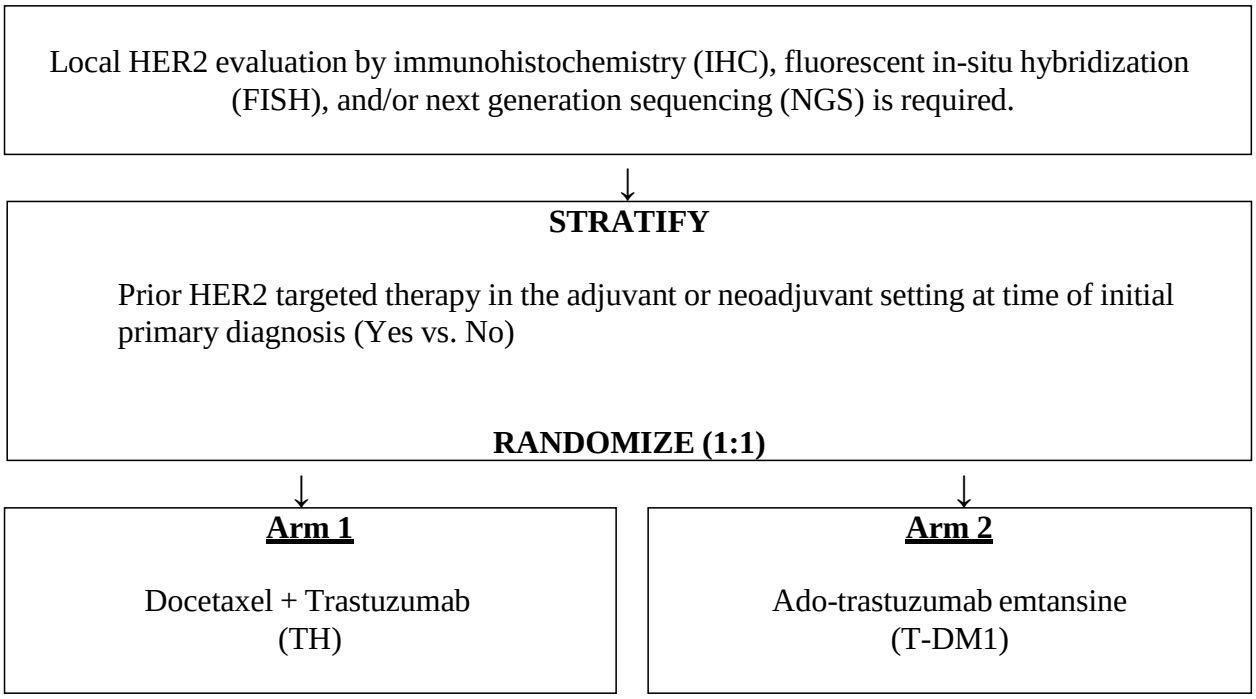
NRG-HN010
SCHEMA



NOTE: Crossover Treatment (see APPENDIX I for more details):

- Patients on Arm 1 treated with docetaxel plus trastuzumab (TH) who experience progression of disease (PD) may cross over to treatment with ado-trastuzumab emtansine (T-DM1) within 30 days of confirming progression.
- Patients on Arm 2 treated with T-DM1 who experience progression of disease (PD) may cross over to treatment with TH within 30 days of confirming progression.

3. ELIGIBILITY AND INELIGIBILITY CRITERIA

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

3.1 Eligibility Criteria

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 HER2-positive salivary gland cancer (SGC).

Note: The majority of HER2-positive SGCs are salivary duct carcinoma (SDCs), but to a lesser extent, other SGC subtypes can be HER2-positive (e.g., adenocarcinomas, mucoepidermoid carcinomas, etc.) and are eligible to be included on the study. Additionally, pathologists may sign out SDCs under other descriptors (e.g., ex-pleomorphic adenoma, adenocarcinoma), and these would be eligible if they are HER2-positive.

Note: HER2 evaluation based on local site immunohistochemistry (IHC), fluorescent in-situ hybridization (FISH), or local/commercial next-generation sequencing (NGS) is required. Any one of the following criteria observed in a primary tumor or metastasis would meet the study definition for "HER2-positive":

- IHC (3+) per the College of American Pathologists (CAP) breast cancer guidelines
- Gene amplification by FISH (HER2/CEP17 ratio $\geq$ 2.0)
- Gene amplification by NGS (fold change $\geq$ 2)

3.1.2 Patients with unresectable disease who are not candidates for curative surgery or radiation OR recurrent OR metastatic disease that is evident on radiologic imaging;

3.1.3 Patients with treated brain metastases are eligible if follow-up brain imaging after CNS-directed therapy shows no evidence of progression.

Patients with new or progressive brain metastases (active brain metastases) or leptomeningeal disease are eligible if the treating physician determines that immediate CNS specific treatment is not required and is unlikely to be required during the first cycle of therapy;

3.1.4 Measurable or non-measurable disease by the RECIST v1.1 criteria;

3.1.5 History/physical examination within 30 days prior to registration;

3.1.6 The following imaging within 60 days prior to registration:

- CT or MRI of the neck (diagnostic quality with contrast, unless contraindicated) AND
- CT scan of the chest (diagnostic quality with contrast, unless contraindicated) AND
- CT or MRI of the abdomen and pelvis, if clinically indicated (diagnostic quality with contrast, unless contraindicated);

3.1.7 Age ≥ 18;

3.1.8 Left ventricular ejection fraction (LVEF) ≥ 50% assessed by echocardiogram or MUGA scan within 30 days prior to registration;

3.1.9 Zubrod (ECOG) Performance Status of 0-2 within 14 days prior to registration;

3.1.10 Adequate hematologic function within 14 days prior to registration defined as follows:
- Absolute neutrophil count (ANC) ≥ 1,500 cells/mm^3
- Platelets ≥ 100,000 cells/mm^3
- Hemoglobin ≥ 9.0 g/dL (Note: The use of transfusion or other intervention to achieve Hgb ≥ 9.0 g/dL is acceptable.)

3.1.11 Adequate renal function within 14 days prior to registration defined as follows:
- Serum creatinine ≤ 1.5 x upper limit of normal (ULN) OR
- Calculated creatinine clearance (CrCl) ≥ 30 mL/min by the Cockcroft-Gault formula:

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

3.1.12 Adequate hepatic function within 14 days prior to registration defined as follows:
- Total bilirubin ≤ 1.5 x institutional ULN (Not applicable to patients with known Gilbert's syndrome)
- AST and ALT ≤ 1.5 x institutional ULN

3.1.13 Known human immunodeficiency virus (HIV) infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months prior to registration are eligible for this trial. Testing is not required for entry into protocol.

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

Note: Known positive test for hepatitis B virus surface antigen (HBV sAg) indicating acute or chronic infection would make the patient ineligible unless the viral load becomes undetectable on suppressive therapy. Patients who are immune to hepatitis B (anti-Hepatitis B surface antibody positive) are eligible (e.g., patients immunized against hepatitis B).

3.1.15 For patients with a known history of hepatitis C virus (HCV) infection, they 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.

3.1.16 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.

3.1.17 Willing to use highly effective contraceptives for participants of childbearing potential (participants who may become pregnant or who may impregnate a partner) during therapy and for 7 months following last dose of study drug; this inclusion is necessary because the treatment in this study may be significantly teratogenic (See Section 9 for definition of highly effective contraception). Women must refrain from donating eggs during this same period.

3.1.18 Men with partners of childbearing potential must be willing to use a highly effective form of non-hormonal contraception or two effective forms of non-hormonal contraception by the patient and/or partner, and to continue the use of contraception for the duration of study treatment and for at least 7 months after the last dose of study treatment. Male patients whose partners are pregnant should use condoms for the duration of the pregnancy. Men must refrain from donating sperm during this same period.

3.1.19 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.

3.1.20 The patient or a legally authorized representative must provide study-specific informed consent prior to study entry and, for patients treated in the U.S., authorization permitting release of personal health information.

3.2 Ineligibility Criteria

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

3.2.1 Prior systemic therapy for the study cancer in the unresectable or recurrent and/or metastatic disease setting.

Note: Prior chemotherapy for a different cancer is allowed; prior androgen receptor targeted therapy in any setting is allowed; prior systemic therapy, including HER2-directed therapies given as neoadjuvant therapy, adjuvant therapy, and/or concurrently with radiation is allowed.

3.2.2 Patients who have had chemotherapy or palliative-intent radiotherapy must have all toxicities related to prior treatment recovered to ≤ Grade 1 prior to registration.

3.2.3 Severe, active co-morbidity defined as follows:

- Unstable angina requiring hospitalization in the last 6 months;
- Myocardial infarction within the last 6 months;
- New York Heart Association Functional Classification III/IV (Note: Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification.);
- Persistent Grade 3-4 (CTCAE version 5.0) electrolyte abnormalities that cannot be reversed despite replacement as indicated by repeat testing;
- Patient must not have an active infection requiring IV antibiotics;

3.2.4 ≥ Grade 3 peripheral neuropathy.

3.2.5 Interstitial lung disease or pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on chest CT scan.

3.2.6 Any hemorrhage or bleeding event Grade ≥ 3 within 28 days prior to registration.

3.2.7 History of allergic reactions to compounds of similar chemical or biologic composition to ado-trastuzumab emtansine, trastuzumab, and/or docetaxel (or any of their excipients).

3.2.8 History of exposure to the following cumulative doses of anthracyclines:

- Doxorubicin or liposomal doxorubicin > 500 mg/m^2
- Epirubicin > 900 mg/m^2
- Mitoxantrone > 120 mg/m^2

Note: If another anthracycline, or more than one anthracycline has been used, the cumulative dose must not exceed the equivalent of doxorubicin 500 mg/m^2.

3.2.9 Pregnancy and individuals unwilling to discontinue nursing.