FAST FACTS

NRG-GY026: A PHASE II/III STUDY OF PACLITAXEL/CARBOPLATIN ALONE OR COMBINED WITH EITHER TRASTUZUMAB AND HYALURONIDASE-OYSK (HERCEPTIN HYLECTA) OR PERTUZUMAB, TRASTUZUMAB, AND HYALURONIDASE-ZZXF (PHESGO) IN HER2 POSITIVE, STAGE I-IV ENDOMETRIAL SEROUS CARCINOMA OR CARCINOSARCOMA

Eligibility Criteria

1. FIGO 2009 Stage IA-IVB, non-recurrent, chemo-naïve, HER2-positive endometrial serous carcinoma or endometrial carcinosarcoma. See Appendix I.
   Histologic confirmation of the original primary tumor is required. Submission of surgical pathology report (or endometrial biopsy pathology report in patients who never undergo hysterectomy) is required.
   Patients must be within 8 weeks of primary surgery (or endometrial biopsy in patients who never undergo hysterectomy) at the time of study registration.
2. Patients may have measurable disease, non-measurable disease, or no measurable disease. In patients with measurable disease, lesions will be defined and monitored by RECIST v 1.1. Measurable disease is defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be ≥ 10 mm when measured by CT or MRI. Lymph nodes must be ≥ 15 mm in short axis when measured by CT or MRI.
   For patients with uterine-confined (stage I) disease, the tumor must be invasive into the myometrium. Any amount of myoinvasion is acceptable for eligibility. Patients with noninvasive disease, endometrial intraepithelial carcinoma alone, or disease confined to a polyp will be excluded.
3. Additionally, patients must have the following histologic types to be eligible:
   a. Serous adenocarcinoma (may include ≤10% non-serous histology)
   b. Carcinosarcoma with serous epithelial component (only the serous component needs to be HER2 positive as defined in Section 3.1.4; may include ≤10% non-serous histology)
   c. In cases where determination of serous is equivocal or challenging, aberrant p53 immunohistochemistry (IHC) (defined as overexpression of p53 compared to internal controls) will be sufficient for inclusion.
4. All patients must have tumors that are HER2 positive as defined by ASCO/CAP 2018 Breast Cancer guidelines (https://documents.cap.org/documents/algorithim-evaluationher2.pdf. In general HER2 positivity is defined as any of the following:
   a. 3+ immunohistochemistry (IHC),
   b. 2+ IHC with positive in situ hybridization (ISH)
   c. Average HER2 copy number ≥ 6.0 signals/cell
   d. Average HER2 copy number ≥ 4.0 and < 6.0 signals/cell, with concurrent IHC 3+
   e. HER2/CEP17 ratio ≥ 4.0 signals/cell
   f. HER2/CEP 17 ratio ≥ 2.0 and < 4.0, with concurrent IHC 3+

   IHC and ISH testing will be done locally, at each participating institution and interpreted by local pathologists. Alternatively, patients could be eligible if next generation sequencing (NGS) demonstrates HER2 (ERBB2) amplification. NGS testing can be performed through any designated labs as per the NCI MATCH/NCI Combo-MATCH

trial (https://ecog-acrin.org/nci-match-eay131-designated-labs).
Pathology report showing results of institutional HER2 testing (or NGS testing results) must be submitted.
Sites must submit all results available (IHC, ISH, and NGS).

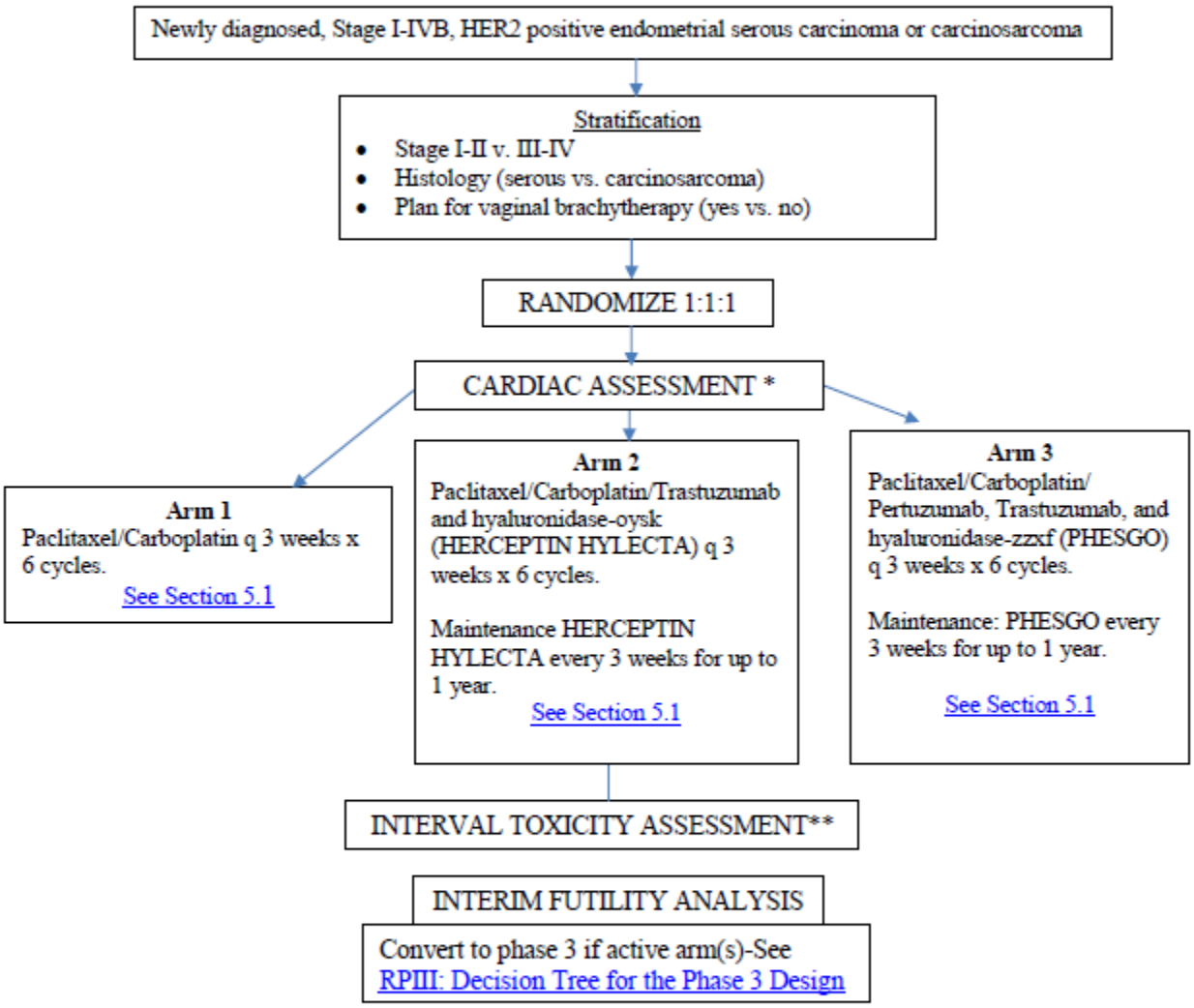
5. ECOG Performance Status of 0, 1 or 2. See Appendix III.
6. Age ≥ 18.
7. Adequate hematologic function within 14 days prior to registration defined as follows:
   • Platelets ≥ 100,000/mcl
   • Absolute neutrophil count (ANC) ≥ 1,500/mcl.
8. Adequate renal function within 14 days prior to registration defined as follows:
   Creatinine ≤ 1.5 x institutional/laboratory upper limit of normal (ULN) or estimated Glomerular filtration rate (eGFR) ≥ 50 mL/min using either the Cockcroft-Gault equation, the Modification of Diet in Renal Disease Study, or as reported in the comprehensive metabolic panel/basic metabolic panel (eGFR).
9. Adequate hepatic function within 14 days prior to registration defined as follows:
   • Total serum bilirubin level ≤ 1.5 x ULN (patients with known Gilbert's disease who have bilirubin level ≤ 3 x ULN may be enrolled)
   • AST and ALT ≤ 3 x ULN.
10. HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months of registration are eligible for this trial.
11. Although the uterus will have been removed in the vast majority of patients, for patients of child-bearing potential: negative urine or serum pregnancy test. If the urine test is positive or cannot be confirmed as negative, a serum pregnancy test is required.
    Patients will be considered of non-reproductive potential if they are either:
    • Postmenopausal (defined as at least 12 months with no menses without an alternative medical cause; in women <45 years of age, a high follicle stimulating hormone [FSH] level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormonal replacement therapy. In the absence of 12 months of amenorrhea, a single FSH measurement is insufficient); OR
    • Have had a hysterectomy and/or bilateral oophorectomy, bilateral salpingectomy or bilateral tubal ligation/occlusion at least 6 weeks prior to registration.
    • Have a congenital or acquired condition that prevents childbearing.
12. 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
13. investigational regimen are eligible for this trial. Patients with evidence of chronic hepatitis B virus (HBV) infection must have an
    undetectable HBV viral load 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.
14. Patients with treated brain metastases are eligible if follow-up brain imaging after CNS directed therapy shows no evidence of progression.
15. 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.

Ineligibility Criteria

1. Prior Therapy:
    a. Patients must NOT have received prior chemotherapy, biologic therapy, or targeted therapy for treatment of endometrial carcinoma.
    b. Patients must NOT have received prior radiation therapy for treatment of endometrial carcinoma. Prior radiation includes external beam pelvic radiation therapy, external beam extended field pelvic/para-aortic radiation therapy, and/or intravaginal brachytherapy.
    NOTE: Vaginal brachytherapy for treatment of endometrial cancer is permitted during study treatment (See Section 5.2). Planned use of vaginal brachytherapy must be declared at time of registration.
    c. Patients may have received prior hormonal therapy for treatment of endometrial carcinoma. All hormonal therapy must be discontinued at least one week prior to registration.
2. Patients may not have a planned interval cytoreduction or hysterectomy, prior to documentation of progression, after study registration.
3. Patients may not have planned external beam radiotherapy, prior to documentation of progression, after study registration.
4. Significant cardiovascular disease including:
    • Uncontrolled hypertension, defined as systolic > 150 mm Hg or diastolic > 90 mm Hg despite antihypertensive medications.
    • Myocardial infarction or unstable angina within 6 months prior to registration.
    • New York Heart Association functional classification II, III or IV (See Appendix IV).
    • Serious cardiac arrhythmia requiring medication. This does not include asymptomatic, atrial fibrillation with controlled ventricular rate.
5. Significant lung disease: dyspnea at rest grade 2 or greater (resulting from extensive tumor involvement or other causes), pneumonitis grade 2 or greater, interstitial lung disease grade 2 or greater, idiopathic pulmonary fibrosis, cystic fibrosis, Aspergillosis, active tuberculosis, or history of opportunistic infections (pneumocystis pneumonia or cytomegalovirus pneumonia).
6. Patients with uncontrolled intercurrent illness including, but not limited to: ongoing or active infection (except for uncomplicated urinary tract infection), uncontrolled interstitial lung disease, symptomatic congestive heart failure, or psychiatric illness/social situations that would limit compliance with study requirements.
7. Treatment with strong CYP2C8 or CYP3A4 inhibitors or inducers within 14 days or 5 drug-elimination half-lives, whichever is longer, prior to registration.
8. Women who are unwilling to discontinue nursing.

NRG-GY026 SCHEMA

RPII: Paclitaxel/Carboplatin vs. Paclitaxel/Carboplatin/Trastuzumab and hyaluronidase-oysk (HERCEPTIN HYLECTA) vs. Paclitaxel/Carboplatin/ Pertuzumab, trastuzumab, and hyaluronidase-zzxf (PHESGO)→ drop inactive arm(s) to Phase III



*All patients will require post-randomization cardiac assessment. Patients with EF<55% will be treated *with the control regimen* (Arm 1) (carboplatin/paclitaxel) regardless of randomization assignment, and will continue to be followed on-study. Please refer to section 4 for updated requirements.

**An Interval Toxicity Assessment (ITA) is included to evaluate the safety and tolerability of Arm 3. The first 12 eligible patients who receive any protocol therapy will be monitored for the specified cardiac events for at least 12 weeks from the start of treatment. See Section 14.4.2.