FAST FACTS

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

Eligibility criteria

i. Patient must be ≥ 18 years of age.

ii. Patient must have histologically confirmed HER2 negative metastatic esophageal or gastric adenocarcinoma (AJCC 8th edition) with knownPDL1 CPS expression.

iii. Patient must have received 3-6 months of first-line systemic therapy for advanced disease within 4 weeks of the date of protocol randomization. Patient must have at least stable disease, with no evidence of disease progression on first-line systemic therapy to be eligible.

iv. Patient must have oligometastatic disease at the time of diagnosis ofmetastatic disease and prior to initiation of the first-line systemic therapy, which is defined as the following:
   1. One to five (1-5) 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. Malignant lymph node mustbe at least 1 cm in short axis or biopsy proven involved bydisease.
   2. Anatomically defined lymphadenopathy will be consideredas 1 metastatic lesion. For example, 2 enlarged paraaorticlymph 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. Intrathoracicnodes, defined as hilar and mediastinal nodes, will be collectively counted as one.
   3. Patients with radiologically evident peritoneal metastasisare not eligible.

v. Patient must have received at least 2 chemotherapy agents during their first-line treatment.

vi. Consultation with radiation oncology must be performed to confirm eligibility. Patient must not have any contraindications to radiation therapy. Prior palliative or definitive radiation or chemoradiation to theprimary site is allowed.

vii. Patient must have an ECOG Performance Status 0-1.

viii. 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.

ix. A patient of childbearing potential must have a serum or urinepregnancy test to rule out pregnancy within 14 days prior to randomization.

x. A patient of childbearing potential is defined as anyone, regardless of sexual orientation

or whether they have undergone tubal ligation, whomeets the following criteria: 1) has achieved menarche at some point,

xi. 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).

xii. Patient must not expect to conceive or father children by using accepted and effective method(s) of contraception or by abstaining from sexual intercourse for the duration of their participation in this study. Patients of childbearing potential must continue contraception measures for 5 months after the last dose of protocol treatment (for patients of childbearing potential). Investigators mustcounsel all patients on the importance of pregnancy prevention and the implications of an unexpected pregnancy.

xiii. Patient must have adequate organ function, obtained within 28 daysprior to randomization, as defined below:

a. Hemoglobin (Hgb) $\geq$ 8 g/dL

   Hgb:_____ Date of Test:_____

b. Platelets $\geq$ 75,000/µL

   Platelets:_____ Date of Test:_____

c. Absolute neutrophil count (ANC) $\geq$ 1.0 10^9/L

   ANC:_____ Date of Test:_____

d. AST/ALT $\leq$ 3.0 × institutional upper limit of normal (ULN)

   AST:_____ Institutional ULN:_____

   Date of Test:_____

   ALT:_____Institutional ULN:_____

   Date of Test:_____

e. Bilirubin $\leq$ 1.5 x institutional ULN (unless suspected Gilbert's disease per treating physician)

   Bilirubin:_____ Institutional ULN:_____

   Date of Test:_____

   Suspected Gilbert's disease? _____ (Yes or No)

f. Serum creatinine $\leq$ 1.5 x institutional ULN or Creatinine Clearance $\geq$ 30 mL/min (estimated using Cockcroft and Gault formula or measured) See Appendix V for calculation information.

   Serum creatinine _____Date of Test:_____

   Institutional ULN:_____

   Creatinine Clearance:_____Date:_____

xiv. 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.

xv. 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.

xvi. 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.

NOTE: Patients previously treated with radio-sensitizing 5-FU andoxaliplatin will be eligible for participation as long as adequate time has elapsed from past treatments. For priordefinitive treatments with curative intent, recurrent diseasemust be diagnosed at least 6 months after treatment completion as detailed in Section 3.1.12.

NOTE: Patients who received systemic chemotherapy or immunotherapy as part of the treatment for their locoregional disease (for example, induction therapy

xvii. 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 developing recurrent disease.

xviii. Any major surgery must have been completed ≥ 4 weeks prior to randomization.

xix. Patient must not have any known CNS metastasis.

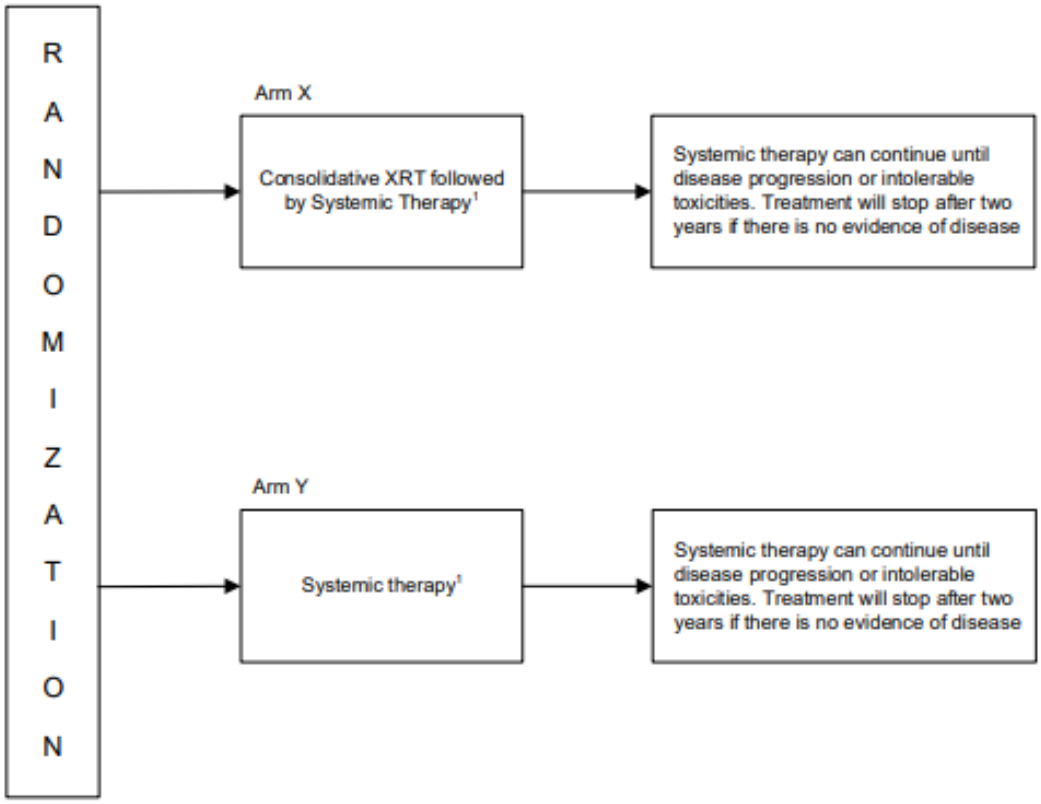
xx. Patient must not have any uncontrolled intercurrent illness including,but not limited to ongoing or active infection requiring treatment, symptomatic congestive heart failure, unstable angina pectoris, clinically significant cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

xxi. Patient must not have had live vaccines within 4 weeks prior to randomization. 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).

Schema

Stratification Factors:

- Number of metastatic sites: 1-2 vs. 3 or more at the time of diagnosis of advanced disease.
- Prior use of anti-PD1 agents (IO) during first-line treatment of advanced disease vs. no prior IO during first-line treatment of advanced disease
- Triplet vs. doublet first-line chemotherapy backbone



N = 216

1. Systemic therapy will consist of standard FDA approved systemic therapy for HER2 negative esophageal and gastric adenocarcinoma as per NCCN guidelines and with the options outlined in Section **5.1**. The selection of the systemic therapy regimen used is at the discretion of the treating physician and in agreement with the patient. Once the regimen has been declared and started, patients may not switch to another regimen option.