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FAST FACTS

NRG GY009 - A RANDOMIZED, PHASE II/III STUDY OF PEGYLATED LIPOSOMAL DOXORUBICIN AND CTEP-SUPPLIED ATEZOLIZUMAB (IND #134427) VERSUS PEGYLATED LIPOSOMAL DOXORUBICIN/BEVACIZUMAB AND CTEP-SUPPLIED ATEZOLIZUMAB VERSUS PEGYLATED LIPOSOMAL DOXORUBICIN/BEVACIZUMAB IN PLATINUM RESISTANT OVARIAN CANCER

Eligibility Criteria

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

1. High grade ovarian cancer, including high grade serous; clear cell; endometrioid, grade 3; and others (adenocarcinoma, NOS; mixed epithelial carcinoma; undifferentiated carcinoma). NOTE: Low grade serous, mucinous and carcinosarcoma histologies are excluded due to their different underlying genomic features and/or clinical behavior. Ovarian cancer = ovarian, fallopian tube or primary peritoneal cancer. Required data element: submission of pathology report.
2. Recurrent, platinum resistant ovarian cancer (defined as progression within < 6 months from completion of platinum based therapy. The date should be calculated from the last administered dose of platinum therapy).
3. 1-2 prior regimens (including primary therapy). Hormonal therapies (*e.g.*, tamoxifen, aromatase inhibitors) will not count toward the prior regimen limit. Parp inhibitors given in the maintenence setting post response to platinum-based therapy will not count as a separate regimen from the preceding platinum-based therapy.
4. Measurable disease (defined by RECIST v 1.1) or evaluable disease (defined as solid and/or cystic abnormalities on radiographic imaging that do not meet RECIST 1.1 definitions for target lesions OR ascites and/or pleural effusion that has been pathologically demonstrated to be disease related in the setting of CA125 ≥ 2xULN).
5. Age ≥ 18
6. The trial is open to females only
7. Performance Status 0, 1 or 2 (see Appendix II)
8. Adequate hematologic function within 14 days prior to registration defined as follows:
    - ANC ≥ 1,500/mcl
    - Platelets ≥ 100,000/mcl
    - Hgb ≥ 8 g/dl
9. Adequate renal function within 14 days prior to registration defined as follows:
    - Creatinine ≤ 1.5 x institutional upper limit of normal (ULN)
    - Urine protein creatinine (UPC) ratio must be < 1.0. If UPC ratio > 1, collection of 24-hour urine measurement of urine protein is recommended (24-hour urine protein level must be < 1000 mg for patient enrollment). If UPC ratio cannot be calculated because the urine protein is below the lower limit of detection of the assay this will not exclude the patient.

    UPC ratio of spot urine is an estimation of the 24-hour urine protein excretion – a UPC ratio of 1 is roughly equivalent to a 24-hour urine protein of 1 gm. UPC ratio is calculated using one of the following formulas:
        - [urine protein]/[urine creatinine] – if both protein and creatinine are reported in mg/dL
        - [(urine protein) x0.088]/[urine creatinine] – if urine creatinine is reported in mmol/L
10. Adequate hepatic function within 14 days prior to registration defined as follows:
    - Total Bilirubin ≤ 1.5 x ULN (patients with known Gilbert disease who have serum bilirubin level ≤ 3 x ULN may be enrolled)
    - AST/ALT ≤ 3 x ULN (AST and/or ALT ≤ 5 x ULN for patients with liver involvement)

11. INR and aPTT ≤ 1.5 x ULN (or on stable dose of therapeutic anticoagulation, such as low-molecular-weight heparin, warfarin or rivaroxaban)
12. TSH within normal limits (Euthyroid patients on thyroid replacement therapy allowed provided TSH < ULN.)
13. The patient or 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

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

1. Patients with prior allogeneic bone marrow transplantation or prior solid organ transplantation.
2. Patients who have had systemic anticancer therapy (*e.g.*, chemotherapy, targeted therapy including PARP inhibitors or bevacaizumab) within 3 weeks prior to entering the study.
3. Patients who have had hormonal therapy (*e.g.*, tamoxifen, aromatase inhibitor) within 1 week prior to entering the study.
4. Patients with prior treatment with anti-PD-1, anti-PD-L1 or anti-CTLA-4 therapeutic antibody or other similar agents.
5. Patients with prior treatment with bevacizumab (or any other anti vascular therapy, e.g., cediranib) for platinum resistant recurrence. (Note: Prior bevacizumab in initial therapy and/or platinum sensitive recurrent setting is allowed.)
6. Patients with prior treatment with PLD. (Pegylated liposomal doxorubicin)
7. Prior radiotherapy to the abdomen or pelvis.
8. Patients who have not recovered from adverse events to < grade 1 (other than alopecia) due to agents administered more than 3 weeks earlier.
   However, the following therapies are allowed:
   - Hormone replacement therapy or oral contraceptives
   - Herbal therapy >1 week prior to Cycle 1, Day 1 (herbal therapy intended as anticancer therapy must be discontinued at least 1 week prior to Cycle 1, Day 1)
   - Palliative radiotherapy for bone metastases >2 weeks prior to Cycle 1, Day 1
9. Treatment with any other investigational agent within 4 weeks prior to Cycle 1, Day 1.
10. Treatment with systemic immunostimulatory agents (including, but not limited to, interferon [IFN]-alpha or interleukin [IL]-2) within 6 weeks prior to Cycle 1, Day 1.
11. Treatment with systemic immunosuppressive medications (including, but not limited to, prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 2 weeks prior to Cycle 1, Day 1.
    - Patients who have received acute, low dose, systemic immunosuppressant medications (*e.g.*, a one-time dose of dexamethasone for nausea or steroids as CT scan contrast premedication) may be enrolled.
    - The use of inhaled corticosteroids and mineralocorticoids (*e.g.*, fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.
12. Patients taking bisphosphonate therapy for symptomatic hypercalcemia within the past 28 days. Use of bisphosphonate therapy for other reasons (*e.g.*, bone metastasis or osteoporosis) is allowed.
13. 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 Cycle 1, Day 1

- 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 28 days prior to Cycle 1, Day 1
  - Screening CNS radiographic study ≥ 4 weeks from completion of radiotherapy and ≥ 2 weeks from discontinuation of corticosteroids

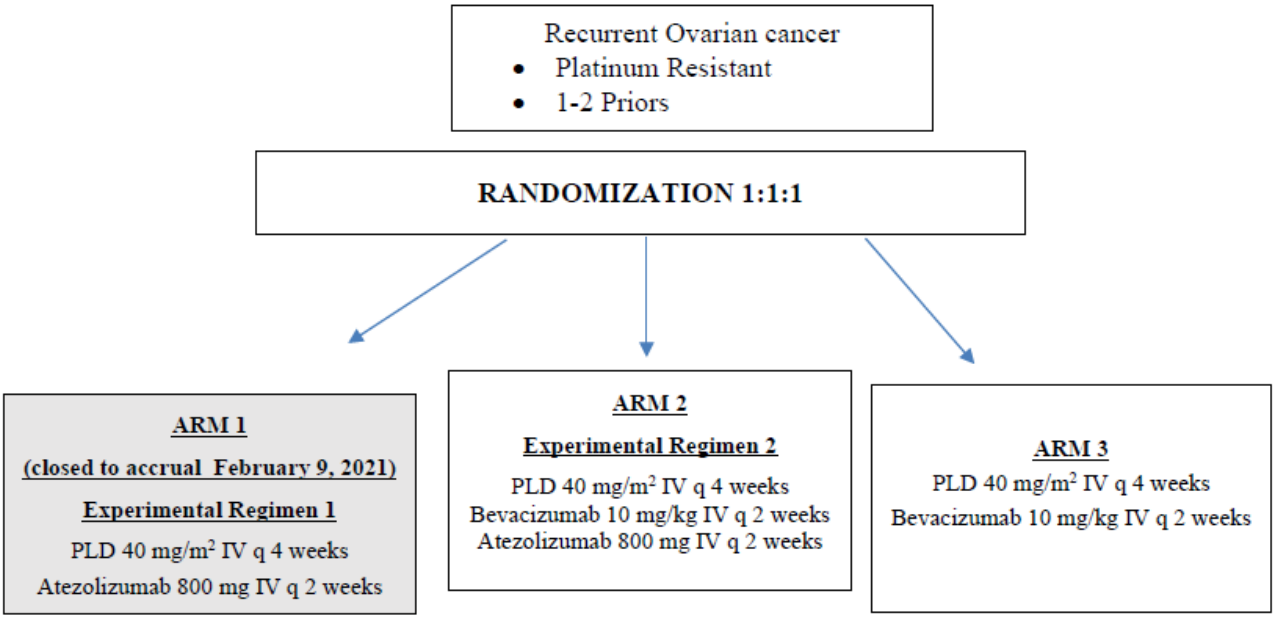
14. Known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies.
15. History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.
16. Patients requiring treatment with a RANKL inhibitor (e.g., denosumab) who cannot discontinue it before treatment with atezolizumab.
17. Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis; cirrhosis; fatty liver; and inherited liver disease.
    - Patients with past or resolved hepatitis B infection (defined as having a negative hepatitis B surface antigen [HBsAg] test and a positive anti-HBc [antibody to hepatitis B core antigen] antibody test) are eligible.
    - Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA.
18. 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, 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 are eligible.
    - Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen or Type 2 diabetes mellitus are eligible.
    - Patients with eczema, psoriasis, lichen simplex chronicus or 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%, alclometasone dipropionate 0.05%)
      - No acute exacerbations of underlying condition 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)
19. History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of

active pneumonitis on screening chest computed tomography (CT) scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

20. Patients with active tuberculosis (TB) are excluded.
21. Severe infections within 4 weeks prior to Cycle 1, Day 1, including but not limited to hospitalization for complications of infection, bacteremia, or severe pneumonia.
22. Signs or symptoms of infection within 2 weeks prior to Cycle 1, Day 1.
23. Received oral or intravenous (IV) antibiotics within 2 weeks prior to Cycle 1, Day 1. Patients receiving prophylactic antibiotics (*e.g.*, for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.
24. Major surgical procedure within 28 days prior to Cycle 1, Day 1 or anticipation of need for a major surgical procedure during the course of the study.
25. Administration of a live, attenuated vaccine within 4 weeks before Cycle 1, Day 1 or anticipation that such a live, attenuated vaccine will be required during the study and up to 5 months after the last dose of atezolizumab.
    - Influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated influenza vaccine within 4 weeks prior to Cycle 1, Day 1 or at any time during the study.
26. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
27. HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.
28. Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years, with the exception of those with a negligible risk of metastases or death, such as carcinoma in situ of the breast or cervix.
29. Severe, active co-morbidity defined as follows:
    - Current (within 28 days of Cycle 1, Day 1) signs and/or symptoms of bowel obstruction
    - Patients who require parental hydration and/or nutrition
    - Patients who require drainage gastrostomy tube
    - Evidence of bleeding diathesis or clinically significant coagulopathy
    - Serious, non-healing or dehiscing wound, active ulcer or untreated bone fracture
    - History of hemoptysis (≥ 1/2 teaspoon of bright red blood per episode) within 1 month of study enrollment
30. Significant cardiovascular or cerebrovascular disease including:
    - Uncontrolled hypertension (SBP >150 and/or DBP >90) (29-JUN-2020)
    - History of myocardial infarction within 6 months
    - Unstable angina
    - New York Heart Association functional classification II, III or IV (See Appendix III)
    - Baseline ejection fraction ≤ 50% as assessed by echocardiogram or MUGA
    - Cerebral vascular accident (CVA) or transient ischemic attack (TIA) within 6 months
    - Significant vascular disease (e.g., aortic aneurysm, requiring surgical repair or peripheral arterial thrombosis) within 6 months
31. History of abdominal/pelvic or tracheoesophageal fistula or gastrointestinal perforation and/or abdominal/pelvic abscess within 6 months prior to initiation of treatment.
32. Pregnant or lactating patients.

Randomized Phase II/III

Note: Arm 1 was permanently closed to accrual with Amendment 11



PLD = pegylated liposomal doxorubicin

Safety Lead-Ins – Limited access (Restricted to NRG Oncology, Participating Institutions for Safety Lead-Ins)

See Section 5.1.1 and Table 4.2 for guidance on PLD dosing if cumulative dose of PLD exceeds 550mg/m^2.