Version 12/14/21 (Add. #2)

NCI National Clinical Trials Network

EA2183

ECOG-ACRIN cancer research group

For Patients with Oligometastatic HER2(-) EGA

EA2183 Available Through ECOG-ACRIN Cancer Research Group

A Phase III Study of Consolidative Radiotherapy in Patients with Oligometastatic HER2 Negative Esophageal and Gastric Adenocarcinoma (EGA)

Patient Population

See Section 3.0 for Complete Eligibility Details

Registration to Step 1:

- ≥ 18 years of age, ECOG PS 0-1, and adequate lab values
- Must have histologically confirmed HER2(-) metastatic esophageal/gastric adenocarcinoma (AJCC 8th ed.) with known PDL1 CPS expression
- Must have oligometastatic disease diagnosed prior to induction systemic therapy/defined per protocol
  - ◊ 1-3 radiologically visible metastatic lesions (not sites), in addition to the primary site
  - ◊ Anatomically defined lymphadenopathy will be considered as 1 metastatic lesion
  - ◊ No radiologically evident peritoneal metastasis
- No contraindications to 5-FU/capecitabine/oxaliplatin/ leucovorin, or RT (consultation with radiation oncologist); patients who received nivolumab must not have any contraindications to immune checkpoint inhibitors
- Patients who had prior definitive treatment for early stage EGA are eligible as long as recurrent disease developed at least 6 months after prior therapy completion (see protocol for details)
- Major surgery must be completed ≥ 4 weeks prior to Step 1 registration
- No patients with CNS metastasis
- Must not have uncontrolled intercurrent illness (see protocol for details)
- No live vaccines within 4 weeks of Step 1 registration (see protocol for details)

Registration to Step 2:

- Arm A, B, G, H: Must have histologically confirmed HER2 (-) metastatic esophageal/gastric adenocarcinoma with stable disease after 4 cycles of FOLFOX or 6 cycles of CAPOX (Step 1 treatment); Arm S: must have completed 4-5 months of systemic induction therapy per protocol
- No evidence of disease progression since systemic induction treatment initiation (Arm A, B, G, H, S); patients with complete radiologic response are eligible for Step 2

Treatment Plan

See Section 5.0 for Complete Treatment Details

Step 1– Induction Systemic Therapy- Treatment Choice Depends on PDL1 CPS Score (Note ≥ 5 Must Receive Nivolumab):

- **Arm A– FOLFOX:** 4 cycles of FOLFOX (8 doses); administered days 1 and 15 of each 28 day cycle; Oxaliplatin 85 mg/m² IV and leucovorin 200 mg/m² IV, followed by 5-FU bolus 400 mg/m², then continuous 5-FU IV over 46-48 hours for a total of 2400 mg/m²
- **Arm B– CAPOX:** 6 cycles given (each cycle is 21 days); Oxaliplatin 130 mg/m² IV on day 1; Capecitabine 1000 mg/m² orally (2x/day) days 1-14
- **Arm G– FOLFOX + Nivolumab:** FOLFOX (same as Arm A); Nivolumab 480 mg IV day 1
- **Arm H– CAPOX + Nivolumab:** CAPOX (same as Arm B); Nivolumab 360 mg IV day 1
- **Arm S–** 4-5 months of induction systemic therapy received prior to study enrollment (regimens above; no evidence of disease progression), go to Step 2

Step 2– Consolidation Systemic Therapy: Continue to receive the same systemic regimen as Step 1, but be randomized for the addition of consolidative radiation (up to 15 treatment days):

- Arm A/S: **Arm C** (RT followed by FOLFOX) or **D** (continue FOLFOX per Arm A)
- Arm B/S : **Arm E** (RT followed by CAPOX) or **F** (continue CAPOX per Arm B)
- Arm G/S: **Arm I** (RT followed by FOLFOX + Nivolumab) or **J** (continue FOLFOX + Nivolumab)
- Arm H/S: **Arm K** (RT followed by CAPOX + Nivolumab) or **L** (continue CAPOX + Nivolumab)

Radiation Therapy: Administered using external beam photon RT, with 3D-CRT, IMRT, SBRT, or SRS per treating radiation oncologist (dose/fractionation per treating radiation oncologist as well)

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Patient Enrollment

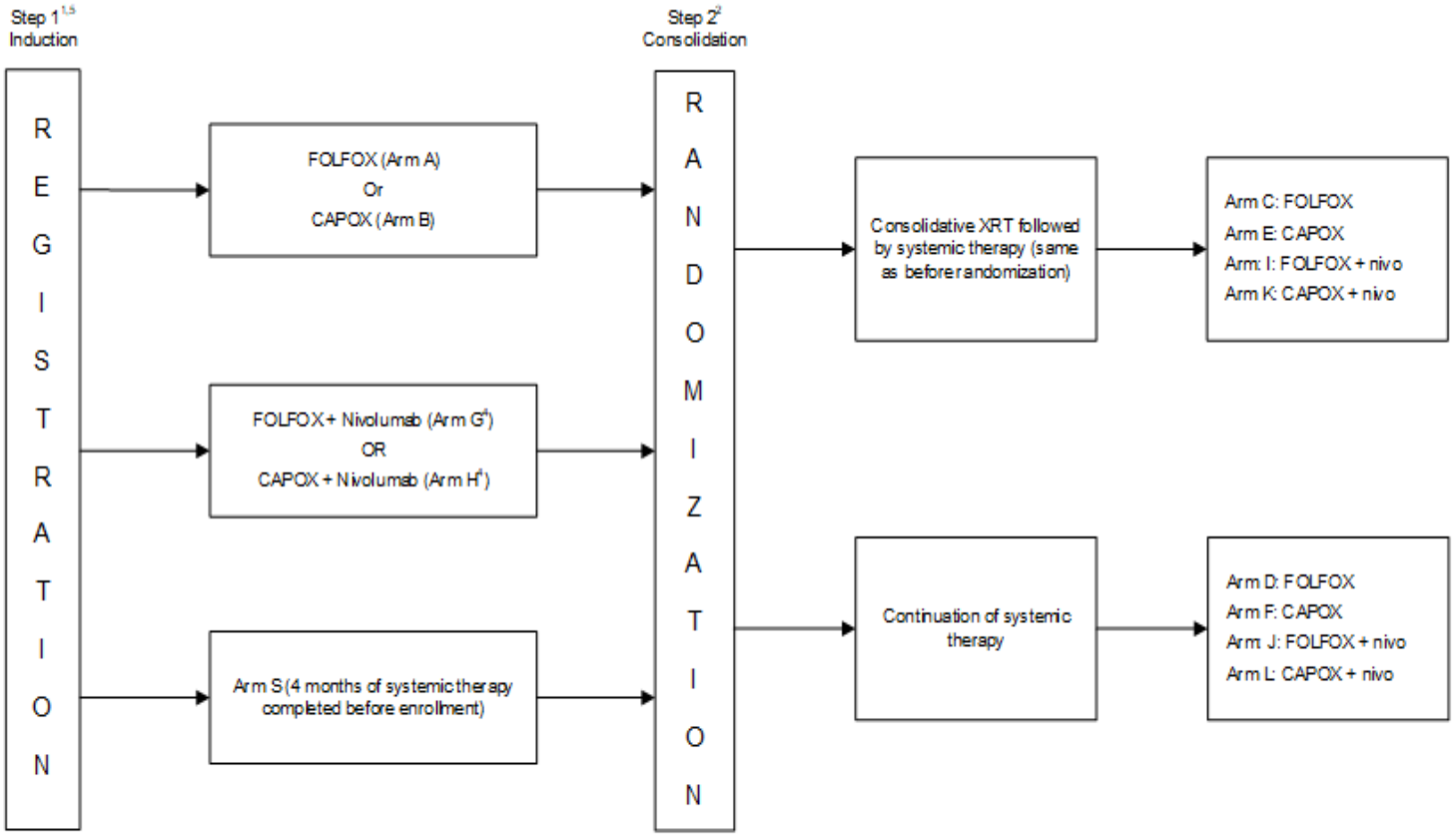
All Sites: Oncology Patient Enrollment Network (OPEN), https://open.ctsu.org

Protocol Information

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

Please Enroll Your Eligible Patients!

EA2183



NOTE: *Consolidation Systemic Therapy as described above in Arms C-F and I-L can continue until disease progression or intolerable toxicities. Treatment will stop after two years if there is no evidence of disease)*

Accrual: Step 1 = 314, Step 2 = 204

FOLFOX Dosing:
Oxaliplatin 85mg/m^2 + Leucovorin 200mg/m^2 at the same time followed by 5-FU 400mg/m^2, followed by continuous infusion 5-FU IV over 46-48 hours for a total dose of 2400mg/m^2 on days 1 and 15 of each cycle.
**Cycle= 28 days. Total 4 cycles.*[6]

CAPOX Dosing:
Oxaliplatin 130mg/m^2 on day 1
Capecitabine 1000 mg/m2 BID on days 1-14.
**Cycle= 21 days. Total 6 cycles.*[6]

Nivolumab Dosing:
For Arms G, I & J: Nivolumab: 480 mg IV on Day 1 of each cycle
**Cycle = 28 days. Total 4 cycles*
For Arms H, K & L: Nivolumab: 360 mg IV on day 1 of each cycle
**Cycle = 21 days. Total 6 cycles*

1. Treatment physician will decide whether to place the patient on a FOLFOX or CAPOX based regimen (Arm A, B, G, or H).
2. Patients with progressive disease during Step 1 will not be randomized and will be removed from the study.
3. Patients are required to have at least a 1 week break between the last dose of Step 1 Induction chemotherapy and the first day of radiation to prevent increased toxicities.
4. Tumors with PDL1 CPS ≥5: nivolumab is mandatory, unless contraindications. Tumors with PDL1 CPS <5: nivolumab use at the discretion of a treating physician.
5. Patients that are registering to the protocol after receiving initial induction treatment (as described in section 5.1.1) will be assigned to Arm S on Step 1 and then will proceed directly to Step 2 randomization.
6. The total number of cycles is applicable to step 1 only. Doses are the same in step 1 and 2.