

FAST FACTS

EA2176 - A Randomized Phase III Study of Immune Checkpoint Inhibition with Chemotherapy in Treatment-Naïve Metastatic Anal Cancer Patients

Eligibility criteria

1. Patient must have inoperable, recurrent, or metastatic disease not amenable to curative therapy.
2. Patient must have histological or cytological confirmation of anal squamous cell carcinoma (includes basaloid and cloacogenic lesions) from the primary tumor or a newly diagnosed recurrent/metastatic lesion.
3. Patient must be ≥ 18 years of age.
4. Patient must have ECOG Performance Status $\leq 0-1$.
5. Patients must have measurable disease according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria version 1.1 and based on radiologic assessment performed <4 weeks prior to randomization.
6. Patient receiving palliative (limited-field) radiation therapy is allowed, as long as the lesion treated for palliation is not a target lesion and is > 7 days from completion from palliative radiation.
7. Patients with brain metastasis are eligible if patient is asymptomatic and if treatment ended > 3 months prior to randomization. Patients with treated brain metastases are eligible if follow-up brain imaging after central nervous system (CNS)-directed therapy shows no evidence of progression within 4 weeks prior to randomization.
8. 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. All females of childbearing potential must have a blood test or urine study with a minimum sensitivity of 25 IU/L or equivalent units of BCG, within 14 days prior to randomization to rule out pregnancy. A female of childbearing potential is defined as 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 2) 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 child bearing potential? _____ (Yes or No)
Date of blood test or urine study: _____
9. Women of childbearing potential and sexually active males must not expect to conceive or father children by using accepted and effective method(s) of contraception or to abstain from sexual intercourse for at least one week prior to the start of treatment, and continue for 5 months after the last dose of protocol treatment for women of childbearing potential and 7 months after the last dose of protocol treatment for males who are sexually active with WOCBP.
10. Patient must have adequate organ and marrow function as defined below , obtained < 14 days prior to randomization:
Absolute neutrophil count $\geq 1,500/\text{mcl}$
ANC: _____ Date of Test: _____
Platelets $\geq 100,000/\text{mcl}$
Platelet: _____ Date of Test: _____
Hemoglobin (Hb) $\geq 9 \text{ g/dL}$ for males and $\geq 9 \text{ g/dL}$ for females
Hgb: _____ Date of Test: _____
Total bilirubin $\leq 1.5 \times$ institutional upper limit of normal (ULN)
Bilirubin: _____ Institutional ULN: _____
Date of Test: _____
AST(SGOT) /ALT(SGPT) $\leq 5 \times$ institutional ULN ALT: _____
Institutional ULN: _____
Date of Test: _____

AST: _____ Institutional ULN: _____

Date of Test: _____

Creatinine \leq 1.5 X institutional ULN

OR

Creatinine clearance (CrCl) \geq 50 mL/min (if using the Cockcroft-Gault formula below):

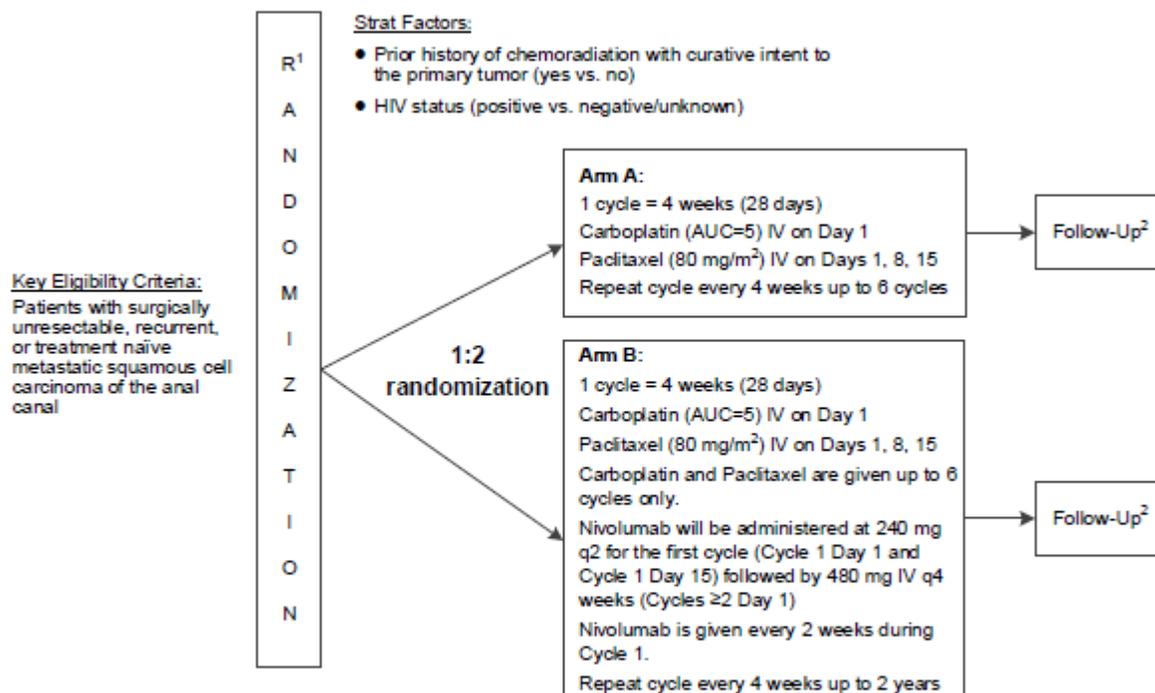
- Female CrCl = (140 - age in years) x weight in kg x 0.85
- 72 x serum creatinine in mg/dL
- Male CrCl = (140 - age in years) x weight in kg x 1.00
- 72 x serum creatinine in mg/dL

11. Human immunodeficiency virus (HIV)-infected patients on effective Anti-Retroviral Therapy (ART) with CD4 count $>$ 200 or have a CD4 count $<$ 200 but an undetectable viral load are eligible.
 - a. All HIV+ patients should be under the care of an Infectious Diseases specialist. If a relationship with an Infectious Diseases specialist is not established, an Infectious Disease specialist should be consulted. Records of all viral counts and peripheral T-cell counts should be documented in order to follow these values over the course of treatment.
 - b. All patients must be willing to undergo testing for HIV testing if not tested within the past 12 months.
12. For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.
13. Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.
14. Patients with known history or current symptoms of cardiac disease, 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. Patients with a history of CHF or who are at risk because of underlying cardiovascular disease or exposure to cardiotoxic drugs must be willing to undergo evaluation of cardiac function including EKG and ECHO as clinically indicated.
15. Patient must have the ability to understand and the willingness to sign a written informed consent document. Patients with impaired decision-making capacity (IDMC) who have a legally authorized representative (LAR) or caregiver and/or family member available will also be considered eligible.
16. Patient must not have had previous use of systemic chemotherapy or other investigational drugs for the treatment of inoperable recurrent or metastatic anal cancer (Previous use of radiotherapy or chemoradiotherapy in this setting is not an exclusion criterion if: 1) non-irradiated target tumor lesions are present at randomization for the purpose of tumor response assessment or 2) in the absence of non-irradiated target tumor lesions, progression of the irradiated tumor lesions according to the RECIST criteria version 1.1 is documented).
17. Patient must not have current or recent (within 30 days prior to randomization) treatment with another investigational drug or participation in another investigational study.
18. Patient must not have had prior immunotherapy.
19. Patient must not have a history of known hypersensitivity reaction to any platinum or taxane-based chemotherapy or monoclonal antibody.
20. Patient must not have active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including chronic prolonged systemic corticosteroids (defined as corticosteroid use of duration one month or greater). These include but are not limited to patients with a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as SLE, connective tissue diseases, scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or anti-phospholipid syndrome. Patients with any of these are ineligible because of the risk of recurrence or exacerbation of autoimmune disease.
21. Patient must not have a condition requiring systemic treatment with either corticosteroids ($>$ 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of randomization. Inhaled or topical steroids and adrenal replacement doses $<$ 10 mg daily prednisone equivalents are

permitted in the absence of active autoimmune disease. Patients are permitted to use topical, ocular, intra-articular, intranasal, and inhalational corticosteroids (with minimal systemic absorption). Physiologic replacement doses of systemic corticosteroids are permitted, even if <10 mg/day prednisone equivalents. A brief course of corticosteroids for prophylaxis (e.g., contrast dye allergy) or for treatment of non-autoimmune conditions (e.g., delayed-type hypersensitivity reaction caused by contact allergen) is permitted.

22. Patient must not have had major surgery performed \leq 28 days prior to randomization.
23. Patient must not have a history of interstitial lung disease (e.g., pneumonitis or pulmonary fibrosis) or evidence of interstitial lung disease on baseline chest CT scan.
24. Patient must not have a serious active infection requiring IV antibiotics at time of randomization.
25. Patient must not have other primary malignancy within the last 3 years, except for adequately treated carcinoma in situ of the cervix or squamous carcinoma of the skin, or adequately controlled limited basal cell skin cancer, or any other cancer from which the patient has been disease-free for at least 3 years.
26. Patient must not have known peripheral neuropathy > grade 1 at the time of randomization (absence of deep tendon reflexes as the sole neurological abnormality does not render the patient ineligible).
27. Patients must agree to not receive live vaccines while on this study.

Schema



1. Randomization is 1:2 (A:B).

2. For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until disease progression, even if non-protocol therapy is initiated, and for survival every 3 months for two years from the date of randomization. All patients must also be followed through completion of all protocol therapy.