STUDY TYPE	Open label, multicenter phase III trial
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CONDITION	colon carcinoma
DESIGN	Open label, multicenter phase III trial
INDICATION	colon adenocarcinoma stage III
OBJECTIVE(S)	**Primary objective**: Aim of the study is to determine whether atezolizumab combined with FOLFOX and its continuation as monotherapy can significantly improve DFS compared to FOLFOX alone in patients with stage III colon cancers and dMMR. **Secondary objectives:** to determine whether atezolizumab combined with FOLFOX and its continuation as monotherapy can significantly improve overall survival compared to FOLFOX alone in patients with stage III colon cancers and dMMR. To assess the adverse events (AE) profile and safety of each treatment arm, using the CTCAE and PRO-CTCAE. The quality of life objective will be to determine the impact of the addition of atezolizumab to FOLFOX on patient-reported neuropathy, health-related QoL, and functional domains of health-related QoL. The quality of life analysis will also access the efficacy of atezolizumab adjusting for baseline QOL and fatigue measurements. Testing of banked specimens will not occur until an amendment to the recent treatment protocol (or separate correlative science protocol) is reviewed and approved.
INTERVENTION(S)	This is a Phase III, randomized, comparative, multicenter, open-label, two-arm study designed to evaluate the efficacy and safety of atezolizumab combined with FOLFOX and its continuation as monotherapy compared to FOLFOX alone. This study will enroll approximately 200 patients in Germany and Austria (and with USA 700 in total) randomized in a 1:1 ratio to one of two treatment arms: Arm 1: mFOLFOX6 for 12 cycles total with atezolizumab starting at Cycle 1 or Cycle 2 of mFOLFOX6 with continuation of atezolizumab for a total of 12 months (6 months of atezolizumab monotherapy). Arm 2: mFOLFOX6 for 12 cycles, which is a total of 6 months. One cycle will be defined as 14 days of treatment. Both arms: Cycle 1 of mFOLFOX6 must be started within 10 weeks of surgical resection of the primary cancer. Please note that best practice is 3 to 6 weeks between surgery and Cycle 1 of chemotherapy. Cycle 1 of mFOLFOX6 may be given prior to registration. Randomization will be stratified according to the following stratification factors: 1. Number of Positive Lymph Nodes: N1 (1-3 positive nodes)/N1C vs. N2 (> 4 positive nodes) (per AJCC 7) 2. T Stage: Tx/T1-T3 vs. T4 3. Primary Tumor Location: proximal (cecum, ascending colon, hepatic flexure, and transverse colon) vs. distal (splenic flexure, descending colon, sigmoid colon, and rectosigmoid junction)

	<u>Treatment discontinuation</u> Patients who continue to be in remission will continue on therapy for a total of 12 cycles mFOLFOX6 + atezolizumab followed by 6 months of atezolizumab alone if assigned to Arm 1 or 12 cycles mFOLFOX6 in total if assigned to Arm 2. After treatment is completed, patients will be followed per the Study Calendar. Remove from protocol therapy any patient with disease recurrence.
BACKGROUND/RATIONALE	The ability of immunotherapy to unleash a patient's own T cells to kill MSI-H tumor cells is expected to occur in the adjuvant setting, as demonstrated in metastatic disease [1], and may result in reduced recurrence and improved patient survival. The rationale for combination of FOLFOX and atezolizumab is based upon the fact that FOLFOX is standard of care as adjuvant therapy for stage III colon cancer and promising data for combining chemotherapy with atezolizumab, including suggestion of immune priming. Since FOLFOX is standard adjuvant chemotherapy for stage III disease [2], it serves as the control arm for studies aiming to further improve patient outcomes. Atezolizumab will be continued as monotherapy for an additional 6 months following completion of FOLFOX for 6 months (12 cycles). The rationale for this approach is late and sustained responders with the use of pembrolizumab in metastatic MSI-H CRC, the importance of a definitive study, and alignment with ongoing/planned adjuvant studies using atezolizumab in other malignancies. Furthermore, sustained stimulation of the immune system may be key for long-term benefit with immunotherapy. There is a precedent with the anti-CTLA-4 antibody ipilimumab that is approved for the adjuvant therapy of melanoma with treatment duration up to 3 years. It is intended for the study outlined in the protocol to be definitive, and regard this study to have the potential to be practice-changing.
KEY INCLUSION CRITERIA	(1) 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) (2) 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. Note: loss of MLH1 and PMS2 commonly occur together. 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 without dMMR screening by IHC. Note that patients who did not show dMMR (loss of MMR protein) are not eligible to participate. Patients whose tumors show MSI-H by polymerase chain reaction (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). (3) Availability of formalin-fixed paraffin-embedded (FFPE) tumor tissue for subsequent retrospective central confirmation of dMMR status. (4) Tumors 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 (5) Entire tumor in the colon (rectal involvement is an exclusion).[Note: 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 versus (vs.) rectal primary.] (6) Age ≥ 18 years (7) Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2 (8) Not pregnant and not nursing. For women of childbearing potential (WOCBP) only, a negative pregnancy test done ≤ 7 days prior to registration is required. A WOCBP is a sexually mature female who: 1) is not naturally postmenopausal (defined as at least 12 consecutive

	months with no menses without an alternative medical cause); OR 2) has not had a hysterectomy and/or bilateral oophorectomy (Note: Women with tubal ligation are still considered of child-bearing potential according to CTFG Guidance). (9) Absolute neutrophil count (ANC) ≥ 1500/mm³ (10) Platelet count ≥ 100,000/mm3; platelets ≥ 75,000/mm³ required for patients who received cycle 1 of mFOLFOX6 prior to registration (11) Creatinine ≤ 1.5 x upper limit of normal (ULN) or Calculated creatinine clearance ≥ 45 mL/min by Cockcroft-Gault equation (12) Total bilirubin ≤ 1.5 x upper limit of normal (ULN), except in the case of Gilbert disease (13) Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) ≤ 2.5 x upper limit of normal (ULN) (14) Thyroid-stimulating hormone (TSH) within normal limits (WNL). 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
KEY EXCLUSION CRITERIA	(1) 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. (2) 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 main protocol. (3) Active known autoimmune disease, including colitis, inflammatory bowel disease (i.e. ulcerative colitis or Crohn's disease), rheumatoid arthritis, panhypopituitarism, adrenal insufficiency (4) Known active hepatitis B or C • Active hepatitis B can be defined as: ▪ Hepatitis B virus surface antigen (HBsAg) detectable for > 6 months; ▪ Serum hepatitis B virus (HBV) DNA 20,000 IU/mL(10^5 copies/mL); lower values 2,000-20,000 IU/mL(10^4-10^5 copies/mL) are often seen in hepatitis B virus e antigen (HBeAg)-negative chronic hepatitis B ▪ Persistent or intermittent elevation in ALT/AST levels ▪ Liver biopsy showing chronic hepatitis with moderate or severe necroinflammation • Active hepatitis C can be defined as: ▪ Hepatitis C antibody (AB) positive AND ▪ Presence of hepatitis C virus (HCV) RNA (5) Known active pulmonary disease with hypoxia defined as: • Oxygen saturation < 85% on room air, or • Oxygen saturation < 88% despite supplemental oxygen (6) Grade ≥ 2 peripheral motor or sensory neuropathy (7) Patient HIV-positive, unless 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/μL, and an undetectable HIV viral load on standard PCR-based tests

	(8) Other planned concurrent investigational agents or other tumor directed therapy (chemotherapy, radiation) while on study (9) Systemic daily treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 7 days of registration (10) Known history of severe allergic anaphylactic reactions to chimeric, human or humanized antibodies, or fusion proteins (11) Known hypersensitivity to Chinese hamster ovary (CHO) cell products or any component of the atezolizumab formulation (12) Known allergy to 5-fluorouracil, oxaliplatin or folinic acid
STATISTICAL ANALYSIS	**Primary Endpoint** The primary endpoint of this study is the disease-free survival (DFS), defined as the time from randomization to first documentation of disease recurrent or death. Patients who do not have a DFS event will be censored for DFS at their last disease assessment date. Confirmed second primary colon cancer and second primaries of other types will not be included as an event for the DFS endpoint. **Secondary Endpoints** *Overall Survival (OS)* The secondary endpoint of this study is the overall survival, defined as the time from randomization to death, from any cause. Patients who do not have an OS event will be censored for OS at the date they were last known to be alive. *Adverse Events (AEs)* CTCAE AEs and the maximum grade for each type of AE will be recorded for each patient separately for the first 12 cycles (mFOLFOX6 +/- atezolizumab) and the 6 months of continuation of atezolizumab. Similarly, scores (0-4) and maximum score for each PRO-CTCAE item will be recorded for each patient separately for these two periods. **Sample Size and Accrual** It is anticipated randomizing a maximum of 700 patients (350 per arm) per statistical design (200 of them in Germany and Austria).
SAMPLE SIZE	N_{total} = 700 patients randomized into 2 arms, each of 350 patients $N_{GER/AT}$=200 patients randomized into 2 arms, each of 100 patients
TRIAL DURATION AND TIMELINE	Enrollment (GER/AT): 18 Months, Maximal duration: 9,5 years (114 months) including follow-up
COUNTRY	USA, GERMANY, AUSTRIA

REFERENCES
[1] Le, D.T., et al., PD-1 Blockade in Tumors with Mismatch-Repair Deficiency. N Engl J Med, 2015. 372(26): p. 2509-20.
[2] André , T., et al., Oxaliplatin, Fluorouracil, and Leucovorin as Adjuvant Treatment for Colon Cancer. New England Journal of Medicine, 2004. 350(23): p. 2343-2351.