

FAST FACTS

EA5181 - Randomized Phase III Trial of MEDI4736 (durvalumab) as Concurrent and Consolidative Therapy or Consolidative Therapy Alone for Unresectable Stage 3 NSCLC

Eligibility criteria

1. Step 1 Eligibility Criteria – Concurrent Therapy

- a. Patient must be ≥ 18 years old.
- b. Patient must have one of the following:
 - Newly diagnosed stage IIIA/B/C NSCLC (per the AJCC 8th Edition) that is unresectable and is histologically and/or cytologically confirmed.
 - Nodal recurrence after surgery for early stage NSCLC. Please see Section 3.1.11 for associated requirements.
- c. Patient must have an ECOG Performance Status of 0 or 1. Refer to Appendix IV.
- d. Patient must have a body weight > 30 kg.
- e. Patient must not have unintentional weight loss greater than 10% within 30 days prior to registration.
- f. Patient must have a baseline ECG obtained within 6 weeks prior to registration.
- g. Patient must have measurable disease per Response Evaluation Criteria in Solid Tumors (RECIST) version v1.1, as defined in Section 6.1. Baseline imaging assessments and measurements used to evaluate all measurable or non-measurable sites of disease must be done within 4 weeks prior to registration.
- h. Patient must have acceptable organ and marrow function as defined below. These values must be obtained ≤ 7 days prior to registration.
 - Absolute neutrophil count (ANC) ≥ 1500 cells/uL
ANC: _____ Date of test: _____
 - White blood cells (WBC) counts ≥ 2500 /uL
WBC: _____ Date of test: _____
 - Platelet count $\geq 100,000$ /uL
Platelets: _____ Date of test: _____
 - Hemoglobin ≥ 9.0 g/dL Hemoglobin: _____
Date of test: _____
 - Total bilirubin ≤ 1.5 x Institutional upper limit of normal (ULN) with the following exception: patients with known Gilbert disease who have serum bilirubin level < 3 x ULN may be enrolled. Total bilirubin: _____ Date of test: _____
Institutional ULN: _____
Known Gilbert disease? _____ (Yes or No)
 - Aspartate aminotransferase (AST) and alanine transaminase (ALT) ≤ 3.0 x Institutional ULN.
AST: _____ Date of test: _____
Institutional ULN (AST): _____
ALT: _____ Date of test: _____
Institutional ULN (ALT): _____
 - Serum creatinine ≤ 1.5 x Institutional ULN or creatinine clearance ≥ 45 mL/min on the basis of the Cockcroft-Gault glomerular filtration rate estimation (see Appendix VI).
Creatinine Clearance: _____ Date of test: _____
Creatinine: _____ Date of test: _____
Institutional ULN: _____

- i. Patient must have pulmonary function tests (PFTs) with both FEV1 and DLCO \geq 40% of predicted, obtained within 5 months prior to registration.
- j. Patient is expected to have Lung V20 of \leq 35%, after radiation oncologist views pre-treatment work up.
- k. Patients with nodal recurrence after surgery for early-stage NSCLC are eligible if the following criteria are met:
 - i. No prior chemotherapy or radiation was ever administered for this lung cancer originally or for recurrence prior to entering this protocol.
 - ii. Prior curative-intent surgery was at least 90 days prior to the nodal recurrence.
 - iii. No prior radiation was administered to the region of study cancer that would cause overlap of treatment fields.
- l. Patients who are Human Immunodeficiency Virus (HIV) positive may participate in the study IF they meet all of the following eligibility requirements:
 - i. They must be stable on their anti-retroviral regimen, and they must be healthy from an HIV perspective.
 - ii. They must have a CD4 count of greater than 250 cells/mcL, obtained within 6 months prior to registration.
 - iii. They must not be receiving prophylactic therapy for an opportunistic infection.
- m. 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. Patients must not have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to registration.
- n. Patient must not be pregnant or breast-feeding due to the potential harm to an unborn fetus and possible risk for adverse events in nursing infants with the treatment regimens being used.
 All patients of childbearing potential must have a negative blood test or urine study, with a minimum sensitivity 50 mIU/L or equivalent units of HCG, within 7 days prior to registration to rule out pregnancy. A patient of childbearing potential is anyone, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy; or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e. has had menses at any time in the preceding 24 consecutive months).
 Patient of childbearing potential? _____ (Yes or No)
 Date of blood test or urine study: _____
- o. Patients must not expect to conceive or father children by using accepted and highly effective method(s) of contraception during sexual intercourse for at least one week prior to the start of treatment, during protocol treatment, and continue for 90 days after the last dose of protocol treatment.
 - i. Highly effective methods of contraception include Etonogestrel-releasing implants (Implanon® or Norplant®), Intravaginal: Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g., NuvaRing, Injection: Medroxyprogesterone injection: e.g., Depo-Provera®, Combined Pill: Normal and low dose combined oral contraceptive pill, Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: e.g., Ortho Evra®, Minipill: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone based pill.
 - ii. Methods that are considered inadequate include male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without

spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).

- p. Patient must not have any active, known or suspected autoimmune disease and neuromuscular paraneoplastic syndromes including, but not limited to myasthenia gravis, Lambert-Eaton myasthenic syndrome, limbic encephalitis, myositis, Guillain-Barré, systemic lupus erythematosus, and systemic sclerosis. Patients with type I diabetes mellitus requiring insulin, hypothyroidism only requiring hormone replacement, skin disorders (such as vitiligo, psoriasis, or alopecia), not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are eligible.
- q. Patient must not have a history of active hepatitis B (chronic or acute) or hepatitis C infection. 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 hepatitis C virus ribonucleic acid (HCV RNA).
- r. Patient must not have a known active tuberculosis infection.
- s. Patient must not have any severe infections within 4 weeks prior to registration including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia.
- t. Patient must not have signs or symptoms of severe infection (sepsis) within 2 weeks prior registration.
- u. Patient must not have been treated with systemic immunostimulatory agents (including but not limited to interferon-a [IFN-a], interleukin [IL]-2) within 6 weeks or five half-lives of the drug (whichever is shorter) prior to registration; or treated with an investigational agent within 4 weeks prior to registration (or within five half-lives of the investigational agent, whichever is longer).
- v. Patient must not have a history of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.
- w. Patient must not have been treated with systemic immunosuppressive medications (equivalent to > 10 mg prednisone per day) or other immunosuppressive medications within 7 days prior to registration. Inhaled or topical steroids and adrenal replacement steroid doses equivalent to > 10 mg prednisone per day are permitted in the absence of active autoimmune disease.
- x. Patient must not have had a prior allogeneic bone marrow transplantation or prior solid organ transplantation.
- y. Patient must not have a 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 within 4 weeks prior to registration.
- z. Patient must not have had any prior systemic treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell costimulation or immune checkpoint pathways.
- aa.

Patient with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment and severity of cardiac symptoms. Symptoms should be stable over the past 3 months. Specifically, patient must not have coronary artery bypass grafting, myocardial infarction, acute coronary

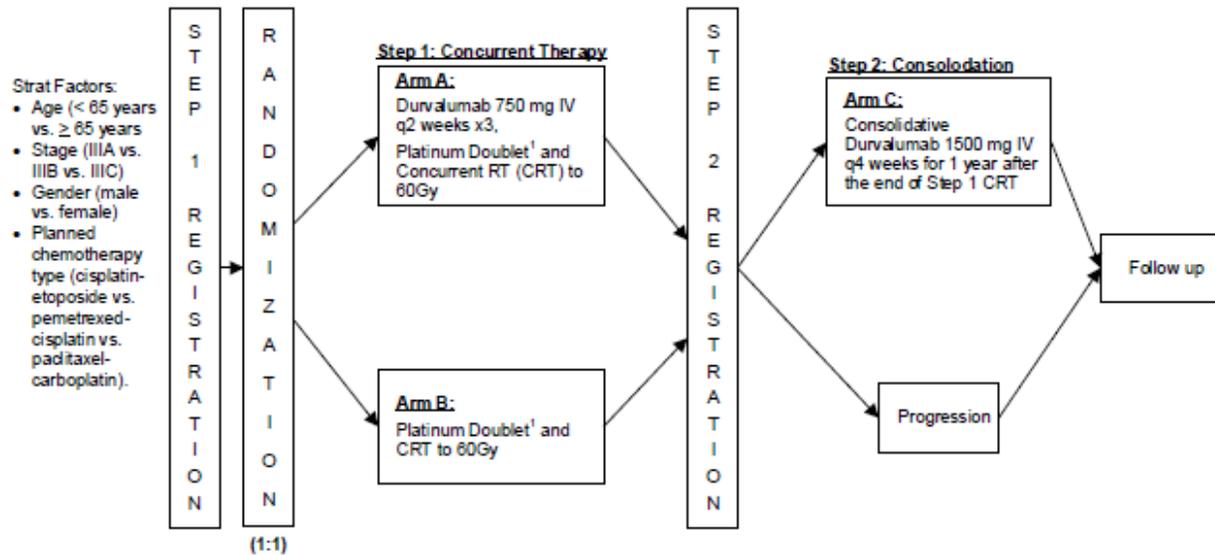
syndrome severe/unstable angina, stroke, transient ischemic attack, or heart failure hospitalization within 3 months prior to registration.

- bb. Patient must not have an uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.
- cc. Patient must not have received a live, attenuated vaccine within 4 weeks prior to registration.
- dd. Patient must not have had past radiation to the current intended treatment site.
- ee. Patient must not donate blood or sperm while on study treatment.

2. Step 2 Eligibility Criteria – Consolidation

- a. Patient must not receive any non-protocol anti-cancer therapy after the end of Step 1 chemo/radiation or during Step 2 consolidation.
- b. Patients with any > Grade 2 non-hematologic or > Grade 3 hematologic toxicities must recover to Grade 2 (or less) within 45 days after the end of Step 1 concurrent chemo/radiation, with the exception of alopecia and vitiligo.
- c. Patients with suspected cases of \geq Grade 2 pneumonitis (non-infectious) are not eligible for Step 2 consolidative MEDI4736 (durvalumab) and will proceed onto follow-up instead.
- d. Patient must not have disease progression on the first post-treatment (Step 1 for concurrent chemo/radiation) chest CT scan, which must be obtained within 14 days after the last dose of radiation therapy. If so, the patient is not eligible for Step 2 consolidative MEDI4736 (durvalumab) and will proceed onto follow-up instead.

Schema



N = 660

Cycle = Step 1 (Arms A & B): 28 days for patients receiving platinum doublet option #1 (see below)
 21 days for patients receiving platinum doublet option #2 (see below)
 7 days for patients receiving platinum doublet option #3 (see below)

Step 2 (Arm C): 28 days for patients on consolidative durvalumab (Arm C).

1. Investigator's Choice for Step 1 (see Section 5.1):

- Option #1: Cisplatin 50 mg/m² IV on C1D1, C1D8, C2D1, C2D8; Etoposide 50 mg/m² IV C1D1-D5; C2D1-D5 (Cycle = 28 days)
- Option #2: Pemetrexed 500 mg/m² IV C1D1, C2D1; Cisplatin 75 mg/m² IV on C1D1, C2D1 (Cycle = 21 days) (nonsquamous only)
- Option #3: Paclitaxel 45 mg/m² IV on D1 of each cycle for 6 cycles; Carboplatin AUC 2 IV on D1 of each cycle for 6 cycles (Cycle = 7 days)