## For Patients with Metastatic Anal Cancer

**EA2176 Available Through ECOG-ACRIN Cancer Research Group**

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

### Patient Population

See Section 3.0 for Complete Eligibility Details

- Age ≥ 18 years, ECOG PS ≤ 0-1, adequate lab values
- Must have inoperable, recurrent, or metastatic disease not amenable to curative therapy
- Must have histological/cytological confirmation of anal squamous cell carcinoma (includes basalogef and cloacogenic lesions) from the primary tumor or a newly diagnosed recurrent/metastatic lesion
- Must have measurable disease (RECIST 1.1); based on radiologic assessment < 4 weeks prior to randomization
- Palliative (limited-field) radiation therapy is allowed, as long as the lesion is not a target lesion and the patient is > 7 days from completion from palliative radiation
- Patients with brain metastasis are eligible per protocol
- HIV, HBV, HCV patients are permitted per protocol
- Patients with known history/current symptoms of cardiovascular disease should be NYHA class 2B or better
- Must not have had previous use of systemic chemotherapy or other investigational drugs for the treatment of inoperable recurrent/metastatic anal cancer (see protocol for exceptions)
- Must not have current/recent (within 30 days) treatment with another investigational drug/participation in another investigational study
- Must not have had prior immunotherapy
- Must not have a history of known hypersensitivity reaction to any platinum or taxane-based chemotherapy or monoclonal antibody
- Must not have active/history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including chronic prolonged systemic corticosteroids
- No history/evidence of interstitial lung disease
- No known peripheral neuropathy > grade 1 at the time of randomization
- No live vaccines while on the study

### Treatment Plan

See Section 5.0 for Complete Treatment Details

**Cycle = 28 days**

**Arm A (Control Arm):**
- First, paclitaxel (80 mg/m²) IV Day 1, 8, and 15
- Followed by carboplatin (AUC= 5) IV Day 1
- Repeat cycles every 4 weeks, up to 6 cycles

**Arm B (Investigational Arm):**
- First, nivolumab 240 mg for the first cycle (cycle 1, day 1 and 15) followed by 480 mg IV q4 weeks (cycles ≥ 2 day 1)
- Then, paclitaxel (80 mg/m²) IV Day 1, 8, and 15
- Followed by carboplatin (AUC= 5) IV Day 1
- Repeat cycles every 4 weeks, up to 6 cycles (carboplatin and paclitaxel will be given for 6 cycles, however, nivolumab may continue as single agent therapy until disease progression or intolerance [max of 2 years])

**Notes:**
- Carboplatin doing is based on Calvert formula, using actual body weight for each cycle
- Paclitaxel doing is based on body surface area, using actual body weight
- Nivolumab is a flat dose
- See protocol 5.1.3 for suggested antiemetic therapy

### Patient Enrollment

All Sites: Oncology Patient Enrollment Network (OPEN), [https://open.ctsu.org](https://open.ctsu.org)

### Protocol Information

ECOG-ACRIN Operations-Boston: 857-504-2900, [http://ecog-acrin.org](http://ecog-acrin.org) (Member Login)

Please Enroll Your Eligible Patients!
The image contains a diagram with the following annotations:

- **Randomization Schema**
- **Eligibility Criteria**
- **Key Factors**

**Eligibility Criteria**:
- HIV status (positive vs. negative/unknown)
- Prior history of chemoradiation with curative intent to the primary tumor (yes/no)
- Prior history of adjuvant chemotherapy (yes/no)
- Metastatic squamous cell carcinoma of the anal canal
- Histology or histopathology of recurrent disease if surgically resected
- Histology or histopathology of recurrent disease if surgically unresected
- Number of metastatic deposits
- Prior neoadjuvant chemotherapy (yes/no)
- Prior adjuvant chemotherapy (yes/no)
- Prior radiation therapy (yes/no)
- Prior radiation therapy for recurrent disease (yes/no)
- Prior radiation therapy for metastatic disease (yes/no)
- Prior radiation therapy for both recurrent and metastatic disease (yes/no)

**Key Factors**:
- History of radiotherapy (yes/no)
- History of chemotherapy (yes/no)
- History of surgery (yes/no)
- History of both radiotherapy and chemotherapy (yes/no)
- History of both radiotherapy and surgery (yes/no)
- History of both chemotherapy and surgery (yes/no)
- History of all three (radiotherapy, chemotherapy, and surgery) (yes/no)

**Randomization Schema**:
- Repeat cycle every 4 weeks up to 2 years
  - CAVE 1: NW regimen is given every 2 weeks during cycles 1 to 7
  - CAVE 2: NW regimen will be administered at 24 mg/m² in the first cycle
  - CAVE 3: Pemetrexed and Paclitaxel are given up to 6 cycles (80 mg/m²) on days 1, 8, and 15
  - CAVE 4: NW regimen is given every 4 weeks (24 mg/m²)

**Follow-up**:
- Cycle every 4 weeks up to 10 cycles
- CAVE 1: NW regimen is given every 2 weeks during cycles 1 to 7
- CAVE 2: NW regimen will be administered at 24 mg/m² in the first cycle
- CAVE 3: Pemetrexed and Paclitaxel are given up to 6 cycles (80 mg/m²) on days 1, 8, and 15
- CAVE 4: NW regimen is given every 4 weeks (24 mg/m²)