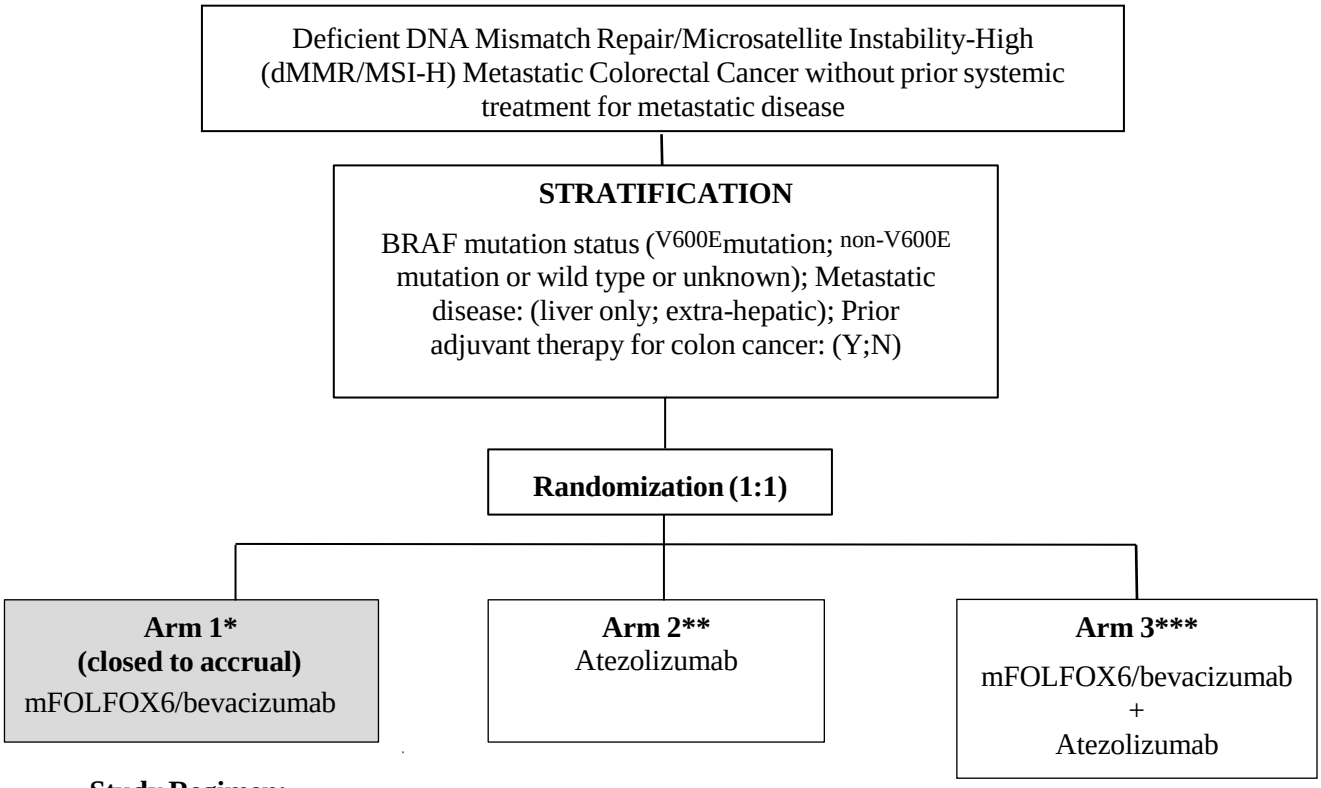
Figure 1. NRG-GI004/SWOG-S1610

NOTE: Arm 2 had been closed to accrual inAmendment #5. With Amendment #6, Arm 2 is restored to accrual and Arm 1 is closed.



Study Regimen:

*** Arm 1:** ***mFOLFOX6/bevacizumab until disease progression. Discontinue oxaliplatin after Cycle 10 (1 cycle = 2 weeks***)

- Oxaliplatin 85 mg/m^2 IV + leucovorin 400 mg/m^2 IV + bevacizumab 5 mg/kg IV+ 5-FU 400 mg/m^2 IV bolus on Day 1 followed by 5-FU 2400 mg/m^2 IV over 46 hours (Days 1 and 2)
- In the event of unacceptable toxicity without disease progression, including grade ≥ 3 neuropathy, individual components of mFOLFOX6/bevacizumab may be discontinued at the physician's discretion. All other components of mFOLFOX6/bevacizumab may be continued at their current dose and schedule.

**** Arm 2:** ***Atezolizumab monotherapy until disease progression and/or unacceptable toxicity or up to and including a maximum of 48 cycles (1 cycle = 2 weeks)***

- Atezolizumab 840 mg IV on Day 1 of every cycle

*****Arm 3:** ***mFOLFOX6/bevacizumab/atezolizumab until disease progression. Discontinue oxaliplatin after Cycle 10; discontinue atezolizumab after Cycle 48 (1 cycle = 2 weeks)***

- mFOLFOX6/bevacizumab same as Arm 1 + atezolizumab 840 mg IV on Day 1 of every cycle
- In the event of unacceptable toxicity without disease progression, including grade ≥ 3 neuropathy, individual components of mFOLFOX6/bevacizumab/atezolizumab may be discontinued at the physician's discretion. All other components of mFOLFOX6/bevacizumab/ atezolizumab may be continued at their current dose and schedule.

Note: *At disease progression, study therapy will be discontinued. Further treatment is at the investigator's discretion; however, patients will continue to be followed for survival.*

3.1 PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Clinical Coordinating Department (CCD).

Investigators also should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

Submission of blood and archived tumor tissue (FFPE) for biobanking and exploratory analyses is optional for the patient.

Investigators should check with their site Pathology department regarding release of tissue before approaching patients about participation in the trial. (See details of tumor tissue and blood sample submissions in Section 10.0).

3.2 Eligibility Criteria

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

3.1.1 The patient must have signed and dated an IRB-approved consent form that conforms to federal and institutional guidelines.

3.2.2 Age ≥ 18 years

3.2.3 ECOG Performance Status of 0, 1 or 2 (see Appendix A).

3.2.4 Diagnosis of metastatic adenocarcinoma of colon or rectum without previous chemotherapy or any other systemic therapy for metastatic colorectal cancer.

3.2.5 Tumor determined to be mismatch-repair deficient (dMMR) by CLIA-certified immunohistochemical (IHC) assay ***with a panel of all four IHC markers, including MLH1, MSH2, PMS2, and MSH6. Alternatively,*** MSI-H diagnosed by ***polymerase chain reaction (PCR)-based assessment of microsatellite alterations*** (either Bethesda markers or Pentaplex panel) or by next-generation sequencing (NGS) are eligible

3.2.6 Documentation by PET/CT scan, CT scan, or MRI that the patient has measurable metastatic disease per RECIST 1.1.

3.2.7 No immediate need for surgical intervention for the primary tumor or palliative diversion/bypass.

3.2.8 Adequate hematologic function based on the most recent test results obtained within 28 days prior randomization and defined as follows:

- ANC must be ≥ 1500/mm^3;
- Platelet count must be ≥ 100,000/mm^3; and
- Hemoglobin must be ≥ 8 g/dL.

3.2.9 Adequate hepatic function based on the most recent test results obtained within 28 days prior randomization and defined as follows:

- total bilirubin must be ≤ 1.5 x ULN (upper limit of normal) for the lab unless the patient has a bilirubin elevation > 1.5 x ULN to 3 x ULN due to Gilbert disease or similar syndrome involving slow conjugation of bilirubin; *and*
- alkaline phosphatase must be ≤ 2.5 x ULN for the lab *with the following exception*: patients with documented liver metastases or bone involvement – alkaline phosphatase must be ≤ 5 x ULN ; *and*

- AST and ALT must be ≤ 3 x ULN for the lab *with the following exception:* for patients with documented liver metastases, AST and ALT must be ≤ 5 x ULN.

3.2.10 Adequate renal function based on test results obtained within 28 days prior to randomization and defined as serum creatinine ≤ 1.5 x ULN for the lab or measured (24 hour urine collection) or calculated creatinine clearance ≥ 30 mL/min (see Appendix B for instructions regarding calculation of creatinine clearance).

3.2.11 A urine sample tested for proteinuria by either the dipstick method, urinalysis (UA), ***or*** a urine protein creatinine (UPC) ratio:

- the dipstick method must indicate 0-1+ protein. If dipstick reading is ≥ 2+, a 24-hour urine must be done and it must demonstrate < 1.0 g of protein per 24 hours (see Appendix B for instructions regarding calculation of urine protein creatinine ratio).
- A urine protein creatinine (UPC) ratio must be < 1.0. If the UPC ratio is ≥ 1.0 a 24-hour urine must be done and it must demonstrate < 1.0 g of protein per 24 hours (See Appendix B for instructions regarding calculation of urine protein creatinine (UPC) ratio).
- Urinalysis must indicate <30 mg/dl. If urinalysis ≥ 30 mg/dl, a 24-hour urine must be done and it must demonstrate < 1.0 g of protein per 24 hours.

3.2.12 International normalized ratio of prothrombin time (INR) and prothrombin time (PT) must be ≤ 1.5 x ULN for the lab within 28 days before randomization. Patients who are therapeutically treated with an agent such as warfarin may participate if they are on a stable dose and no underlying abnormality in coagulation parameters exists per medical history, regardless of PT/INR results.

3.2.13 Pregnancy test done within 14 days prior randomization must be negative (for women of childbearing potential only). Pregnancy testing should be performed according to institutional standards.

Administration of atezolizumab or mFOLFOX6/bevacizumab/atezolizumab may have an adverse effect on pregnancy and poses a risk to the human fetus, including embryo-lethality. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately.

Women of child-bearing potential and men must agree to use adequate contraception methods that result in a failure rate of < 1% per year during the treatment period (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation, and for 5 months (150 days) after the last dose of atezolizumab, 6 months after the last dose of bevacizumab, and 6 months after the last dose of mFOLFOX6.

A woman is considered to be of childbearing potential if she is not postmenopausal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), and has not undergone surgical sterilization (removal of ovaries and/or uterus).

Examples of contraceptive methods with a failure rate of < 1% per year include: bilateral tubal ligation; male partner sterilization; intrauterine devices.

The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical study and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not acceptable methods of contraception. Men must refrain from donating sperm during this same period.

3.3 **Ineligibility Criteria**

Patients with one or more of the following conditions are NOT eligible for this study.

3.2.1 Patients with CNS metastases are excluded, with the following exceptions:

- Patients with asymptomatic untreated CNS metastases may be enrolled, provided all eligibility criteria are met, as well as the following:
  - Evaluable or measurable disease outside the CNS
  - No metastases to brain stem, midbrain, pons, medulla, cerebellum, or within 10 mm of the optic apparatus (optic nerves and chiasm)
  - No history of intracranial hemorrhage or spinal cord hemorrhage
  - No ongoing requirement for dexamethasone for CNS disease; patients on a stable dose of anticonvulsants are permitted.
  - No neurosurgical resection or brain biopsy within 28 days prior to randomization.
- Patients with asymptomatic treated CNS metastases may be enrolled, provided all eligibility criteria are met, as well as the following:
  - No radiographic demonstration and no evidence of interim progression between the completion of CNS-directed therapy and the screening radiographic study
  - No stereotactic radiation or whole-brain radiation within 28 days prior to randomization
  - Screening CNS radiographic study ≥ 28 days from completion of radiotherapy and ≥ 14 days from discontinuation of corticosteroids.

3.2.2 Known hypersensitivity to Chinese hamster ovary cell products or other recombinant human antibodies, fluoropyrimidines, folic acid derivatives or oxaliplatin.

3.2.3 Uncontrolled high blood pressure defined as systolic BP > 150 mmHg or diastolic BP > 90 mmHg with or without anti-hypertensive medication. Patients with initial BP elevations are eligible if initiation or adjustment of BP medication lowers pressure to meet entry criteria.

3.2.4 Any of the following cardiac conditions:

- Documented NYHA Class III or IV congestive heart failure
- Myocardial infarction within 6 months prior to randomization
- Unstable angina within 6 months prior to randomization
- Symptomatic arrhythmia.

3.2.5 Serious or non-healing wound, skin ulcer, or bone fracture.

3.2.6 History of TIA, CVA, GI perforation or arterial thrombotic event within 6 months prior to randomization, symptomatic peripheral ischemia, or other medical condition in the opinion of the treating oncologist that makes the risk of cardiovascular or bleeding complications with bevacizumab use unacceptably high.

3.2.7 Other malignancies are excluded unless the patient has completed therapy for the malignancy ≥ 12 months prior to randomization and is considered disease-free. Patients with the following cancers are eligible if diagnosed and treated within the past 12 months: in situ carcinomas or basal cell and squamous cell carcinoma of the skin.

3.2.8 Known DPD (dihydro pyrimidine dehydrogenase) deficiency.

3.2.9 Symptomatic peripheral sensory neuropathy ≥ grade 2 (CTCAE v5.0).

3.2.10 Prior treatment with oxaliplatin chemotherapy within 6 months prior to randomization.

3.2.11 Prior treatment with anti-PD-1, or anti-PD-L1 therapeutic antibody or pathway-targeting agents. Patients who have received prior treatment with anti-CTLA-4 may be enrolled provided the following requirements are met:
- Minimum of 12 weeks from the first dose of anti-CTLA-4 and > 6 weeks from the last dose to randomization
- No history of severe immune-related adverse effects (CTCAE Grade 3 and 4) from anti-CTLA-4.

3.2.12 Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events (other than alopecia) due to agents administered more than 4 weeks earlier are excluded; however, the following therapies are allowed:
- Hormone-replacement therapy or oral contraception
- Herbal therapy > 7 days prior to randomization (herbal therapy intended as anticancer therapy must be discontinued at least 1 week prior to randomization)
- Palliative radiotherapy for bone metastases >14 days prior to randomization

3.2.13 Treatment with systemic immunostimulatory medications (including, but not limited to interferon [IFN]-α or interleukin [IL]-2 within 42 days prior to randomization.

3.2.14 Treatment with systemic immunosuppressive medications (including, but not limited to prednisone, cyclophosphamide, azathioprine, methotrexate, thalidomide, and anti-tumor necrosis factor [anti-TNF] agents) within 14 days prior to randomization; however,
- Patients who have received acute, low dose, systemic immunosuppressant medications (e.g., a one-time dose of dexamethasone for nausea; or chronic daily treatment with corticosteroids with a dose of $\leq$ 10 mg/day methylprednisolone equivalent) may be enrolled.
- The use of inhaled corticosteroids and mineralocorticoids (e.g., fludrocortisone) for patients with orthostatic hypotension or adrenocortical insufficiency is allowed.

3.2.15 Patients taking bisphosphonate therapy for symptomatic hypercalcemia. Use of bisphosphonate therapy for other reasons (e.g., bone metastasis or osteoporosis) is allowed.

3.2.16 Patients requiring treatment with a RANKL inhibitor (e.g., denosumab) who cannot discontinue it before treatment with atezolizumab.

3.2.17 Treatment with any other investigational agent within 4 weeks prior to randomization.

3.2.18 Known clinically significant liver disease, including active viral, alcoholic, or other hepatitis; cirrhosis; fatty liver; and inherited liver disease; however,
- Patients with past or resolved hepatitis B infection (defined as having a negative hepatitis B surface antigen [HBsAg] test and a positive anti-HBc [antibody to hepatitis B core antigen] antibody test) are eligible if polymerase chain reaction (PCR) for HBV RNA is negative per local guidelines.
- Patients positive for hepatitis C virus (HCV) antibody are eligible only if polymerase chain reaction (PCR) is negative for HCV RNA per local guidelines.

3.2.19 History or risk of autoimmune disease, including, but not limited to, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, vascular thrombosis associated with antiphospholipid syndrome, Wegener's granulomatosis, Sjögren's syndrome, Bell's palsy, Guillain-Barré syndrome, multiple sclerosis, autoimmune thyroid disease, vasculitis, or glomerulonephritis; however,
- Patients with a history of autoimmune hypothyroidism on a stable dose of thyroid replacement hormone may be eligible.
- Patients with controlled Type 1 diabetes mellitus on a stable insulin regimen may be

eligible.

- Patients with eczema, psoriasis, lichen simplex chronicus or vitiligo with dermatologic manifestations only (*e.g.*, patients with psoriatic arthritis would be excluded) are permitted provided that they meet the following conditions:
  - Patients with psoriasis must have a baseline ophthalmologic exam to rule out ocular manifestations
  - Rash must cover less than 10% of body surface area (BSA)
  - Disease is well controlled at baseline and only requiring low potency topical steroids (*e.g.*, hydrocortisone 2.5%, hydrocortisone butyrate 0.1%, flucinolone 0.01%, desonide 0.05%, aclometasone dipropionate 0.05%)
  - No acute exacerbations of underlying condition within the last 12 months (not requiring psoralen plus ultraviolet A radiation [PUVA], methotrexate, retinoids, biologic agents, oral calcineurin inhibitors; high potency or oral steroids)

3.2.20 History of idiopathic pulmonary fibrosis, pneumonitis (including drug induced), organizing pneumonia (i.e., bronchiolitis obliterans, cryptogenic organizing pneumonia, etc.), or evidence of active pneumonitis on screening chest computed tomography (CT) scan. History of radiation pneumonitis in the radiation field (fibrosis) is permitted.

3.2.21 History of severe allergic, anaphylactic, or other hypersensitivity reactions to chimeric or humanized antibodies or fusion proteins.

3.2.22 Patients with known active tuberculosis (TB) are excluded.

3.2.23 Severe infections within 28 days prior to randomization, including but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia.

3.2.24 Signs or symptoms of infection within 14 days prior to randomization.

3.2.25 Received oral or intravenous (IV) antibiotics within 14 days prior to randomization. Patients receiving prophylactic antibiotics (e.g., for prevention of a urinary tract infection or chronic obstructive pulmonary disease) are eligible.

3.2.26 Major surgical procedure, open biopsy, or significant traumatic injury within 28 days prior to randomization or anticipation of need for a major surgical procedure during the course of the study.

3.2.27 Administration of a live, attenuated vaccine within 28 days prior to randomization or anticipation that such a live, attenuated vaccine will be required during the study and up to 5 months after the last dose of atezolizumab. Note: influenza vaccination should be given during influenza season only (approximately October to March). Patients must not receive live, attenuated influenza vaccine within 28 days prior to randomization or at any time during the study.

3.2.28 Psychiatric illness/social situations that would limit compliance with study requirements.

3.2.29 Pregnant women are excluded from this study because atezolizumab is an agent with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with atezolizumab, breastfeeding should be discontinued if the mother is treated with atezolizumab. These potential risks may also apply to other agents used in this study. *(Note: Pregnancy testing should be performed within 14 days prior to randomization according to institutional standards for women of childbearing potential.)*

3.2.30 HIV-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

3.2.31 Patients with prior allogeneic bone marrow transplantation or prior solid organ transplantation.