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.
    d. Body weight > 30 kg of patients.
    e. Patient should have a life expectancy greater than 12 weeks.
    f. Patient must have a baseline ECG obtained within 6 weeks of 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
    Leukocytes: _____ Date of test: _____
    • Platelet count ≥ 100,000/uL
    Platelets: _____ Date of test: _____ • Hemoglobin ≥ 9.0 g/dL Hemoglobin: _____
    Date of test: _____
    • Total bilirubin ≤ 1.5 x 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. Bilirubin: _____ Date of test: _____
    Institutional ULN: _____
    Known Gilbert disease? _____ (Yes or No)
    • Aspartate aminotransferase (AST) and alanine transaminase (ALT) ≤ 3.0 x ULN.
    AST: _____ Date of test: _____
    Institutional ULN (AST): _____
    ALT: _____ Date of test_____
    Institutional ULN (ALT): _____
    • Serum creatinine ≤ 1.5 x ULN or creatinine clearance ≥ 50 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: _____

• International normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤ 1.5 x ULN. INR: _____ Date of test: _____
Institutional ULN (INR): _____
aPTT: _____ Date of test:_____
Institutional ULN (aPTT): _____

i. Patient must have pulmonary function tests (PFTs) with both FEV1 and DLCO ≥ 40% of predicted, obtained within 5 months of registration.
j. Patient should be expected to have Lung V20 of ≤ 35%.
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.
    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.
    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. Women 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. Patients must also not expect to conceive or father children from the time of registration, while on study treatment, and until 90 days after the last dose of study treatment.
    All females 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 female of childbearing potential is any woman, 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).
    Female of childbearing potential? _____ (Yes or No)
    Date of blood test or urine study: _____
o. Women of childbearing potential (WOCBP) and males who are sexually active with WOCBP must use 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® , Minipillc: 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, 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 of 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 of 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 of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better. For example, patients must not have the following:

i. Unstable angina and/or congestive heart failure requiring hospitalization within 180 days prior to registration.

ii. Uncontrolled cardiac arrhythmia within 180 days 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 unintentional weight loss > 10% within 30 days prior to registration.

ee. Patient must not have had past radiation to the current intended treatment site.

ff. Patient must not donate blood while on study treatment.

2. Step 2 Eligibility Criteria – Consolidation

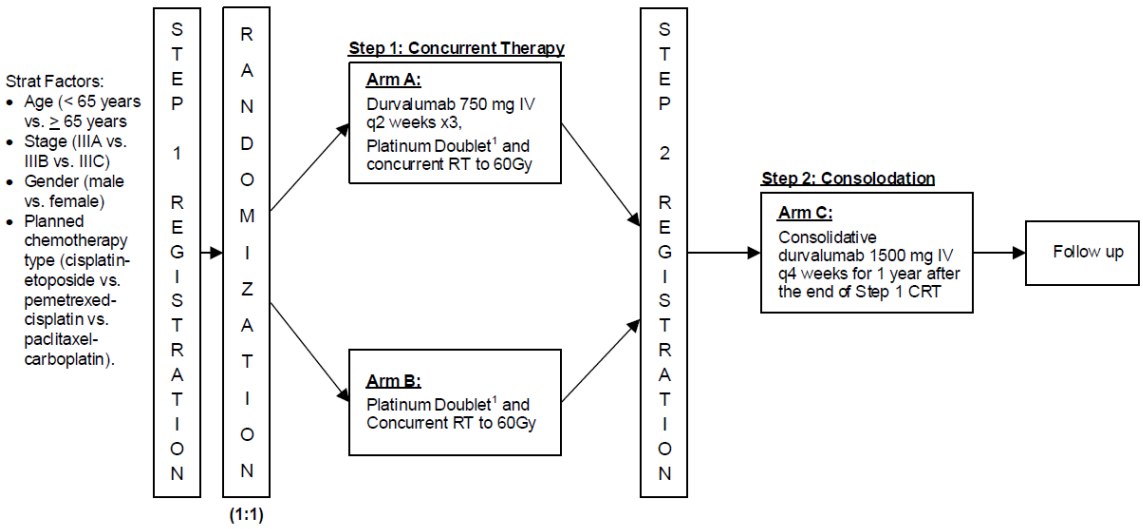
a. Patients must not receive any non-protocol anti-cancer therapy after the end of chemo/radiation or during consolidation.

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 concurrent chemo/radiation, with the exception of alopecia, vitiligo, and the laboratory values defined in the inclusion criteria.

c. Patients with suspected cases of ≥ Grade 2 pneumonitis (non-infectious) are not eligible for consolidative MEDI4736 (durvalumab) and will proceed onto follow-up instead.

d. Patients must not have disease progression on the first post-treatment (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 consolidative MEDI4736 (durvalumab) and will proceed onto follow-up instead.

Schema


Strat Factors:
• Age (< 65 years vs. ≥ 65 years
• Stage (IIIA vs. IIIB vs. IIIC)
• Gender (male vs. female)
• Planned chemotherapy type (cisplatin-etoposide vs. pemetrexed-cisplatin vs. paclitaxel-carboplatin).
STEP 1 REGISTRATION
RANDOMIZATION
(1:1)
Step 1: Concurrent Therapy
Arm A:
Durvalumab 750 mg IV q2 weeks x3,
Platinum Doublet[1] and concurrent RT to 60Gy
Arm B:
Platinum Doublet[1] and Concurrent RT to 60Gy
STEP 2 REGISTRATION
Step 2: Consolodation
Arm C:
Consolidative durvalumab 1500 mg IV q4 weeks for 1 year after the end of Step 1 CRT
Follow up