Cancer Research Consortium
of West Michigan
P: 616.391.1230 | 800.336.6299 | www.crcwm.org

FAST FACTS

EA2183 - A Phase III Study of Consolidative Radiotherapy in Patients with Oligometastatic Esophageal and Gastric Adenocarcinoma

Eligibility criteria

Registration to Step 1: Eligibility Criteria

1. Patient must be ≥ 18 years of age.
2. Patient must have histologically confirmed HER2 negative metastatic esophageal or gastric adenocarcinoma (AJCC 8th edition) with knownPDL1 CPS expression.
3. Patient must have oligometastatic disease at the time of diagnosis of metastatic disease and prior to initiation of induction systemic therapy,which is defined as the following:
    a. One to three (1-3) radiologically visible metastatic lesions (not sites), in addition to the primary site. CT or MRI scanswill be performed for staging purposes. Patients with oligometastatic sites that are only detected with PET/CT will be eligible for participation, as long as radiation planning and administration is feasible after discussion with treating radiation oncologist. Malignant lymph node must be at least 1 cm in size or biopsy proven involved bydisease.
    b. Anatomically defined lymphadenopathy will be considered as 1 metastatic-lesion. For example, 2 enlarged paraaortic lymph nodes will be considered as one lesion, and 2 additional lesions will be allowed to meet protocol definitionof oligometastatic disease. However, if supraclavicular or cervical nodes are involved for distal esophageal tumors orgastric tumors, these are counted separately from intrathoracic nodes. For upper thoracic/cervical esophageal tumors, the involvement of celiac nodes are counted separately from intrathoracic nodes. Intrathoracic nodes, defined as hilar and mediastinal nodes, will be collectively counted as one.
    c. Patients with radiologically evident peritoneal metastasisare not eligible.
4. Patient must have baseline imaging done within 4 weeks prior to Step1 registration. For patients registering to Arm S, scans must demonstrate at least stable disease after induction systemic therapy.
5. Patient must not have any contraindications to 5-FU, capecitabine,leucovorin, or oxaliplatin.
6. Patients who receive(d) nivolumab in addition to chemotherapy mustnot have any contraindications to immune check point inhibitors.
    a. Patient must not have active autoimmune disease that hasrequired systemic treatment within 2 years prior to Step 1 registration. Patients are permitted to receive immunotherapy if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger (precipitating event).
    b. Patient must not have a condition requiring systemic treatment with either corticosteroids (>10 mg/day prednisone equivalents) or other immunosuppressive medications within 14 days prior to Step 1 registration. Inhaled or topical steroids and adrenal replacement doses (≤10 mg/day prednisone equivalent) are permitted.
    c. Patients with prior immune mediated adverse events related to immunotherapy that resulted in permanent treatment discontinuation with these agents are ineligible.
7. Patient must not have any contraindications to radiation therapy based on consultation with a radiation oncologist. Formal radiation oncology evaluation will be required for eligibility purposes. Prior palliative or definitive radiation or chemoradiation to the primary site is allowed. Palliative treatments must be completed at least 2 weeks prior to registration.

8. Patient must have an ECOG performance status 0-1.
9. Patient must not be pregnant or breast feeding due to the potential harm to unborn fetus and possible risk for adverse events in nursinginfants with the treatment regimens being used.

   A patient of child bearing potential must have a serum or urine pregnancy test to rule out pregnancy within 14 days prior to Step 1registration.

   A patient of childbearing potential is defined as anyone, regardless ofsexual orientation or whether they have undergone tubal ligation, whomeets 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 cancertherapy 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).

   Patient of child bearing potential?_____(Yes or No)

   Date of blood test or urine study: _____
10. Patients must not expect to conceive or father children by using accepted and effective method(s) of contraception (both double barrier contraception and birth control pills or implants) or by abstaining from sexual intercourse while on protocol treatment (for allpatients) and continue for 5 months after the last dose of protocol treatment (for patients of child bearing potential). Investigators must counsel all patients on the importance of pregnancy prevention and the implications of an unexpected pregnancy.
11. Patient must have adequate organ function, obtained within 28 daysprior to Step 1 registration, as defined below:

    Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/LANC:_____Date of Test:___

    Hemoglobin (Hgb) ≥ 8 g/dL

    Hgb:___Date of Test:___

    Platelet ≥ 100 x 10^9/L

    Platelet:_____Date of Test:___

    AST/ALT ≤ 3.0 × institutional upper limit of normal (ULN)AST:___Institutional ULN:_____

    Date of Test:___

    ALT:___Institutional ULN:_____ Date of Test:__

    Bilirubin ≤ 1.5 x institutional ULN

    Bilirubin:_____Institutional ULN:_____

Date of Test:___

Serum creatinine ≤ 1.5 x institutional ULN (Cockcroft and Gaultformula)

Serum creatinine_____Date of Test:___

Please refer to Appendix V for the formula to estimate renal functionusing serum creatinine.

Albumin > 2.5 g/dL

Albumin:_____Date of Test:___

12. Patient must be able to understand and willing to sign and date the written voluntary informed consent form prior to any protocol-specificprocedures. 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.
13. Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months areeligible for this protocol and must have CD4 > 200 within 6 months prior to registration.

    NOTE: HIV testing is not required for eligibility.
14. Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety orefficacy assessment of the investigational regimen are eligible for thisprotocol.
15. Patients who had prior definitive treatment for early stage EGA areeligible for participation as long as recurrent disease developed at least 6 months after completion of all prior therapies.
    a. For patients registering to Arms A, B, G or H, patient mustnot have had any prior systemic treatment for metastatic disease.

       NOTE: Patients previously treated with radiosensitizing 5-FU and oxaliplatin will be eligible for participation as long as adequate time has elapsed from past treatments. If treatments were palliative in nature, 2 week washout is required (Section 3.1.6). For prior definitive treatments withcurative intent, recurrent disease must be diagnosed at least 6 months after treatment completion as detailed in Section 3.1.14.

       NOTE: Patients who received systemic chemotherapy or immunotherapy as part of the treatment for their locoregional disease (for example, induction therapy before chemoradiation or adjuvant therapy after resection) are eligible for participation, as long as all definitive therapyhas been completed at least 6 months prior to Step 1 registration.
    b. For patients registering to Arm S, patient must have completed at least 4 months, but not more than 5 months of systemic induction therapy for advanced disease (with CAPOX, FOLFOX, CAPOX plus nivolumab, or FOLFOX plus nivolumab) as defined in Section 5.2.1.
16. Any major surgery must have been completed ≥ 4 weeks prior to Step1 registration.
17. Patients with known CNS metastasis will be excluded from protocolparticipation, regardless of the status of the CNS disease.

18. Patient must not have any uncontrolled intercurrent illness including,but not limited to ongoing or active infection requiring treatment, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
19. Patient must not have had live vaccines within 4 weeks prior to Step 1registration. 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. Patients are permitted to receive inactivated vaccines and any non-live vaccines including those for the seasonal influenza and COVID-19 (Note: intranasal influenza vaccines, such as Flu-Mist® are live attenuated vaccines and are not allowed). If possible, it is recommended to separate studydrug administration from vaccine administration by about a week (primarily, in order to minimize an overlap of adverse events).

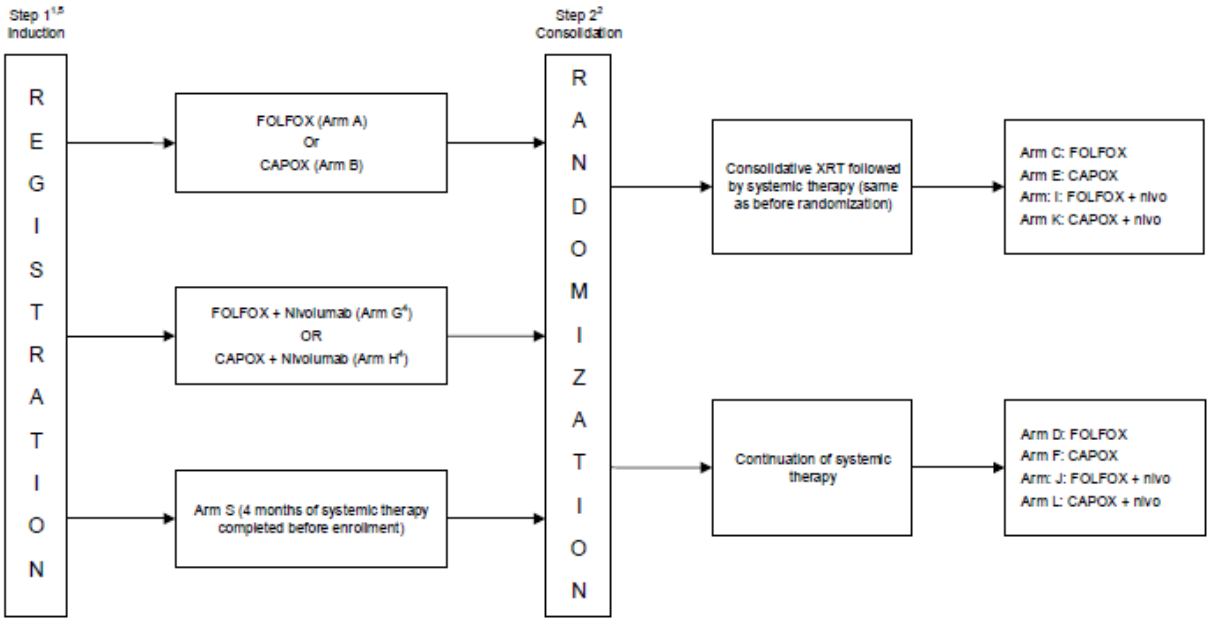
Randomization to Step 2: Eligibility Criteria

1. For patients registered to Arms A, B, G or H on Step 1, the patient must have histologically confirmed HER2 negative metastatic esophageal or gastric adenocarcinoma (AJCC 8th edition) with stabledisease after 4 cycles of FOLFOX or 6 cycles of CAPOX (Step 1 treatment).
   For patients registered to Arm S on Step 1, patients must have completed at least 4 months, but not more than 5 months of systemicinduction therapy for advanced disease (with CAPOX, FOLFOX, CAPOX plus nivolumab, or FOLFOX plus nivolumab), as defined in Section 5.2.1.
2. Patient must have no evidence of disease progression since systemicinduction treatment initiation (all patients on Arms A, B, G, H and S). Imaging must be done within 7 days prior to Step 2 randomization. Patients with complete radiologic response are eligible for Step 2.
3. Patient must have an ECOG performance status 0-1.
4. For patients registered to Arms A, B, G or H on Step 1 must have aserum or urine pregnancy test to rule of pregnancy within 14 days prior to Step 2 randomization.

Schema

Stratification Factors:

- Number of Metastatic Sites: 1 vs >1 at the time of Step 1 Registration
- Choice of Immunotherapy (IO) therapy and PD-L1 CPS Score
  - *Not choosing IO:*
    PD-L1 CPS<5 and not choosing IO at physician discretion vs. CPS ≥ 5 but not choosing IO due to contraindication
  - *Choosing IO Therapy:*
    PDL-1 CPS <5 and choosing IO at physician discretion vs. CPS ≥5 and choosing IO per recommendation
- Enrollment Status: Registering to study before vs. After induction systemic therapy



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.