

NRG ONCOLOGY

NRG-HN001

Randomized Phase II and Phase III Studies of Individualized Treatment for Nasopharyngeal Carcinoma Based on Biomarker Epstein Barr Virus (EBV) Deoxyribonucleic Acid (DNA)

SCHEMA (4/14/16)

STEP 1 REGISTRATION

All Patients

*Pre-treatment collection and submission of plasma for required EBV DNA analysis or documentation of previous testing within 28 days at a credentialed central lab
Note: Patients can proceed with treatment while the EBV DNA is being tested, if necessary. Sites must follow the instructions in Section 5.4.

Patients with Detectable Plasma EBV DNA from Pre-Treatment Analysis — the site completes STEP 2 REGISTRATION to register the patient to Weekly cisplatin (40 mg/m²) and IMRT over 33 days**

STEP 2 REGISTRATION

Patients with Undetectable Plasma EBV DNA from Pre-Treatment Analysis — the site completes STEP 2 REGISTRATION to indicate that the patient goes off study.

Within 1 Week after Completion of Chemoradiation

*Post-treatment collection of plasma and required EBV DNA analysis

STEP 3 REGISTRATION: Patients with detectable plasma EBV DNA from post-treatment analysis proceed to phase II study (see next page). Patients with undetectable plasma EBV DNA from post-treatment analysis proceed to phase III study (see next page). Note: The site completes Step 3 registration to indicate that the patient goes off study (e.g. if the patient progresses, refuses, etc.). These patients are treated off study as clinically indicated and are followed for 3 years.

* Sites are required to complete to Step 1 registration before submitting specimens for EBV DNA analysis. Plasma will be collected from all patients for the mandatory plasma EBV DNA testing at pre-treatment and within 1 week after concurrent chemoradiation but prior to the start of adjuvant chemotherapy. Blood also will be collected for translational science from patients consenting to participate. See [Section 10.0](#) for details. For patients who have detectable plasma EBV DNA tested at one of the credentialed central labs (listed on the EBV DNA Testing Specimen Transmittal form) within 28 days prior to Step 1 registration: that test result can be used for eligibility without the need for re-testing. To use this test result for eligibility, the central lab must enter the test result through the pathology portal, and the site must follow the instructions in Section 5.4. **Note: If the patient needs to start chemoradiation prior to the results of the pre-treatment plasma EBV DNA being known, then sites must follow the instructions in Section 5.4.**

** IMRT: PTV_{69.96} for the GTV: 69.96 Gy; PTV_{59.4} for the high risk CTV: 59.4 Gy; PTV₅₄ for the low risk CTV: 54.12 Gy. See [Section 5.0](#) for credentialing required prior to patient registration. See [Section 7.0](#) for details of drug therapy.

Schema continued on next page

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SCHEMA (Continued)

S T R A T I F Y	N Stage	R A N D O M I Z E	Randomized Phase II: Detectable Plasma EBV DNA Cohort
	1. N0-1 2. N2-3		Arm 1 (Control Arm, "PF"): Cisplatin (80 mg/m ²) and 5-FU (1000 mg/m ² /d x 4 d IVCI) Every 28 days for 3 cycles beginning 4 weeks after completion of radiation
	T Stage		Arm 2 (Experimental Arm, "GT"): Gemcitabine (1000 mg/m ²) days 1 and 8 and Paclitaxel (80 mg/m ²) days 1 and 8 every 21 days for 4 cycles beginning 4 weeks after completion of radiation
	1. T1-2 2. T3-4		
Y	Zubrod Performance Status		
	1. 0		
	2. 1		

S T R A T I F Y	N Stage	R A N D O M I Z E	Phase III: Undetectable Plasma EBV DNA Cohort
	1. N0-1 2. N2-3		Arm 3 (Control Arm, "PF"): Cisplatin (80 mg/m ²) and 5-FU (1000 mg/m ² /d x 4 d IVCI) Every 28 days for 3 cycles beginning 4 weeks after completion of radiation
	T Stage		Arm 4 (Experimental Arm): Observation
	1. T1-2 2. T3-4		
Y	Zubrod Performance Status		
	1. 0		
	2. 1		

3.1 PATIENT SELECTION (4/14/16)

NOTE: PER NCI GUIDELINES, EXCEPTIONS TO ELIGIBILITY ARE NOT PERMITTED. For questions concerning eligibility, please contact the study data manager.

3.2 Conditions for Patient Eligibility (9/2/15)

3.2.1 Biopsy proven (from primary lesion and/or lymph nodes) diagnosis of cancer of the nasopharynx;

3.2.2 Sites are required to complete Step 1 registration before submitting specimens for EBV DNA analysis.

- Patients must have detectable pretreatment plasma EBV DNA, determined by the central lab prior to Step 2 registration (see Section 10.2 for details of specimen submission).
- For patients who have detectable plasma EBV DNA tested at one of the credentialed central labs (listed on the EBV DNA Testing Specimen Transmittal form) within 28 days prior to Step 1 registration: that test result can be used for eligibility without the need for re-testing. To use this test result for eligibility, the central lab must enter the test result through the pathology portal, and the site must follow the instructions in Section 5.4.

3.2.3 Stage II-IVB disease (AJCC, 7th ed.) with no evidence of distant metastasis, based upon the following minimum diagnostic workup:

- History/physical examination by a Medical Oncologist or Clinical Oncologist or Radiation

- Oncologist or ENT, which must include an endoscopic evaluation, a complete list of current medications, and assessment of weight and weight loss in the past 6 months within 21 days prior to registration;
- Evaluation of tumor extent with MRI of the nasopharynx and neck within 28 days prior to registration; if MRI is medically contraindicated, obtain CT scan with ≤ 3 mm contiguous slices with contrast and bone windows (to evaluate base of skull involvement). **Note:** If a treatment planning CT scan is used, it must be with ≤ 3 mm contiguous slices with contrast and be read by a radiologist.
 - To rule out distant metastasis, patients must undergo the following imaging within 28 days prior to registration:
 - 1) a CT scan with contrast of the chest, abdomen, and/or pelvis or a total body PET/CT scan (non-contrast PET/CT is acceptable);
 - 2) a bone scan only when there is suspicion of bone metastases (a PET/CT scan can substitute for the bone scan).
- 3.2.4** Zubrod Performance Status 0-1 within 21 days prior to registration;
- 3.2.5** Age ≥ 18 ;
- 3.2.6** CBC/differential obtained within 21 days prior to registration, with adequate bone marrow function defined as follows:
- Absolute neutrophil count (ANC) $\geq 1,500$ cells/mm³;
 - Platelets $\geq 100,000$ cells/mm³;
 - Hemoglobin ≥ 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.);
- 3.2.7** Adequate hepatic function within 21 days prior to registration, defined as follows:
- Total bilirubin ≤ 1.5 x institutional ULN;
 - AST or ALT ≤ 1.5 x institutional ULN;
 - Alkaline phosphatase ≤ 1.5 x institutional ULN.
- 3.2.8** Adequate renal function within 21 days prior to registration, defined as follows:
- Serum creatinine ≤ 1.5 mg/dl or calculated creatinine clearance (CC) ≥ 50 ml/min determined by 24-hour urine collection or estimated by Cockcroft-Gault formula:
- $$\text{CCr male} = \frac{[(140 - \text{age}) \times (\text{wt in kg})]}{[(\text{Serum Cr mg/dl}) \times (72)]}$$
- $$\text{CCr female} = 0.85 \times (\text{CrCl male})$$
- 3.2.9** Negative serum pregnancy test within 14 days prior to registration for women of childbearing potential;
- 3.2.10** Women of childbearing potential and male participants who are sexually active must agree to use a medically effective means of birth control throughout protocol treatment;
- 3.2.11** Patient must provide study specific informed consent prior to study entry, including the mandatory pre-treatment plasma EBV DNA assay.
- 3.3 Conditions for Patient Ineligibility**
- 3.3.1** Prior invasive malignancy (except node negative, non-melanomatous skin cancer) unless disease free for a minimum of 1095 days [3 years] (For example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible);
- 3.3.2** Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable; however, at least 6-weeks recovery is necessary if the last regimen included nitrosourea or mitomycin.
- 3.3.3** Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;
- 3.3.4** Patients with hearing loss assessed to be primarily sensorineural in nature, requiring a hearing aid, or intervention (i.e. interfering in a clinically significant way with activities of daily living); a conductive hearing loss from tumor-related otitis media is allowed.
- 3.3.5** \geq grade 2 peripheral sensory neuropathy (CTCAE, v. 4.0);
- 3.3.6** Severe, active co-morbidity, defined as follows:
- Major medical or psychiatric illness, which in the investigator's opinion would interfere with

- the completion of therapy and follow up or with full understanding of the risks and potential complications of the therapy;
- Unstable angina and/or uncontrolled congestive heart failure;
 - Myocardial infarction within the last 6 months;
 - Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration; note that patients switched from IV antibiotics and currently on oral antibiotics whose infection is assessed to be adequately treated or controlled are eligible.
 - Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days prior to registration;
 - Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive.
- 3.3.7** Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception;
- 3.3.8** Prior allergic reaction to the study drug(s) involved in this protocol;
- 3.3.9** Patients with undetectable pre-treatment plasma EBV DNA.