Cancer Research Consortium of West Michigan
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# FAST FACTS

## EA2165 - A Randomized Phase II Study of Nivolumab After Combined Modality Therapy (CMT) in High Risk Anal Cancer

**Registration to Step 1 Eligibility Criteria**

1. Age ≥ 18 years.
2. Patients must have histologically proven stage IIB (T3N0M0 only), IIIA (T2N1M0), IIIB (T4N0M0), or IIIC (T3N1M0, T4N1M0) invasive squamous cell carcinoma of the anus or anorectum, according to the AJCC 8th edition. This may include tumors of non-keratinizing histology such as basoloid, transitional cell, or cloacogenic histology. Individuals with squamous cell carcinoma of the anal margin are eligible if there is evidence of extension of the primary tumor into the anal canal.
3. For patients registering to Arm T, patients must not have received prior chemoradiotherapy for anal cancer.
4. Patients must have ECOG performance status of 0-2.
5. Adequate hematologic function must be documented within 2 weeks prior to registration:
    a. Patients must have hemoglobin levels of > 9g/dL.
    b. Patient must have a platelet count of > 100,000/mm3.
    c. Patient's ANC level must be > 1500/mm3.
    d. Serum creatinine must be ≤ 2X ULN.
6. Adequate hepatic function must be documented within 2 weeks prior to registration
    a. Total bilirubin must be < 2 X ULN. AST (SGOT)/ALT (SGPT) ≤ 2.5 X institutional upper limit of normal
    b. Albumin ≥ 3.0 g/dL
7. Human immunodeficiency virus (HIV)+ patients with CD4>200 and Serum HIV viral load of < 200 copies/mm3 are permitted.
    a. Participants must be PPD negative. Alternatively, the QuantiFERON-TB Gold In-Tube (QFT-GIT) assay (Cellestis Limited, Carnegie, Australia) can be used. An individual is considered positive for M. tuberculosis infection if the IFN-γ response to TB antigens is above the test cut-off (after subtracting the background IFN-γ response in the negative control). The result must be obtained within 12 weeks prior to enrollment. PPD positive (or Quantiferon assay positive) participants are permitted if prophylaxis has been completed prior to enrollment.
    b. No history of AIDS-related complications within past year other than a history of low CD4+ T-cell count >200/mm3 prior to initiation of combination antiretroviral therapy. On study CD4+ T-cell count may not be informative due to chemoradiotherapy and should not be used as an exclusion criterion if low.
    c. Patient must be healthy on the basis of HIV disease with high likelihood of near normal life span were it not for the anal cancer
    d. Participants MUST receive appropriate care and treatment for HIV infection, including antiretroviral medications when clinically indicated, and should be under the care of a physician experienced in HIV management. Participants will be eligible regardless of antiretroviral medication (including no antiretroviral medication) provided there is no intention to initiate therapy or the regimen has been stable for at least 4 weeks with no intention to change the regimen within 12 weeks following enrollment.
    e. Patient must have ≤ grade 2 diarrhea (participants with grade 1 diarrhea are eligible provided stool for ova/parasites and stool cryptosporidium studies are negative

8. For patients registering prior to start of chemoradiotherapy, baseline scans must have been completed within 4 weeks prior to registration
9. Patients with an allogenic bone marrow/stem, cell or solid organ transplant are excluded.
10. Women of child bearing potential and sexually active males must use accepted and effective method(s) of contraception and/or abstain from sexual intercourse while on protocol treatment and for at least 5 months after the last dose of nivolumab (for female patients) and for at least 7 months after the last dose of nivolumab (for male patients).
11. Women MUST NOT be pregnant or breast-feeding due to the potential teratogenic harm or abortifacient effects to an unborn fetus and possible risk for adverse events in nursing infants with the treatment regimens being used. All patients must also not expect to conceive or father children from study registration and throughout their time on study treatment. For female patients this must continue until at least 5 months after the last dose of nivolumab and for male patients until at least 7 months after the last dose of nivolumab. All females of child bearing potential must have a serum or urine pregnancy test to rule out pregnancy within 2 weeks prior to registration.
    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 child bearing potential? _____ (Yes or No)
    Date of blood test or urine study: _____
12. Patients will be excluded if they have a T1, T2N0 or M1 cancer
13. Patients must not have had prior potentially curative surgery (abdominal, peritoneal resection) for carcinoma of the anus.
14. Participants may not be receiving any other standard anti-cancer therapy or experimental agent concurrently with the study drugs.
15. Any surgery must have been completed ≥ 4 weeks prior to starting study treatment
16. No 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.
17. Individuals with a history of a different malignancy are ineligible except if they have been disease-free for at least 2 years and are deemed by the investigator to be at low risk for recurrence. Individuals with the following cancers are eligible if diagnosed and treated within the past 5 years: cervical cancer in situ, and basal cell or squamous cell carcinoma of the skin.
18. Patient must not have active autoimmune disease Rev. Add2 in the past 2 years. NOTE: This does not include patients with autoimmune disease controlled by medication, such as hypothyroidism.
19. No prior treatment with an immune checkpoint inhibitor (anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA4 monoclonal antibody)
20. No patients with immunodeficiency or receiving systemic steroid therapy equivalent to > 10 mg prednisone per day or any other form of immunosuppressive therapy within 7 days prior to step 1 registration.. Topical corticosteroid or occasional inhaled corticosteroids are allowed.
21. No live vaccines within 30 days prior to registration. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines and are not allowed.
    **NOTE:** No live vaccines may be administered while participating in the trial

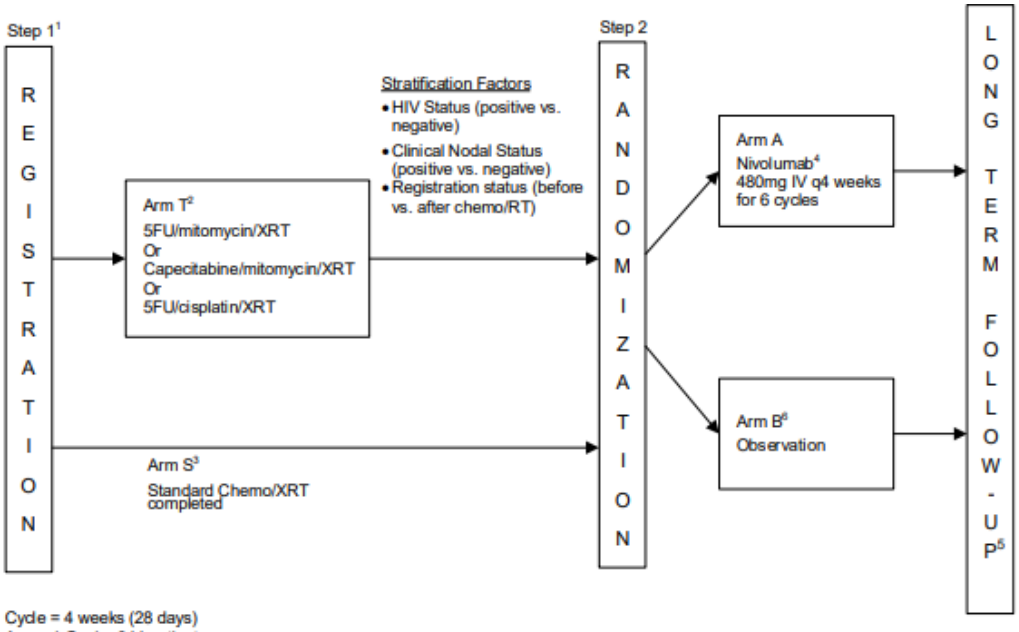
22. Patients must not have known interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity
23. Radiation therapy data are submitted to IROC Rhode Island for quality review. See Section 4.4 for submission requirements.

**Registration to Step 2 Eligibility Criteria**

1. Patients will be registered no sooner than 4 weeks following completion of standard chemoradiation for anal cancer. Standard chemoradiation therapy is as defined in Appendix VII.
2. Patients must have histologically proven stage IIB (T3N0M0 only), IIIA (T2N1M0), IIIB (T4N0M0), or IIIC (T3N1M0, T4N1M0) invasive squamous cell carcinoma of the anus or anorectum, according to the AJCC 8th edition. This may include tumors of non-keratinizing histology such as basoloid, transitional cell, or cloacogenic histology. Individuals with squamous cell carcinoma of the anal margin are eligible if there is evidence of extension of the primary tumor into the anal canal.
3. Patients must not have received less than 54 Gy of radiation for the treatment of the anal cancer.
4. Patients must have ECOG performance status of 0-2.
5. Adequate hematologic function must be documented within 2 weeks prior to registration:
    a. Patients must have hemoglobin levels of > 10g/dL.
    b. Patient must have a platelet count of > 100,000/mm3.
    c. Patient's ANC level must be > 1500/mm3.
    d. Serum creatinine must be ≤ 2 X ULN.
6. Adequate hepatic function must be documented within 2 weeks prior to registration:
    a. Total bilirubin must be < 2 X ULN. AST (SGOT)/ALT (SGPT) ≤ 2.5 X institutional upper limit of normal
    b. Albumin ≥ 3.0 g/dL.
7. Human immunodeficiency virus (HIV) + patients with CD4 > 200 and Serum HIV viral load of < 200 copies/mm3 are permitted.
    a. Participants must be PPD negative. Alternatively, the QuantiFERON-TB Gold In-Tube (QFT-GIT) assay (Cellestis Limited, Carnegie, Australia) can be used. An individual is considered positive for M. tuberculosis infection if the IFN-γ response to TB antigens is above the test cut-off (after subtracting the background IFN-γ response in the negative control). The result must be obtained within 12 weeks prior to enrollment. PPD positive (or Quantiferon assay positive) participants are permitted if prophylaxis has been completed prior to enrollment.
    b. No history of AIDS-related complications within past year other than a history of low CD4+ T-cell count >200/mm3 prior to initiation of combination antiretroviral therapy. On study CD4+ T-cell count may not be informative due to chemoradiotherapy should not be used as an exclusion criterion if low.
    c. Patient must be healthy on the basis of HIV disease with high likelihood of near normal life span were it not for the anal cancer
    d. Participants MUST receive appropriate care and treatment for HIV infection, including antiretroviral medications when clinically indicated, and should be under the care of a physician experienced in HIV management. Participants will be eligible regardless of antiretroviral medication (including no antiretroviral medication) provided there is no intention to initiate therapy or the regimen has been stable for at least 4 weeks with no intention to change the regimen within 12 weeks following enrollment.
    e. Patient must have ≤ grade 2 diarrhea (participants with grade 1 diarrhea are eligible provided stool for ova/parasites and stool cryptosporidium studies are negative).
8. Scans done within 4 weeks of randomization to Step 2
9. Patient must be able to have recovered from all toxicities associated with chemoradiotherapy for anal cancer, to Grade ≤ 1 with the exception of alopecia.

10. Patients with an allogenic bone marrow/stem, cell or solid organ transplant are excluded
11. Women of child bearing potential and sexually active males must use accepted and effective method(s) of contraception and/or abstain from sexual intercourse while on protocol treatment and for at least 5 months after the last dose of nivolumab (for female patients) and for at least 7 months after the last dose of nivolumab (for male patients).
12. Women MUST NOT be pregnant or breast-feeding due to the potential teratogenic harm or abortifacient effects to an unborn fetus and possible risk for adverse events in nursing infants with the treatment regimens being used. All patients must also not expect to conceive or father children from study registration and throughout their time on study treatment. For female patients this must continue until at least 5 months after the last dose of nivolumab and for male patients until at least 7 months after the last dose of nivolumab. All females of child bearing potential must have a serum or urine pregnancy test to rule out pregnancy within 2 weeks prior to registration.
    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 child bearing potential? _____ (Yes or No)
    Date of blood test or urine study: _____
13. Pregnant women are excluded from this study because the study agents have the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk of adverse events in nursing infants secondary to treatment of the mother with the study agents, breastfeeding should be discontinued.
14. Patients must not have had prior potentially curative surgery (abdominal, peritoneal resection) for carcinoma of the anus.
15. Participants may not be receiving any other standard anti-cancer therapy or experimental agent concurrently with the study drugs.
16. No 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.
17. Individuals with a history of a different malignancy are ineligible except if they have been disease-free for at least 2 years and are deemed by the investigator to be at low risk for recurrence. Individuals with the following cancers are eligible if diagnosed and treated within the past 5 years: cervical cancer in situ, and basal cell or squamous cell carcinoma of the skin.
18. No prior treatment with an immune checkpoint inhibitor (anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA4 monoclonal antibody)
19. No prior treatment with an immune checkpoint inhibitor (anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA4 monoclonal antibody)
20. No patients with immunodeficiency or receiving systemic steroid therapy equivalent to > 10 mg prednisone per day or any other form of immunosuppressive therapy within 7 days prior to the first dose of study medication. Topical corticosteroid or occasional inhaled corticosteroids are allowed.
21. No live vaccines within 30 days prior to the first dose of trial treatment and while participating in the trial. Examples of live vaccines include, but are not limited to, the following: measles, mumps, rubella, chicken pox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed; however, intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines and are not allowed.

22. Patients must not have known interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity
23. Patients must not have a history of allergic reactions attributed to compounds of similar chemical or biologic composition to nivolumab.




1. High Risk Anal Cancer: Stage IIB (T3N0M0 only), IIIA (T2N1M0), IIIB (T4N0M0), or IIIC (T3N1M0, T4N1M0) invasive squamous cell carcinoma of the anus or anorectum, according to the AJCC 8th edition. This may include tumors of non-keratinizing histology such as basoloid, transitional cell, or cloacogenic histology. Individuals with squamous cell carcinoma of the anal margin are eligible if there is evidence of extension of the primary tumor into the anal canal. Patients can be registered prior to standard chemo/XRT or after completion of standard chemo/XRT.
2. Per treating physician.
3. Patients are eligible if completed standard chemo/XRT per Section 5.1.1.
4. Maximum of 6 cycles.
5. Patients will be followed for up to 5 years from date of registration.
6. The total duration of observation should not exceed 6 months, at which point the patient will go into Long-term Follow-up.