.5 Global Reporting/Monitoring

Data for this study will be submitted via the Data Mapping Utility (DMU). Cumulative protocol- and patient-specific data will be submitted weekly to CTEP electronically via the DMU. DMU Light reporting consists of Patient Demographics, On/Off Treatment Status, Abbreviated Treatment and Course information, and Adverse Events as applicable. Instructions for setting up and submitting data via DMU are available on the CTEP Website: (https://ctep.cancer.gov/protocolDevelopment/dmu.htm).

**Note**: All adverse events (both routine and serious) that meet the protocol mandatory reporting requirements must be reported via DMU in addition to expedited reporting of serious adverse events via CTEP-AERS.

## 14. STATISTICAL CONSIDERATIONS

### 14.1 Study Design

This is a prospective randomized phase III trial comparing the platinum-gemcitabine-nivolumab combination to platinum-gemcitabine in the first-line treatment of recurrent and/or metastatic NPC. Patients will be stratified by:

- Disease: locoregional only vs. lung metastases vs. other distant metastases;
- Zubrod/ECOG performance status: 0 vs. 1;
- Prior platinum-gemcitabine neoadjuvant (induction) therapy and/or adjuvant chemotherapy for primary non-metastatic/recurrent NPC more than 6 months prior to registration: yes vs. no.

After being stratified, patients will be randomized to both arms using a 1:1 ratio.

### 14.2 Study Endpoints

#### 14.2.1 Primary Endpoint

- Overall survival (OS) *(failure – death due to any cause)*.

#### 14.2.2 Secondary Endpoints

- Locoregional failure and distant metastases.
- Progression-free survival (PFS) *(failure – progression or death due to any cause).*
- Tumor response according to RECIST 1.1.
- Toxicity based on CTCAE v5.0.
- Patient-reported symptomatic toxicities measured by PRO-CTCAE.
- QOL as measured by EORTC QLQ-C30.
- Fatigue, as measured by MFI.
- PFS based on PD-L1 CPS/TPS cut-off.

#### 14.2.3 Exploratory Endpoints

- OS based on PD-L1 CPS/TPS cut-off.

- Changes in QOL as measured by EORTC QLQ-C30, and in fatigue as measured by MFI-20, between and within arms over time.
- Translational research studies.

## 14.3 Primary Objectives Study Design

### 14.3.1 Primary Hypothesis and Endpoints

This study hypothesizes that the platinum-gemcitabine-nivolumab combination would result in a better OS than platinum-gemcitabine in the first-line treatment of recurrent and/or metastatic NPC.

### 14.3.2 How Primary Endpoints Will Be Analyzed

Overall survival rates for both treatment arms will be estimated using the Kaplan-Meier method (Kaplan 1958). The comparison of OS distributions between treatment arms will be done using a logrank test (Mantel 1966). More details on the primary endpoint analysis are given in Section 14.6.2. Multivariate analysis will be also performed using the Cox proportional hazards model evaluating the stratification factors listed in Section 14.1, country (Asian sites vs. Non-Asian sites), keratinizing squamous carcinoma, prior definitive RT for NPC, gender, age, and PD-L1 status (CPS). Variable selection based on BIC and AIC will be performed to determine relevant covariates in the multivariate models. Hazard ratios and their respective 95% confidence intervals will be provided.

### 14.3.3 Sample Size and Power Calculations:

To date, the 1-yr OS rate of cisplatin-gemcitabine has only been formally reported in a phase II study to be 62% [16]. In the phase III study by Zhang et al, the 1-yr OS rate can only be estimated to be 70-80% from the OS curve (Zhang 2016). Therefore, it is reasonable to assume that the 1-yr OS is around 71-75% for this clinical setting. In the KEYNOTE-048 study, HR for OS is 0.77 (95% CI: 0.63-0.93; p=0.0034) for unselected patients for pembrolizumab-chemotherapy relative to the EXTREME regimen, whereas the HR for OS is 0.61 (95% CI: 0.45-0.83) for patients with PD-L1 CPS score $\geq$ 20%. Thus, a HR for OS should be somewhere between 0.61-0.93 for patients unselected for PD-L1 expression in NPC. In the KEYNOTE-048 study, patients in the control arm received cetuximab maintenance, but there is no level 1 evidence on maintenance therapy in NPC. Most centers would give 6 to 8 cycles of 1$^{st}$ line chemotherapy followed by observation. The KEYNOTE-189 study met the primary endpoints with a 19.8% difference in the 1-yr OS favoring the chemo-PD-1 inhibitor arm (HR=0.49). In the study of camrelizumab (Fang 2014), the 1-yr PFS of 61% appears to be more than double of the rate reported with cisplatin-gemcitabine by the same group in China (27%). Thus, we speculated that the magnitude of benefit of adding nivolumab to chemo should be larger than previously estimated.

After being stratified (see Section 14.1), patients will be randomized in a 1:1 ratio to receive either platinum-gemcitabine with nivolumab (experimental arm) or without nivolumab (control arm). The primary endpoint is OS defined as the time from randomization to death due to any cause. It is hypothesized that OS will be superior for patients on platinum-gemcitabine with nivolumab (followed by maintenance with nivolumab alone) as compared to patients on the platinum-gemcitabine without nivolumab arm. The hypothesized effect size is a HR of 0.67 in favor of the nivolumab arm, corresponding to an increase in 1-year OS from 75% to 82.5% under

the exponential distribution assumption (i.e. an increase in the median survival time from 28.9 months to 43.2 months). With a 1-sided type I error rate of 0.025, 80% power, and two interim analyses, the log-rank test requires **200 OS events** from 300 randomized patients. After an adjustment of 5% due to loss to follow-up, **the target accrual is 316 randomized patients**.

### 14.4 Study Monitoring of Primary Objectives

**Interim Analysis for the DMC**

The NRG Oncology Data Monitoring Committee (DMC) will review the study twice a year with respect to patient accrual and morbidity. The DMC also will review the study on an "as needed" basis in between regularly scheduled meetings.

**Interim Analysis to Monitor Study Progress**

Interim reports with statistical analyses will be prepared twice per year until the initial treatment results have been presented/published. In general, the interim reports will contain the following information: patient accrual rate with a projected completion date (while the study is still accruing), total patients accrued, distributions of important pretreatment and prognostic baseline variables, and the frequencies and severity of adverse events by treatment arm. The interim reports will not contain the results from the treatment comparisons with respect to the primary endpoint, OS, or any secondary endpoints, with the exception of reporting of adverse events.

**Significance Testing for Early Termination and/or Reporting**

Two interim efficacy analyses based on the O'Brien-Fleming boundary will be performed when 50% and 75% (100 and 150) of the OS events have occurred. These are projected to occur approximately 54 and 69 months from study activation, respectively. The nominal significance levels and the corresponding HRs for rejecting the $H_0$ at the interim analyses are shown in the table below. If a boundary is crossed, then recommendations will be made to the NRG Oncology Data Monitoring Committee (DMC) relative to stopping accrual (if applicable) and/or reporting the study results early, otherwise, accrual to the trial and/or follow-up (as applicable) will continue until the final analysis. There will be two interim futility analyses at the same time points. The statistical monitoring boundaries for futility are based on the LIB20 method at the same times as the efficacy analyses (Haybittle 1971, Freidlin 2010). The last column in Table 1 provides the decision rule for the interim futility analysis.

Table 1. Nominal significance level and HR for interim analyses

| | | **Efficacy Boundary** | | **Futility boundary (LIB20)** |
|---|---|---|---|---|
| Interim Analysis | Number of Events (% Information) | Reject $H_0$ if $p \leq$ | Reject $H_0$ if HR(Exp./Control) $\leq$ | Reject $H_1$ if HR(Exp./Control) $\geq$ |
| #1 | 100 (50%) | 0.0015 | 0.55 | 1.00 |
| #2 | 150 (75%) | 0.0092 | 0.68 | 0.96 |

In addition to the routine reporting of accrual, distributions of pretreatment characteristics, and frequency/severity of adverse events, the interim efficacy/futility results will be reported to the NRG DMC, following the required number of events for the planned interim analyses.

**Analysis for Reporting the Initial Treatment Results**

The primary hypothesis of the study is to determine if adding nivolumab to platinum-gemcitabine as first-line treatment improves OS for patients with recurrent and/or metastatic NPC. The primary analysis will happen when 200 OS events (deaths) have been observed, which is projected to require 33 months of follow-up after accrual closure (approx. 92 months from study activation). The primary analysis will be done in the intent-to-treat (ITT) population.

The analysis report will include: tabulation of all cases entered and those excluded from the analyses with the reasons for exclusion given, distributions of important prognostic baseline variables, the frequencies and severity of adverse events by treatment arm, compliance rate of treatment delivery, observed results with respect to the primary and secondary endpoints. The primary hypothesis of improved OS, assuming the two interim analyses have been carried out, will be tested with a 1-sided significance level of 0.022.

## 14.5 Accrual/Study Duration Considerations

The expected accrual rate is 6 patients/month, thus around 59 months (4.9 years) are expected for the total accrual including a 6-month period of minimal accrual after study activation. The follow-up period will take approximately 33 months (2.75 years) after accrual closure to reach the required events for primary endpoint analysis. Total study duration is 92 months (~7.7 years) from activation.

## 14.6 Alternative Design if Accrual is Higher than Projected

The study team will monitor accrual of this trial to determine the feasibility of increasing the sample size based on a slightly higher hazard ratio than the hypothesized value (HR=0.67) used in the original design in Sections 14.3-14.5. This increase in HR, or equivalently, a decrease in the treatment effect size, is motivated by the possible dilution of the treatment effect given that no immune-selection based on PD-L1 expression has been implemented in this trial. The study team will examine the monthly accrual rate for quarters 5-6. If the observed accrual rate for quarters 5-6 is at least 7 patients/month then a biomarker-guided design will be proposed to allow for parallel testing of the treatment effect in the overall population and a biomarker-defined subgroup. This redesign will imply a change in the PD-L1 expression from an integrated to an integral biomarker since the PD-L1 expression will be involved in the primary efficacy analysis. If warranted, the protocol amendment process to increase the sample size will be initiated once the accrual for quarters 5-6 is available and the protocol amendment will be submitted to NCI/CTEP by the end of quarter 8 accrual.

### **14.6.1** *Fully Specified Biomarker-Guided Design*

This section presents the alternative design for this trial if the actual accrual rate for quarters 5-6 supports changing the accrual parameter to 7 patients/month. Under this scenario and using the PD-L1 CPS cutpoint parameter of 20, the protocol will be amended to adopt the design shown in this section instead of the current design shown in Sections 14.3-14.5. This alternative design will use a parallel testing after allocating a one-sided alpha level of 0.015 for the primary efficacy testing in the overall population and 0.010 for the biomarker-defined subgroup analysis, as explained later (overall one-sided alpha level of 0.025). This design recognizes the possibility of a treatment effect on OS in the overall population while allowing for the testing of the

treatment effect on OS in a biomarker-defined subgroup that is likely to show a more profound treatment benefit.

*Overall population analysis*: The hypothesized effect size for the overall population is a HR of 0.70 in favor of the nivolumab arm, corresponding to an increase in 1-year OS from 75% to 81.8% under the exponential distribution assumption (i.e. an increase in the median survival time from 28.9 months to 41.3 months). Note that the target HR is along the observed HR for the pembroluzimab+chemotherapy vs. EXTREME regimen in the overall population in the KEYNOTE-048 trial (HR=0.72, 95% IC [0.60, 0.87]) (Burtness et al 2019). With a 1-sided type I error rate of 0.015, 80% power, and two interim analyses at 50% of 75% of information, the log-rank test requires **290 OS events** from 430 randomized patients. After an adjustment of 5% due to loss to follow-up, **the target accrual is 452 randomized patients**. The boundaries for rejecting the $H_0$ (efficacy) and $H_1$ (futility) at the interim analyses are shown in the table below. The first interim analysis is projected to occur around 60 months into accrual (~80% of accrual target), and the second interim look around 76 months from trial activation.

Nominal significance level and HR for interim analyses

| | | **Efficacy Boundary** | | **Futility boundary (LIB20)** |
|---|---|---|---|---|
| Interim Analysis | Number of Events (% Information) | Reject $H_0$ if $p \leq$ | Reject $H_0$ if HR(Exp./Control) $\leq$ | Reject $H_1$ if HR(Exp./Control) $\geq$ |
| #1 | 145 (50%) | 0.0006 | 0.58 | 0.99 |
| #2 | 218 (75%) | 0.0048 | 0.70 | 0.96 |

The primary efficacy analysis for the overall population will be performed when 290 OS events (deaths) have been observed, which is projected to occur around 99 months from study activation. This analysis will be done in the intent-to-treat (ITT) population. The primary hypothesis of improved OS, assuming the two interim analyses have been carried out, will be tested with a 1-sided significance level of 0.0134.

*Biomarker-defined subgroup analysis*: Under this alternative design, a one-sided alpha level of 0.010 is allocated for the biomarker-subgroup analysis based on OS for patients with CPS $\geq$ 20, which is assumed to be 40% of patients (Burtness et al. 2018). This assumption translates into a monthly accrual rate of 2.8 patients for this cohort. The hypothesized effect size for this biomarker subgroup is a HR of 0.55 in favor of the nivolumab arm, a reasonable figure according to the results from the KEYNOTE-048 trial for chemotherapy plus pembroluzimab vs. the EXTREME regimen in recurrent and metastatic HNSCC patients: HR=0.60 (95% CI [0.45, 0.82]). With a 1-sided type I error rate of 0.010, 80% power, the log-rank test requires **113 OS events** from 182 randomized patients with CPS $\geq$ 20.

| | **Overall Population** | **Biomarker-defined subgroup CPS $\geq$ 20*** |
|---|---|---|
| Monthly accrual rate | 7 | 2.8 |
| One-sided alpha level | 0.015 | 0.010 |
| Power | 80% | 80% |

| | | |
|---|---|---|
| Targeted HR (exp./control) | 0.70 | 0.55 |
| # of randomized patients | 452 | 182 |
| # OS events | 290 | 113 |

*About 40% NPC patients with CPS ≥ 20, according to KEYNOTE-048.

Under this alternative design, an optimal cut-off point finding algorithm based on OS and the Procedure A in Jiang et al (2007) will be also added as an exploratory objective/endpoint. Note that this exploratory objective is still reasonable given the current evidence on the role of PD-L1 expression in NPC. All these details will be added to the amended protocol if this design is adopted given the accrual rule specified in this section.

**Accrual and Study Duration Considerations for the Biomarker-Guided Design**

The expected accrual rate for this alternative design is 7 patients/month, thus around 70 months (~5.8 years) are expected for the total accrual including a 6-month period of minimal accrual after study activation. The follow-up period will take approximately 29 months (~2.4 years) after accrual closure to reach the required events for primary endpoint analysis. Total study duration is 99 months (~8.2 years) from activation. The time required to enroll the patients in the biomarker-defined subgroup and to reach the number of OS events for the primary efficacy analysis in this cohort is about the same as for the overall population, as shown in the table below. Adjustments to the operating characteristics of this trial could be performed as the result of the actual accrual rate for quarters 5-6.

| | **Overall Population** | **Biomarker-defined subgroup CPS ≥ 20*** |
|---|---|---|
| Monthly accrual rate | 7 | 2.8 |
| Accrual duration | 70 mo. (~5.8 yrs) | 70 mo. (~5.8 yrs) |
| Study duration | 99 mo. (~8.2 yrs) | 103 mo. (~8.6 yrs) |

*About 40% NPC patients with CPS ≥ 20, according to KEYNOTE-048.

**14.6.2** *Further design considerations*

Currently, the PD-L1 (CPS) has been not validated in NPC, unlike recurrent and metastatic HNSCC (KEYNOTE-048). The Mainland China study with chemotherapy and chemotherapy plus camrelizumab in the first-line of R/M NPC (NCT03707509), and also the KEYNOTE-122 (NCT02611960), a study with platinum pre-treated R/M NPC, may provide further evidence on the utility of PD-L1 CPS in R/M NPC. Therefore, the proposed alternative design in Section 14.6.1 could be modified after considering the new data evidence on PD-L1 expression from the aforementioned trials. If the actual monthly accrual rate for quarters 5-6 is at least 7 and discussions are needed about modifications to any of the design parameters in the alternative design shown in Section 14.6.1, then the design modification process will be carried out by an independent statistician who has no knowledge of the study outcome and biomarker data. The decision about any modifications to the alternative design will be made by the study chairs and the independent statistician, without any knowledge of outcome data from NRG-HN007.

## 14.7 Secondary/Exploratory Hypothesis and Endpoints (including correlative science aims)

**14.7.1** Secondary Hypotheses and Endpoints

- Locoregional failure (LRF)

*Hypothesis:* The platinum-gemcitabine-nivolumab combination would result in lower LRF rates.

- Distant metastasis (DM)
  *Hypothesis:* The platinum-gemcitabine-nivolumab combination would result in lower DM rates.
- Progression-free survival (PFS)
  *Hypothesis:* The platinum-gemcitabine-nivolumab combination would result in superior PFS.
- Tumor response according to RECIST 1.1
  *Hypothesis:* The platinum-gemcitabine-nivolumab combination would result in better objective response rate (RECIST 1.1).
- Toxicity based on CTCAE v5.0
  *Hypothesis:* The platinum-gemcitabine-nivolumab combination would have a similar toxicity profile as the platinum-gemcitabine arm.

**14.7.2** Definitions of Secondary Endpoints and How These Will Be Analyzed

Except for within PRO endpoints, no multiplicity adjustments will be done for other secondary endpoints.

*Time-to-Event Endpoints*

The distribution of the progression-free survival (PFS), defined as the time from randomization to disease *progression or death due to any cause* will be estimated using the Kaplan-Meier method and between-arm differences compared using the log-rank test (Kaplan 1958).

All other secondary time to event endpoints have precluding events that act as competing risks. Failure events and competing risks for local-regional and distant metastasis failure endpoints is outlined in the table below.

| **First event** | **Local-regional failure** | **Distant metastasis** |
|---|---|---|
| None | Censored | Censored |
| Local-regional progression or recurrence | Failure | Competing risk |
| Distant metastasis | Competing risk | Failure |
| Death due to study cancer or unknown causes | Failure | Competing risk |
| Death due to any other reason | Competing risk | Competing risk |

Time to locoregional failure will be measured from the time of randomization to the date of failure, date of precluding event, or last known follow-up date. Time to distant metastasis will similarly be measured from the time of randomization to the date of distant metastasis, date of precluding event, or last known follow-up date. The cumulative incidence estimator will be used to estimate time to event distributions for locoregional failure and distant metastasis with between arm differences tested using cause-specific log-rank test.

For all efficacy endpoints, Cox proportional hazards models will be used to determine hazard ratios (cause-specific hazard ratios in the case of endpoints with competing risks) and to assess the effects of covariates of interest mentioned in Section 14.3.2 (Cox 1972). The Fine-Gray

subdistribution hazards model may be applied to further explore outcomes by treatment arm and other covariates for endpoints with competing risks (Fine and Gray 1999).

All efficacy endpoints will be reported at the time of the primary endpoint analysis. A two-sided significance level of 0.05 will be used to determine significance for these secondary endpoints. All the analysis for secondary time-to-event endpoints will be done in the intent-to-treat (ITT) population.

*Tumor Response*

Tumor response in patients with measurable disease will be assessed according to RECIST 1.1. The Objective Response Rate (ORR), defined as the proportion of confirmed complete and partial response will be calculated with their respective 95% confidence intervals (CI). An estimate of the difference in ORR between the experimental and control arms along with the 95% CI will be also provided. Between-arm difference in ORR will be assessed using a chi-square test for proportions based on normal approximation. The confidence intervals will be also based on a normal approximation. A two group chi-square test with a 5% one-sided significance level will have 89% power to detect the difference between arms of 60% (control arm; Zhang et al 2016) and 75% (experimental arm) with 316 randomized patients.

*Toxicity*

Adverse events (AEs) will be graded using CTCAE v5.0. Counts of all AEs by grade will be provided by treatment arm. Counts and frequencies will be provided for the worst grade AE experienced by the patient by treatment arm. The number of patients with at least 1 grade 3 or higher AE will be compared between the treatment arms. All comparisons will be tested using a chi-Square test, or Fisher's exact test if cell frequencies are $< 5$, with a significance level of 0.05. Toxicity analyses will be based on an as-treated population, which includes all patients who received at least one dose of the assigned trial treatment.

The mean number of grade 3-4 adverse events after adjusting by follow-up time between arms will be compared using a negative binomial regression (Tang 2015). The mean toxicity ratio between arms and its 95% confidence interval (CI) will be reported. As recommended by Trotti and colleagues (Trotti 2007), further toxicity analyses separated by cycles (concurrent and maintenance) will be explored.

All toxicity analyses will be conducted at the time of the primary endpoint analysis.

*PRO-CTCAE*

Adverse events will also be assessed using PRO-CTCAE items. The specific symptoms to be evaluated for this study are listed in the table in Section 7.4.1. Assessments will be collected at the same time points as the PROs. For each symptom, counts and frequencies will be provided for the worst score experienced by the patient by treatment arm. The proportion of patients with scores $\geq 1$ and $\geq 3$ will be compared between groups using a Chi-square test, or Fisher's exact test if cell frequencies are $< 5$, using a significance level of 0.05. Analysis of changes in patient reported outcomes over time will analyzed by fitting GEE models using a logit link (dichotomizing the symptom scores as 0 vs. $> 1$ and 0-2 vs. 3-4) with time of assessment, treatment arm, and treatment-by-time interaction terms in the model.

*Patient-Reported Outcomes (PROs)*
The EORTC QLQ-C30 and Multidimensional Fatigue Inventory (MFI)-20 are the two PRO tools in this trial, collected at time points specified in Section 4.0 - Study Assessment Calendars. A description of these tools and background information can be found in Section 11.1. The primary PRO endpoint is the global health status (GHS/QOL) from the EORTC QLQ-C30 at the end of cycle 6 (end of the chemo doublet or 18 weeks from start of treatment). This subscale comprises two items with a score ranging from 0 to 100 with a higher scale score representing better functioning. The selection of the GHS from EORTC QLQ-C30 as the primary PRO objective will allow an easy comparison with other published immunotherapy trials, because the majority have used the global health status from EORTC QLQ-C30 as the primary endpoint (Hall 2019). The secondary PRO endpoint is the MFI overall score at the end of cycle 6. The MFI overall score is the sum of the 20 items or the sum of the five dimensions, ranging from 20 to 100 with a higher score representing more fatigue. Fatigue is a multidimensional symptom including physical, emotional, and/or cognitive tiredness. The overall score of MFI is a good measure for burden from fatigue in cancer patients and a valid summary score for people with fatiguing illnesses (Lin 2009, Hinz 2020).

The following are the PRO objectives and hypotheses in this trial:

- *Primary PRO Objective*: To assess quality of life (QOL), as measured by EORTC QLQ-C30, between the two arms.
  *Primary PRO Hypothesis:* The EORTC QLQ-C30 GHS/QOL mean score change from baseline to cycle 6 will be non-inferior in the platinum-gemcitabine-nivolumab combination arm compared to the control arm.
- *Secondary PRO Objectives*: To assess fatigue, as measured by Multidimensional Fatigue Inventory (MFI-20), between the two arms.
  *Secondary PRO Hypothesis:* The MFI overall mean score change from baseline to cycle 6 will be non-inferior in the platinum-gemcitabine-nivolumab combination arm compared to the control arm.
- *Exploratory PRO Objective:* To determine changes in patient QOL and fatigue as measured by the EORTC QLQ-C30 and the MFI-20, respectively, between and within arms over time until the end of the nivolumab maintenance.

Cycle 6 was selected for the primary and secondary PRO objectives based on the following reasons: 1) cycle 6 is the end the chemo doublet and beginning of nivolumab maintenance phase, which will allow us to capture patients' acute responses to treatment, platinum-gemcitabine-nivolumab combination vs. chemo doublet; 2) current literature has suggested that most PRO studies in immunotherapy trials have used acute changes in PROs as the endpoints (ranging from 12-24 weeks from baseline; Hall 2019) and shown similar to favorable findings in PROs for immunotherapy arms; and 3) given the potential attrition rate in PRO measures for longitudinal follow-ups, using PRO at the end of chemo doublet would reduce potential attrition and improve the study power.

An exploratory aim has been added into the study to examine the long-term changes in PROs between and within the arms. Since the nivolumab maintenance will continue up to 2 years, it is important to study the long-term effect on PROs up to 2 years as well. The assessment at 1 year

will allow us to study the effect of nivolumab in the middle of the maintenance phase.

Analysis Plan for PROs

The EORTC QLQ-C30 subscales (global health status, five functional subscales, and three multi-item symptom subscales – Fatigue; Nausea and Vomiting; and Pain) and the change score from baseline to each time point will be summarized using descriptive statistics (e.g. mean, standard deviation, etc.). Similarly, descriptive statistics will be reported for the five subscales (general fatigue, physical fatigue, mental fatigue, reduced motivation, and reduced activity) and overall score in the MFI.

To test the primary and secondary PRO hypotheses, an ANCOVA model using the scores at the end of cycle 6, baseline scores, the stratification factors, and important prognostic factors in NPC (keratinizing squamous carcinoma and prior definitive RT) will be used. No variable selection will be performed for the main analyses. The proposed adjusted ANCOVA estimator has shown desirable statistical properties even under the presence of missing data (Tsiatis 2008, Wang 2019). For the primary non-inferiority hypothesis, a 97.5% confidence interval (CI) for the treatment effect at the end of cycle 6 will be calculated using the proposed model (one-sided alpha of 0.0125). If the lower bound of this CI > -10, the MID for the GHS score, then the experimental arm will be declared non-inferior to the control arm in terms of the global health-related QOL. The non-inferiority margin was based on the MID, which in turn is based on a moderate change in a subjective significance questionnaire associated with mean change in scores about 10 to 20 points in the EORTC QLQ-C30 domains (Osoba 1998, Mazieres 2019).

For the secondary PRO hypothesis based on the MFI overall score, a 97.5% CI will be used to determine if the MFI overall mean scores at the end of cycle 6 for the experimental arm is non-inferior to the control arm after adjusting for the baseline scores and additional covariates mentioned previously (one-sided alpha of 0.0125). If the upper bound of this CI < 9, the MID for the MFI overall score, then the experimental will be declared non-inferior to the control arm in terms of fatigue. The MID for the MFI overall score in cancer populations is currently not available. According to data from non-cancer patients, the MID for the MFI overall score ranges from 7-13 points (Nordin 2016). A range of 5%-10% differences in instrument range has been recommended for clinical meaningful changes (Ringash 2007), if no specific MID is proposed for patient-reported outcomes. So conservatively speaking, a MID of 9 points is used in this study.

The proposed hypothesis testing and alpha levels for the primary and secondary PRO endpoints will keep control of the type-1 error at 0.025 (one-sided alpha).

In addition to the primary and secondary PRO analyses, exploratory analyses with each of the subscales of the EORTC QLQ-C30 and MFI will be performed. A longitudinal ANCOVA model involving all the time points (discrete), the treatment factor and its interaction, and the same covariates as before, will be adjusted for each of the subscales in the EORTC QLQ-C30 and MFI tools (Liu et al 2009). A reduced model without the treatment by time interaction terms will be also adjusted. Using the previous two models, a likelihood ratio test will be done to determine if treatment arms differ for a given subscale in at least one time point (alpha level of 0.05). If the null hypothesis of no difference at all time points is rejected then 95% CIs for the between arms

difference will be reported at every time point. No multiplicity adjustment due to subscales or time points or missing data imputation will be performed with these exploratory analyses. These analyses aim at describing changes in quality of life or symptoms between and within arms over time. The same 10 points will be used as the MID for the EORTC QLQ-C30 domains for purposes of these exploratory analyses. For purposes of interpretations of the MFI results in these exploratory analyses, the following MIDs will be used: 2.1 for the general fatigue, 2.1 for physical fatigue, 2.4 for reduced activity, 1.6 for reduced motivation, and 1.6 for mental fatigue (Purcell 2010).

Handling Missing PRO Data

Prior to performing analyses, an evaluation of the amount, reasons and patterns of missing data will be performed, using the well-known categories of missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR) (Fairclough 1998, 2010; Verbeke 2000). If > 20% of the data is missing at any time point for the PROs, patient and tumor characteristics will be compared between patients with completed assessments and those with missing assessments using, for instance, a logistic model and a variable selection model. If any are found to differ significantly, they will be included in the analytic models, which assumes that the data is MAR. Multiple imputation under the MAR assumption could also be considered (Rubin 1987). Given that non-ignorable missing data is a concern in health-related QOL studies, other methods to handle MNAR data will be applied. Specifically, a joint model that allows a shared parameter between the repeated measurements and time to death or drop out can be used if considered MNAR due to the high number of patient deaths or dropouts (Rizopoulos 2012). Other options for MNAR data are pattern mixture, selection models and single-step full-likelihood methods for the outcome and missing data models (Little 1995, Fairclough 2010, Gomes 2019). More recent approaches to assess the nonignorability assumption in the MAR approaches could be also explored (Yuan 2014, Xie 2018). Sensitivity analyses will be performed to compare the results of different missing data handling strategies.

Sample size justification and Power for PROs

The following assumptions were used to calculate the power for the primary PRO endpoint analysis:

- The compliance rate at the end of cycle 6 for the EORTC QLQ-C30 tool is estimated to be around 70% based on PRO compliance data from the randomized phase II/III NRG-HN001 trial, an international study with non-recurrent/non-metastatic nasopharyngeal cancer.
- The non-inferiority margin for the between arms difference at the end of cycle 6 is based on the MID of 10 points for the GHS score (Mazieres 2019). That is, the experimental arm is allowed to be, on average, worse than the control arm but the detriment in health-related QOL has to be within the MID or non-inferiority margin (i.e. a non-clinically meaningful detriment).
- The common standard deviation (SD) of the GHS scores at the end of cycle 6 is around 18-22 points. These figures are based on the data from Keynote 141, a randomized phase III trial for recurrent and metastatic SCC of the head and neck (Harrington et al 2017).
- The power calculations are based on a t-test for two independent groups. The proposed ANCOVA model is expected to have a higher power since the adjusted estimator is more efficient than the one based on the t-test (Wang 2019).

- A one-sided alpha level of 0.0125 is used for the non-inferiority test, or equivalently, a 97.5% CI.
- Under the null inferiority hypothesis, no difference between arms in terms of the GHS scores at the end of cycle 6 is assumed.

**Power of the test for the non-inferiority (primary) PRO hypothesis based on 220 evaluable patients (70% compliance rate; target accrual is 316 randomized patients)**

| SD of GHS scores at the end of cycle 6 (EORTC QLQ-C30) | Cohen's Effect Size | Power |
|---|---|---|
| 18 | 0.56 | 97% |
| 19 | 0.53 | 95% |
| 20 | 0.50 | 93% |
| 22 | 0.45 | 87% |

Based on the power figures in the previous table, the proposed statistical method to test the non-inferiority hypothesis will have good power to reject the inferiority hypothesis on the global health score at the end of cycle 6 on the experimental arm compared to the control arm. This power analysis is based on small to moderate Cohen's effect sizes.

The following assumptions were used to calculate the power for the secondary PRO endpoint analysis related to the MFI overall score:

- The non-inferiority margin is based on the MID for the MFI overall score which is taken to be 9 points.
- The common standard deviation (SD) of the MFI overall scores at the end of cycle 6 is assumed to be around 18-21 points (Lin et al. 2009, Hinz 2020).
- A one-sided alpha level of 0.0125 is used for the non-inferiority test, or equivalently, a 97.5% CI.
- Under the null inferiority hypothesis, no difference between arms in terms of the MFI overall mean scores at the end of cycle 6 is assumed.

**Power of the test for the secondary PRO hypothesis based on 220 evaluable patients (70% compliance rate; target accrual is 316 randomized patients)**

| SD of MFI overall scores at the end of cycle 6 | Cohen's Effect Size | Power |
|---|---|---|
| 18 | 0.50 | 93% |
| 19 | 0.47 | 89% |
| 20 | 0.45 | 86% |
| 21 | 0.43 | 82% |

Based on the power figures in the previous table, the proposed statistical method to test the secondary PRO hypothesis will have good power to reject the inferiority hypothesis on the MFI overall mean score at the end of cycle 6 for the experimental arm compared to the control arm. This power analysis is based on small to moderate Cohen's effect sizes.

*PFS analysis based on PD-L1 CPS cut-off*

*Hypothesis:* A subset of patients based on a cutoff for PD-L1 CPS is more likely to benefit in terms of PFS from the platinum-gemcitabine-nivolumab combination.

The finding of an optimal cutoff value for PD-L1 CPS on PFS will be performed according to the two-step testing procedure (Procedure A) suggested by Jian et al (2007). This analytical proposal assumes that the underlying true Cox model between PFS and PD-L1 CPS is a cut-point model, that is, only a subset of patients will benefit from the experimental therapy. The steps involved in this algorithm are given next.

- A biomarker-subset effect will determined using the maximum of the log likelihood ratio test for the treatment effect limited to patients with PD-L1 CPS $\geq c$, where $c$ is restricted to a subinterval on the CPS scale. Existing data suggest that 85% of patients with HNSCC have CPS $\geq 1$ and about 40% have CPS $\geq 20$ in the KEYNOTE-048 trial (Burtness 2018).
- The p-value associated with the previous test statistic will be calculated using a permutation test based on permutations of the treatment labels. A two-sided alpha level of 0.020 will be used for the testing of the treatment effect in the overall population (Step 1) and 0.030 for the biomarker-defined subset effect (Step 2). The overall two-sided alpha level for this analysis is 0.05.
- If a treatment effect in a subset of patients is determined by the previous steps then an estimate of the optimal cutoff value for PD-L1 CPS will be obtained by maximizing the partial log likelihood.

The table below shows the statistical power for the proposed method to find the optimal cutoff value based on PFS (i.e. find a biomarker-defined subset effect). Power calculations in the table below are based on a simulation study under the following assumptions: survival times were generated from a Cox-exponential model using the method proposed by Bender et al. (2005), biomarker values are assumed to follow a (0, 1) uniform distribution, PFS at 1 year is 20% (Zhang et al. 2016), 300 patients enrolled, and 500 simulations for each scenario with 300 samples to calculate the permutation distribution of the maximum test statistic. The PFS-based analysis is projected to occur when 295 PFS events have been observed. The listed HRs for the biomarker subgroup were chosen to illustrate scenarios in which the power to detect an overall treatment effect is relatively low at the final analysis. For instance, if the HR=0.53 for 40% of patients with high CPS ($\geq 0.60$ in the [0,1] scale) then the proposed method will have a reasonable power (77%) to detect a treatment effect in this biomarker subgroup while the overall test will have a lower power (69%). With a two-sided alpha of 0.020, the test for the overall treatment effect on PFS will have an 81% power to detect a HR of 0.69 with the number of PFS events expected at the final analysis based on the current design.

| **Model** | **Biomarker subgroup HR (exp./control)** | **Empirical Power Procedure A (%)** |
|---|---|---|
| Only patients with $c \geq 0.50$ benefit from experimental therapy (i.e., 50% of patients) | 0.50 | 94% |
| | 0.55 | 77% |
| | 0.60 | 74% |
| Only patients with $c \geq 0.60$ benefit from experimental therapy (i.e., 40% of patients) | 0.45 | 94% |
| | 0.50 | 88% |

| | | |
|---|---|---|
| | 0.53 | 77% |
| Only patients with $c \geq 0.75$ benefit from experimental therapy (i.e., 25% of patients) | 0.40 | 84% |

*Quantile of PD-L1 CPS. Cutoff values on interval [0.2, 0.9].

A similar approach will be used to examine the role of PD-L1 TPS on PFS.

**14.7.3** Exploratory Hypotheses and Endpoints

*OS analysis based on PD-L1 CPS cut-off*
The recent KEYNOTE-048 study on the first-line therapy for recurrent or metastatic head and neck squamous cell carcinoma (HNSCC) concluded that pembrolizumab/chemotherapy had superior overall survival in the PD-L1 CPS ≥ 20, CPS ≥ 1, and total populations, with comparable safety, compared to cetuximab/chemotherapy (Burtness 2018). Although this is already being established in HNSCC, the role of PD-L1 in recurrent and metastatic NPC is not well understood. Therefore, an exploratory objective in this trial is to determine whether a subset of patients will more likely to benefit in terms of OS from the experimental arm.

*Hypothesis:* A subset of patients based on a cutoff for PD-L1 CPS is more likely to benefit in terms of OS from the platinum-gemcitabine-nivolumab combination.

If the statistical test for the overall population based on OS, discussed in Section 14.3.2, is not significant then an algorithm to find an optimal cutoff value for PD-L1 will be executed based on the second step of the biomarker-adaptive threshold design (see details in Section 14.7 and Procedure A in Jiang et al 2007). A two-sided alpha level of 0.05 will be used for this exploratory analysis. A similar approach will be used to examine the role of PD-L1 TPS on OS.

### 14.8 Gender/Ethnicity/Race Distribution

The expected racial/ethnicity/gender distribution for this trial is based on data from a phase II trial of nivolumab for treating patients with recurrent and/or metastatic NPC cancer (NCT02339558) and the data from the ongoing NRG-HN001 study, a phase II/III trial of individualized treatment based on EBV DNA for non-recurrent/metastatic NPC patients (NCT02135042). It is assumed a 50%-50% distribution for domestic and international enrollment, respectively.

| **Racial Categories** | **DOMESTIC PLANNED ENROLLMENT REPORT** | | | | |
|---|---|---|---|---|---|
| | **Ethnic Categories** | | | | |
| | Not Hispanic or Latino | | Hispanic or Latino | | Total |
| | Female | Male | Female | Male | |
| American Indian/Alaska Native | 0 | 0 | 0 | 0 | 0 |
| Asian | 26 | 64 | 0 | 0 | 90 |
| Native Hawaiian or Other Pacific Islander | 3 | 3 | 1 | 0 | 7 |
| Black or African American | 5 | 7 | 0 | 0 | 12 |
| White | 7 | 34 | 1 | 6 | 48 |
| More Than One Race | 0 | 1 | 0 | 0 | 1 |
| Total | 41 | 109 | 2 | 6 | 158 |

| **Racial Categories** | **INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT** | | | | |
|---|---|---|---|---|---|
| | **Ethnic Categories** | | | | |
| | Not Hispanic or Latino | | Hispanic or Latino | | Total |
| | Female | Male | Female | Male | |
| American Indian/Alaska Native | 0 | 2 | 0 | 0 | 2 |

| | | | | | |
|---|---|---|---|---|---|
| Asian | 31 | 110 | 0 | 2 | 143 |
| Native Hawaiian or Other Pacific Islander | 0 | 2 | 0 | 0 | 2 |
| Black or African American | 0 | 0 | 0 | 0 | 0 |
| White | 3 | 7 | 0 | 0 | 10 |
| More Than One Race | 0 | 1 | 0 | 0 | 1 |
| Total | 34 | 122 | 0 | 2 | 158 |

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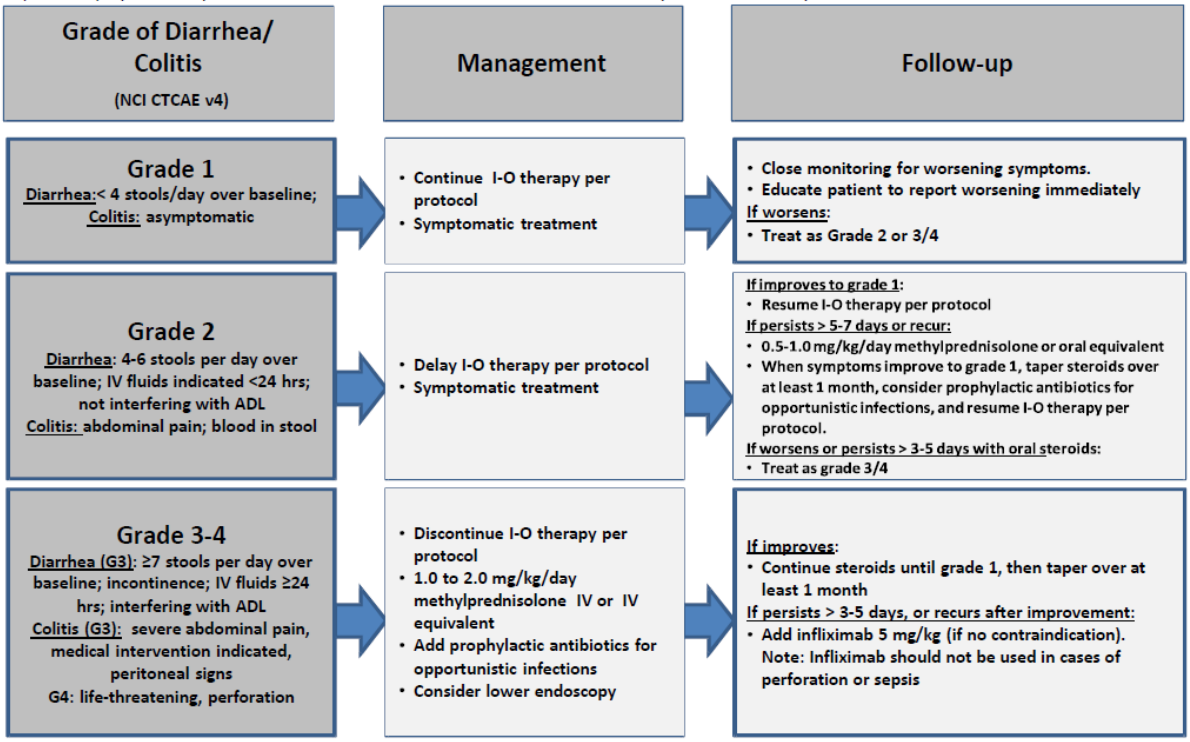
## APPENDIX I: NIVOLUMAB TOXICITY MANAGEMENT ALGORITHMS

### GI Adverse Event Management Algorithm

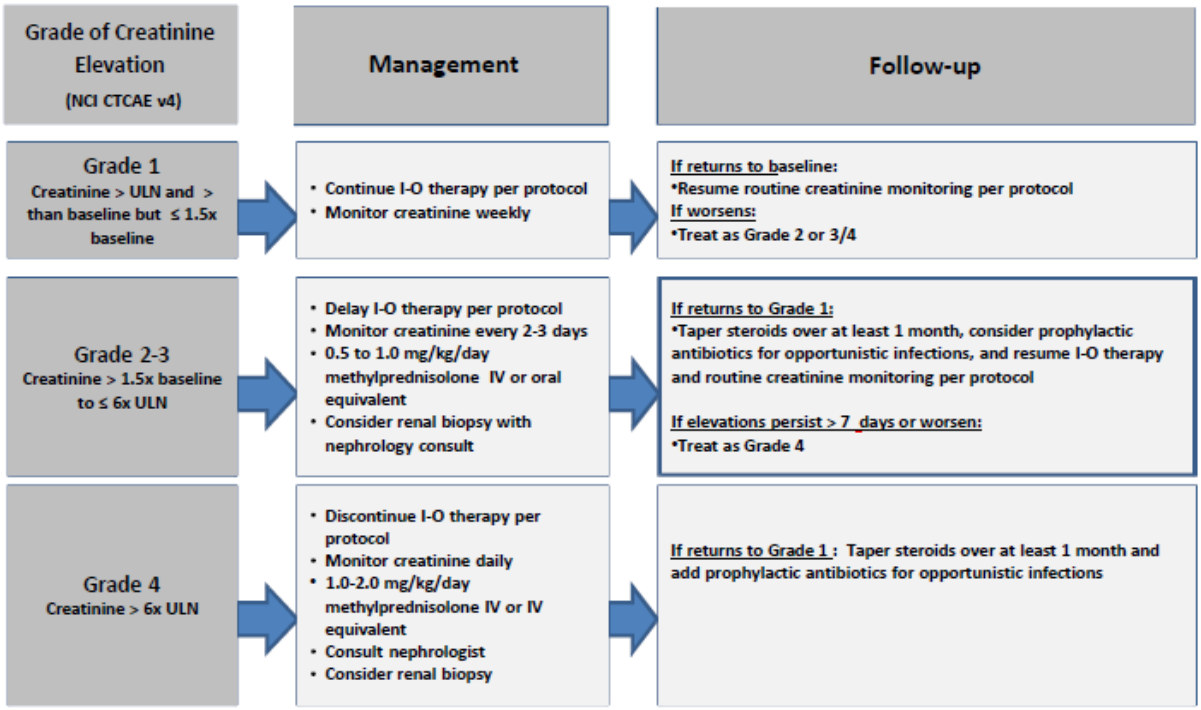
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.




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

# Renal Adverse Event Management Algorithm

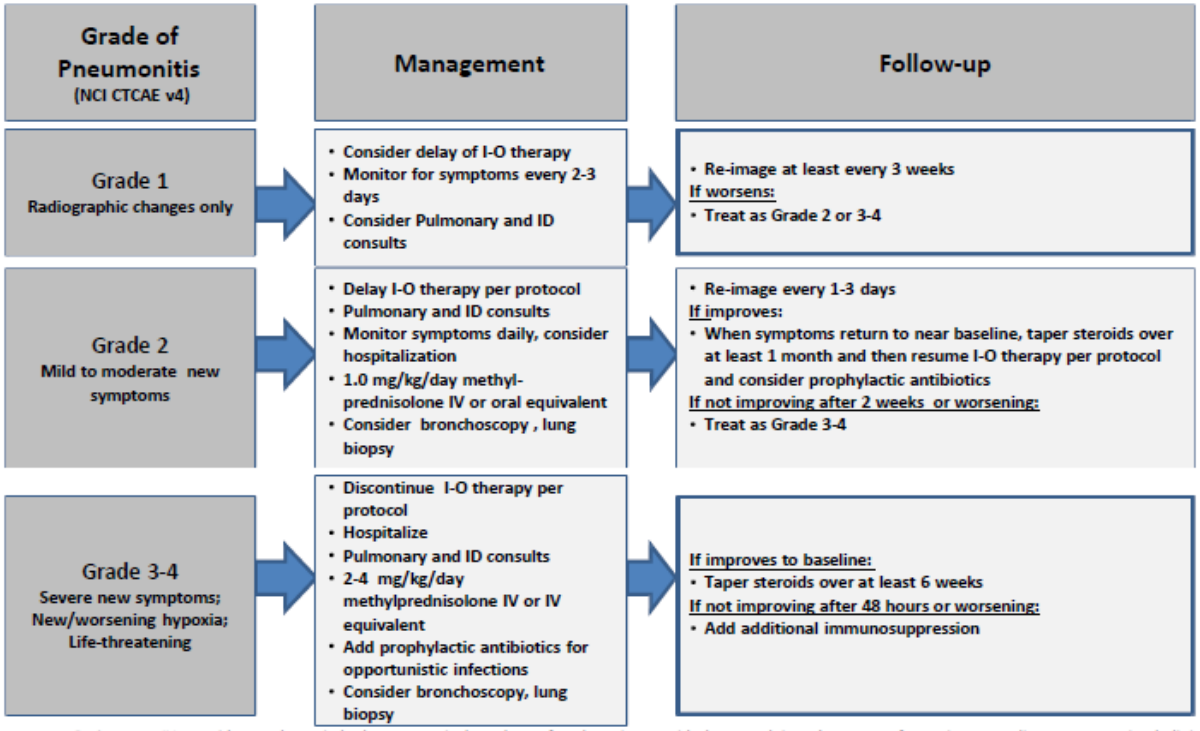
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.




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.

# Pulmonary Adverse Event Management Algorithm

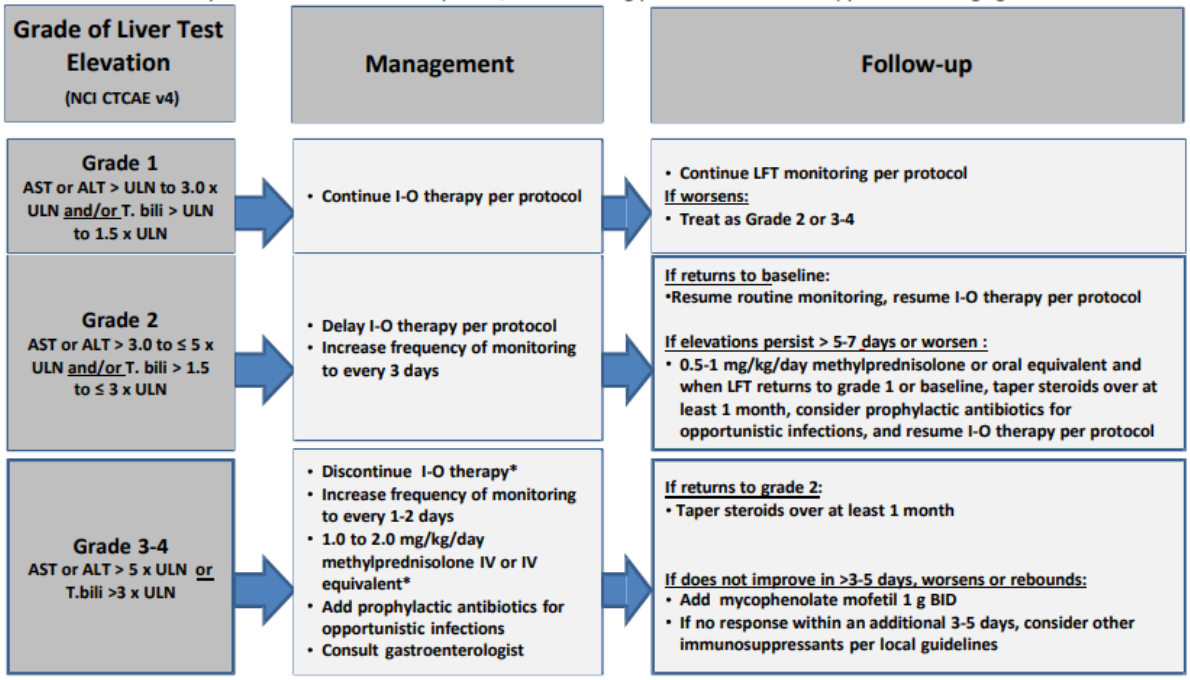
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.




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

# 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.

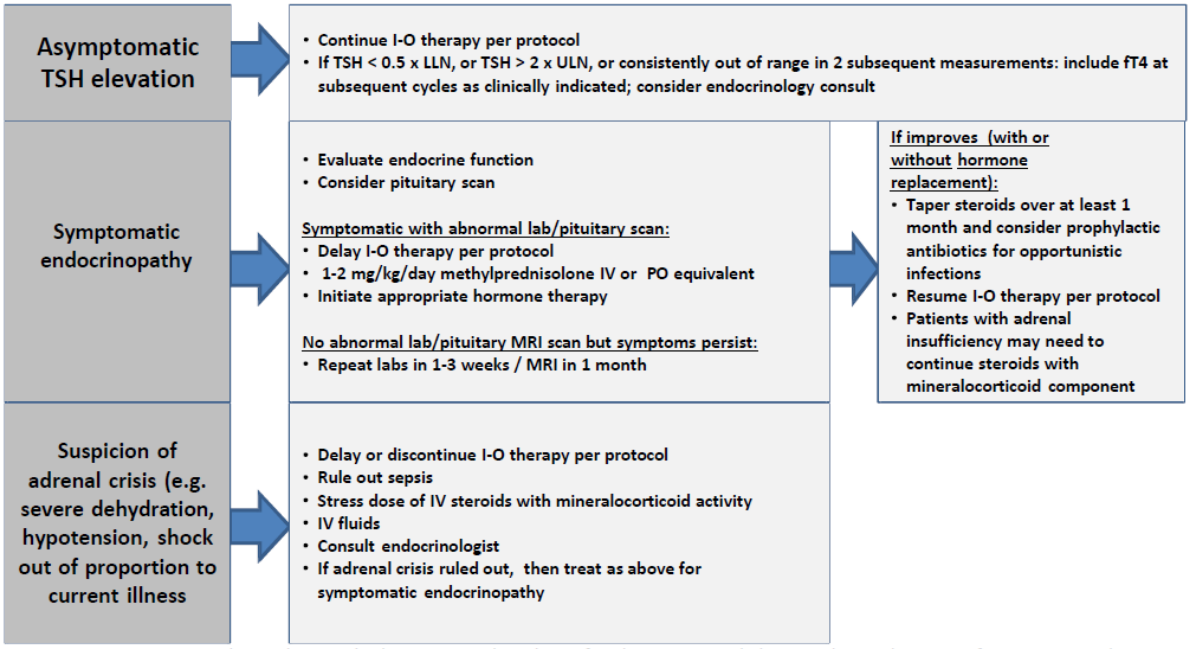



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

# Endocrinopathy Adverse Event Management Algorithm

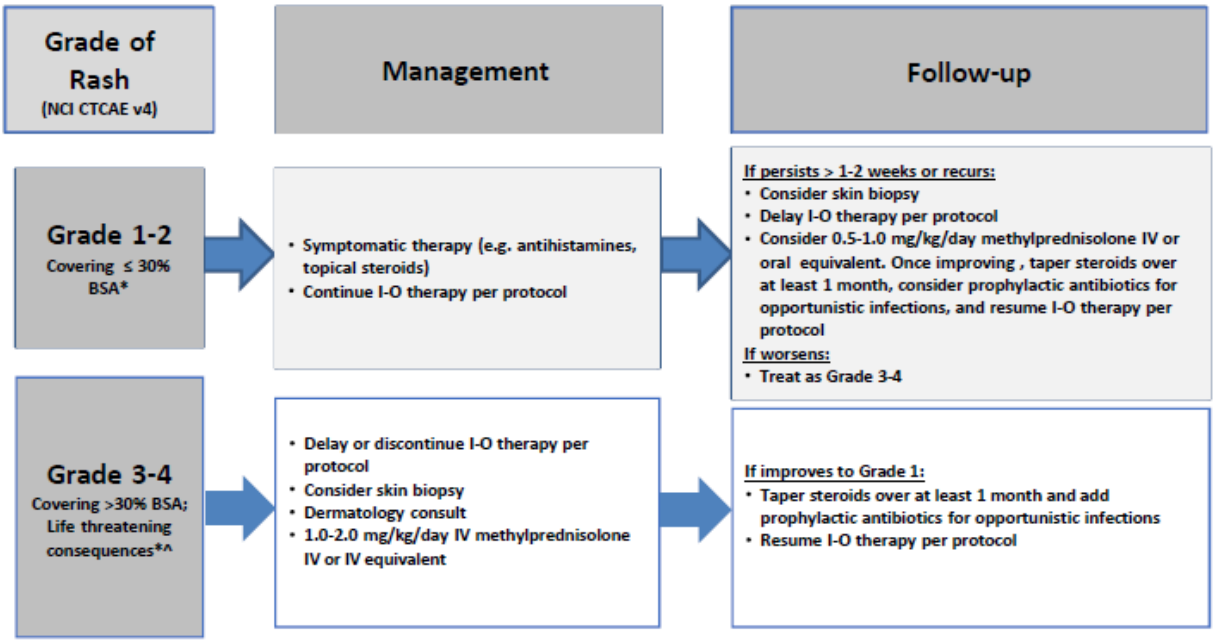
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.




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.



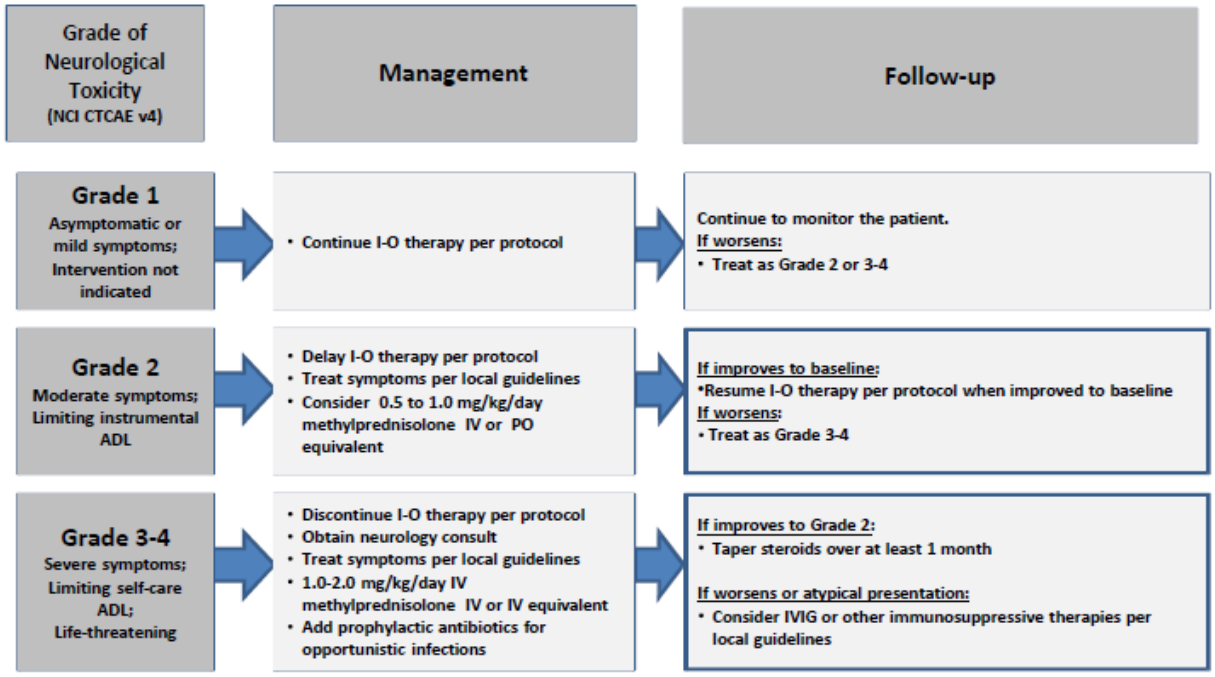

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.

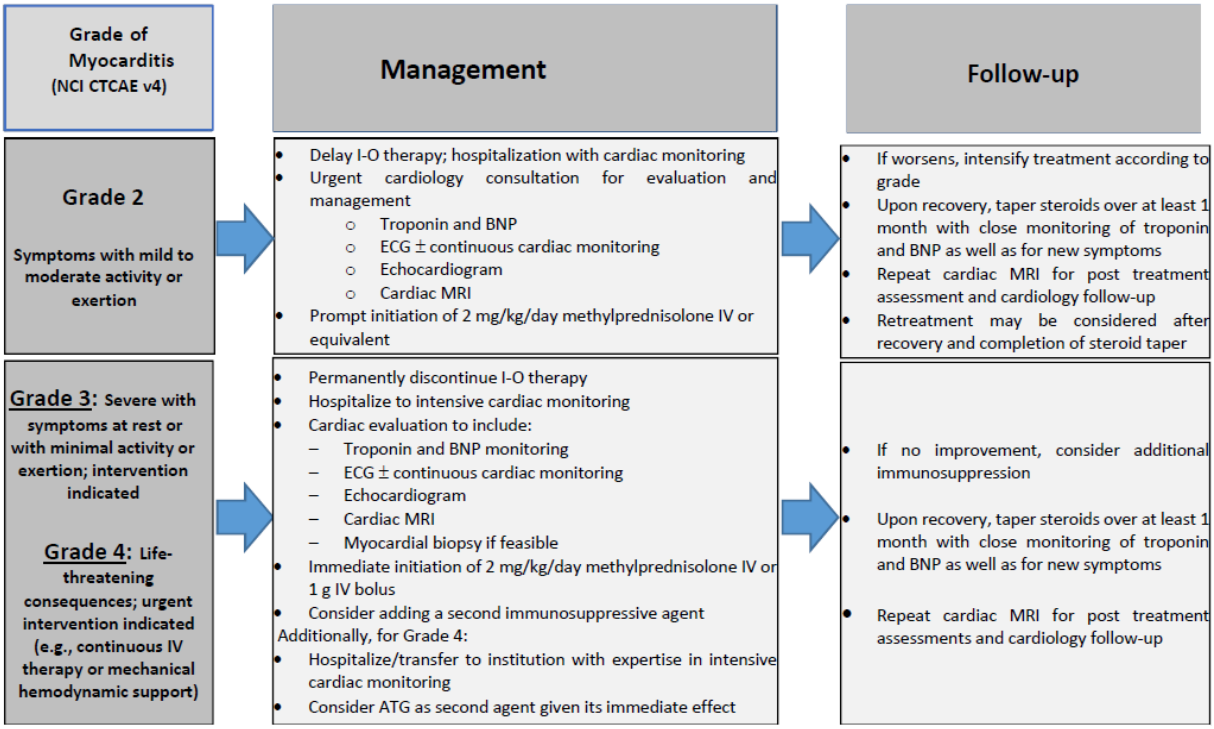
# Neurological Adverse Event Management Algorithm

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.

# Myocarditis Adverse Event Management Algorithm




Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (eg, 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.
Prophylactic antibiotics should be considered in the setting of ongoing immunosuppression.
ATG = anti-thymocyte globulin; BNP = B-type natriuretic peptide; ECG = electrocardiogram; IV = intravenous; MRI = magnetic resonance imaging

## APPENDIX II: MEDIDATA PATIENT CLOUD EPRO OPERATIONAL INSTRUCTIONS

### 1.1 Introduction

Electronic collection of patient-reported outcomes (ePRO) through Medidata Patient Cloud ePRO is preferred but not mandatory. Traditional paper submission is the other option. Patients who will be submitting PRO data via Patient Cloud ePRO must be registered to Patient Cloud ePRO by an authorized site user after the patient has been registered to the study. Patients may use their own device or one provisioned by the site.

Sites can use a site-specific tablet for multiple study patients. If a site-specific tablet is used, CRAs need to setup the tablet for multiple users. Multi-user mode lets multiple study patients log in to Patient Cloud ePRO with their passwords or their PIN codes on the same device.

**ePRO Application Download**

Note that there are multiple versions of the Medidata Patient Cloud ePRO Application. Patients should be instructed to download the version chosen by the study team for the protocol. The patient will receive an error if the wrong version is downloaded.

**Patient Cloud ePRO**

**Patient Cloud**

### 1.2 CRA Site Users

Site users of Patient Cloud ePRO require the same access as Rave. Access to the trial in the Patient Cloud ePRO is granted through the iMedidata. Site users will receive an invitation to Patient Cloud ePRO and the site user must accept the invitation to begin patient registration. Users who have not previously activated their iMedidata/Rave account at the time of initial approval of site registration 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). Please note, site users will not be able to access the study in the Patient Cloud ePRO until all required Rave and study specific trainings are completed.

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.

### 1.3 CRA Instructions for Setting the Patient Cloud ePRO App to Multi-User Mode

Sites conducting studies entirely on-premise, where patients travel to the sites to fill out questionnaires, can use multi-user mode. Multi-user mode lets multiple study patients log in to Patient Cloud with their passwords or their PIN codes on the same device. . If patients will be using devices supplied by the institution, site staff will need to help the patient to access the

device if the device is locked.

The study provider will download the Patient Cloud ePRO app to the device and set the Patient Cloud ePRO App to multi-user mode if applicable.
To switch from personal mode (default setting) to multi-user mode:

1. Tap **About** at the bottom of the log in screen.
2. Scroll to the bottom and tap **Advanced User**.
3. Tap **Mode**, then select **Multi-User**.
4. Tap **Yes** to confirm.
5. Tap the back arrows to return to the log in screen.

**Note:** If enabling multi-user mode on a device, it is highly recommended that completion reminders are turned off on that device.

For a video demonstration, see Show Me How to Switch to Multi-User Mode.

**1.4 Patient Users**
To use the Patient Cloud ePRO, patients will need to use their own device (IOS, Android phone or tablet). Short term data will only appear on the patient's device until responses are completed and submitted. The patient data will import directly into the database once the patient selects the "Submit" button and will no longer be visible on the patient's device.

Sites can provide a site-specific tablet for multiple study patients use on site. If a site-specific tablet is used, study staff need to setup the tablet for multiple users. Multi-user mode lets multiple study patients log into Patient Cloud ePRO with their passwords or their PIN codes on the same device. **Refer to Appendix E on Setting the Patient Cloud ePRO App to Multi-User Mode.**

**1.5 Patient Instructions for Accessing the Patient Cloud Using Your Personal Device**
Downloading the Patient Cloud ePRO App
If you are using your personal device, and you do not have the Patient Cloud ePRO app, use the following instructions. When downloading the app, you must use the Apple ID or Google account associated with the device. If the Patient Cloud ePRO app is already on the device, or if you are using a provider's device, you can skip this section.

You will need an email address that you agree to use for this purpose. The e-mail address is needed to identify you on the Patient Cloud Application and for you to receive notifications to let you know when forms are due. Your e-mail address will only be used for this survey study, and will not be used for mail or marketing purposes.

If you decide to use the electronic method to complete the questionnaires, and do not have an e-mail address, you may sign up for one at no charge at many different websites. A few sites that are commonly used and will allow you to create an email address very easily are Yahoo, Gmail, and Outlook.

For iOS:

1. An Apple ID is required for downloading the Patient Cloud ePRO app.
2. Tap the *App Store* icon.
3. Search for *Medidata Patient Cloud* and follow the installation instructions.

Note: Patient Cloud ePRO is listed as an iPhone App in the App store. When using an iPad, please view the search results under iPhone apps.

For Android:

1. A Google account is required for downloading the Patient Cloud ePRO app
2. Tap the *Play Store* icon.
3. Search for *Medidata Patient Cloud* and follow the installation instructions.

Registering

You must register in order to complete and submit your study forms. When you register, you will create a username, which is your email address, and a password that allows you to log in to the Patient Cloud ePRO app.

Note**:** You must have an activation code to begin this process. If you do not have an activation code, please contact your provider.

There are two possible ways to register. Your provider may have sent you a link to a web address where you may register from any web browser, including the one on your device. The other way to register is on the Patient Cloud ePRO app.

1. If registering from the Patient Cloud app, tap Register on the bottom of the log in page. If registering on the web, open the URL shield.imedidata.com on a web browser.
2. Enter your activation code and tap Activate.
3. On the next page, read the instructions and tap Next.
4. Read the privacy notice and tap I agree. Then tap OK to confirm.
5. Enter and confirm your email address. Tap Next.
6. Enter and confirm your password. Tap Next.
7. Choose a security question by scrolling through the dropdown menu to display the question of your choice.
8. Enter your security question response.
9. Tap Create my account to complete your registration.

If you registered on the Patient Cloud ePRO app, it automatically logs you out. If you registered on the web, you are presented with the option to download the Patient Cloud ePRO app. You can then proceed to log in with the credentials you created.

Logging in to the App

1. Enter your Email and Password that you created during the registration process. (If you previously set a PIN code, just enter your four-digit PIN.)
2. Tap Log in.

Note: If you do not remember your password, tap **Forgot Password**, and follow the instructions provided.

Setting a PIN Code

The first time you log in to the Patient Cloud ePRO app, you are given the option to create a PIN code. A PIN code allows you to bypass the step of entering your email and password every time you need to log in to the Patient Cloud ePRO app. Instead, you can enter a four-digit PIN.

1. If you wish to set a PIN code the first time you log in, tap Yes when prompted.
2. Note: You can also set your PIN at a later time by tapping the options menu on the top left of most pages and selecting Set PIN.
3. Enter a four-digit PIN.
4. Re-enter the four-digit PIN to confirm.

If you forget your PIN code, tap **Forgot PIN** and you can access the app using your email and password. You may reset your PIN by tapping the options menu on the top left of most pages and selecting Set PIN.

Resetting Your Password

You can reset your password by using the options menu at the top left of most pages.

1. Tap the options menu icon.
2. Tap Reset Password.
3. Follow the instructions to reset your password.

Completing and Submitting Forms

Once logged in, forms related to your study display on the Tasks page. If you are enrolled in multiple studies, select the appropriate study first, and then select a form. New forms can appear on the Tasks page at any time, depending on how the study is designed.

There are two types of forms displayed on the Task List page:

- *Scheduled Forms* (with a  icon): These forms have a "Due Date" indicator in them so you are aware of the last day by which you will need to complete the form. If the form is due in less than one day, you will see the due time in hours.
- *Anytime Forms* (with a  icon): These forms have "Last Completed Time" indicator on them which tells the most recent date or time when you completed the form. If you start a form, but do not complete it, you will see an 'Incomplete" status beneath the form name, along with a half-moon icon.

1. Select the appropriate form.
2. Follow the on-screen instructions until you reach the end of the form where you are given the opportunity to review and change your responses prior to submitting.
3. Review your responses by scrolling down the list.
4. If you need to change an answer, tap the question to go back and change the answer.
5. When you are ready to submit, tap Submit Your Data.

Note: Once a form is submitted, you will be unable to edit any of your responses. In some cases, you may be asked to acknowledge your submission by entering your password.

**1.6 Patient Compliance**

The patient data imports directly from a device into the Rave database. There are no documents to audit. The patient-submitted electronic responses are the source documentation.

**1.7 Security**

All data is encrypted on the device (256 bit encryption and Hyper Text Transfer Protocol Secure [https]) and the app requires each user to have a unique username and password for access. If the user is idle for too long (5 minutes inactivity time), the app will time out and the user will need to log in again.

The data will only reside on the device for a short period of time. Once the user clicks "Submit," the data is securely transferred over HTTPS between the device and internal relay to the Rave database. Except for the patient's email address, no identifying information is stored in iMedidata. The email address is stored for what purpose? The patient's email links the device (used) and (ePRO) account to where the data is stored. The patient's email is not visible to anyone in the system.

The Patient information (email/password) does not reside in Medidata Rave EDC and the patient accounts are hidden in iMedidata from sites and LPOs.

The Patient Cloud ePRO application is 21 CFR Part 11 compliant and acts as a gateway between the device and Medidata Clinical Cloud (MCC).

Messages and information communicated to and from the Patient Cloud ePRO are encrypted and therefore this information cannot be read if intercepted while in transit.

**1.8 Site checklist for activities prior to consenting a patient**

Site staff must have already completed required eLearning for the Patient Cloud ePRO application. See last bullet with hyperlink to training video library. Contact the LPO to request appropriate Rave access to register patients in Patient Cloud ePRO

Accept study invitation at iMedidata.com

- Note: you must be rostered in RSS and have received an invitation to Patient Cloud ePRO

Verify the IOS or Android operating system is using the most current version

Verify Patient Cloud ePRO app is using the most current version

If using institutional shared devices, first patient only: Verify Patient Cloud ePRO app is in Multi-User mode

Refer to Review Quick Reference Guides for videos and other procedural information

**1.9 Patient withdraws study consent or withdraws consent from participating on ePRO**

CRA must instruct the patients that are participating on ePRO who decide to withdraw consent to delete the App from their smart phones. This will prevent QOL reminders from being sent to the patient.

## APPENDIX III: CARBOPLATIN DOSE CALCULATION INSTRUCTIONS

1) The Cockcroft-Gault formula will be used in NRG Oncology trials.

**Dosing of Carboplatin:**

1) The carboplatin dose will be calculated to reach a target area under the curve (AUC) according to the Calvert formula using creatinine clearance (mL/min) from the Cockcroft-Gault formula.

2) In patients with an abnormally low serum creatinine (less than 0.7 mg/dl), the creatinine clearance should be estimated using **a minimum value of 0.7 mg/dL.**

3) The initial dose of carboplatin must be calculated using GFR. In the absence of renal toxicity greater than or equal to CTCAE Grade 2 (serum creatinine >1.5 x ULN) or toxicity requiring dose modification, the dose of carboplatin will not need to be recalculated for subsequent cycles, but will be subject to dose modification for toxicity as noted in the protocol.

4) Carboplatin doses are required to be recalculated if the patient has a weight change of greater than or equal to 10%. Patients are permitted to have chemotherapy doses recalculated for < 10% weight changes.

5) At the time of dose modification, if the patient's age had changed (the patient has had a birthday), the site can use the current age.

CALVERT FORMULA:
Carboplatin dose (mg) = target AUC x (GFR [or estimated CrCl] + 25)

NOTE: the GFR used in the Calvert formula should not exceed 125 ml/min.
**Maximum** carboplatin dose (mg) = target AUC (mg/ml x min) x 150 ml/min.

**The maximum allowed doses of carboplatin are:**
**AUC 6 = 900 mg**
**AUC 5 = 750 mg**
**AUC 4 = 600 mg**

For the purposes of this protocol, the GFR is considered to be equivalent to the estimated creatinine clearance. The estimated creatinine clearance (mL/min) is calculated by the method of Cockcroft-Gault using the following formula:

$$\textbf{Creatinine Clearance (mL/min)} = \frac{\textbf{[140-Age (years)] x actual body Weight* (kg)}}{\textbf{72 x serum creatinine (mg/dl)}} \quad \textbf{\{x 0.85 } \textit{\textbf{if female}}\textbf{\}}$$

Notes:
1) Weight in kilograms (kg):
   a. Body Mass Index (BMI) should be calculated for each patient.

   b. Actual weight should be used for estimation of GFR for patients with BMI of less than 25.

c. **Adjusted** weight should be used for estimation of GFR for patients with **BMI of greater than or equal to 25**

d. Adjusted weight calculation:
**Ideal weight (kg) = (((Height (cm)/2.54) – 60) x 2.3) (+ 45.5 females) or (+ 50 for men)**
**Adjusted weight (kg) = ((Actual weight – Ideal weight) x 0.40) + Ideal weight**

**At the time of a dose modification for toxicity:**
If the creatinine at the time of a dose modification is lower than the creatinine used to calculate the previous dose, use the previous (higher) creatinine; if the creatinine at the time of a dose modification is higher than the creatinine used to calculate the previous dose, use the current (higher) creatinine. This will ensure that the patient is actually receiving a dose reduction.

## APPENDIX IV: COLLABORATIVE AGREEMENTS

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

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

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

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

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

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

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

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

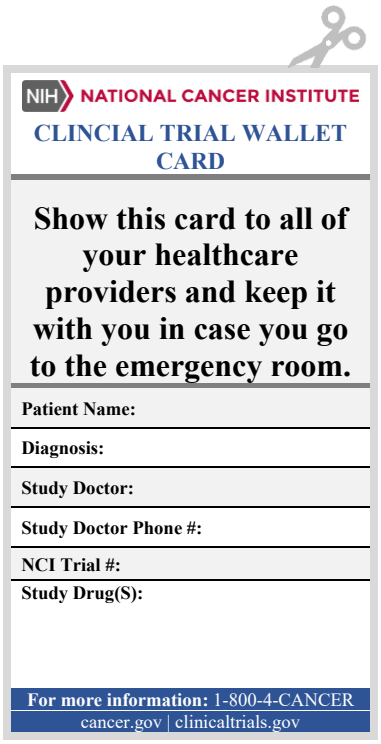
5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

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

   Email: ncicteppubs@mail.nih.gov

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

## APPENDIX V: PATIENT CLINICAL TRIAL WALLET CARD



NIH NATIONAL CANCER INSTITUTE

**CLINCIAL TRIAL WALLET CARD**

**Show this card to all of your healthcare providers and keep it with you in case you go to the emergency room.**

**Patient Name:**

**Diagnosis:**

**Study Doctor:**

**Study Doctor Phone #:**

**NCI Trial #:**

**Study Drug(S):**

**For more information:** 1-800-4-CANCER

cancer.gov | clinicaltrials.gov