Cancer Research Consortium of West Michigan
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FAST FACTS

EA2212: A Randomized Phase II Study of Perioperative Atezolizumab +/- Chemotherapy in Resectable MSIH/dMMR Gastric and Gastroesophageal Junction (GEJ) Cancer.

ELIGIBILITY CRITERIA

1. Patient must be ≥ 18 years of age.

2. Patient must have histologically or cytologically confirmed diagnosis of gastric or gastroesophageal junction adenocarcinoma that is MSIH/dMMR (microsatellite instability-high/mismatch repair deficient) as determined by one of three methods:

   2.1 Deficient DNA Mismatch Repair Protein (MMR) Expression Status: MMR status must be assessed by immunohistochemistry (IHC) for MMR protein expression (MLH1, MSH2, MSH6, PMS2) where loss of one or more proteins indicates dMMR. dMMR may be determined either locally or by site-selected reference lab by CLIA-certified assay.

   NOTE: Loss of MLH1 and PMS2 commonly occur together.

   2.2 Polymerase chain reaction (PCR) determined microsatellite instability.

   2.3 MSI-H tumor status determined by next-generation sequencing.

3. Patient must have previously untreated localized gastric, or Siewert type II or III GEJ (gastroesophageal junction) adenocarcinoma. Tumors must be staged as T2 or greater primary lesion or be any T stage with the presence of positive locoregional lymph nodes- N+ (clinical nodes) without evidence of metastatic disease.
   - Siewert Type II tumors: tumors located between 1 cm proximal and 2 cm distal to the GEJ.
   - Siewert Type III tumors: tumors located between 2 and 5 cm distal to GEJ.

4. Patient must be amenable to surgical resection with therapeutic intent.

5. Patient must have an ECOG Performance Status 0-2.

6. Patient must demonstrate adequate organ and marrow function as defined below (these labs must be obtained ≤ 14 days prior to randomization):

   - Absolute neutrophil count (ANC) ≥ 1,500/mcL

ANC:_____ Date of Test:_____

- Platelets ≥ 100,000/mcL
  Platelets:_____ Date of Test:_____

- Hemoglobin ≥ 9 g/dL
  Hemoglobin:_____ Date of Test:_____

- Total bilirubin ≤ 1.5 x institutional upper limit of normal (ULN) OR Direct bilirubin ≤.ULN (for patients with total bilirubin > 1.5 x ULN)
  Total Bilirubin:_____ Institutional ULN:_____
  Direct Bilirubin:_____Institutional ULN:_____
  Date(s) of Test(s):_____

- AST(SGOT)/ALT(SGPT): × ≤3 institutional ULN
  AST:_____ Institutional ULN:_____
  Date of Test:_____
  ALT: _____Institutional ULN:_____

- Creatinine ≤ 1.5 x institutional ULN OR glomerular filtration rate (GFR) > 50mL/min/1.73m2
  Creatinine: _____ Institutional ULN:_____
  Date of Test:_____
  GFR:_____ Date of Test:_____

- Albumin ≥ 2.5 g/dL
  Albumin:_____ Date of Test:_____

- International Normalized Ratio (INR) OR Prothrombin Time (PT) < 1.5 x ULN (unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants)
  INR:_____ Institutional ULN:_____
  Date of Test:_____
  PT:_____ Institutional ULN:_____
  Date of Test:_____
  Patient on anticoagulants? _____ (Yes or No)

- Activated Partial Thromboplastin Time (aPTT) < 1.5 x ULN (unless patient is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants)
  aPTT:_____ Institutional ULN:_____

Date of Test:_____
Patient on anticoagulants? _____ (Yes or No)

7. Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

8. Patient must have no contraindications to receive one of the chemotherapy regimens: FLOT or mFOLFOX / CAPOX.

9. Patient must not have had prior potentially curative surgery for carcinoma of the stomach/GEJ.

10. Patient must not receive any other standard anti-cancer therapy or experimental agent concurrently with the study drugs.

11. Patient must have recovered from clinically significant adverse events of their most recent therapy/intervention prior to randomization.

12. 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.

13. 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.

14 Patient must have chest/abdomen/pelvis CT completed within 4 weeks prior to randomization.

15 Patient may not have received prior treatment with an immune checkpoint inhibitor (anti-PD-1, anti-PDL-1, anti-PDL-2, anti-CTLA4 monoclonal antibody).

16 Patient must not have received any live vaccines within 30 days prior to randomization and while participating in the study. 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 study drug administration from vaccine administration by about a week (primarily, in order to minimize an overlap of adverse events.

17. Patient must not have active autoimmune disease or history of autoimmune disease that might recur, which may affect vital organ function or require immune suppressive treatment including systemic corticosteroids. These include but are not limited to patients with a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain- Barre syndrome, myasthenia gravis; systemic autoimmune disease such as SLE, connective tissue disease, scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis and hepatitis. Patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome are ineligible because of the risk of recurrence or exacerbation of disease. Patients with vitiligo, endocrine deficiencies including thyroiditis managed with replacement hormones including physiologic corticosteroids are eligible. Patients with rheumatoid arthritis and other arthropathies, Sjogren's syndrome and psoriasis controlled with topical medication and patients with positive serology, such as antinuclear antibodies (ANA), anti-thyroid antibodies should be evaluated for the presence of target organ involvement and potential need for systemic treatment but otherwise are eligible. Patients are permitted to enroll 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).

18. Patients must not be receiving systemic steroid therapy equivalent to > 10 mg prednisone per day or any other form of immunosuppressive therapy within 7 days prior to randomization. Topical corticosteroid or occasional inhaled corticosteroids are allowed.

19. Patient must not have known interstitial lung disease that is symptomatic or may interfere with the detection or management of suspected drug-related pulmonary toxicity, and must not have a known history of prior pneumonitis requiring treatment with steroids, or any evidence of active, non-infectious pneumonitis.

20. Patient must not have a known history of active TB (Bacillus Tuberculosis)

21. Patient must not have any hypersensitivity to Atezolizumab or any of

its excipients.

22. Patient must not have received any prior chemotherapy, targeted small molecule therapy, or radiation therapy for their MSI-H/dMMR gastric and GEJ cancer.

23. Patient must not have had an allogenic bone marrow/stem, cell or solid organ transplant.

24. Patient must not have a history or current evidence of any condition (e.g., known deficiency of the enzyme dihydropyrimidine dehydrogenase [DPD]), therapy, or laboratory abnormality that might confound the results of the trial, interfere with the patient's participation for the full duration of the trial, or is not in the best interest of the patient to participate, in the opinion of the treating investigator.

25. Patient must not have any condition that would interfere with the cooperation with the requirements of this trial.

26. Patient must not be pregnant or breast-feeding due to the potential harm to an unborn fetus and possible risk for adverse events in nursing infants with the treatment regimens being used.
All patients of childbearing potential must have a blood test or urine study within 14 days prior to randomization to rule out pregnancy.
A patient of childbearing potential is defined as anyone, regardless of sexual orientation or whether they have undergone tubal ligation, who meets 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 cancer therapy 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: _____

27. Patient must not expect to conceive or father children by using accepted and effective method(s) of contraception or by abstaining from sexual intercourse while on protocol treatment. Patients of childbearing potential must continue contraception measures for 5 months after the last dose of atezolizumab and for 9 months after the last dose of chemotherapy. Male patients with partners of

childbearing potential must continue contraception measures for 6 months after the last dose of chemotherapy. Patients of childbearing potential must also not breastfeed while on treatment and for 5 months after the last dose of atezolizumab and for 3 months after the last dose of chemotherapy.

28. Patient must have the ability to understand and the willingness to sign a written informed consent document. 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.

29. For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, ifindicated.

30. Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment, they are eligible if they have an undetectable HCV viral load.

31. The investigator must declare the chemotherapy regimen their patient will receive (FLOT or mFOLFOX / CAPOX) prior to randomization.

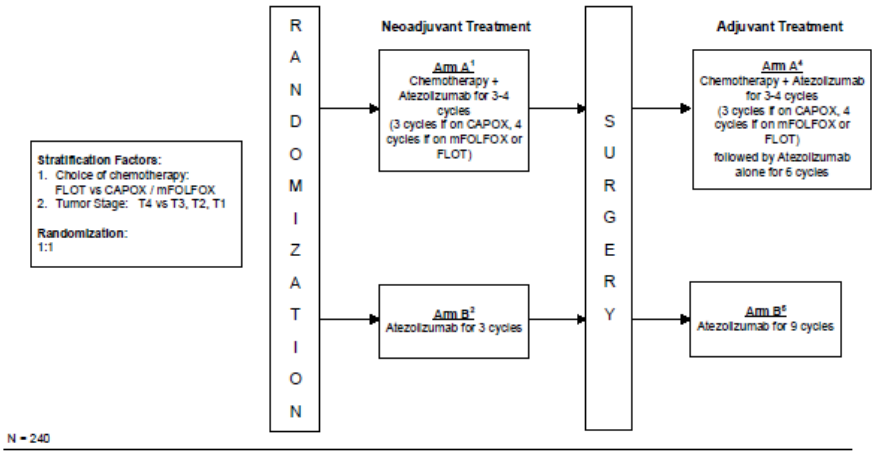
Chemotherapy Regimen selected: _____

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

Schema



1. Arm A Neoadjuvant: Prior to randomization, the treatment physician must select one of the following chemotherapy regimens outlined below (see Section 5.2 for detailed administration guidelines).

   Arm A Option 1 FLOT: Day 1 Docetaxel 50 mg/m^2 IV, Oxaliplatin 85 mg/m^2 IV, Leucovorin 200 mg/m^2 IV, Fluorouracil (5-FU) 2600 mg/m^2 IV continuous infusion over 24 hours, Atezolizumab 840mg mg IV. Repeat cycle every 14 days for 4 cycles.

   Arm A Option 2 mFOLFOX: Day 1 Oxaliplatin 85 mg/m^2 IV, Leucovorin 400 mg/m^2 IV, Fluorouracil (5-FU) bolus of 400 mg/m^2 followed by Fluorouracil (5-FU) 2400 mg/m^2 IV continuous infusion over 46 hours, Atezolizumab 840mg mg IV. Repeat cycle every 14 days for 4 cycles.

   Arm A Option 3 CAPOX: Day 1 Oxaliplatin 130 mg/m^2 IV infusion and Atezolizumab 1200mg IV; Capecitabine 1000 mg/m^2 twice a day by mouth on Days 1-14 of each cycle. Repeat cycle every 21 days for 3 cycles.

2. Arm B Neoadjuvant: Day 1 Atezolizumab 1200 mg IV. Repeat cycle every 21 days for 3 cycles.

3. Surgery: Refer to Section 5.2.4 for details for those patients that do not go on to surgery

4. Arm A Adjuvant: The same regimen used in the neoadjuvant setting will be used in the adjuvant setting. Repeat cycle every 14 days for 4 cycles for FLOT +Atezolizumab or mFLOFOX + Atezolizumab and repeat cycle every 21 days for 3 cycles for CAPOX + Atezolizumab. After adjuvant Chemotherapy + Atezolizumab is complete, patient will receive Atezolizumab 1200mg mg IV alone for 6 cycles.

5. Arm B Adjuvant: Day 1 Atezolizumab 1200 mg IV. Repeat cycle every 21 days for 9 cycles.