FAST FACTS

NRG LU007 - RAndomized Phase II/III Trial Of Consolidation Radiation + Immunotherapy for ES-SCLC: RAPTOR trial

Eligibility Criteria

1. Pathologically proven diagnosis of extensive stage small cell lung cancer;
2. Partial response (PR) or stable disease (SD) after 4-6 cycles of etoposide/platinum (E/P) doublet plus atezolizumab by re-staging scans (PET/CT scan, diagnostic CT scan, MRI optional per treating physician); atezolizumab should continue through randomization. Patients must be randomized within 9 weeks of last dose of etoposide/platinum or 6 weeks from completion of PCI.
3. At the time of enrollment, patients must have had measurable disease (per RECIST) and 3 or fewer observable liver metastases and no evidence of progressive disease (per RECIST) at time of enrollment.
4. Patients presenting with a pleural effusion will be eligible if thoracentesis is cytologically negative and non-bloody or if pleural fluid is too small a volume to effectively sample by thoracentesis and does not show increased metabolic activity on CT/PET imaging.
5. Appropriate stage for study entry based on the following diagnostic workup:
    a. History/physical examination within 14 days prior to registration;
    b. Imaging within 42 days prior to registration to include:
        i. Imaging within 42 days prior to registration to include:
        ii. CT chest, abdomen and pelvis or whole body PET/CT scan after the fourth cycle of chemotherapy
6. Age ≥ 18;
7. ECOG Performance Status of 0-2 at the time of registration;
8. Required laboratory values within 14 days prior to registration:

ANC	≥1,000/cells/mm^3
Platelets	≥75,000 cells/mm^3
Hemoglobin	≥8 g/dL
Total Bilirubin	≤1.5 x ULN
AST (SGOT) and ALT (SGPT)	≤3.0 x ULN (AST and/or ALT ≤5 ULN for patients with liver involvement)
Alkaline phosphatase	≤2.5 × ULN (≤5 ULN for patients with documented liver involvement or bone metastases)
Serum Creatinine	≤2.0 x ULN
Adequate renal function	Adequate renal function within 30 days prior to registration defined as follows: Glomerular filtration rate (GFR) ≥ 40 mL/min/1.73 m^2 (See Appendix I for eGFR calculations)

9. Upfront central nervous system (CNS) radiotherapy for treatment of brain metastases is permitted provided there is no evidence of CNS progression at the time of randomization and patients are clinically stable on a dose of steroids <10 mg prednisone a day or

equivalent. Upfront radiation therapy of symptomatic metastatic site is permissible if causing patient pain or impending fracture.

10. Patients with bone metastases are eligible. However, to assess response after radiation for bone metastases, must order at least diagnostic CT scan to measure response.
11. For women of childbearing potential, a negative serum or urine pregnancy test within 14 days prior to registration.
    Note: Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
    • Women < 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
    • Women ≥ 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).
12. The patient or a legally authorized representative must provide study-specific informed consent prior to study entry.

Ineligibility Criteria

1. Metastatic disease invading the liver (>3 metastases), heart or >10 metastatic sites detectable after induction systemic therapy. Each visible bone metastasis on radiographic scan count as one site. For site of bony metastases, must order diagnostic CT scan for assessment of response.
2. Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for 5 years prior to randomization. Cancers with a negligible risk of metastasis or death (e.g., expected 5-year OS >90%) treated with expected curative outcome are eligible (such as adequately treated carcinoma in situ of the cervix or oral cavity; localized prostate cancer treated surgically with curative intent, or ductal carcinoma in situ treated surgically with curative intent);
3. Prior radiotherapy except in the thorax, where there may be some overlap in the mediastinum and spine, as long as overlap fields meet dose constraints.
4. History of autoimmune disease, including, but not limited to: systemic lupus erythematosus; rheumatoid arthritis; inflammatory bowel disease (e.g. Crohn's, ulcerative colitis); vascular thrombosis associated with antiphospholipid syndrome; Wegener's granulomatosis; Sjögren's syndrome; Guillain-Barré syndrome; multiple sclerosis; vasculitis; or glomerulonephritis. Note: the follow are eligible:
    • 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 are 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:
    o Patients with psoriasis must not have ocular manifestations within the past year
    o Rash must cover less than 10% of body surface area (BSA)

o Disease is well controlled on topical steroids (e.g., hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, fluocinolone 0.01%, desonide 0.05%, alclometasone dipropionate 0.05%)
o 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 or oral steroids)

5. Severe, active co-morbidity defined as follows:
• Any other diseases, 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;
• Active tuberculosis;
• Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis; cirrhosis; fatty liver; and inherited liver disease.
i. 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.
ii. Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA. (The HCV RNA test must be performed for patients who have a positive HCV antibody test.)
• Known immunosuppressive disease, for example history of bone marrow transplant or CLL;
• Patients positive for human immunodeficiency virus (HIV) are allowed on study, but HIV-positive patients must have:
o A stable regimen of highly active anti-retroviral therapy (HAART)
o No requirement for concurrent antibiotics or antifungal agents for the prevention of opportunistic infections
o A CD4 count above 250 cells/mcL and an undetectable HIV viral load on standard PCR-based tests
• Chronic obstructive pulmonary disease (COPD) requiring chronic oral steroid therapy of > 10 mg prednisone daily or equivalent at the time of registration. Inhaled corticosteroids are not exclusionary;
• Unstable angina and/or congestive heart failure requiring hospitalization within the last 3 months;
• History of recent myocardial infarction within 6 months prior to registration.
• Clinically significant interstitial lung disease
6. Pregnancy: 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 (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study treatment, and for 5 months (150 days) after the last dose of study agent. 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.
7. Women who are breastfeeding and unwilling to discontinue.
8. History of allogeneic organ transplant.
9. Patients who have had immunotherapy-induced pneumonitis.

NRG-LU007
SCHEMA

PATIENT POPULATION:
Patients with extensive stage small cell lung cancer (ES-SCLC), stable disease (SD) or partial response (PR) after 4-6 cycles of etoposide/platinum (E/P) doublet plus atezolizumab

STRATIFICATION

- Number of sites receiving radiation therapy (fields 1-3 vs >3)
- Partial Response (PR) vs Stable Disease (SD)
- ECOG Performance Status (0/1 vs 2)

RANDOMIZE

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Arm 1	**Arm 2**
Atezolizumab maintenance	Standard RT: (Daily up to 5 sites) Thoracic or Liver RT: 45 Gy or 30 Gy Extra-Thoracic RT: 30 Gy or 20 Gy + Atezolizumab maintenance