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

Study Schema

Step 1*

Arm S‡
Standard chemo/XRT completed

Arm T†
5FU/mitomycin/XRT or Capecitabine/mitomycin/XRT or 5FU/cisplatin/XRT

Stratification Factors
• HIV status (positive vs negative)
• Clinical nodal status (positive vs negative)
• Registration status (before vs after chemo/RT)

Step 2

Arm A
Nivolumab§ 480 mg IV q 4 weeks for 6 cycles

Arm B† Observation

Long-term Follow-up

Accrual goal = 200 patients.
Cycle = 4 weeks (28 days).
*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 nonkeratinizing histology such as basaloid, 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.
†Per treating physician.
‡Patients are eligible if completed standard chemo/XRT per Section 5.1.1.
§Maximum of 6 cycles.
¶Patients will be followed for up to 5 years from date of registration.
†The total duration of observation should not exceed 6 months, at which point the patient will go into Long-term Follow-up.
5FU = fluorouracil; XRT = radiotherapy.
Overall EA2165 Study Objective
To examine whether the addition of nivolumab, a monoclonal antibody specific for human programmed death-1 (PD-1) receptor expressed on T cells, after chemoradiation can provide a survival benefit in patients with locally advanced high-risk anal cancer

Study Objectives
Primary Objective
• Evaluate whether therapy with nivolumab following CMT improves disease-free survival (DFS), compared with observation

Secondary Objectives
• Compare nivolumab following CMT with observation regarding
  – Objective response rate (complete [CR] or partial [PR]), stable disease, and progression
  – Severe toxicity interval
  – Colostomy-free survival
  – Overall survival
  – Toxicity

Eligibility Criteria*
Main Inclusion Criteria
Step 1
• ≥ 18 years of age with 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. May include tumors of nonkeratinizing histology, such as basaloid, transitional cell, or cloacogenic histology. Eligible if there is evidence of extension of the primary tumor (squamous cell carcinoma of the anal margin) into the anal canal

*When evaluating patients for this study, please refer to the full protocol for the complete list of eligibility criteria.
• ECOG performance status of 0-2
• Adequate hematologic and hepatic function documented within 2 weeks prior to registration
• HIV positivity with exceptions
• Baseline scans completed within 4 weeks prior to the start of chemoradiation registration
• Surgery completed ≥ 4 weeks prior to starting study treatment
• Use of accepted and effective contraception and/or abstinence

Step 2
• Registered within 63 days following completion of standard chemoradiation for anal cancer

• Received ≥ 54 Gy of radiation to the planning target volume (PTV) for the primary tumor (PTVp) and 45 Gy to PTV for the elective nodal region (PTVn) to treat anal cancer
• Scans completed within 4 weeks of randomization to Step 2
• Recovered from all toxicities associated with chemoradiation for anal cancer to grade ≤ 1, except for alopecia

Main Exclusion Criteria
Step 1
• Arm T: prior chemoradiation for anal cancer
• Allogenic bone marrow/stem cell or solid organ transplant

• T1 or M1, and T2N0 cancer
• Prior potentially curative surgery (abdominal, peritoneal resection) for carcinoma of the anus
• Receiving any other anticancer therapy or experimental agent concurrently with the study drugs
• 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

(Continued)
Main Exclusion Criteria (cont)

- History of a different malignancy except if disease-free for at least 2 years and deemed by the investigator to be at low risk for recurrence. Cervical cancer in situ and basal cell or squamous cell carcinoma of the skin are allowable if diagnosed and treated within the past 5 years.
- Active autoimmune disease in the past 2 years (note: does not include autoimmune disease controlled by medication, such as hypothyroidism).
- Immunodeficiency or receiving Nivolumab 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 or occasional inhaled corticosteroids are allowed.
- Live vaccines within 30 days prior to registration.
- Interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity.
- Pregnancy or breastfeeding.

Step 2

- Allergic reactions attributed to compounds of similar chemical or biologic composition to nivolumab.