COG-ARAR2221: A Phase 2 Study Using Chemoimmunotherapy with Gemcitabine, Cisplatin and Nivolumab in Newly Diagnosed Nasopharyngeal Carcinoma (NPC)

FAST FACTS
Eligibility Reviewed and Verified By
_____ MD/DO/RN/LPN/CRA Date _____
_____ MD/DO/RN/LPN/CRA Date _____
Consent Version Dated_____

PATIENT ELIGIBILITY:
Important note: The eligibility criteria listed below are interpreted literally and cannot be waived (per COG policy posted 5/11/01). All clinical and laboratory data required for determining eligibility of a patient enrolled on this trial must be available in the patient's medical research record which will serve as the source document for verification at the time of audit.

___1. Prior to obtaining informed consent and enrolling a patient, a reservation must be made.

___2. Timing
Patients must be enrolled before treatment begins. The date protocol therapy is projected to start must be no later than **five (5)** calendar days after the date of study enrollment. **Patients who are started on protocol therapy prior to study enrollment will be considered ineligible.**
All clinical and laboratory studies to determine eligibility must be performed within 7 days prior to enrollment unless otherwise indicated in the eligibility section below.

___3. **Patient Eligibility Criteria**

Laboratory Studies
All laboratory studies to determine eligibility must be performed within 7 days prior to *enrollment* unless otherwise indicated.

Clinical Studies
Clinical studies (e.g., cardiac imaging, pulmonary function tests), if applicable, must be obtained within 21 days prior to *enrollment* and *start of protocol therapy* (repeat if necessary).

Disease/Staging Imaging
Disease/staging imaging studies, if applicable, must be obtained within 21 days prior to *enrollment* and *start of protocol therapy* (repeat if necessary).

___4. Age
Patients must be ≤ 21 years of age at the time of study enrollment.

___5. Diagnosis
Newly diagnosed AJCC Stage II-IV nasopharyngeal carcinoma (NPC)
- Patients must have had histologic verification of the malignancy at original diagnosis.
- Although submission of tumor tissue for the Molecular Characterization Initiative is not required for eligibility, it is strongly recommended. See Section 3.1.1 for more information.

___6. Performance Level
Patients must have a Lansky (for patients ≤ 16 years of age) or Karnofsky (for patients > 16 years of age) performance status score of ≥ 60%.
See https://members.childrensoncologygroup.org/prot/reference_materials.asp under Standard Sections for Protocols.

___7. Organ Function Requirements

- Adequate Bone Marrow Function Defined As:
  - Peripheral absolute neutrophil count (ANC) ≥ 1000/µL
  - Platelet count ≥ 100,000/µL (transfusion independent)

- Adequate Renal Function Defined As:
  - - Creatinine clearance or radioisotope GFR ≥ 60 mL/min/1.73 m^2 or
  - - A serum creatinine based on age/gender as follows:

Age	Maximum Serum Creatinine (mg/dL)	
	Male	Female
1 month to < 6 months	0.4	0.4
6 months to < 1 year	0.5	0.5
1 to < 2 years	0.6	0.6
2 to < 6 years	0.8	0.8
6 to < 10 years	1	1
10 to < 13 years	1.2	1.2
13 to < 16 years	1.5	1.4
≥ 16 years	1.7	1.4

The threshold creatinine values in this Table were derived from the Schwartz formula for estimating GFR (Schwartz et al. J. Peds, 106:522, 1985) utilizing child length and stature data published by the CDC.

- Adequate Liver Function Defined As:
  - Total bilirubin ≤ 1.5 x upper limit of normal (ULN) for age, and
  - SGPT (ALT) ≤ 135 U/L*

  ** Note: For the purpose of this study, the ULN for SGPT (ALT) has been set to the value of 45 U/L*

- Adequate Cardiac Function Defined As:
  - Shortening fraction of ≥ 27% by echocardiogram, or
  - Ejection fraction of ≥ 50% by radionuclide angiogram.

- Adequate Pulmonary Function Defined As:
  - No evidence of dyspnea at rest, no exercise intolerance, and a pulse oximetry > 94% if there is clinical indication for determination.

___8. HIV Status

HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months and T-cell count above the lower limit of normal are eligible for this trial.

___9. HBV and HCV Status

For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

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.

Assent: The CIRB has determined that assent of children age 14 and older is a necessary condition for proceeding with the research.

Note: This trial has a protocol supplied wallet card that is required to be provided to the patient. See Appendix IV.

EXCLUSION CRITERIA

___1. Patients who received prior radiotherapy to the head or neck.
___2. Patients who received prior chemotherapy or radiation for the treatment of any cancer in the last 3 years. These patients must also be in remission.
___3. Patients with a diagnosis of immunodeficiency.
___4. Patients with an active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease-modifying agents, corticosteroids, or immunosuppressive agents). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.
Note: Patients with well-controlled asthma and no need for systemic steroids for the treatment of asthma in the last 12 months will not be excluded.
___5. Patients with a condition requiring systemic treatment with either corticosteroids (> 0.25 mg/kg (10 mg) daily prednisone equivalent) within 14 days or other immunosuppressive medications within 30 days of enrollment. Inhaled or topical steroids, and adrenal replacement steroid doses > 0.25 mg/kg (10 mg) daily prednisone equivalent, are permitted in the absence of active autoimmune disease.
___6. Patients with a history of (non-infectious) pneumonitis that required steroids or current pneumonitis.
___7. Patients with detectable viral load of Human Immunodeficiency Virus (HIV), Hepatitis B or Hepatitis C, or active tuberculosis. See Sections 3.2.5 and 3.2.6 for more information regarding HIV Status and HBV and HCV Status.
___8. Patients who have undergone solid organ or allogeneic hematopoietic transplant at any time.
___9. Pregnancy and Breastfeeding

- Due to risks of fetal and teratogenic adverse events as seen in animal studies, a negative pregnancy test must be obtained in females of childbearing potential, defined as females who are post-menarchal. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.
- Females of childbearing potential that are sexually active must agree to either practice 2 medically accepted highly-effective methods of contraception at the same time or abstain from heterosexual intercourse from the time of signing the informed consent through 5 months after the last dose of nivolumab, 6 months after the last dose of gemcitabine, and 14 months after the last dose of CISplatin, whichever is longer.
- Males of childbearing potential that are sexually active must agree to either practice a medically accepted highly-effective methods of contraception or abstain from heterosexual intercourse from the time of signing the informed consent through 3 months after the last dose of gemcitabine, and 11 months after the last dose of CISplatin, whichever is longer.
- Lactating females are not eligible unless they have agreed not to breastfeed their infants starting with the first dose of study therapy through 5 months after the last dose of nivolumab.

REQUIRED OBSERVATIONS:

Required Observations – Induction Chemoimmunotherapy (CIT), Cycles 1-3

All baseline studies must be performed prior to starting protocol therapy unless otherwise indicated below.

a. Physical exam with vital signs (including O2 saturation), height and weight
b. CBC, differential and platelets as clinically indicated but strongly recommended.
c. Creatinine, Bilirubin.
d. Electrolytes, BUN, Ca++, PO4, Mg++ as clinically indicated but strongly recommended.
e. AST, ALT, Albumin.
f. TSH, free T4 as clinically indicated but strongly recommended.
g. Urinalysis
h. Pregnancy test. Female patients of childbearing potential require a negative pregnancy test prior to starting treatment and on Day 1 of each cycle.
i. ECG pre-treatment as clinically indicated but strongly recommended1
j. MUGA or ECHO required pre-treatment1
k. Audiogram required pre-treatment1 and in Cycle 32
l. Tumor Imaging – MRI head and neck with and without contrast required pre-treatment1 and once in Day 15-21 of Cycle 3.
m. FDG PET required pre-treatment1 and once in Day 15-21 of Cycle 3.
n. CT Chest with contrast required pre-treatment1 and once in Day 15-21 of Cycle 3.
o. Dental x-ray: perform once only, at any time before the start of radiation. (Radiation will be administered during Consolidation.)
p. Tissue and blood for banking (optional): pre-treatment only, at any time from enrollment prior to start of Cycle 1. See Sections 15.1.1 and 15.1.3.
q. Plasma for banking (optional) pre-treatment, at any time from enrollment prior to start of Cycle 1. In Cycle 1 collect on Day 8. Not collected in Cycle 2. In Cycle 3 collect once during Day 15-21. See Section 15.1.2.
r. Stool for microbiome (optional) collect pre-treatment, at any time from enrollment to before Day 8 of Cycle 1. See Section 15.1.4.
s. Questionnaires (mFOIS, Pediatric EAT-10, and PROMIS-25 v 2.0, or PROMIS-29 v 2.1) Pre-treatment, at any time from enrollment prior to start of Cycle 1. Not collected in Cycle 2. In Cycle 3 perform once during Day 1-8. See Section 15.2.

[1] **Pre-treatment means within 21 days prior to start of Cycle 1. Additionally, beyond the required timepoint(s), perform as clinically indicated throughout Induction.**

[2] **During Cycle 3 perform once after Day 15 but prior to start of treatment on Day 1 of Cycle 1 of Consolidation/CRIT.**

TOXICITIES AND DOSAGE MODIFICATIONS:

See Section 5.0.

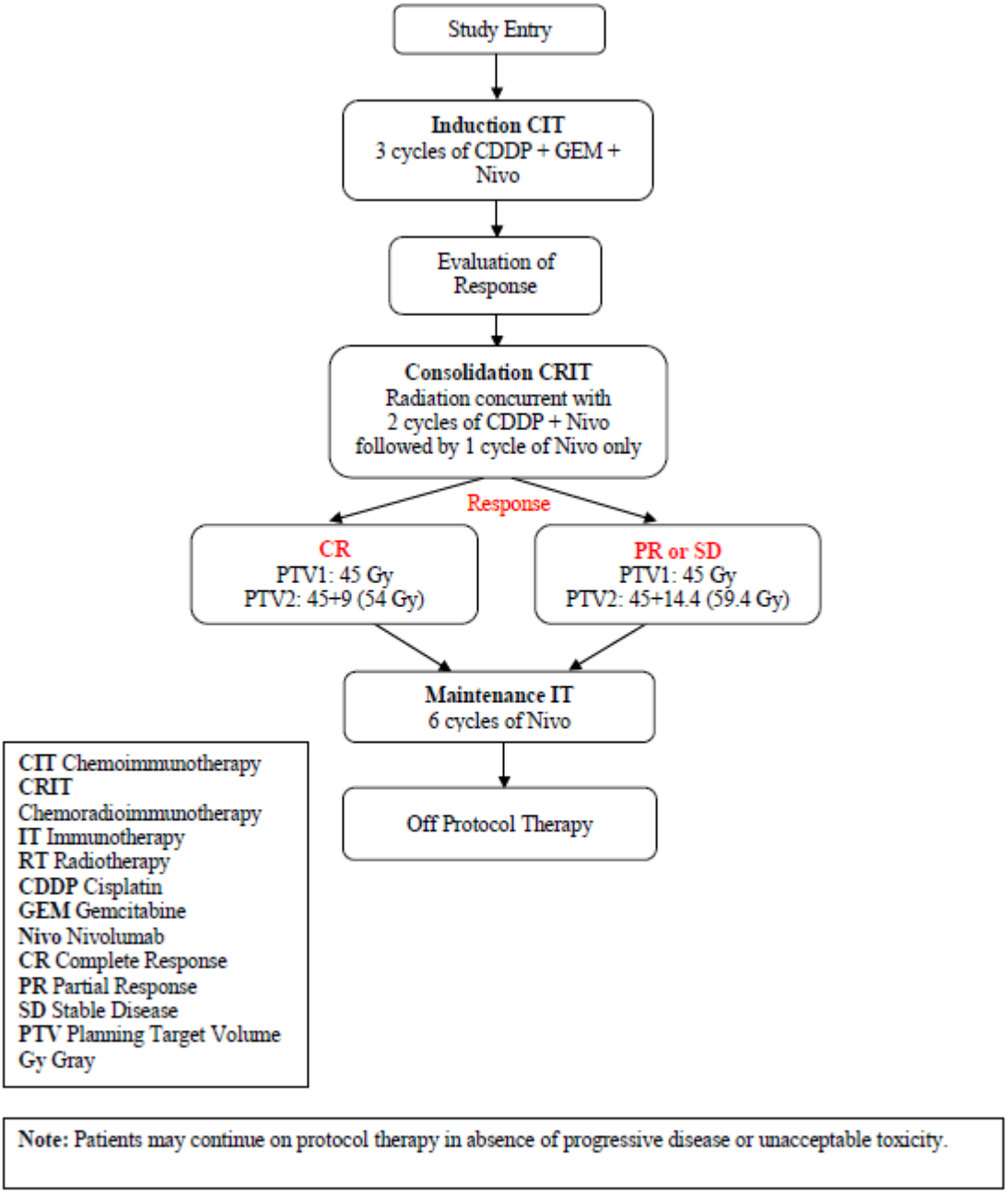
OPTIONAL QUALITY OF LIFE

Patients will be asked to consent to participation in health-related quality of life studies. See Section 15.2.

BIOLOGY REQUIREMENTS:

See Section 15.1 for optional blood serum and stool details.

TREATMENT PLAN:



Note: Patients may continue on protocol therapy in absence of progressive disease or unacceptable toxicity.