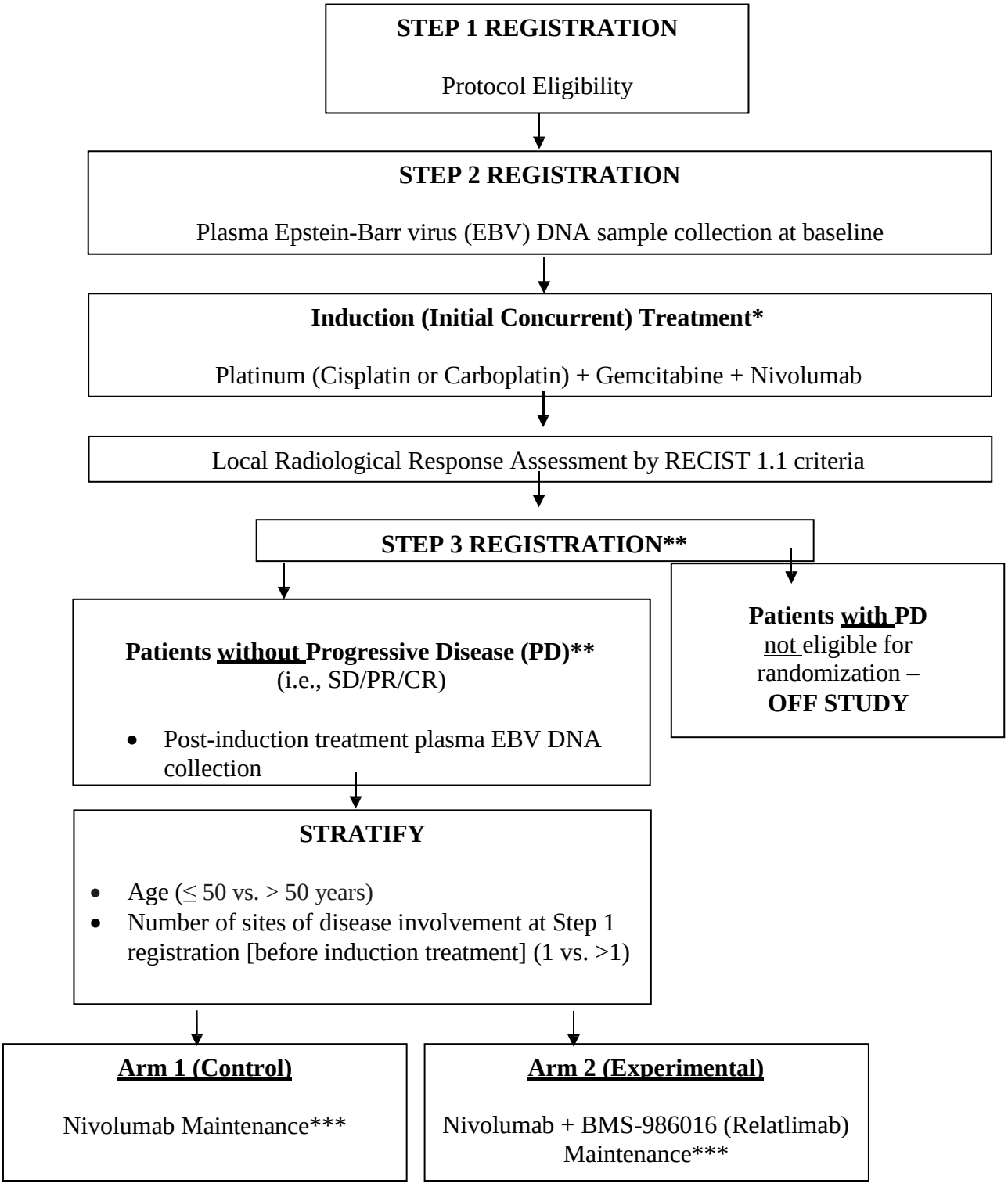
NRG-HN011
SCHEMA



*See section 5.1 for induction treatment details.
**See section 3.2.11 for Step 3 registration details.
***See section 5.2 for maintenance treatment details.

3. ELIGIBILITY CRITERIA

Notes: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility see protocol cover page.

3.1 On Study Guidelines

This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. Investigators should consider all relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

Physicians should consider the following when evaluating if the patient is appropriate for this protocol:

- Patients must have the adequate health that permits completion of the study requirements and required follow up.
- Patients with HIV, HBV, and/or HCV infection:
    - HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial **ONLY** if the enrolling site is experienced and can provide adequate medical management of patients with HIV who are undergoing chemotherapy and immunotherapy.
    - For patients with evidence of chronic hepatitis B virus (HBV) infection, the plasma HBV DNA must be undetectable on anti-viral 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 (HCV-RNA negative).
- Patient must be willing to undergo blood sampling for plasma EBV DNA at the protocol-specified time points.
- Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.

In addition:

- Participants of childbearing potential (participants who may become pregnant or who may impregnate a partner) must be willing to use highly effective contraceptives during therapy and for up to 5 months after completing study treatment because the treatment in this study may be significantly teratogenic (see protocol section 9 for definition of highly effective contraception).

3.2 Eligibility Criteria

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

Prior to Step 1 Registration

3.2.1 Documentation of Disease

Pathologically (histologically or cytologically) proven diagnosis of nasopharyngeal carcinoma (NPC) that has recurred locoregionally and/or is present at distant sites. Patients who present with metastatic disease (de novo) at diagnosis are also eligible. For locoregional recurrence, the disease must not be amenable to potentially curative surgery or re-irradiation.

Eligible patient must have the following characteristics:

- Tumor showing (histological/cytological) EBER-positivity (e.g., In situ hybridization, immunohistochemistry)
  OR
- A known history of detectable plasma EBV DNA (via a PCR-based assay) at any time point since the initial diagnosis of NPC.

3.2.2 Definition of Disease

Measurable disease as defined by RECIST 1.1 criteria. Lesion(s) that have been irradiated previously can be counted as measurable as long as radiological progression after the prior radiation therapy has been demonstrated.

- Contrast enhanced CT scan of the chest. The contrast enhanced CT component of a whole-body PET-CT is also acceptable. The plain (non-contrast) CT component of a PET-CT is not acceptable.
- CT the abdomen and pelvis, if clinically indicated (diagnostic quality with contrast, unless contraindicated).
- Patients **with** known locoregional disease must have contrast enhanced MRI or CT of the nasopharynx and neck as this disease site(s) may be assessed as target lesions. For patients without known locoregional disease, imaging of the nasopharynx and neck is optional.
- Symptomatic and active brain metastases and/or leptomeningeal metastasis on CT and/or MRI imaging: Patients who have prior therapies for brain and leptomeningeal metastasis or cord/cauda compression who are clinically stable for ≥ 2 months prior to registration and have discontinued systemic steroids therapy (> 10 mg/day prednisone or equivalent) > 4 weeks prior to registration are eligible.
- Patients with base of skull involvement by NPC are allowed unless their disease is directly invading the brain parenchyma, associated with clinical symptoms and/or significant vasogenic edema on radiological imaging.

3.2.3 Age ≥ 18 years

3.2.4 ECOG (Zubrod) Performance Status of 0-2

3.2.5 Not Pregnant and Not Nursing

Negative urine or serum pregnancy test (in persons of childbearing potential) within 14 days prior to registration. Childbearing potential is defined as any person who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal.

3.2.6 Required Initial Laboratory Values

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 (Hgb)	≥ 8.0 g/dL (Transfusion is accepted. Erythropoietin dependency not accepted.)
Hepatic	
Total bilirubin	≤ 1.5 × institutional upper limit of normal (ULN) OR direct bilirubin ≤ ULN for patients with total bilirubin levels >1.5 × ULN. Patients with known Gilbert's disease who have serum bilirubin level ≤ 3 × ULN may be enrolled.
ALT (SGPT)	≤ 3 × ULN (≤ 5 × ULN for patients with liver metastases)
Renal	
Serum creatinine OR Calculated creatinine clearance (CrCl) based on Cockcroft-Gault equation	≤ 1.5× ULN OR ≥ 30 mL/min for patients with serum creatinine levels > 1.5 × ULN. 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. CrCl must be > 50 mL/min for cisplatin to be used.
Albumin-Adjusted calcium level based on corrected calcium equation	≤ 1.5× ULN (patients are allowed to have treatment for hypercalcemia prior to starting treatment).

Legend:

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

$$\text{CrCl (mL/min)} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg / dL)}} \quad \{\times 0.85 \text{ for female patients}\}$$

- Corrected calcium equation:
  Corrected Ca (mg/dL) = [0.8 x (normal albumin - patient's albumin)] + serum Ca

3.2.7 Prior Treatment

- No prior systemic treatment for recurrent/metastatic (R/M) NPC including cytotoxic chemotherapy. Prior treatment for non-recurrent and non-metastatic NPC is allowed.

- No prior treatment with a PD-1 inhibitor (except if given as adjuvant or neoadjuvant therapy for NPC), PD-L1 inhibitor, anti-PD-L2 inhibitor, LAG-3 inhibitor, CTLA-4 inhibitor (except if given as adjuvant or neoadjuvant therapy for non-recurrent and non-metastatic NPC), or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways.
- The interval between the last dose of curative-intent treatment for non-recurrent, non-metastatic NPC, including definitive radiotherapy (RT) and/or induction, concurrent, or adjuvant chemotherapy and recurrence must be > 6 months.
- Clinically significant toxicities from any prior systemic therapy or radiotherapy must have resolved to grade 0 or 1 as per NCI CTCAE v5.0 – **except alopecia, dry mouth, dysgeusia, dysphagia, and fatigue.** Patients with a history of grade 3-4 cisplatin related neuropathy must have recovered to grade 0-2 prior to registration. Patients with a history of hearing impairment, or ototoxicity from prior cisplatin, of any grade are allowed.
- No prior palliative RT within 30 days prior to registration. This includes RT given with palliative intent to recurrent/metastatic sites. The irradiated sites must not be the only sites of measurable recurrent disease.
- No major surgical procedures within 30 days prior to registration.

3.2.8 Comorbid Conditions

- No history of unstable angina requiring hospitalization within the last 6 months;
- No history of myocardial infarction within the last 6 months;
- New York Heart Association Functional Classification II or better (NYHA Functional Classification III/IV are not eligible). Patients with symptomatic coronary artery disease, congestive heart failure or a known history of having a left ventricular ejection fraction < 50% must be stably controlled with medication in the opinion of the treating physician, in consultation with a cardiologist if appropriate.
- No prior history of myocarditis;
- No active infection requiring IV antibiotics, IV antiviral, or IV antifungal treatments at the time of study registration;
- No history of (non-infectious) pneumonitis that required steroids or current pneumonitis requiring steroids and/or immunosuppressive therapy, idiopathic pulmonary fibrosis, drug-induced pneumonitis, organizing pneumonia (i.e., bronchiolitis obliterans), or idiopathic pneumonitis;.
- No history of multi-drug resistant mycobacterium tuberculosis (TB) or active TB, as defined by systemic treatment received ≤ 2 years prior to registration. **Note:** Patients who had a history of treated TB > 2 years prior to registration are allowed.
- No prior solid organ transplant or bone marrow transplant;
- No conditions requiring systemic treatment with either immunosuppressive doses of 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.

- No active autoimmune disease requiring systemic treatment (i.e., disease modifying agents, corticosteroids, or immunosuppressive drugs) within the past 2 years. These may include (but 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 disease, ulcerative colitis, autoimmune hepatitis, glomerulonephritis; and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome.

  Note: Patients are permitted to enroll if they have vitiligo; type I diabetes mellitus; hypothyroidism, pituitary or adrenal insufficiency requiring only hormone replacement; alopecia; and/or psoriasis not requiring systemic treatment. Conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- No prior live vaccine within 30 days prior to registration. 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. COVID-19 vaccines that are approved by the local drug regulatory authority of the participating region are allowed.

3.2.9 Allergies

- No known history of grade 3-4 allergic reaction or hypersensitivity reaction to cisplatin, carboplatin, or gemcitabine.
- No known history of grade 4 hypersensitivity (or infusion) reaction to any monoclonal antibody. Patients who had prior grade 3 hypersensitivity (or infusion) reaction but could tolerate resumption of the antibody treatment after appropriate pre-medication are eligible.

3.2.10 Prior to Step 2 Registration

Plasma EBV DNA

Collection of plasma EBV DNA at baseline is mandatory for all patients prior to Step 2 registration and induction treatment. Step 1 eligibility assessments do not need to be repeated for purposes of meeting study eligibility but may be performed as clinically indicated per standard of care.

Note: Submission of the baseline sample will be batch shipped (see Section 10 for details).

3.2.11 Prior to Step 3 Registration/Randomization: Patients <u>without</u> Progressive Disease (PD) ONLY

Step 1 eligibility assessments do not need to be repeated for purposes of meeting study eligibility but may be performed as clinically indicated per standard of care.

- All patients must have received minimum of 3 cycles, and up to a maximum of 6 cycles of induction treatment within 20 weeks from cycle 1, day 1 of induction treatment (i.e.,

patients must have completed all induction treatment within 20 weeks from cycle 1 day 1, including the treatment breaks). Patients must have completed 6 cycles of induction treatment, except in the following circumstances:

a. Significant dose delays as a result of treatment-related toxicities

b. Intercurrent illness(s), that rendered the patient unable to continue induction treatment

Note: If a patient received < 6 cycles of induction treatment for reasons other than the above circumstances, they will not be eligible for randomization.

- A CT scan within 30 days prior to Step 3 registration/randomization is required. If the most recent scan performed is not within this timeframe, a repeat scan is required to assess response.
- Did not meet any criteria that result in permanent discontinuation of study treatment during induction treatment phase, as outlined in section 5.4.
- Must meet the criteria for starting/resuming a new cycle of maintenance treatment in section 6.1.1.
- Did not experience any nivolumab-related autoimmune toxicities as outlined in section 6.5 that would result in permanent discontinuation of nivolumab during the induction treatment phase.
- Collection of the plasma EBV DNA post-induction treatment is mandatory.

  Note: Submission of the post-induction sample will be batch shipped (see Section 10 for details).