

## FAST FACTS

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### NRG-GY025: A RANDOMIZED PHASE II TRIAL OF NIVOLUMAB AND IPILIMUMAB COMPARED TO NIVOLUMAB MONOTHERAPY IN PATIENTS WITH DEFICIENT MISMATCH REPAIR SYSTEM RECURRENT ENDOMETRIAL CARCINOMA

#### 3. ELIGIBILITY AND INELIGIBILITY CRITERIA

##### 3.1 ELIGIBILITY CRITERIA

3.1.1 Patients with measurable or non-measurable (detectable) recurrent endometrial cancer.

3.1.1.1 Measurable disease will be defined and monitored by RECIST v 1.1. Measurable disease is defined per RECIST 1.1 criteria as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded). Each lesion must be  $\geq 10$  mm when measured by CT or MRI. Lymph nodes must be  $\geq 15$  mm in short axis when measured by CT or MRI.

3.1.1.2 Non-measurable (detectable) disease in a patient is defined in this protocol per RECIST 1.1 criteria as one who does not have measurable disease but has at least one of the following conditions:

- All other lesions (or sites of disease), including small lesions (longest diameter  $<10$  mm or pathological lymph nodes with  $\geq 10$  to  $<15$  mm short axis), are considered non-measurable disease.
- Ascites and/or pleural effusion attributed to tumor.
- Solid and/or cystic abnormalities on radiographic imaging that do not meet RECIST 1.1 (see [Section 12](#)) definitions for target lesions.

3.1.2 Patients must have endometrial cancer with deficient mismatch repair system. All patients must have institutional immunohistochemistry (IHC) and/or microsatellite instability (MSI) testing to determine mismatch repair (MMR) status. MMR deficiency is defined as lack of expression of one or more mismatch repair proteins (MLH1, PMS2, MSH2, MSH6, EPCAM) by immunohistochemistry and/or presence of microsatellite instability high using the NCI-5plex and Promega v1.2 assays, or institutional standards (e.g. NGS panel).

Method(s) of detection of MMR deficiency will be recorded for each patient. An institutional pathology report, and additional reports if available, documenting these results must be submitted. Patients with “equivocal” results on MMR testing by immunohistochemistry may be eligible if they have documented evidence of microsatellite instability by MSI testing or by next generation sequencing assays. MMR testing by IHC may be used to resolve equivocal/indeterminate MSI results.

- 3.1.3 Histologic confirmation of the original primary tumor is required (submission of pathology report(s) is required). Patients with the following histologic types are eligible: Endometrioid adenocarcinoma, mucinous adenocarcinoma, dedifferentiated/undifferentiated carcinoma, clear cell adenocarcinoma, mixed epithelial carcinoma, adenocarcinoma not otherwise specified (N.O.S.).
- 3.1.4 Prior Therapy:
- Patients may have received 1-2 prior lines of systemic therapy.
    - Prior anti-PD1/PD-L1 therapy is allowed if given in combination with chemotherapy or radiation therapy in adjuvant or primary metastatic/recurrent settings. Patients must have had a complete response and have disease progression/relapse with treatment-free interval of 12 months or more from last dose of therapy with immune check inhibition.
  - Patients may have received prior radiation therapy for treatment of endometrial cancer. Prior radiation therapy may have included pelvic radiation therapy, extended field pelvic/para aortic radiation therapy, intravaginal brachytherapy, and/or palliative radiation therapy. All radiation therapy must be completed at least 4 weeks prior to registration.
  - Patients may have received prior hormonal therapy for treatment of endometrial cancer. All hormonal therapy must be discontinued at least three weeks prior to registration.
  - Any other prior therapy directed at the malignant tumor including chemotherapy, targeted agents, biologic agents, immunologic agents, and any investigational agents, must be discontinued at least 4 weeks prior to registration (6 weeks for nitrosoureas or mitomycin C).
- 3.1.5 Age  $\geq$  18.
- 3.1.6 ECOG Performance Status of 0, 1, or 2 (see [Appendix II](#)).
- 3.1.7 Adequate hematologic function within 14 days prior to registration defined as follows:
- Platelets  $\geq$  100,000/mcl
  - Absolute neutrophil count (ANC)  $\geq$  1,500/mcl
- 3.1.8 Adequate renal function within 14 days prior to registration defined as follows:
- Creatinine  $\leq$  1.5 x institutional/laboratory upper limit of normal (ULN)
- 3.1.9 Adequate hepatic function within 14 days prior to registration defined as follows:
- Total serum bilirubin level  $\leq$  1.5 x ULN (patients with known Gilbert's disease who have bilirubin level  $\leq$  3 x ULN may be enrolled)
  - AST and ALT  $\leq$  3 x ULN
- 3.1.10 Adequate oxygen saturation via pulse oximeter (CTCAE v.5.0 hypoxia < grade 2 within 28 days prior to registration).
- 3.1.11 TSH within normal limits (TSH <ULN allowed in euthyroid patients on thyroid replacement therapy). TSH testing is only required if clinically indicated.

- 3.1.12 Patients must have recovered from effects of recent surgery, radiotherapy or chemotherapy. At least 4 weeks must have elapsed since major surgery.
- 3.1.13 As clinically indicated, 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. To be eligible for this trial, patients should be class 2B or better and have a corrected QT (QTc) interval <450 msec. (See [Appendix III](#)).
- 3.1.14 The effects of nivolumab, and ipilimumab on the developing human fetus are unknown. For this reason and because nivolumab and ipilimumab are known to be teratogenic, women of child-bearing potential (WOCBP) must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for 5 months after the last dose of investigational drug. Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of nivolumab. Women must not be breastfeeding. Women who are not of childbearing potential (*i.e.*, who are postmenopausal or surgically sterile) do not require contraception.

WOCBP is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes. In addition, women under the age of 55 must have a documented serum follicle stimulating hormone (FSH) level less than 40 mIU/mL.

- 3.1.15 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.
- 3.1.16 HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months of registration are eligible for this trial.
- 3.1.17 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.

- 3.1.18 Patients with treated brain metastases are eligible if follow-up brain imaging after CNS- directed therapy shows no evidence of progression and the patient is stable off steroids for at least one month.
- 3.1.19 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

3.2.1 Patients with a diagnosis of endometrial serous carcinoma or carcinosarcoma.

3.2.2 Patients who received prior anti-PD1/PD-L1 therapy and had grade 3-4 or recurring grade 2 immune-related toxicities that led to dose delay or discontinuation of immunotherapy due to those toxicities.

Patients who received anti-CTLA-4 therapy or other immunotherapeutic agents beyond that indicated in [Sec 3.1.4](#).

3.2.3 Patients on chronic steroid therapy except those on replacement therapy at a daily dose of 10mg or less prednisone or equivalent.

3.2.4 Patients on immunosuppressive therapy, with the exception of:

- Intra-nasal, inhaled, topical or local steroid injections
- Premedication for hypersensitivity reaction

3.2.5 Patients with active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including systemic corticosteroids, should be excluded. These include but are 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, connective tissue diseases, scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, hepatitis; and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome should be excluded because of the risk of recurrence or exacerbation of disease.

Patients with vitiligo, endocrine deficiencies including thyroiditis managed with replacement hormones including physiologic corticosteroids are eligible.

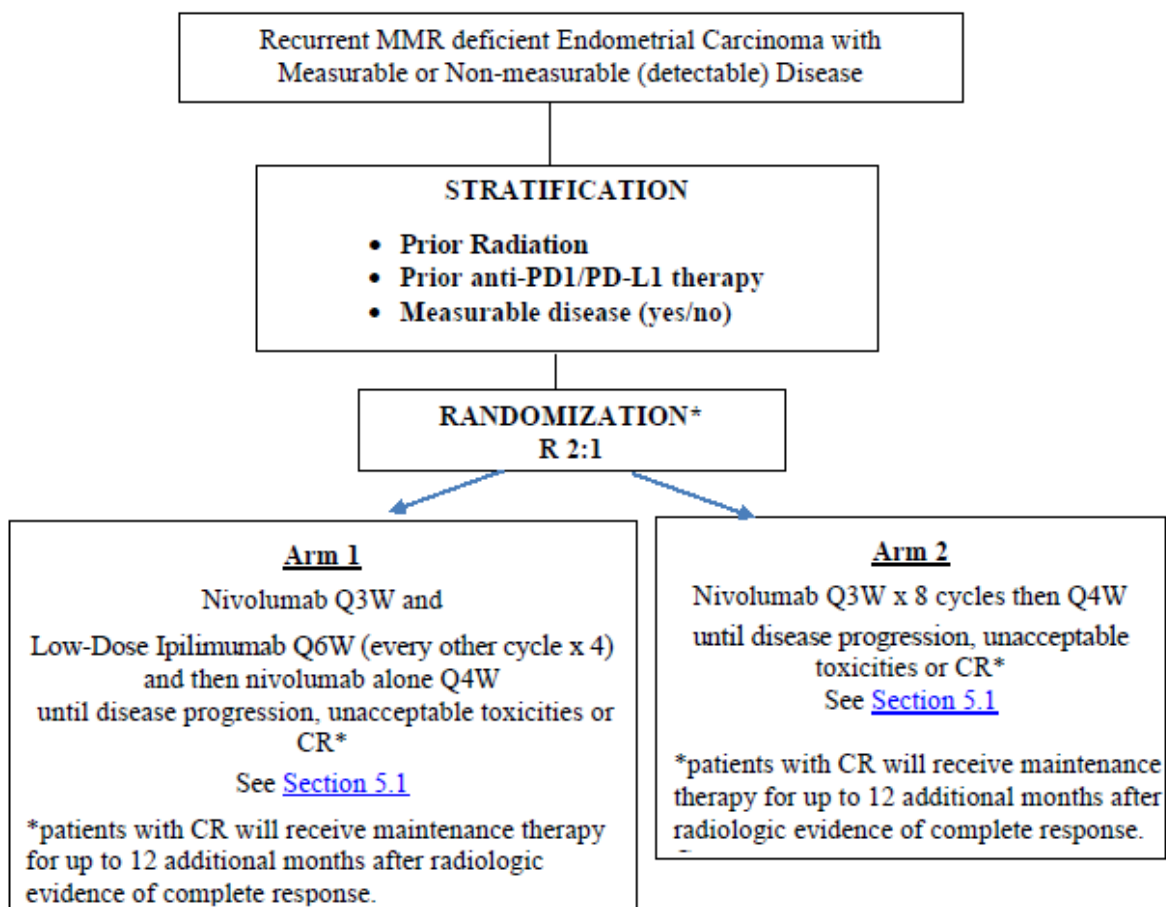
Patients with rheumatoid arthritis and other arthropathies, Sjögren's syndrome and psoriasis controlled with topical medication and patients with positive serology, such as antinuclear antibodies (ANA), anti-thyroid antibodies should be evaluated for the presence of target organ involvement and potential need for systemic treatment but should otherwise be eligible.

3.2.6 Patients with known immune impairment who may be unable to respond to anti-CTLA-4 antibody.

3.2.7 Patients with uncontrolled intercurrent illness including, but not limited to: ongoing or active infection (except for uncomplicated urinary tract infection), interstitial lung disease or active, non-infectious pneumonitis, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.8 Women who are pregnant or unwilling to discontinue nursing.

- 3.2.9 Prior therapy with CTLA-4 inhibitors, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways. Prior anti-PD1/PD-L1 therapy is allowed if criteria outlined in [Section 3.1.4](#) is met.
- 3.2.10 History of allergic reactions attributed to compounds of similar chemical or biologic composition to nivolumab, and/or ipilimumab including severe hypersensitivity reactions to any monoclonal antibody.



\*Randomization is 2:1 (Arm 1 vs Arm 2). Twice as many patients will be randomized to Arm 1.