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Committed to Community Cancer Research & Education

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FAST FACTS

NRG-BR004
A Randomized, Double-Blind, Phase III Trial of Paclitaxel/Trastuzumab/Pertuzumab with Atezolizumab or Placebo in First-Line HER2-Positive Metastatic Breast Cancer

Eligibility Criteria

1. The patient must have signed and dated an IRB-approved consent form that conforms to federal and institutional guidelines.
2. The trial is open to female and male patients.
3. Patients must be ≥ 18 years old.
4. Patient must have an ECOG Performance Status of 0 or 1 (see Appendix A).
5. Histologically confirmed adenocarcinoma of the breast with locally recurrent, unresectable disease or metastatic disease ***confirmed as described below***. Eligible patients include those with either:
   - De novo metastatic disease presenting without prior history of HER2-positive breast cancer:
     - Diagnosis should have been made from a biopsy of a metastatic disease site, but biopsy from the breast primary or involved regional lymph nodes is acceptable if biopsy of the metastatic sites was thought to carry excessive risk for the patient.
   - Locally recurrent or metastatic disease following prior therapy for early breast cancer:
     - Diagnosis must have been made from the biopsy of the locally recurrent or metastatic disease.
     - There must be an interval of ≥ 6 months between completion of neoadjuvant/adjuvant HER2-targeted therapy and documentation of locally recurrent or metastatic HER2-positive disease by biopsy.
6. Patients must have measurable disease based on RECIST 1.1, as determined by the site, to be eligible.
7. The tumor specimen obtained at the time of diagnosis of locally recurrent or metastatic disease must have been determined to be HER2-positive based on ***central testing*** according to ASCO/CAP guidelines (Wolff 2018). HER2 status will initially be assessed using a FDA-cleared IHC assay. Positive is defined as IHC 3+ staining intensity. If HER2 IHC results are equivocal (2+), then HER2 status will be determined using a FDA-cleared HER2 ISH test according to ASCO/CAP guidelines. Sites can send biopsy specimens for central testing which have been determined to be HER2-positive or initially equivocal by either IHC or ISH on local testing.
8. The tumor specimen obtained at the time of diagnosis used for HER2 testing must also have ***central testing*** for PD-L1 status. Patients will be eligible irrespective of PD-L1 testing result including PD-L1 indeterminant.
9. The tumor specimen obtained at the time of diagnosis used for HER2 and PD-L1 testing should also have ***central testing*** for ER and PgR according to current ASCO/CAP Guideline Recommendations for hormone receptor testing (http://www.asco.org). Patients with < 1% ER and PgR staining by IHC will be classified as negative. If sufficient material for central confirmation of ER and PgR is unavailable, local testing results for ER and PgR may be used for eligibility.
10. Localized palliative radiation therapy is allowed for symptom management if completed ≥ 14 days prior to randomization.

11. Patients must have imaging of the chest/abdomen/pelvis, preferably with a CT scan, and a bone scan within 4 weeks prior to randomization. (Note: If a patient is unable to receive CT contrast, a MRI of the abdomen/pelvis and non-contrast chest CT should be performed. PET/CT ***is not*** an acceptable alternative.)

12. MRI of the brain (or contrast CT scan of the brain if patients are unable to undergo MRI) must be obtained in patients with symptoms suggesting possible central nervous system (CNS) metastatic disease. Neuroimaging is recommended but not required in asymptomatic patients.

13. Adequate hematologic function within 14 days prior to randomization defined as follows:
- ANC must be ≥ 1200/mm3;
- Platelet count must be ≥ 100,000/mm3;
- Hemoglobin must be ≥ 8 g/dL.

14. Adequate hepatic function within 14 days prior to randomization:
- total bilirubin must be ≤ 1.5 x ULN for the lab or direct bilirubin ≤ ULN for patients with bilirubin levels > 1.5 x ULN;
- AST and ALT must be ≤ 2.5 x ULN for the lab or ≤ 5 x ULN for patients with liver metastases.

15. Adequate renal function determined within 14 days prior to randomization defined as the most recent serum creatinine ≤ 1.5 x ULN or measured or calculated creatinine clearance ≥ 50 mL/min using the Cockroft-Gault formula for patients with creatinine levels > 1.5 x ULN for the lab.

For Women

$$\text{Creatinine Clearance (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)} \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

For Men

$$\text{Creatinine Clearance (mL/min)} = \frac{(140 - \text{age}) \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

16. Patients not receiving anti-coagulant therapy must have PT and INR ≤ 1.5 x ULN within 14 days prior to randomization. For laboratories that do not report an ULN for the INR assay, use ≤ 1.5 as the value for the ULN. Patients receiving anti-coagulants should have a baseline INR assessed, but the value does not affect eligibility.

17. A serum TSH and AM (morning) cortisol must be obtained within 14 days prior to randomization to obtain a baseline value. Patients with abnormal TSH or AM cortisol baseline levels should be further evaluated and managed per institutional standards. Asymptomatic patients who require initiation or adjustment of medication or are followed without initiating treatment based on endocrinologist's recommendations are eligible.

18. LVEF assessment must be performed within 6 weeks prior to randomization. (LVEF assessment performed by echocardiogram is preferred; however, MUGA scan may be substituted based on institutional preferences.) The LVEF must be ≥ 55% regardless of the cardiac imaging facility's lower limit of normal.

19. Administration of atezolizumab may have an adverse effect on pregnancy and poses a risk to the human fetus, including embryo-lethality. Women of child-bearing potential and men must agree to use adequate contraception (non-hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 5 months (150 days) after the last dose of atezolizumab/placebo and 7 months after the last dose of trastuzumab and pertuzumab. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

Ineligibility Criteria

1. Patients with known primary central nervous system (CNS) malignancy or symptomatic CNS metastases are excluded, with the following exceptions:
   • Patients with asymptomatic untreated CNS disease may be enrolled, provided all of the following criteria are met:
      − Evaluable or measurable disease outside the CNS
      − No metastases to brain stem, midbrain, pons, medulla, cerebellum, or within 10 mm of the optic apparatus (optic nerves and chiasm)
      − No history of intracranial hemorrhage or spinal cord hemorrhage
      − No ongoing requirement for dexamethasone for CNS disease; patients on a stable dose of anticonvulsants are permitted.
      − No neurosurgical resection or brain biopsy within 28 days prior to randomization.
   • Patients with asymptomatic treated CNS metastases may be enrolled, provided all the criteria listed above are met as well as the following:
      − Radiographic demonstration of improvement upon the completion of CNS directed therapy and no evidence of interim progression between the completion of CNS directed therapy and the screening radiographic study
      − No stereotactic radiation or whole-brain radiation within 4 weeks prior to randomization.
      − Screening CNS radiographic study at least 4 weeks from completion of radiotherapy and at least 2 weeks from discontinuation of corticosteroids.
2. Known leptomeningeal carcinomatosis.
3. Patients with metastatic disease limited to the CNS.
4. History of systemic anti-cancer therapy (e.g., chemotherapy, targeted therapy) for MBC with the exception of:
   a. aAdministration of trastuzumab or lapatinib concurrently with radiation therapy for brain metastases. Toxicities related to lapatinib should be ≤ grade 1, per the CTCAE v5.0, and the lapatinib must have been completed at least 2 weeks prior to randomization.
   b. The loading doses of trastuzumab and pertuzumab may be administered prior to randomization. Patients who receive a loading dose with transtuzumab biosimiliar will not be eligible.
5. History of exposure to cumulative doses of doxorubicin greater than 360 mg per square meter of body-surface area or its equivalent.
6. Prior treatment with mTOR inhibitors or CDK 4/6 inhibitors in combination with endocrine therapy for treatment of metastatic disease.
7. Prior treatment with CD137 agonists or immune checkpoint-blockade therapies, including anti-CD40, anti-CTLA-4, anti-PD-1, and anti-PD-L1 therapeutic antibodies.
8. History of *non-breast* malignancies (except for in situ cancers treated only by local excision and basal cell and squamous cell carcinomas of the skin) within 5 years prior to randomization.
9. Uncontrolled hypertension defined as sustained systolic BP > 150 mmHg or diastolic BP > 90 mmHg. (Patients with initial BP elevations are eligible if initiation or adjustment of BP medication lowers pressure to meet entry criteria.)
10. History of asymptomatic LVEF decline to < 40% during or after prior HER2-targeted therapy.
    Cardiac disease (history of and/or active disease) that would preclude the use of the drugs included in the treatment regimens. This includes but is not confined to:
    Active cardiac disease
    • angina pectoris that requires the current use of anti-anginal medication;
    • ventricular arrhythmias except for benign premature ventricular contractions;

• supraventricular and nodal arrhythmias requiring a pacemaker or not controlled with medication;
• conduction abnormality requiring a pacemaker;
• valvular disease with documented compromise in cardiac function; or
• symptomatic pericarditis.

History of cardiac disease

• prior myocardial infarction documented by elevated cardiac enzymes or persistent regional wall abnormalities on assessment of LV function;
• history of documented CHF defined as symptomatic heart failure with an LVEF < 40%; or
• documented cardiomyopathy.

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12. Nervous system disorder (paresthesia, peripheral motor neuropathy, or peripheral sensory neuropathy) ≥ grade 2, per the CTCAE v5.0.

13. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.

14. Known hypersensitivity to biopharmaceuticals produced in Chinese hamster ovary cells or other recombinant antibodies.

15. Known allergy or hypersensitivity to the components of the atezolizumab formulation or to any of the study drugs or excipients, (e.g., Cremophor® EL).

16. History or risk of autoimmune disease, including, but not limited to, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis.

• Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone may be eligible.
• Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be eligible.
• Patients with eczema, psoriasis, lichen simplex chronicus of vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:

- − Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations
- − Rash must cover less than 10% of body surface area (BSA)
- − Disease is well controlled at baseline and only requiring low-potency topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, aclometasone dipropionate 0.05%)
- − No acute exacerbations of underlying conditions within the last 12 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors; high potency or oral steroids)

17. Treatment with systemic immunomodulatory medications (including but not limited to interferons, IL-2) within 4 weeks or 5 half-lives of the drug, whichever is longer, prior to randomization.

18. Treatment with systemic immunosuppressive medications (including but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and ***anti-tumor*** necrosis [anti-TNF] factor agents) within 14 days prior to randomization or anticipation of need for systemic immunosuppressive medications during the study. Note: Intranasal and inhaled corticosteroids or systemic corticosteroids at doses that do not exceed 10 mg/day of prednisone or an equivalent corticosteroid are allowed.

19. Has a diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 2 weeks prior to randomization.

20. Active hepatitis B virus (HBV) infection, defined as having a positive hepatitis B surface antigen (HBsAg) test at screening.
Patients with a past or resolved HBV infection, defined as having a negative HBsAg test and a positive total hepatitis B core antibody (HBcAb) test at screening, are eligible for the study if active HBV infection is ruled out on the basis of HBV DNA viral load per local guidelines.

21. Active hepatitis C virus (HCV) infection, defined as having a positive HCV antibody test at screening confirmed by a polymerase chain reaction (PCR) positive for HCV RNA.

22. Patients with clinically active tuberculosis.

23. Patients known to be HIV positive are eligible if they meet the following criteria within 4 weeks prior to randomization:
• A stable regimen of highly active anti-retroviral therapy (HAART) ***and;***
• No requirement for concurrent antibiotics or antifungal agents for the prevention of opportunistic infections; ***and***
• A CD4 count above 250 cells/mcL and an undetectable HIV viral load on standard PCR-based tests.

24. Severe infection within 4 weeks prior to randomization, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia.

25. Prior allogeneic stem cell or solid organ transplantation.

26. Symptomatic peripheral ischemia.

27. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, idiopathic pneumonitis, or evidence of active pneumonitis ***or*** ≥ grade 1 pulmonary fibrosis, per the CTCAE v5.0, on screening chest CT scan.

28. Administration of a live, attenuated vaccine within 4 weeks prior to randomization or anticipation that such vaccine will be required during the study.
Patients must agree not to receive live, attenuated influenza vaccine (e.g., FluMist□) within 4 weeks prior to randomization, during treatment or within 5 months following the last dose of atezolizumab/placebo.

29. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding giving reasonable suspicion of a disease or condition that contraindicates the use of an investigational drug or that may affect the interpretation of the results or render the patient at high risk from treatment complications.

30. Psychiatric or addictive disorders or other conditions that, in the opinion of the investigator, would preclude the patient from meeting the study requirements or interfere with interpretation of study results.

31. Pregnancy or lactation at the time of randomization or intention to become pregnant during the study. ***(Note: Pregnancy testing according to institutional standards for women of childbearing potential must be performed within 3 day prior to randomization.)***

32. Use of any investigational product within 4 weeks prior to randomization.

Figure 1.
NRG-BR004 SCHEMA