

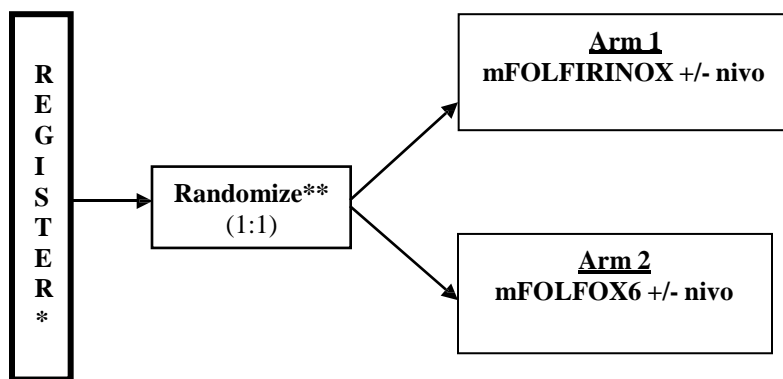
RANDOMIZED PHASE III TRIAL OF mFOLFIRINOX +/- NIVOLUMAB VS. FOLFOX +/- NIVOLUMAB FOR FIRST-LINE TREATMENT OF METASTATIC HER2-NEGATIVE GASTROESOPHAGEAL ADENOCARCINOMA

Eligibility Criteria (see Section 3.0)

- HER2 negative gastroesophageal adenocarcinoma with known PD-L1 CPS
- Measurable disease or non-measurable but evaluable disease as defined by RECIST 1.1
- No prior treatment for metastatic disease (see Section 3.2 for prior neoadjuvant and/or adjuvant therapy parameters)
- Not pregnant and not nursing
- Age \geq 18 years
- ECOG performance status 0 or 1
- Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.
- No allogeneic tissue/organ transplant
- No known Gilbert’s Syndrome or known homozygosity for UGAT1A1 *28 polymorphism
- No grade \geq 2 peripheral neuropathy, neurosensory toxicity, or neuromotor toxicity per CTCAE v5.0 regardless of causality
- No medical condition such as uncontrolled infection, uncontrolled diabetes mellitus or cardiac disease which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- No active autoimmune disease requiring systemic treatment with disease modifying agents or immunosuppressive drugs within 6 months.
- No history of noninfectious pneumonitis requiring steroids

Required Initial Laboratory Values	
ANC	$\geq 1500/\text{mm}^3$
Platelet count:	$\geq 100,000/\text{mm}^3$
Creatinine:	$\leq 1.5 \times$ upper limit of normal (ULN) OR
Calc. creatinine clearance	$\geq 30 \text{ mL/min}$
Total bilirubin:	$\leq 1.5 \times$ ULN
AST/ALT:	$\leq 3 \times$ ULN (< 5 x ULN if clearly attributable to liver metastases)

Schema



* Patients with newly diagnosed advanced unresectable or metastatic HER2 negative gastric, GEJ, esophageal adenocarcinoma

** Stratification: Tumor location (gastric vs GEJ vs esophagus); Measurable disease vs not; planned nivo use vs not; PD-L1 CPS ≥ 5 vs < 5.

Patients will be treated using 14-day cycles until disease progression or discontinuation of treatment for other reasons (e.g. unacceptable adverse events, withdrawal, etc.); oxaliplatin will be given up to 12 cycles.

NOTE: Patients whose tumors have PD-L1 CPS ≥ 5 MUST receive nivolumab on this study; Patients whose tumors have CPS < 5 may receive Nivolumab per treating physician's discretion, unless there are contraindications to immunotherapy use as indicated in [Section 3.2](#)

NOTE: The use of nivolumab in patients with prior exposure to immunotherapy during the course of treatment of early-stage disease will be allowed if the last dose of immunotherapy was at least 1 year from registration to this study.

Treatment is to continue until disease progression or unacceptable adverse event. Patients will be followed for 3 years or until death, whichever comes first.

Please refer to the full protocol text for a complete description of the eligibility criteria and treatment plan.

3.2 Eligibility Criteria

Use the spaces provided to confirm a patient's eligibility by indicating Yes or No as appropriate. It is not required to complete or submit the following page(s).

When calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test were done on a Monday, the Monday one week later would be considered Day 7.

A female of childbearing potential is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 12 consecutive months (i.e., has had menses at any time in the preceding 12 consecutive months).

3.2.1 Documentation of Disease:

Histologic Documentation: HER2 negative adenocarcinoma as defined by ASCO CAP Guidelines (Bartley et al., JCO 2017) with known PD-L1 CPS (Any CPS is allowed, but should be known prior to registration)

Stage: unresectable or metastatic

Tumor Site: esophagus, gastroesophageal junction, or stomach

3.2.2 Measurable disease or non-measurable but evaluable disease as defined by RECIST 1.1.

3.2.3 Prior Treatment

- No prior treatment for unresectable or metastatic disease.
- Prior neoadjuvant or adjuvant cytotoxic chemotherapy or adjuvant immunotherapy is allowed as long as it was completed at least 1 year prior to registration.

3.2.4 Not pregnant and not nursing, because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects.

Therefore, for women of childbearing potential only, a negative serum or urine pregnancy test done ≤ 7 days prior to registration is required.

Absolute Neutrophil Count (ANC)	$\geq 1,500/\text{mm}^3$
Platelet Count	$\geq 100,000/\text{mm}^3$
Creatinine	$\leq 1.5 \times$ upper limit of normal (ULN) OR
Calc. Creatinine Clearance	$\geq 30 \text{ mL/min}$
Total Bilirubin	$\leq 1.5 \times$ ULN
AST and ALT	$\leq 3 \times$ ULN
3.2.5	Age > 18 years.
3.2.6	(in patients with liver metastasis: $\leq 5 \times$ ULN if clearly attributable to liver metastases)
3.2.6	ECOG Performance Status 0 or 1

3.2.8 Comorbid conditions Required Initial Laboratory Values:

- Patients with a prior or concurrent malignancy whose natural history or treatment does not have the potential to interfere with the safety or efficacy assessment of the investigational regimen are eligible for this trial.
- Patients positive for HIV are eligible only if they meet all of the following:
 - On effective anti-retroviral therapy
 - Undetectable HIV viral load by standard clinical assay ≤ 6 months of registration

- No known Gilbert's Syndrome or known homozygosity for UGAT1A1*28 polymorphism
- No baseline grade ≥ 2 peripheral neuropathy, neurosensory toxicity, or neuromotor toxicity per CTCAE v5.0 regardless of causality
- No medical condition such as uncontrolled infection or uncontrolled diabetes mellitus which, in the opinion of the treating physician, would make this protocol unreasonably hazardous for the patient.
- Patients with known history or current symptoms of cardiac disease, or history of treatment with cardiotoxic agents, should have a clinical risk assessment of cardiac function using the New York Heart Association Functional Classification. To be eligible for this trial, patients should be class 2B or better.
- No untreated, symptomatic brain metastasis. Patients with treated brain metastases are eligible if the following criteria are met: 1) follow-up brain imaging done at least in 4 weeks after central nervous system (CNS)-directed therapy shows no evidence of progression and 2) the patient no longer requires steroids, or is on a stable steroid dose for more than four weeks.
- No allogeneic tissue/organ transplant
- Patients who will receive nivolumab in addition to chemotherapy must not have any contraindications to immune checkpoint inhibitors
 - Patients must not have active autoimmune disease that has required systemic treatment within 6 months prior to registration. Patients are permitted to receive immunotherapy if they have vitiligo, type I diabetes, 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).
 - Patients must not have a condition requiring systemic treatment with either corticosteroids ($>10\text{mg/day}$ prednisone equivalents) or other immunosuppressive medications within 14 days prior to registration. Inhaled or topical steroids and adrenal replacement doses ($\leq 10\text{mg/day}$ prednisone equivalent) are permitted.
 - Patients must not have a history of noninfectious pneumonitis requiring steroids
 - Patients with prior immune mediated adverse events related to immunotherapy that resulted in permanent treatment discontinuation with these agents are ineligible.

3.2.9 Language

This study includes the use of the mandatory patient completed measure, PRO-CTCAE. For this study the PRO-CTCAE is available in English, Spanish, Korean, Chinese (Simplified), and Russian, hence patients must be able to speak, understand and read in these languages. Ad-hoc translation of patient-reported measures is not permitted.