Cancer Research Consortium of West Michigan
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FAST FACTS

ALLIANCE A021502 - RANDOMIZED TRIAL OF STANDARD CHEMOTHERAPY ALONE OR COMBINED WITH ATEZOLIZUMAB AS ADJUVANT THERAPY FOR PATIENTS WITH STAGE III COLON CANCER AND DEFICIENT DNA MISMATCH REPAIR
(ATOMIC: Adjuvant Trial of Deficient Mismatch Repair in Colon Cancer)

On Study Guidelines

1. This clinical trial can fulfill its objectives only if patients appropriate for this trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. Physicians should consider the risks and benefits of any therapy, and therefore only enroll patients for whom this treatment is appropriate.
2. Physicians should consider whether any of the following may render the patient inappropriate for this protocol:
   a. Psychiatric illness which would prevent the patient from giving informed consent.
   b. 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.
   c. Patients with a "currently active" second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are free of disease for ≥ 3 years, had a gastric or bowel carcinoid < 1 cm, or DCIS /LCIS of the breast without invasive cancer, or endometrial dysplasia/carcinoma in situ.
   d. Patients are not considered to have a "currently active" malignancy if they had a sebaceous neoplasm (sebaceous adenoma, sebaceous epithelioma, sebaceous adenocarcinoma, keratoacanthoma, and squamous cell carcinoma) that was noninvasive.

   In addition:

   Women and men of reproductive potential should agree to use an appropriate method of birth control throughout their participation in this study due to the teratogenic potential of the therapy utilized in this trial. Appropriate methods of birth control include abstinence, oral contraceptives, implantable hormonal contraceptives, or double barrier method (diaphragm plus condom). For women, birth control should begin at least 28 days prior to the start of therapy and continue for 5 months after completion of therapy. For men, birth control should begin prior to registration and continue for 5 months after completion of therapy.

Eligibility Criteria

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.

1. Documentation of Disease
   - Histologically proven stage III colon adenocarcinoma (any T [Tx, T1, T2, T3, or T4], N1-2M0; includes N1C). Tumors must be deemed to originate in the colon including tumors that extend into/involve the small bowel (e.g. those at the ileocecal valve).
   - DNA Mismatch Repair (MMR) Status: Presence of deficient (d) DNA mismatch repair (dMMR). 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.
   - Note: loss of MLH1 and PMS2 commonly occur together.

   FFPE tumor tissue is required for subsequent retrospective central confirmation of dMMR status. Patients with testing that did not show dMMR (loss of MMR protein) are not eligible to participate. Patients whose tumors show MSI-H by PCR-based assay are not eligible to participate unless they also have MMR testing by IHC and are found to have dMMR (i.e. loss of one or more MMR proteins).

   Patients who are known to have Lynch Syndrome and have been found to carry a specific germline mutation in an MMR gene (*MLH1*, *MSH2*, *MSH6*, *PMS2*) are eligible to participate.

2. Disease Status
   - Tumors must have been completely resected. In patients with tumor adherent to adjacent structures, en bloc R0 resection must be documented in the operative report or otherwise confirmed by the surgeon. Near or positive radial margins are acceptable so long as en bloc resection was performed. Proximal or distal margin positivity is not permitted.
   - Entire tumor must be in the colon (rectal involvement is an exclusion). Surgeon confirmation that entire tumor was located in the colon is required only in cases where it is important to establish if the tumor is a colon vs. rectal primary. . Patients with more than one primary colon adenocarcinoma are eligible if the qualifying stage III tumor is confined to the colon, and not rectum, and the other cancers of lower stage are removed in the en bloc R0 resection.
   - Based upon the operative report and other source documentation, the location of the primary tumor will be categorized as proximal or distal to the splenic flexure (included with distal), and further categorization will be as follows: cecum/ascending, transverse, descending, sigmoid colon, or rectosigmoid colon.
   - No evidence of residual involved lymph node disease or metastatic disease at the time of registration based on clinician assessment of imaging. The treating physician will determine if incidental lesions on imaging require workup to exclude metastatic disease. If based on review of images, the treating physician determines the patient to be stage III, then the patient is eligible.
3. Prior Treatment
   - No prior medical therapy (chemotherapy, immunotherapy, biologic or targeted therapy) or radiation therapy for the current colon cancer except for one cycle of mFOLFOX6. Cycle 1 of mFOLFOX6 must have been administered per Appendix III.
4. Age ≥ 18 years
5. ECOG Performance Status ≤ 2
6. Not Pregnant and Not Nursing
   - This study involves: 1) an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown; and 2) an agent that has known genotoxic, mutagenic, and teratogenic effects.
   - Therefore, for women of childbearing potential only, a negative pregnancy test done ≤ 7 days prior to registration is required.
   - 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).
7. Required Initial Laboratory Values:
   - Absolute Neutrophil Count (ANC) ≥ 1500 mm3
   - Platelet Count ≥ 100,000 mm3*
   - Creatinine ≤ 1.5 x upper limit of normal (ULN)

   or

     Calculated Creatinine Clearance ≥45 mL/min**
   - Total Bilirubin ≤ 1.5 x upper limit of normal (ULN)***
   - AST / ALT ≤ 2.5 x upper limit of normal (ULN)
   - TSH WNL****

   * Platelets ≥ 75,000 required for patients who received Cycle 1 of mFOLFOX6 prior to registration
   ** By Cockcroft-Gault equation
   *** Except in the case of Gilbert disease
   **** Supplementation is acceptable to achieve a TSH WNL. In patients with abnormal TSH, if Free T4 is normal and patient is clinically euthyroid, patient is eligible.
8. Comorbid Conditions

- No active known autoimmune disease, including colitis, inflammatory bowel disease (i.e. ulcerative colitis or Crohn's disease), rheumatoid arthritis, panhypopituitarism, adrenal insufficiency.

- No known active hepatitis B or C.

a. Active Hepatitis B can be defined as:
   - HBsAg detectable for > 6 months;
   - Serum HBV DNA 20,000 IU/ml (105 copies/ml); lower values 2,000-20,000 IU/ml (104-105 copies/ml) are often seen in HBeAg-negative chronic hepatitis B;
   - Persistent or intermittent elevation in ALT/AST levels;
   - Liver biopsy showing chronic hepatitis with moderate or severe necroinflammation.

b. Active Hepatitis C can be defined as:
   - Hepatitis C AB positive, AND
   - Presence of HCV RNA

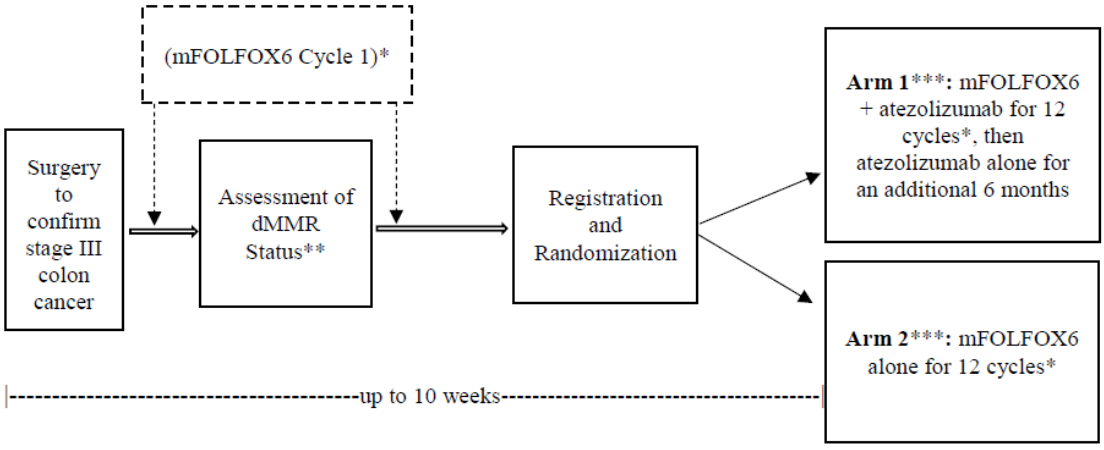
Excluded if known active pulmonary disease with hypoxia defined as:
- Oxygen saturation < 85% on room air, or
- Oxygen saturation < 88% despite supplemental oxygen

No grade ≥ 2 peripheral motor or sensory neuropathy.

Patients positive for HIV are eligible only if they meet all of the following:
- A stable regimen of highly active anti-retroviral therapy (HAART)
- No requirement for concurrent antibiotics or antifungal agents for the prevention of opportunistic infections
- A CD4 count above 250 cells/mcL, and an undetectable HIV viral load on standard PCR-based tests

9. Concomitant Medications
   - No other planned concurrent investigational agents or other tumor directed therapy (chemotherapy, radiation) while on study.
   - No systemic daily treatment with either corticosteroids (>10 mg daily prednisone equivalents) or other immunosuppressive medications within 7 days of registration.
10. Allergies
   - No known history of severe allergic anaphylactic reactions to chimeric, human or humanized antibodies, or fusion proteins.
   - No known hypersensitivity to CHO cell products or any component of the atezolizumab formulation.
   - No known allergy to 5-fluorouracil, oxaliplatin, or leucovorin.

Schema



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