ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

PROTOCOL UPDATE TO 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

[X] **Update:**	[ ] **Status Change:**
[ ] Eligibility changes	[ ] Activation
[X] Therapy / Dose Modifications / Study Calendar changes	[ ] Closure
[ ] Informed Consent changes	[ ] Suspension / temporary closure
[ ] Scientific / Statistical Considerations changes	[ ] Reactivation
[X] Data Submission / Forms changes	
[X] Editorial / Administrative changes	
[X] Other: CTSU template language	

No recommended IRB level of review is provided by the Alliance as the CIRB is the IRB of record for this trial. The site has 30 days after the posting of this amendment to implement it at their site. Please refer to the CIRB amendment application and guidelines for further instructions.

UPDATES TO THE PROTOCOL:

Cover Page (p.1)

- Language has been added to the cover page regarding the status as an FDA registration trial.
- The spelling of Dr. [redacted] name has been corrected.
- [redacted] has been removed as study Co-Chair
- [redacted] has replaced [redacted] as the nursing contact.

Study Resources (p. 2)

- The Alliance Biorepository information has been updated.

CTSU Address and contact information (p. 3)

- CTSU Template language has been updated.

Section 5.0 (Study Calendar)

- Survival follow-up information has been removed from footnote *** and replaced with 'See Section 12.0.'

- In footnote #9, a second sentence has been added as follows: 'After the end of FOLFOX treatment, the timing of CEA testing should correspond with timing of radiographic imaging studies, where possible, but more frequent testing is at provider discretion.'
- A new section, **5.1 Vital Status (Survival)** has been added.

Section 6.1 (Data Collection and Submission)

- CTSU Template language has been updated.
- In section 6.1.1, the following information has been added to the list of baseline reports: 'Germline mutation testing report when requested by Alliance Statistics and Data Management Center to resolve discordant data entries.'

Section 11.1 (Schedule of Evaluations)

- A third sentence has been added to the second bullet point: 'After the end of FOLFOX treatment, the timing of CEA should correspond with the timing of radiographic imaging, where possible, but more frequent testing is at provider discretion.

Section 12.0 (End of Treatment)

- **Sections 12.4** (Survival Follow-Up) and **12.5** (Lost to Follow-up) have been added.

Appendix V (AIO Sites and Investigators) has been added back into the protocol. It was removed by mistake in a previous update. The remaining appendices have been renumbered.

'Gender' has been replaced with 'Sex' throughout the protocol document (schema, eligibility and Correlative Science Companion Studies sections) as directed by NCI.

UPDATES TO THE MODEL CONSENT:

No changes to the model consent form.

A replacement protocol and consent document have been issued.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

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)

NCI-supplied agent: Atezolizumab (NSC #783608, IND #[redacted]; IND holder: NCI DCTD
Commercial agent(s): 5-fluorouracil, leucovorin, oxaliplatin

This is an FDA registration trial.

ClinicalTrials.gov Identifier: NCT02912559

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Study Resources

Expedited Adverse Event Reporting http://eapps-ctep.nci.nih.gov/ctepaers/	**Medidata Rave® iMedidata portal** https://login.imedidata.com
OPEN (Oncology Patient Enrollment Network) https://open.ctsu.org	**Biospecimen Management System** http://bioms.allianceforclinicaltrialsinoncology.org

Protocol Contacts

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Please refer to the Correlative Science Manual on the A021502 study page on the CTSU website.

Protocol-related questions may be directed as follows:

Questions	Contact (via email)
Questions regarding patient eligibility, treatment, and dose modification:	Study Chair, Nursing Contact, Protocol Coordinator, and (if applicable) Data Manager
Questions related to data submission, Rave, or patient follow-up:	Data Manager
Questions regarding the protocol document and model informed consent:	Protocol Coordinator
Questions related to IRB review:	Alliance Regulatory Inbox *regulatory@allianceNCTN.org*
Questions regarding CTEP-AERS reporting:	Pharmacovigilance Inbox *pharmacovigilance@allianceNCTN.org*
Questions regarding drug supply:	Pharmaceutical Management Branch (PMB)
Questions regarding specimens/specimen submissions:	Alliance Biorepository at Mayo Clinic

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

For regulatory requirements:	**For patient enrollments:**	**For data submission:**
Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal. (Sign in at https://www.ctsu.org, and select the Regulatory > Regulatory Submission.) Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately at by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support. Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878) or CTSURegHelp@coccg.org for regulatory assistance.	Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org Contact the CTSU Help Desk with any OPEN-related questions by phone or email : 1-888-823-5923, or ctsucontact@westat.com	Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific page located on the CTSU members' website (https://www.ctsu.org). Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.		
For clinical questions (i.e. patient eligibility or treatment-related) see Protocol Contacts, Page 2.		
For non-clinical questions (i.e., unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or email: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		

RANDOMIZED TRIAL OF STANDARD CHEMOTHERAPY ALONE OR COMBINED WITH ATEZOLIZUMAB AS ADJUVANT THERAPY OF PATIENTS WITH STAGE III COLON CANCER WITH DEFICIENT DNA MISMATCH REPAIR

Eligibility Criteria (see Section 3.0)

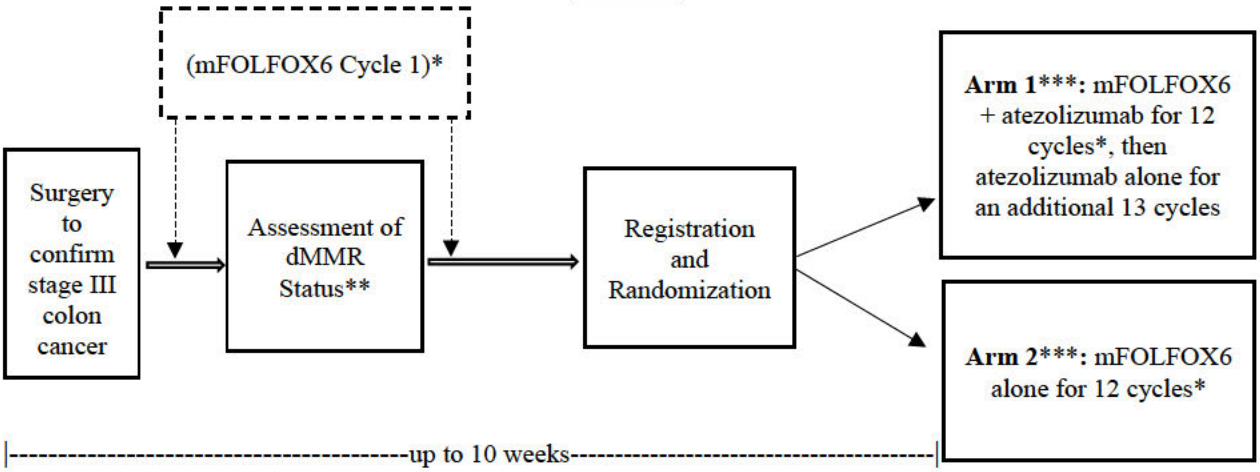
Histologically proven stage III colon adenocarcinoma
Presence of deficient MMR (dMMR) via IHC
Completely resected tumors
Entire tumor in colon
No evidence of residual involved lymph node disease or metastatic disease
Patients known to have Lynch Syndrome are eligible
No other planned concurrent investigational agents or other tumor directed therapy
No active autoimmune disease, including colitis, panhypopituitarism, adrenal insufficiency
No known active hepatitis B or C infection
No active pulmonary disease with hypoxia
No grade ≥ 2 peripheral motor or sensory neuropathy
Non-pregnant, non-nursing
Age ≥ 12 years
Performance Status: Lansky ≥ 50% (patients <16 years), Karnofsky ≥ 50% (patients 16 to <18 years), or ECOG PS≤ 2 (patients ≥ 18 years)

Required Initial Laboratory Values

Absolute Neutrophil Count (ANC)	≥ 1500/mm^3
Platelet Count	≥ 100,000/mm^3*
AST/ALT	≤ 2.5 x ULN
Bilirubin	≤ 1.5 x ULN***
TSH	WNL****
Creatinine	≤ 1.5 x ULN
OR	
Calculated Creatinine Clearance	≥ 45 mL/min**

* Platelets ≥ 75,000 for patients who received Cycle 1 of mFOLFOX6 prior to registration
** By Cockcroft-Gault equation. Alternatively, for patients <18 years of age, maximum serum creatinine ≤ the age-sex-specific norms listed in Section 3.2.7
*** Except in the case of Gilbert disease
**** Supplementation is acceptable to achieve a TSH WNL

Schema



* 1 cycle = 14 days. One cycle of mFOLFOX6 is allowed prior to registration. If Cycle 1 of mFOLFOX6 is started prior to registration, then the first post-registration cycle will be mFOLFOX6 Cycle 2. For patients who received Cycle 1 of mFOLFOX6 prior to registration and who are randomized to Arm 1, atezolizumab will start with Cycle 2 of mFOLFOX6.

** Assessment of dMMR status for eligibility may be performed locally or at a site-selected reference laboratory. Retrospective central confirmation of dMMR testing is required for all patients to gauge the false-positive rate in local testing (not for eligibility). See Section 6.2 for specimen submission requirements.

*** The standard of care for the time window between the end of mFOLFOX6 Cycle 1 and the start of mFOLFOX6 Cycle 2 is 14 days; however, up to 28 days are allowed between the end of Cycle 1 and the start of Cycle 2 if delays are made due to toxicity.

Patients will be followed for recurrence and survival every 6 months for the first two years after registration, then survival every 6 months and recurrence once annually for years 3-5 after registration, and then survival every 6 months for years 5-8 after registration.

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1.0 BACKGROUND

1.1 Colorectal Cancer

In the United States, colorectal cancer (CRC) is the fourth most common malignancy and the second most frequent cause of cancer-related death [1]. Surgery is the primary modality of treatment for non-metastatic CRC, and a resection with 'curative intent' occurs in 80-85% of patients with stages I-III disease. Among patients with potentially curable CRC, pathologic stage (including depth of invasion into the bowel wall, involvement of regional lymph nodes, and distant metastasis) is critical in determining prognosis and whether chemotherapy treatment in addition to surgery is necessary. Overall, 35-40% of CRC patients have stage III disease at diagnosis (~50,000 people in the United States annually) [2]. Among patients with stage III colon cancer, ~30-50% will develop cancer recurrence (dependent on substage of stage III disease and other factors) despite curative-intent surgery and postoperative adjuvant chemotherapy.

Pediatric Colorectal Cancer

Colorectal cancer (CRC) is rare in the pediatric population, with approximately 350 patients ages 19 and under in the U.S. per year. Compared to adults, pediatric patients with CRC are more likely to have tumors with unfavorable histology and stage 3 and 4 disease [3]. Prognosis for these patients remains poor, with 5-year overall survival of approximately 40% [4]. Despite this, no pediatric specific CRC studies have been performed to date. Instead, the majority of pediatric patients are treated using adult protocols despite lack of data on pediatric outcomes [3]. CRC in the pediatric age group is often hereditary of which the most common hereditary susceptibility is due to Lynch Syndrome [5]. In patients with Lynch Syndrome, CRC usually presents after the 4th decade of life; fewer cases have been reported in children and adolescents. Pediatric and adult colon cancers from patients with Lynch Syndrome show deficient DNA mismatch repair and are thus, potential candidates for participation in A021502.

1.2 Adjuvant Chemotherapy

The current standard of care for the adjuvant therapy of stage III colon cancer is oxaliplatin coupled with 5-fluorouracil infusion (FOLFOX-6) for 12 cycles (every 2 weeks) or 6 months. In 2003, the first analysis of the Multicenter International Study of Oxaliplatin/Fluorouracil/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIC) study was presented and showed a statistically significant improvement in disease-free survival with the addition of oxaliplatin to 5-fluorouracil plus leucovorin in stage III patients.[6] An update of the MOSAIC trial demonstrated a 5-year disease-free survival of 66% with FOLFOX compared to 59% with 5-fluorouracil and leucovorin that was limited to stage III patients.[7] The addition of oxaliplatin to fluoropyrimidine therapy increases the risk of toxicities, including bone marrow suppression and neurosensory symptoms, of which the latter is particularly problematic for some patients. At the completion of therapy in the MOSAIC trial, 12% of patients had grade 3 peripheral neuropathy and 92% had some level of neuropathy [8]. In a recent update, 15% of patients still had some level of residual neuropathy 4 years after the completion of adjuvant therapy.[7] Progress in the adjuvant therapy of colon cancer has stalled overall based upon the failure of targeted agents including anti-VEGF (bevacizumab) or anti-EGFR (cetuximab or panitumumab) antibodies to improve outcomes in patients with stage III disease in contrast to evidence of benefit in the metastatic setting [9-11].

Clinical trials being conducted in the U.S. and Europe are testing the hypothesis that 3 months of adjuvant FOLFOX or XELOX is non-inferior to 6 months. The IDEA (International Duration Evaluation of Adjuvant Chemotherapy) steering committee was formed to prospectively pool data from multiple ongoing trials. The TOSCA trial in Italy is randomizing 3450 high-risk stage II and stage III patients to 3 versus 6 months of adjuvant FOLFOX with an option for additional randomization to bevacizumab in stage IIIC patients. The SCOT trial in the UK is randomizing approximately 6500 stage II and III colon and rectal cancer patients to 3 versus 6 months of adjuvant FOLFOX/XELOX. In addition, the GERCOR and C80702 trials are each enrolling 2000-2500 patients with stage III colon cancer to an adjuvant trial of 3 versus 6 months of FOLFOX, and smaller trials are also being conducted in Japan and Greece. Results of the IDEA pooled analysis of over 12,000 patients has been published and did not meet the non-inferiority cutoff. A non pre-specified risk analysis stratified patients into low and high risk based on T and N stage. Among patients with low risk tumors (T1-3N1), 3 months of therapy was non inferior to 6 months. However, 3 months of the FOLFOX regimen was inferior to 6 months in patients with high-risk tumors (T4 and/or N2) [12]. Importantly, the study did not analyze tumors for dMMR status, so no data is yet available for this tumor subset. Accordingly, the duration of FOLFOX will remain 6 months in the ATOMIC trial as risk stratification in IDEA is unknown for patients with dMMR tumors.

1.3 DNA Mismatch Repair Deficient Colon Cancers

Two primary pathways of CRC have been described and include tumors with chromosomal instability (CIN) or those with microsatellite instability (MSI). MSI colon cancers are typically right-sided, poorly differentiated and contain abundant tumor infiltrating lymphocytes (TILs). MSI is a consequence of deficient DNA mismatch repair (dMMR) that is sporadic in origin in two-thirds of cases and is hereditary in one-third due to Lynch Syndrome (LS). LS is caused by a germline mutation in one of four MMR genes (MLH1, MSH2, MSH6, PMS1) with those in *MLH1* or *MSH2* accounting for more than 90% or cases [13]. Epigenetic inactivation of *MLH1* occurs in sporadic MSI CRCs and such tumors are enriched in $BRAF^{V600E}$ mutations [14]. CRCs with MSI/dMMR have been generally reported to have a better prognosis compared to tumors with proficient (p) MMR that are microsatellite stable (MSS). Data indicate that the association of dMMR/MSI with favorable prognosis is stronger in stage II versus stage III patients [15]. In this regard, dMMR status was not significantly associated with better overall survival in stage III colon cancers treated with the standard FOLFOX regimen in pooled data from 3 recent adjuvant chemotherapy trials (NCCTG N0147, PETACC-8, NSABP C-08) (unpublished data). Of note, the frequency of N2 disease (4 or more metastatic regional lymph nodes) which is a poor prognostic factor was similar among dMMR compared to pMMR colon cancers in the NCCTG N0147 trial [16]. Accordingly, there is an unmet need to improve outcomes in patients with stage III dMMR/MSI colon cancers.

1.4 MSI and Immune Checkpoint Inhibition

MSI/dMMR CRCs are hypermutated and express abundant neopeptides that elicit a robust T cell immune response characterized by abundant tumor infiltrating lymphocytes (TILs) [17]. These TILs include cytotoxic CD8+ T cells as well as activated Th1 cells, characterized by IFNγ production and the Th1 transcription factor, TBET [17]. However, recent data indicate that this robust immune reaction fails to eradicate the tumors due to immune checkpoint proteins that are overexpressed in MSI/dMMR tumors compared to p(MSS cancers [17]. These findings link tumor genotype with the immune microenvironment, and may explain why MSI/dMMR tumors are not eliminated despite the anti-tumor Th1/CTL microenvironment. They further suggest that

blockade of specific checkpoints may be selectively efficacious in the MSI/dMMR subset of CRC. In this regard, checkpoint inhibitors can enable a patient's own T cells to eradicate tumor cells which appears to underlie the observed efficacy of an anti-programmed death-1 (PD-1) antibody in cancers with MSI-H. Specifically, a recent phase II study in patients with MSI-H metastatic CRCs and MSI-H non CRCs (from Lynch Syndrome patients) showed that antiPD-1 antibody, pembrolizumab, as monotherapy produced a 57% response rate in MSI-H tumors compared to 0% in MSS tumors, and PFS has not yet been reached [18]. This modest size patient cohort included CRC patients with Lynch Syndrome (LS), some sporadic MSI-H tumors, and extracolonic malignancies associated with LS. While only 4% of metastatic CRCs are MSI-H, the clinical benefit was very substantial and a similar experience is emerging in clinical practice. The anti-tumor efficacy of a checkpoint inhibitor may well apply to stage III disease where 10-15% of tumors are MSI-H [19].

Targeting PD-L1 is a similarly promising approach to targeting PD-1. In addition to binding to PD-1, PD-L1 is believed to exert negative signals on T cells by interacting with B7, and this interaction is blocked by PD-L1, but not PD-1, antibodies. PD-L1 inhibitors have shown objective anti-tumor responses in patients with a variety of solid tumors including GI malignancies [20-22] and a small number of MSI-H colon cancers (Genentech, unpublished data). As stated, the mechanism underlying the clinical benefit of PD-1/PD-L1 inhibitors in MSI-H tumors is believed to be related to hypermutation [23] with production of mutant proteins and expression of abundant neoantigens that elicit an enhanced immune response [24]. In this regard, neoantigen load is associated with clinical benefit from pembrolizumab in NSCLC and may be predictive in other tumor types [25]. Based primarily on the data for pembrolizumab in metastatic MSI-H tumors, MSI-H is the only biomarker that has been shown to predict the efficacy of checkpoint inhibitor therapy in CRCs. MSI tumors selectively demonstrated highly upregulated expression of multiple immune checkpoints, including five-PD-1, PD-L1, CTLA-4, LAG-3, and IDO [26]. Furthermore, PD-1 and/or PD-L1 may provide prognostic information in patients with nonmetastatic CRCs [27] [28]. Some, but not other, PD-L1-positive cancers have demonstrated higher response rates to anti-PD-1/PD-L1 therapies, suggesting that PD-L1 expression may enrich for anti-tumor responses. However, data indicate that PD-L1-negative tumors can respond favorably to checkpoint inhibitors indicating that PD-L1 is not a universal predictive biomarker. PD-L1 is expressed on immune cells as well as tumor cells in various cancers.

1.5 Atezolizumab

Atezolizumab is a humanized IgG1 monoclonal antibody that targets PD-L1 on immune cells and/or tumor cells and prevents interaction with either PD-1 receptor or B7.1 (CD80), both of which function as inhibitory receptors expressed on T cells. Interference of the PD-L1: PD-1 and PD-L1:B7.1 interactions may enhance the magnitude and quality of the tumor-specific T-cell response through increased T-cell priming, expansion, and/or effector function [29]. Atezolizumab was engineered to have minimal binding to Fc receptors and, by eliminating Fc-effector function and antibody-dependent cell-mediated cytotoxicity (ADCC), antibody-mediated clearance of activated effector T cells is eliminated. Overall, the nonclinical pharmacokinetic (PK) behavior observed for atezolizumab is consistent with that expected for a humanized IgG1 monoclonal antibody. Atezolizumab has shown anti-tumor activity in preclinical models and cancer patients, and is being investigated as a single agent in advanced cancer and in adjuvant therapy settings, as well as in combination with chemotherapy, targeted therapy, and cancer immunotherapy. Based upon results from randomized clinical trials, the FDA has granted priority review to atezolizumab, for patients with locally advanced or

metastatic non-small cell lung cancer (NSCLC) who express PD-L1 and have progressed after a platinum-containing regimen. Furthermore, atezolizumab was also granted priority review by the FDA for the treatment of patients with metastatic bladder cancer.

To date, the use of PD-1/PD-L1 inhibitors in combination with chemotherapy has produced promising results in selected tumor types. Several preclinical studies indicate that certain chemotherapeutic agents can have an immunostimulatory effect [30] and in this regard, oxaliplatin can alter tumor immune status to transiently increase inflammation [31] [32]. This so called 'immune priming' may extend the inflammatory state to achieve enhanced and more durable responses. Unpublished data from Roche/Genentech indicate that FOLFOX alone or combined with bevacizumab and atezolizumab can increase cytotoxic $CD8^+$ T cells and PD-L1 expression in colorectal metastases which demonstrates immune priming. Data exist for the combination of the PD-L1 inhibitor, atezolizumab (MPDL3280A) with FOLFOX in patients with metastatic CRC. Single agent atezolizumab produced a 7.1% objective response rate (ORR) in 14 MSS CRCs, and responses were also seen for atezolizumab + bevacizumab in MSI tumors although the data remain premature in this subset. A phase I study evaluated the combination of atezolizumab (20 mg/kg q 3 weeks) combined with standard dose FOLFOX plus bevacizumab versus atezolizumab plus bevacizumab in patients with metastatic CRC [33]. In the atezolizumab + bevacizumab + FOLFOX study arm (n=23), there were 12 partial responses with an ORR of 52.2% and a median PFS of 14.1 months vs. an expected mPFS for FOLFOX + bevacizumab of 10-11 months (J Clin Oncol 33, 2015 (suppl. 3; abstr. 704)). All 23 patients had MSS tumors and in the FOLFOX-containing study arm, 70% of patients were previously untreated. A favorable safety profile was observed for both study arms containing atezolizumab and bevacizumab with or without FOLFOX and there was no increase in Grade 3 adverse events (AEs). Atezolizumab is being examined in patients with CRC as part of the biomarker-driven MODUL trial (NCT02291289) [34].

The phase I/II iMATRIX-atezolizumab study (NCT02541604, study GO29664) evaluated the safety, tolerability, PK, immunogenicity, and preliminary efficacy of atezolizumab monotherapy in pediatric and young adult patients with solid tumors [35]. This multicenter, open-label trial enrolled 87 patients with solid tumors with known or expected PD-L1 pathway involvement for which prior treatment was proven to be ineffective or intolerable, and for whom there was no curative standard-of-care treatment. The study included 69 patients aged < 18 years, each of whom received a weight-adjusted dose of atezolizumab (15 mg/kg every 3 weeks [q3w]; maximum 1200 mg). Patients aged 18 years and older received a flat dose (1200 mg q3w). A total of 431 atezolizumab serum concentrations were used for the population-PK (popPK) analysis, which was compared to a prior two-compartment intravenous infusion input adult popPK model. Atezolizumab clearance and volume of distribution estimates were 0.217 L/day and 3.01 L, respectively. Atezolizumab geometric mean trough exposures were ~ 20% lower in pediatric patients versus young adults; this was not clinically meaningful as both groups achieved the target concentration (6 µg/mL). Safety was similar between pediatric and young adult patients with no exposure-safety relationship observed. A comparable rate (13% vs. 11%) of atezolizumab anti-drug antibodies was seen in pediatric and young adult patients. Overall, a similar exposure-safety profile of atezolizumab was demonstrated in pediatric and young adult patients, supporting weight-based dosing in pediatric patients.

Safety and Tolerability

The risks identified in the nonclinical studies conducted with atezolizumab are consistent with the primary pharmacology of PD-L1/PD-1 pathway inhibition. Atezolizumab has been

administered to approximately 3200 patients, with efficacy and safety findings consistent with non-clinical data. No dose limiting toxicities have been observed at any dose level and no maximum tolerated dose (MTD) was established. While inhibition of PD-L1/PD-1 may lead to anti-tumor immune activity and is generally well tolerated, it may also increase the risk of immune-mediated adverse events (IMAEs). Atezolizumab has been well-tolerated as monotherapy with the majority of AEs being Grade 1-2 and manageable (patients continue atezolizumab). The combination of atezolizumab with chemotherapy has not been associated with additive toxicity and is consistent with the known profile for each study treatment. There is long term safety data from randomized trial of atezolizumab versus docetaxel in NSCLC [36] where 11% of patients in atezolizumab groups versus 39% in docetaxel group had treatment related grade 3 to grade 4 adverse events.

1.6 Rationale for the Proposed Clinical Trial

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 [37], 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 [38], 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. We intend for the study outlined in this protocol to be definitive, and regard this study to have the potential to be practice-changing.

2.0 OBJECTIVES

2.1 Primary Objective

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.

2.2 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 (among patients aged ≥ 18 years).

2.3 Quality of Life Objective

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. Patient-reported outcomes will not be assessed in patients aged 12 to <18 years.

2.4 Potential Correlative Science Objectives

Testing of banked specimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

2.4.1 To determine if the "Immunoscore" can predict the efficacy of atezolizumab for disease-free survival among patients with stage III colon cancer.

2.4.2 To assess whether circulating immune cell populations can predict the efficacy of atezolizumab as adjuvant therapy for stage III colon cancer.

2.4.3 To explore the associations of genomic alterations identified in cfDNA with DFS in patients treated with FOLFOX with or without atezolizumab.

2.4.4 To assess whether soluble markers of systemic inflammation in blood can predict the efficacy of atezolizumab as adjuvant therapy for stage III colon cancer.

2.4.5 To assess the relationship between baseline plasma 25(OH) D levels, change in 25(OH)D levels, and DFS and OS in patients with stage III colon cancer receiving FOLFOX +/- atezolizumab.

2.4.6 To determine the ability of using fecal microbiota and their metabolic products to predict survival benefit from anti-PD-L1 antibody therapy in dMMR colon cancer patients.

2.4.7 To determine if hypermutation or hyper-indel status is associated with response to atezolizumab.

2.4.8 To determine if unique mRNA expression signatures are predictive of disease-free survival among patients receiving adjuvant chemotherapy for stage III colon cancer.

2.4.9 To determine if the efficacy of atezolizumab differs among dMMR cancers due to germline MMR mutation (MLH1, MSH2, MSH6, PMS2) versus those with MLH1 hypermethylation and CIMP in patients with stage III colon cancer.

2.4.10 To identify overall mutational burden and number of putative tumor neoantigens in colon carcinoma specimens.

The following objectives apply to patients aged 12 to <18 years to evaluate the impact of atezolizumab on growth and development patterns in this population:

2.4.11 To determine changes in growth patterns compared to baseline (relative to age-specific standards for height and weight).

2.4.12 To determine changes in development patterns compared to baseline (relative to onset of menarche [for females] and pubertal changes).

3.0 PATIENT SELECTION

For questions regarding eligibility criteria, see the Study Resources page. Please note that the Study Chair cannot grant waivers to eligibility requirements.

3.1 On-Study Guidelines

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.

Physicians should consider whether any of the following may render the patient inappropriate for this protocol:

- Psychiatric illness which would prevent the patient from giving informed consent.
- 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.
- 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.
- 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.

3.2 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.

3.2.1 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, have been found to carry a specific germline mutation in an MMR gene (*MLH1, MSH2, MSH6, PMS2*), and have been shown to be dMMR by IHC are eligible to participate.

3.2.2 Disease Status

Tumors must have been completely resected. In patients with tumor adherent to adjacent structures, en bloc R_0 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 R_0 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.

3.2.3 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**.**

3.2.4 Age ≥ 12 years

3.2.5 Performance Status:

- **Patients <16 years of age: Lansky ≥ 50%**
- **Patients 16 to <18 years of age: Karnofsky ≥ 50%**
- **Patients ≥18 years of age: ECOG Performance Status ≤ 2**

3.2.6 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).

3.2.7 Required Initial Laboratory Values:

Absolute Neutrophil Count (ANC)	≥ 1500 mm^3
Platelet Count	≥ 100,000 mm^3*
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. Alternatively, for patients < 18 years of age, maximum serum creatinine ≤ the below age-sex-specific norms:

	Creatinine (mg/dL)	
Age	Male	Female
12 years	1.2	1.2
13 to <16 years	1.5	1.4
16 to <18 years	1.7	1.4

*** 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.

3.2.8 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.

- 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.
- 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

3.2.9 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.

3.2.10 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.

4.0 PATIENT REGISTRATION

4.1 Investigator and Research Associate Registration with CTEP

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy requires all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and to renew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person registration application with electronic signature and document submission capability.

RCR utilizes five person registration types.

- Investigator (IVR)—MD, DO, or international equivalent;
- Non Physician Investigator (NPIVR)—advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- Associate Plus (AP)—clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System (RUMS), OPEN, Rave; acting as a primary site contact, or with consenting privileges
- Associate (A)—other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB)—individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Addition to a site roster;

- Selection as the treating, credit, or drug shipment investigator or consenting person in OPEN;
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval; and
- Assignment of the Clinical Investigator (CI) task on the Delegation of Tasks Log (DTL).

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, or as the CI on the DTL must be rostered at the enrolling site with a participating organization.

For questions, please contact the **RCR Help Desk** by email at RCRHelpDesk@nih.gov.

4.2 Cancer Trials Support Unit Registration Procedures

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the Cancer Trials Support Unit (CTSU) members' website.This study is supported by the NCI CTSU.

IRB Approval

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.orgto establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an active CTEP status;
- Have an active status at the site(s) on the IRB/REB approval (*applies to US and Canadian sites only*) on at least one participating organization's roster;
- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- Lists all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol.

Additional Site Registration Requirements

Additional site requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number;
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only); and
- Compliance with all applicable protocol-specific requirements (PSRs).

4.2.1 Downloading Site Registration Documents

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log in to the CTSU members' website (https://www.ctsu.org)
- Click on *Protocols* in the upper left of the screen
    - Enter the protocol number in the search field at the top of the protocol tree, or
    - Click on the By Lead Organization folder to expand, the select *Alliance* and protocol number *A021502.*
- Click on *Documents*, *Protocol Related Documents, and* use the *Document Type* filter and select *Site Registration* to download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU)

4.2.2 Submitting Regulatory Documents

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU members' website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the *Regulatory* section and select *Regulatory Submission.*

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support.

NOTE: Until institutions receive a formal notice from the Alliance regarding termination to patient follow-up, institutions must not close this trial with the IRB of record for the study. Alliance members may refer to section 6.14 of the Alliance's Policy and Procedures for additional information about study termination, or institutions may contact the Alliance Regulatory team at regulatory@alliancenctn.org with any questions.

4.2.3 Checking Site Registration Status

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration*; and
- Enter the site's 5-character CTEP Institution Code and click on Go.
  - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as outlined within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

4.2.4 Delegation of Tasks Log (DTL)

Each site must complete a protocol-specific Delegation of Tasks Log (DTL) using the DTL application in the Delegation Log section on the CTSU members' website. The Clinical Investigator (CI) is required to review and electronically sign the DTL prior to the site receiving an approved site registration status and enrolling patients to the study. To maintain an approved site registration status the CI must re-sign the DTL at least annually and when a new version of the DTL is released; and activate new task assignments requiring CI sign-off. Any individual at the enrolling site on a participating roster may initiate the site DTL. Once the DTL is submitted for CI approval, only the designated DTL Administrators or the CI may update the DTL. Instructions on completing the DTL are available in the Help Topics button in the DTL application and describe DTL task assignments, CI signature, and CTEP registration requirements, as well as include a Master Task List.

4.3 Patient Registration Requirements

Informed Consent: For patients ≥ 18 years of age: the patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedure to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Current human protection committee approval of this protocol and a consent form is required prior to patient consent and registration. Patients with impaired decision

making capacity may be enrolled on this study, where institutional policy and IRB of record allow. For patients aged 12 to <18 years: patients and/or their parents or legal guardians must sign and give written informed consent and assent in accordance with institutional and federal guidelines.

Protected Health Information: Some of the tissue specimens collected for this study will be sent directly to a central laboratory agreed upon by the Alliance and the drug company supporting this study. These samples (or the required requisition form) will be labeled with study ID, surgical pathology number/block ID, and collection date. Some of the blood specimens collected for this study will be sent directly to Duke University. These samples will be labeled with patient initials, study ID, and collection date.

Patient-completed Booklets: Patient questionnaire booklets are to be ordered prior to the registration of any patients. Patient completed booklets can be ordered by downloading and completing the CTSU supply request form (located under the site registration documents section of the A021502 CTSU site) and submitting it through the CTSU regulatory portal. Samples of the booklets are found in Appendix I, which are to be used for reference and IRB submission only. They are not to be used for patient completion. There is one booklet for PRO-CTCAE which is required per the study calendar for all patients. There is a second QOL booklet for patients who consent for the Quality of Life study. There is no booklet for the Registration Fatigue/Uniscale assessment (first page of Appendix I, required for all patients per the study calendar). If needed, the first page of Appendix I can be adapted to use as a source document.

4.4 Patient Registration/Randomization Procedures

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- If a Delegation of Tasks Log (DTL) is required for the study, the registrars must hold the OPEN Registrar task on the DTL for the site; and
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their Form FDA 1572 in RCR. If a DTL is required for the study, the IVR or NPIVR must be assigned the appropriate OPEN-related tasks on the DTL.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.orgor from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

COG Patient Registration Enrollment Information

For COG Credited Enrollments ONLY: Prior to enrollment on this study, patients enrolling must be assigned a COG patient ID number. This number is obtained via the Patient Registry module in OPEN once authorization for the release of protected health information (PHI) has been obtained. The COG patient ID number is used to identify the patient in all future interactions with COG. If you have problems with the registration, please refer to the online help. For additional help or information, please contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Note: This COG patient ID number is different from the A021502 patient ID which will be assigned during registration (Step 1) to this trial.

4.5 Registration to Correlative Studies

There are three substudies within Alliance A021502. These correlative science studies must be offered to all patients ≥ 18 years of age enrolled on Alliance A021502 (although patients may opt to not participate); patients 12 to < 18 years of age may not participate in the Quality of Life Study (A021502-HO1), but must be offered the other two substudies. These substudies do not require separate IRB approval. The substudies included within Alliance A021502 are:

- Quality of Life Study A021502-HO1 (Section 14.1)
- Biomarker Study A021502-ST1 (Section 14.2)
- Pharmacogenetic Study A021502-PP1 (Section 14.2)

If a patient answers "yes" to "I choose to take part in the Quality of Life study and will fill out these forms," Question #1 in the model consent, they have consented to participate in the substudy described in Section 14.1. The patient should be registered to Alliance A021502-HO1 at the same time they are registered to the treatment trial (A021502). Questionnaires should be submitted per Section 6.4.

If a patient answers "yes" to "I agree to have my tissue collected, and I agree that my tissue samples and related information may be kept in a Biobank for use in future health research," "I agree to have my blood collected, and I agree that my blood samples and related information may be kept in a Biobank for use in future health research," or "I agree to have my stool collected, and I agree that my stool samples and related information may be kept in a Biobank for use in future health research," questions #2-4 in the model consent, they have consented to participate in the A021502-ST1 substudy described in Section 14.2. If a patient answers "yes" to "I agree to have my blood collected, and I agree that my blood samples and related information may be kept in a Biobank for use in future health research," Question #2 in the model consent, they have consented to participate in the A021502-PP1 substudy described in Section 14.2. The patient should be registered to Alliance A021502-ST1 and/or A021502-PP1 at the same time they are registered to the treatment trial (A021502). Samples should be submitted per Section 6.2.

4.6 Stratification Factors and Treatment Assignments

Permuted Block

After a patient is registered, they will be assigned to one of the two treatment arms (Arm 1 vs. Arm 2) in a **1:1** ratio utilizing a permuted block schedule [39]. The stratification factors for this study are as follows:

- Number of Positive Lymph Nodes: N1 (1-3 positive nodes)/N1C vs. N2 (≥4 positive nodes) (per AJCC 7)
- T Stage: Tx/T1-T3 vs. T4
- Primary Tumor Location: proximal (cecum, ascending colon, hepatic flexure, and transverse colon) vs. distal (splenic flexure, descending colon, sigmoid colon, and rectosigmoid junction)

When combined, these stratification factors create eight stratum levels, each of which having its own patient allocation schedule. The possible block size for this study is four.

5.0 STUDY CALENDAR

The pre-study testing intervals are guidelines only. Laboratory and clinical parameters during treatment are to be followed using individual institutional guidelines and the best clinical judgment of the responsible physician. It is expected that patients on this study will be cared for by physicians experienced in the treatment and supportive care of patients on this trial.

Pre-Study Testing Intervals

- To be completed ≤ 28 DAYS before registration: Laboratory studies, history and physical; dMMR testing may be completed at any point prior to registration for the present tumor.
- To be completed ≤ 80 DAYS before registration: Any imaging used to confirm lack of evidence of definitive metastatic disease (pre-surgery scans are acceptable)

	Prior to Registration*	**Arm 1:** Day 1 of each cycle*	**Arm 2:** Day 1 of each cycle*	End of treatment follow-up**	Post-treatment follow-up ***
Tests & Observations					
History and Physical, Weight, PS	A	A	A	X	X
Height	X	X(1)	X(1)	X(1)	
Pulse, Blood Pressure	X	X	X	X	
O_2 Saturation	X(2)	X(2)		X(2)	
CTCAE Adverse Event Assessment		X(3)	X(3)	X(3)	X(3)
PRO-CTCAE Adverse Event Assessment	X(4)	X(4)	X(4)	X(4)	
Registration Fatigue/ Uniscale Assessment	X(5)				
Colonoscopy	B				B
Tanner Staging	X(1)	C(1)	C(1)	X(1)	X (1)
Laboratory Studies					
Complete Blood Count, incl. Diff.	X	X	X	X	
Chemistry	X(6)	X(6)	X(6)	X(6)	
TSH	X(7)	X(7)			
Hep B Surface Ag & Hep C ab (Physician Discretion)	X				
Serum or Urine HCG	X(8)				
CEA	X(9)	X(9)	X(9)		X(9)
CD4 Count & Viral Load	X(10)				
dMMR Testing	X				
Staging					
CT of Chest/Abd/Pelvis or MRI of Chest/Abd/Pelvis	D	E	E	E	E
Correlative Studies: For patients who consent to participate					
QOL Assessments	*Arm 1: At registration, prior to Cycles 4, 7, and 13, at the end of treatment, and 3 years from registration. Arm 2: At registration, prior to Cycles 4 and 7, at the end of treatment, 12 months from registration, and 3 years from registration. See Sections 6.4, 14.1, and Appendix I.*				

Tissue, Blood, and Stool Samples	*See Sections 6.2 and 14.2.*

* Labs and visits completed prior to registration may be used for Day 1 of Cycle 1 (or Day 1 of Cycle 2) tests if obtained ≤ 14 days prior to treatment. For subsequent cycles, labs and visits may be obtained ≤ 2 business days prior to day of treatment.

** Physical examination, adverse event assessment, labs (CBC and chemistry), and staging scans (if due per footnote D) are required 1 month (+/- 7 days) after the last day of the last treatment cycle.

*** Patients will be followed for recurrence every 6 months (+/- 1 month) for the first two years after registration, and then once annually (+/- 1 month) for years 3-5 after registration. Recurrence follow-up will continue per the schedule above for 5 years after registration or until evidence of relapse, whichever comes first. See Section 12.0 for survival follow-up.

1 For patients aged 12 to <18 years. Staging should be performed until the patient has reached Tanner Stage V.

2 Oxygen saturation should be assessed at rest and after 1 minute walk.

3 Solicited AEs are to be collected starting prior to treatment until off-treatment (see Section 9.1). Routine AEs are to be collected starting after registration until the end of survival follow-up. For patients who complete one cycle of FOLFOX prior to registration, the first routine AE assessment should take place after registration but prior to Day 1 Cycle 2 of FOLFOX; see Section 9.3 for expedited SAE reporting.

4 Patients aged ≥ 18 years complete PRO-CTCAE by paper booklet ordered through the CTSU website. See Section 9.1 for administration instructions. See Appendix I for PRO-CTCAE assessments for IRB submission and review only. See Section 4.3 for ordering instructions. PRO-CTCAE booklets should be administered at the following time points: ≤ 14 days prior to registration; Day 1 of each Cycle, and at the end of treatment.

5 To be completed after registration but ≤ 21 days prior to treatment. See Appendix I.

6 Albumin, alkaline phosphatase, total bilirubin, bicarbonate (or total CO2), BUN, calcium, chloride, serum creatinine, glucose, potassium, total protein, SGOT (AST), SGPT (ALT), and sodium.

7 Perform at baseline and then every 8 weeks (+/- 14 days).

8 For women of childbearing potential (Section 3.2.6). Must be done ≤ 7 days prior to registration.

9 Perform at baseline, 6 weeks (+/- 7 days) after end of FOLFOX, then every 6 months (+/- 1 month) for 3 years, then every 12 months (+/- 1 month) for an additional 2 years, or until relapse. After the end of FOLFOX treatment, the timing of CEA testing should correspond with timing of radiographic imaging studies, where possible, but more frequent testing is at provider discretion.

10 HIV-positive patients should complete a CD4 count and viral load ≤ 28 days prior to registration.

A Drug dosages need not be changed unless the calculated dose changes by ≥ 10%, however, if the site recalculates the dose for a lower percentage dose changes (i.e. dose changes that are < 10%) to adhere to institutional policy, then this will not be considered a protocol deviation.

B Patients who did not receive a colonoscopy to the cecum prior to surgery are required to have a full colonoscopy no later than 6 weeks after the completion of chemotherapy, but exact timing within the specified window is per treating physician discretion. If recurrence is observed or suspected on imaging and it has colonic or rectal involvement that is not in close proximity to the surgical anastomosis, then a colonoscopy with biopsy is required to exclude a new primary malignancy in the colorectum. Colonoscopy and pathology reports from all additional colonoscopies performed during the treatment and follow-up periods should be submitted if possible. See Section 11.3.1 for details on follow-up and Lynch Syndrome.

C Perform only on Day 1 of Cycle 1 and Day 1 of Cycle 7.

D Baseline abdominal/pelvic scans can include either: 1) a CT ABD/PELV, or 2) a MRI ABD/PELV. Chest imaging can be either chest CT or chest MRI. CT scans should be of diagnostic quality and performed with oral and IV contrast unless there is a medical contraindication. MRIs should be performed with IV contrast unless there is a medical contraindication. Supporting documentation is to be submitted, per Section 6.1.1.

E The same imaging modality used at baseline must be used for all subsequent scans. Every 6 months (+/- 1 month) for the first 2 years after registration, and then annually (+/- 3 months) for years 3-5 after registration or until evidence of relapse, whichever comes first. Imaging and reports are to be submitted per Section 6.3. Upon relapse documented by imaging, reports should be submitted for retrospective review by Study Chair per Section 6.1.1.

5.1 Vital Status (Survival)

To ensure current and complete survival data are available, updated vital status (survival) may be requested by the Alliance. The primary focus of a vital status (survival) determination is to identify if a trial participant is deceased.

In support of regulatory requests to minimize missingness for safety and overall survival analysis, public record searches to obtain vital status (survival) for participants who withdrew consent from study or who were lost to follow-up may be requested by the Alliance.

Per FDA Guidance: Data Retention When Subjects Withdraw from FDA-Regulated Clinical Trials (October 2008): If a subject withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the investigator must not access for purposes related to the study the subject's medical record or other confidential records requiring the subject's consent. However, an investigator may review study data related to the subject collected prior to the subject's withdrawal from the study, and may consult public records, such as those establishing survival status.

A public record search would utilize information about the participant, from the time the participant consented to the study, to obtain an updated vital status (survival). No participants should be contacted during a public record search by the site research team.

6.0 DATA AND SPECIMEN SUBMISSION

6.1 Data Collection and Submission

Medidata Rave is the clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems; and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only or Rave SLA role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

This study has a Delegation of Tasks Log (DTL). Therefore, those requiring write access to Rave must also be assigned the appropriate Rave tasks on the DTL.

Upon initial site registration approval for the study in the Regulatory application, all persons with Rave roles assigned on the appropriate roster will be sent a study invitation email from iMedidata. To accept the invitation, site staff must either click on the link in the email or log in to iMedidata via the CTSU members' website under *Data Management* > *Rave Home* and click to *accept* the invitation in the *Tasks* pane located in the upper right corner of the iMedidata screen. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the eLearning link in the *Tasks* pane located in the upper right corner of the iMedidata screen. If an eLearning is required for a study and has not yet been taken, the link to the eLearning will appear under the study name in the *Studies* pane located in the center of the iMedidata screen; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will replace the eLearning link under the study name

Action will be required by site staff (to activate their account) who have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application. Account activation instructions are located on the CTSU website in the Data Management section under the Data Management Help Topics > Rave Resources > Medidata Account Activation and Study Invitation (to activate your iMedidata account). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management Rave Resources section or by contacting the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com.

A **Data Submission Schedule** is available on the Alliance study webpage within the Case Report Forms section. A Data Submission Schedule is also available on the CTSU website within the study-specific folders.

Patient-completed questionnaire booklets for this study are to be ordered prior to the registration of any patients (see Section 4.3). Samples of questionnaire booklets are available in Appendix I for reference and IRB submission only. They are not to be used for patient completion. Booklets must be given to patients to complete and patients should be instructed to return the booklets to site staff in person, and site staff will enter patient responses into Rave.

Major and critical protocol deviations for this study are to be reported in Rave according to the A021502 Deviations Guidance Memorandum available on the Alliance and CTSU websites.

6.1.1 Supporting Documentation to be Submitted to the Alliance

This study requires supporting documentation for diagnosis, DNA mismatch repair (dMMR) status, recurrence, and other reports as specified in data submission. Additional source documentation is required for the protocol-specific central data monitoring plan; see Section 13.6 of this protocol and the Data Submission Schedule accompanying the All Forms Packet for further guidance.

- **Baseline**: H&P, colonoscopy report*, radiologic images (submit to IROC Ohio see section 6.3), imaging report, pathology report from colonoscopy and surgery, operative report, result of dMMR testing (including methodology used, e.g. antibody names), laboratory reports for protocol-specified labs, clinic notes. **Germline mutation testing report when requested by Alliance**

Statistics and Data Management Center to resolve discordant data entries.

*If a patient did not receive a colonoscopy to the cecum prior to surgery due to an obstructing tumor or other factors, then the patient is required to have a full colonoscopy no later than 6 weeks after the completion of chemotherapy, but exact timing within the specified window is per treating physician discretion, to exclude a new primary malignancy in the colorectum.

- **Treatment**: Laboratory reports for protocol-specified labs
- **Restaging**: Radiologic images (submit to IROC Ohio see section 6.3), imaging reports
- **Follow-up**: Colonoscopy report* (if applicable)
- **Recurrence:** Radiologic images (submit to IROC Ohio see section 6.3), imaging report, pathology report (if applicable), colonoscopy report* (if applicable), operative report (if applicable), laboratory reports for protocol-specified labs, clinic notes.

  ***If recurrence is observed or suspected on imaging and it has colonic or rectal involvement that is not in close proximity to the surgical anastomosis, then a colonoscopy with biopsy is required to exclude a new primary malignancy in the colorectum.** Female patients with isolated recurrence involving the uterus should undergo biopsy to exclude a primary endometrial carcinoma, which is the most common extracolonic malignancy in patients with Lynch Syndrome.

All supporting documentation is to be submitted via Rave (with the exception of radiologic images, which should be submitted to IROC Ohio per Section 6.3). Imaging reports should be submitted via Rave and to IROC Ohio per Section 6.3 along with radiologic images.

In the event of a second primary or secondary malignancy, pathology reports, colonoscopy reports (if applicable), imaging reports (if applicable), and surgical reports (if applicable) are to be submitted.

Additionally, colonoscopy and pathology reports (if applicable) from any colonoscopies performed during the treatment and clinical follow-up periods should be submitted wherever possible.

Documentation of administration of all agents, including standard of care drug(s), should include total dose and start/stop dates for prolonged IV infusions ≥ 24 hours. (Paraphrased from the CTMB Guidelines).

6.1.2 Data Quality Portal

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms, DQP Form Status and the DQP

Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available on the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help Topics button displayed on the Rave Home, DQP Queries, DQP Delinquent Forms, DQP Form Status, and DQP Reports modules.

6.2 Specimen Collection and Submission

Correlative Science Manual (CSM): **The Alliance A021502 Correlative Science Manual (CSM) contains instructions for specimen collection, processing, and shipping.** The manual can be found on the study-specific webpage on the Alliance, BioMS, and CTSU websites. Questions regarding the CSM should be directed to the contact(s) specified in the manual.

For all patients registered to Alliance A021502: Retrospective dMMR confirmation testing and retrospective pathology review and biomarker testing will be performed using the paraffin embedded tissue from the surgical resection specimens. **The submission of these samples for dMMR confirmation testing is required for all patients registered to this study.**

For patients registered to substudy A021502-ST1 and A021502-PP1: All participating institutions must ask patients for their consent to participate in the correlative substudies planned for Alliance A021502-ST1 and A021502-PP1, although patient participation is optional. Biomarker and pharmacogenomic studies will be performed. Rationale and methods for the scientific components of these studies are described in Section 14.2. For patients who consent to participate in A021502-PP1, buffy coats from the A021502-ST1 collection will be used. For patients who consent to participate in A021502-ST1, tissue, blood, and/or stool specimens will be collected at the time points listed below.

	Prior to treatment (blood kit 1)	4 weeks (+/- 1 wk) after initiation of treatment (blood kit 2)	4.5 months (+/- 1 wk) after initiation of treatment (blood kit 1)	6 months (+/- 1 month) after end of therapy (blood kit 1)	Time of recurrence (blood kit 3)
Mandatory for all patients registered to A021502:					
10 Superfrost® Plus Micro Slides	X				
H&E slide AND FFPE tumor block	X				
FFPE normal block	X				

	For patients registered to A021502-ST1 and/or A021502-PP1 submit the following:				
FFPE tumor block	X				X
EDTA platelet poor plasma & buffy coats in lavender top	3 x 10 mL		3 x 10 mL	3 x 10 mL	3 x 10 mL
Whole blood in ACD yellow top	3 x 8.5 mL	3 x 8.5 mL	3 x 8.5 mL	3 x 8.5 mL	
Stool (fecal kit)	3 x 25 mL		3 x 25 mL	3 x 25 mL	

6.3 Imaging Submission - Required for All Patients

Collection of CT or MRI images is required for patients consented on A021502. Quality images will be collected digitally for archival purposes. The same imaging modality (i.e. multiphase CT or MRI) used at baseline for each patient should be used for all subsequent evaluations to ensure accurate comparison. Images and local interpretation reports will be collected digitally at the following time points:

- Baseline
- Restaging (performed every 6 months [+/- 1 month] for the first 2 years after registration, then annually [+/- 3 months] for years 3-5 after registration)
- Recurrence/relapse

The complete CT or MRI scan data in digital DICOM format should be **submitted electronically to the Imaging and Radiation Oncology Core at Ohio (IROC Ohio)** upon patient registration or upon image acquisition completeness (restaging and/or recurrence) within the following time frames:

- For imaging performed after the issuance of Update #14: submit within 30 business days
- For imaging performed before the issuance of Update #14: submit within 60 business days of protocol amendment release

BMP files, JPG files, or hard copies (films) are not acceptable.

Imaging data should be submitted electronically to IROC Ohio via TRIAD (Section 6.3.1). The standard TRIAD based data transfer approach will be provided separately through IROC efforts via the specific trial e-mail, Alliance021502@irocohio.org, per the request of participating sites before their first imaging data submission.

If the TRIAD approach is not achievable at a site, alternatively the site needs to de-identify the patient data using institutional procedures to remove patient name and medical record number while preserving the Alliance patient ID number (e.g. 112136) and protocol number (e.g. A021502), and use the following electronic approaches for data submission:

1) Web Transfer (http://upload.imagingcorelab.com)

   Any PCs with internet access and web browser (e.g. Internet Explorer, Mozilla Firefox) can be used to web transfer DICOM images and other required files to IROC Ohio. The standard Web Transfer information will be provided separately through the specific trial e-mail, Alliance021502@irocohio.org, per the request of participating sites before the first imaging data submission.

2) FTP Transfer

Any FTP software can be used to initiate access to the secure FTP Server of IROC Ohio. The standard FTP access information will be provided separately through the specific trial e-mail, Alliance021502@irocohio.org, per the request of participating sites before the first imaging data submission.

3) Mail/CD Shipment

If neither of the electronic data transfer approaches can be achieved, then the de-identified images in digital DICOM format may be burned to a CD and mailed to IROC Ohio (however, electronic submission is preferred). Submit only one of the patient's images per CD, with the Alliance patient ID number, study type, date of scans, and name of submitting institution.

Submit these data to:

IROC Ohio
Attn: A021502
University of Cincinnati
Digital Futures Research Building
3080 Exploration Avenue, Suite 310
Cincinnati, OH 45206
Tel: 513-556-7919
E-mail: Alliance021502@irocohio.org

If the imaging data submission is done via web transfer, FTP transfer, or mail/CD shipment, send an e-mail to IROC Ohio at the specific trial email, Alliance021502@irocohio.org, to inform them that the study has been submitted from the institution. Please include the following basic information of submitted data sets:

1) Alliance Patient ID Number
2) Scan Time Point (i.e. Baseline)
3) Date of Scans
4) Institution Name

IROC Ohio will notify the site of receipt via the trial specific email Alliance021502@irocohio.org within the following time frames:

- For imaging performed after the posting of Update #14: IROC Ohio will notify the site within 5 business days of the data receipt and within 3 business days following the data receipt of the quality check report
- For imaging performed before the posting of Update #14: IROC Ohio will notify the site within 10 business days of the data receipt and within 3 business days following the data receipt of the quality check report

6.3.1 Digital Imaging Data Submission Using Transfer of Images and Data (TRIAD)

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

6.3.1.1 TRIAD Access Requirements

TRIAD Access Requirements:

- A valid Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) (CTEP-IAM) account.
- Registration and Credential Repository (RCR) registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR) registration type. Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- TRIAD Site User role on an NCTN or ETCTN roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

6.3.1.2 TRIAD Installations

To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

6.3.1.3 Procedures for Data Submission via TRIAD

The standard TRIAD-based data transfer approach will be provided separately through IROC efforts via the specific trial e-mail, Alliance021502@irocohio.org, per the request of participating sites before their first imaging data submission.

6.4 Quality of Life Assessments

Patient-completed questionnaire booklets for this study are to be ordered prior to the registration of any patients (see Section 4.3). Samples of questionnaire booklets are available in Appendix I for reference and IRB submission only. They are not to be used for patient completion. Booklets must be given to patients to complete and patients should be instructed to return the booklets to site staff in person and site staff will enter patient responses into Rave. At visits in which booklets are to be completed, the booklet should be given to the patient before any discussion of the patient's health status or test results. Booklet administration schedule is provided below. Please note that PRO-CTCAE is contained in a separate booklet and is required for all patients 18 years or older per the study calendar. The schedule below only pertains to patients aged ≥ 18 years who consent to participate in the Quality of Life study.

ARM 1: mFOLFOX6 + atezolizumab	≤ 14 Days Prior to Registration	Prior to Cycles 4, 7, & 13 (+/-3 days)	End of Treatment Visit (+/-7 days)	3 Years after Registration (+/-28 days)
For patients registered to A021502-HO1, submit patient-completed questionnaires* at the following time points:				
	X	X	X	X

ARM 2: mFOLFOX6	≤ 14 Days Prior to Registration	Prior to Cycles 4 & 7 (+/-3 days)	End of Treatment Visit (+/-7 days)	12 Months after Registration (+/-14 days)	3 Years after Registration (+/-28 days)
For patients registered to A021502-HO1, submit patient-completed questionnaires* at the following time points:					
	X	X	X	X	X

*See Appendix I for FACT-C, FACT/GOG-NTX, and EQ-5D-5L questionnaires for IRB submission and review only. Patients must complete the questionnaires in booklet format. See Section 4.3 for ordering instructions.

Submission of Completed Booklets: The data from the booklets are to be entered into Medidata Rave by site staff. Data entry should correlate with the cycles notes in the above schedules (e.g. entered within Cycles 4, 7, or 13).

7.0 TREATMENT PLAN/INTERVENTION

Protocol treatment is to begin within 14 days after registration.

It is acceptable for individual therapy doses to be delivered ≤ a 24-hour (business day) window before and after the protocol-defined date for a scheduled dose. For example, if the treatment due date is a Friday, the window for treatment includes the preceding Thursday through the following Monday. In addition, patients are permitted to have a new cycle of immunotherapy/chemotherapy delayed up to 7 days for major life events (e.g. serious illness in a family member, major holiday, vacation that cannot be rescheduled) without this being considered a protocol violation. Documentation to justify this delay should be provided.

Patients with stage III, dMMR colon cancer will be randomized in 1:1 fashion to receive either 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, i.e. 13 cycles of atezolizumab monotherapy), or Arm 2: mFOLFOX6 for 12 cycles, which is a total of 6 months. One cycle will be defined as 14 days of treatment.

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. Once results of the local dMMR testing are complete and patients are found to have dMMR, patients may register and will then be randomized to Arm 1 or Arm 2. The standard of care for the time window between the start of mFOLFOX6 Cycle 1 and start of mFOLFOX6 Cycle 2 is 14 days, however, up to 28 days are allowed between Day 14 of Cycle 1 and Day 1 of Cycle 2 to allow for delays due to toxicity or patient decision making.

For patients who received one cycle of mFOLFOX6 prior to registration and who are on Arm 1, atezolizumab will start with Cycle 2 of mFOLFOX6. If Cycle 1 of mFOLFOX6 is administered prior to registration, it must be administered per Appendix III. For patients who did not have a cycle of mFOLFOX6 prior to registration and who are on Arm 1, atezolizumab will start with Cycle 1 of mFOLFOX6.

Chemotherapy and immunotherapy must be administered at the registering institution, including the one cycle of mFOLFOX6 the patient may have received prior to registration. Treatment will continue until disease recurrence or unacceptable adverse event or inability to tolerate treatment occurs (despite all allowed dose reductions). Otherwise treatment will continue until completion of the full treatment program and entrance onto clinical follow-up. Also, see Section 12.0 for additional information regarding discontinuation of treatment. Administration of atezolizumab should be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

The initial dose of atezolizumab will be delivered over 60 (±15) minutes. If the first infusion is tolerated without infusion associated AEs, the second infusion may be delivered over 30 (±10) minutes. If the 30-minute infusion is well tolerated, all subsequent infusions may be delivered over 30 (±10) minutes. For the first infusion, the patient's vital signs (heart rate, respiratory rate, blood pressure, and temperature) should be determined within 60 minutes before, during (every 15 [±5] minutes), and 30 (±10) minutes after the infusion. For subsequent infusions, vital signs should be collected within 60 minutes before and within 30 minutes after the infusion. Vital signs should be collected during the infusion only if clinically indicated. Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study physician if they develop such symptoms.

No premedication will be allowed for the first dose of atezolizumab. Premedication may be administered for Cycles ≥ 2 at the discretion of the treating physician.

7.1 Arm 1: mFOLFOX6 Plus Atezolizumab

The agents in the table below are listed in the order of intended administration.

Agent	Dose	Route	Duration	Days	Cycle
Atezolizumab	840mg*	IV	Over 60 min (+/- 15 min) for 1st dose, then Over 30min (+/- 10 min) for all subsequent doses	Day 1	Every 14 days
Oxaliplatin	85mg/m^2	IV	Over 2 hours (+/- 30 min)	Day 1	Every 14 days
Leucovorin**	400mg/m^2	IV	Over 2 hours (+/- 30 min)	Day 1	Every 14 days
Fluorouracil	400mg/m^2 + 2400mg/m^2	IV	Bolus + Over 46 hours (+/- 4 hours)	Day 1 + Days 1-3	Every 14 days

* Patients 12 to < 18 years of age will receive a dose of 10 mg/kg up to a maximum flat dose of 840 mg. The patient's age on the day of treatment should be used to determine whether to use weight-based dosing.

** Alternatively, leucovorin may be administered (via separate infusion containers) concurrently with oxaliplatin. Infusion duration may be adjusted according to institutional practice.

Note: If the minimum durations are followed and/or concurrent administration of leucovorin and oxaliplatin occurs, then fluorouracil administration could be completed on Days 1-2.

Atezolizumab should be the first drug administered regardless of cycle number as no premedication is allowed prior to the first dose of atezolizumab; see Section 7.0 and Section 8.1.4 for additional details.

Patients should receive 6 months (12 cycles total) of mFOLFOX6, including the cycle that may have been received prior to registration.

For patients who started mFOLFOX6 after registration, atezolizumab should start on Day 1 Cycle 1 of mFOLFOX6 (12 cycles in combination with mFOLFOX6 followed by 13 cycles as monotherapy for a total of 25 cycles of atezolizumab).

For patients who receive one cycle of mFOLFOX6 prior to registration, atezolizumab should start on Day 1 Cycle 2 of mFOLFOX6 (11 cycles in combination with mFOLFOX6 followed by 13 cycles as monotherapy for a total of 24 cycles of atezolizumab).

7.2 Arm 2: mFOLFOX6

The agents in the table below are listed in the order of intended administration.

Agent	Dose	Route	Duration	Days	Cycle
Oxaliplatin	85mg/m^2	IV	Over 2 hours (+/- 30min)	Day 1	Every 14 days
Leucovorin*	400mg/m^2	IV	Over 2 hours (+/- 30 min)	Day 1	Every 14 days
Fluorouracil	400mg/m^2 + 2400mg/m^2	IV	Bolus + Over 46 hours (+/- 4 hours)	Day 1 + Days 1-3	Every 14 days

* Alternatively, leucovorin may be administered (via separate infusion containers) concurrently with oxaliplatin. Infusion duration may be adjusted according to institutional practice.

Note: If the minimum durations are followed and/or concurrent administration of leucovorin and oxaliplatin occurs, then fluorouracil administration could be completed on Days 1-2.

Patients should receive 6 months (12 cycles total) of mFOLFOX6, including the cycle that may have been received prior to registration.

8.0 DOSE AND TREATMENT MODIFICATIONS

8.1 Ancillary Therapy, Concomitant Medications, and Supportive Care

8.1.1 Patients should not receive any other agent which would be considered treatment for the primary neoplasm or impact the primary endpoint.

8.1.2 Patients should receive full supportive care while on this study.

This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.

8.1.3 Treatment with hormones for cancer treatment or other chemotherapeutic agents may NOT be administered. Exceptions include:

- Steroids given for adrenal failure (steroid supplementation should be at physiologic dosing or as described in Section 8.1.12)
- Hormones administered for non-disease-related conditions (e.g. insulin for diabetes)
- Intermittent use of dexamethasone as an antiemetic (see Section 8.1.4 for maximum dose requirements).

8.1.4 Antiemetics may be used at the discretion of the attending physician, with the exception of steroids above.

As this regimen has high emetogenic potential, it is recommended that all subjects on study should receive an aggressive prophylactic antiemetic regimen, consisting of a 5HT-3 antagonist +/- NK1 antagonist. Steroids are permitted for antiemetic prophylaxis during mFOLFOX6 chemotherapy, but must be limited to a maximum of equivalent dexamethasone 10 mg daily for 2 days every 14 days, see Section 8.1.12 below for additional details.

8.1.5 Diarrhea management is per the discretion of the treating physician.

For symptoms of diarrhea (and/or abdominal cramping) that occur at any time during a treatment cycle, it is suggested that patients should be instructed to take an anti-diarrheal, such as loperamide. It is recommended that the anti-diarrheal should be started at the earliest sign of: (1) a poorly formed or loose stool; (2) an increase in bowel movements by 1 to 2 episodes per day compared to baseline, or (3) an increase in stool volume or liquidity. Additional anti-diarrheal measures may be implemented at the discretion of the treating physician. Patients should also be instructed to increase fluid intake to help maintain fluid and electrolyte balance during episodes of diarrhea, and IV

fluids should be considered for severe diarrhea, at the discretion of the treating physician.

8.1.6 Radiation therapy may not be administered while a subject is on the study.

8.1.7 Surgery

Patients who require surgery during protocol treatment may proceed as such, unless the surgery involves resection of recurrent colon cancer. Study drug can be held for a maximum of 42 days. If the patient requires an interruption of > 42 days, then they will be removed from protocol therapy.

8.1.8 Alliance Policy Concerning the Use of Growth Factors

- Please note that during treatment on mFOLFOX6, WBC growth factors are NOT required and may be used at the discretion of the physician.
- Blood products and growth factors should be utilized at the discretion of the treating physician as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology 2015 Clinical Practice Guidelines Update to the Recommendations for the Use of WBC Growth Factors. J Clin Oncol 33(28): 3199-212, 2015.
- The use of erythropoiesis–stimulating agents (ESAs) are NOT allowed, as this is an adjuvant therapy trial and use of ESAs is against the FDA label.
- If filgrastim/pegfilgrastim, tbo-filgrastim, or sargramostim are used, they must be obtained from commercial sources.

8.1.9 Hypersensitivity/Infusion Reactions

Chemotherapy infusion reactions: Treat hypersensitivity and infusion reactions as per institutional standards.

8.1.10 Neurologic Toxicity Due to Oxaliplatin

Patients receiving oxaliplatin on this study should be counseled to avoid cold drinks, chewing of ice chips, and exposure to cold water or air because the neurotoxicity often seen with oxaliplatin appears to be exacerbated by exposure to cold. The period of time during which the patient is at risk for these cold-induced sensory neuropathies is not well documented. Patients should exercise caution regarding cold exposure during the treatment period. Peripheral sensory neuropathies can occur at any time after receiving oxaliplatin therapy.

Supportive care is allowed at the discretion of the treating physician. For pharyngo-laryngeal dysesthesia, it is recommended to increase the duration of oxaliplatin infusion to 6 hours for subsequent cycles.

8.1.11 Extravasation

Extravasation of oxaliplatin has been associated with necrosis. Extravasation should be treated according to institutional guidelines.

8.1.12 Fatigue

Fatigue is the most common adverse event associated with immune checkpoint inhibitor therapy. This may be associated with a flu-like illness. Consider evaluation for associated or underlying organ involvement including pituitary disease, thyroid disease, and liver disease, or muscle inflammation.

8.1.13 Fever

Patients may experience isolated fever during infusion reactions or up to several days after infusion. Continued fever over the course of 1-2 weeks may represent autoimmune events, or infection. Appropriate workup should be initiated, at the discretion of the treating physician.

8.1.14 Supplementation

Electrolyte abnormalities should be adequately corrected with appropriate supplementation upon discovery.

8.1.15 Vaccination

Flu vaccine, pneumococcal vaccine, and any other relevant vaccines are recommended PRIOR to initiation of protocol therapy, at the discretion of the treating physician. Patients should not receive live attenuated vaccines while on study treatment.

8.2 Dose Modification General Guidelines

- If multiple adverse events are seen, administer dose based on greatest reduction required for a single adverse event observed. Reductions or holds for new cycles of treatment are based on treatment given in the preceding cycle and adverse events observed since the prior dose (with the exception of blood counts which should use Day 1 of cycle counts).
- Dose modifications of 5-FU, oxaliplatin, and atezolizumab may occur independently of each other, based on the pattern of toxicity. Patients unable to tolerate one or more drugs due to toxicity will remain on treatment with the other drugs. If oxaliplatin is omitted, 5-FU and leucovorin should both continue to be given.
- During mFOLFOX6, if 5-FU is omitted, leucovorin should also be omitted.
- Once the dose of any drug has been reduced, the dose cannot be re-escalated.
- There are no further dose reductions beyond those listed in the tables below for each drug. If further dose reduction is required, that drug should be discontinued.
- CTEP-AERS reporting may be required for some adverse events (see Section 9.4).
- **NOTE**: PRO-CTCAE data should not be used for determining attribution, dose modifications, or reporting of serious adverse events.

8.2.1 Dose Modifications for mFOLFOX6

Dose Level	5-FU bolus (mg/m^2)	5-FU infusion (mg/m^2)	Leucovorin (mg/m^2)	Oxaliplatin (mg/m^2)
0*	400	2400	400	85
-1	320	1920	400	65
-2	270	1600	400	50
-3	230	1360	400	40

*Dose level 0 refers to the starting dose. If 5-FU is skipped, leucovorin is also skipped.

If a dose reduction beyond level -3 is required for oxaliplatin, oxaliplatin will be discontinued. Continue 5-FU/leucovorin.

If a dose reduction beyond level -3 is required for 5-FU, discontinue mFOLFOX6.

If more than one dose reduction applies, use the most stringent (i.e. the greatest dose reduction).

If mFOLFOX6 is delayed due to toxicity for ≥ 4 weeks, counting from the originally scheduled day of treatment that was held, discontinue mFOLFOX6.

8.2.1.1 Hematologic Toxicity

For **grade 2 neutrophil count decreased** on Day 1, delay 5FU and oxaliplatin until grade ≤ 1, then resume oxaliplatin and 5FU at same dose.

For **grade 3 neutrophil count decreased** on Day 1, delay 5FU and oxaliplatin until grade ≤ 1, then resume with one dose level decreased of oxaliplatin and 5FU.

For **recurring grade 3 neutrophil count decreased**, delay 5FU and oxaliplatin until grade ≤ 1, then discontinue 5FU bolus and resume 5FU infusion and oxaliplatin with one dose level decreased.

For **grade 4 neutrophil count decreased or febrile neutropenia (defined as grade 3 or 4 neutropenia and T ≥ 38.5°C)**, delay 5FU and oxaliplatin until grade ≤ 1, then discontinue 5FU bolus and resume 5FU infusion and oxaliplatin with one dose level decreased.

For **recurring grade 4 neutrophil count decreased or recurring febrile neutropenia**, delay 5FU and oxaliplatin until grade ≤ 1, then discontinue 5FU bolus and resume 5FU infusion and oxaliplatin with two dose levels decreased.

For **grade 2 platelet count decreased**, delay 5FU and oxaliplatin until grade ≤ 1, then resume oxaliplatin with one dose level decreased and 5FU at same dose.

For **grade 3 or 4 platelet count decreased**, delay 5FU and oxaliplatin until grade ≤ 1, then resume 5FU and oxaliplatin with one dose level decreased.

8.2.1.2 Gastrointestinal Toxicity with Optimal Medical Management

For **grade 2 diarrhea**, delay 5FU and oxaliplatin until recovery to grade ≤ 1, then resume 5FU and oxaliplatin at the same dose level.

For **grade 3 diarrhea**, delay 5FU and oxaliplatin until recovery to grade ≤ 1, then resume oxaliplatin at the same dose level and 5FU with one dose level decreased.

For **grade 4 diarrhea**, delay 5FU and oxaliplatin until recovery to grade ≤ 1 or baseline, then resume 5FU and oxaliplatin at the next lower dose level.

For **grade 3 nausea or vomiting or grade 4 vomiting**, delay 5FU and oxaliplatin until recovery to grade ≤ 1, then resume 5FU and oxaliplatin at the next lower dose level.

8.2.1.3 Mucositis

For **grade 3 mucositis**, delay 5FU and oxaliplatin until recovery to grade ≤ 1, then resume oxaliplatin at the same dose level and 5FU at the next lower dose level.

For **grade 4 mucositis**, delay 5FU and oxaliplatin until recovery to grade ≤ 1, then resume 5FU and oxaliplatin at the next lower dose level.

8.2.1.4 Neuropathy (Sensory or Motor)

Toxicity Scale for the Sensory Neuropathies Associated with Oxaliplatin (using the Oxaliplatin Specific Neurotoxicity Scale)

	Symptoms
Grade 1	Paresthesias/dysesthesias* of short duration that resolve and do not interfere with function.
Grade 2	Paresthesias/dysesthesias* interfering with function, but not with activities of daily living (ADL)
Grade 3	Paresthesias/dysesthesias* with pain or with functional impairment that also interfere with ADL.
Grade 4	Persistent paresthesias/dysesthesias* that are disabling or life threatening.
	* May be cold-induced

For **grade 2 neurotoxicity persisting between treatments**, continue mFOLFOX6 with one dose level reduction of oxaliplatin for all subsequent cycles.

For **grade 3 neurotoxicity resolving to grade ≤ 2 between treatments**, continue mFOLFOX6 with one dose level reduction of oxaliplatin for all subsequent cycles.

For **grade 3 neurotoxicity persisting between treatments**, discontinue oxaliplatin.

For **grade 4 neurotoxicity**, discontinue oxaliplatin.

For **laryngopharyngeal dysesthesia**, increase the duration of oxaliplatin infusion to 6 hours for all subsequent cycles.

8.2.1.5 Hepatobiliary Toxicity

For **grade 3 or 4 bilirubin increased,** delay 5FU and oxaliplatin until recovery to grade ≤ 1, then resume 5FU and oxaliplatin at the next lower dose level.

For **grade 3 or 4 ALT/AST increased**, discontinue 5FU and oxaliplatin.

8.2.1.6 Renal Insufficiency

For **grade 3 or 4 creatinine increased and NOT attributed to study treatment**, delay 5FU and oxaliplatin until grade ≤ 1, then restart at the same doses.

8.2.1.7 Pulmonary Toxicities

For ≥ **grade 3 cough, dyspnea, hypoxia, pneumonitis, or pulmonary infiltrates,** delay oxaliplatin until interstitial lung disease is ruled out. Continue 5FU/leucovorin. Discontinue all protocol therapy if interstitial lung disease is confirmed.

8.2.1.8 Thrombotic Microangiopathy

For ≥ **grade 3 hemolytic uremic syndrome (HUS)**, discontinue oxaliplatin.

8.2.1.9 Cardiovascular Toxicities

For **grade 3 or 4 myocardial infarction**, discontinue mFOLFOX6.

For **grade 2 ischemia cerebrovascular**, discontinue mFOLFOX6.

8.2.2 Dose Modifications for Atezolizumab

Administration of atezolizumab will be performed in a setting with emergency medical facilities and staff who are trained to monitor for and respond to medical emergencies.

Premedication is not permitted for the first dose of atezolizumab. Premedication with antihistamines or antipyretics/analgesics (e.g., acetaminophen) may be administered for subsequent infusions at the discretion of the treating physician. The management of Infusion Related Reactions will be according to severity as follows:

- In the event that a patient experiences a Grade 1 Infusion Related Reaction during Cycle 1, the infusion rate should be reduced to half the rate being given at the time of event onset. Once the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. If tolerated, the infusion rate may then be increased to the original rate.
- In the event that a patient experiences a Grade 2 Infusion Related Reaction, or flushing, fever, or throat pain, the infusion should be immediately interrupted and the patient should receive aggressive symptomatic treatment. The infusion should be restarted only after the symptoms have adequately resolved to baseline grade. The infusion rate at restart should be half of the infusion rate that was in progress at the time of the onset of the Infusion Related Reaction. For subsequent infusions, administer oral premedication with antihistamine and anti-pyretic and monitor closely for Infusion Related Reactions.
- For Grade 3 or 4 Infusion Related Reactions, the infusion should be stopped immediately, and aggressive resuscitation and supportive measures should be initiated (e.g., oral or IV antihistamine, anti-pyretic, glucocorticoids, epinephrine, bronchodilators, oxygen). Atezolizumab should be permanently discontinued. Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-related event; retreatment requires consultation with, and consent of, the trial Principal Investigator (PI).

<u>General AE Management and Dose Modification Guidelines</u>

There will be no dose reduction for atezolizumab in this study.

Patients may temporarily suspend study treatment for up to 84 days (12 weeks) beyond the scheduled date of delayed infusion if study drug-related toxicity requiring dose suspension is experienced. If atezolizumab is held because of AEs for 84 days beyond the scheduled date of infusion, the patient will be discontinued from atezolizumab and will be followed for safety and efficacy as specified in this protocol. If the AE resolves within 84 days and the patient is receiving corticosteroid therapy for the event, atezolizumab may be held for longer than 84 days (up to 4 weeks) in order to allow tapering of the steroid dose to ≤10 mg oral prednisone or equivalent.

Dose interruptions for reasons other than toxicity, such as surgical procedures, may be allowed. The acceptable length of interruption will be at the discretion of the study PI in consultation with CTEP.

The primary approach to grade 1 to 2 irAEs is supportive and symptomatic care with continued treatment with atezolizumab; for higher-grade irAEs, atezolizumab should be withheld and oral and/or parenteral steroids administered. Recurrent grade 2 irAEs may also mandate withholding atezolizumab or the use of steroids. Assessment of the benefit risk balance should be made by the investigator, with consideration of the totality of information as it pertains to the nature of the toxicity and the degree of clinical benefit a given patient may be experiencing prior to further administration of atezolizumab. Atezolizumab should be permanently discontinued in patients with life threatening irAEs.

Management of Specific AEs

Management of certain AEs of concern, including immune-related pneumonitis, hepatitis, colitis, endocrinopathies, pancreatitis, neuropathies, meningoencephalitis, and potential ocular toxicities are presented in the Atezolizumab Investigator's Brochure. See the Agent Administration Guidelines including the "**Administration of First and Subsequent Atezolizumab Infusions**" table for guidelines for the management of Infusion Related Reactions and Anaphylaxis.

Atezolizumab has been associated with risks such as the following: IRRs and immune-related hepatitis, pneumonitis, colitis, pancreatitis, diabetes mellitus, hypothyroidism, hyperthyroidism, adrenal insufficiency, hypophysitis, Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, facial paresis, myelitis, meningoencephalitis, myocarditis, pericardial disorders, nephritis, myositis, and severe cutaneous adverse reactions. Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis and macrophage activation syndrome. Neutropenia and lymphopenia associated with chemotherapy may increase the risk for developing an infection in patients receiving atezolizumab in combination with chemotherapy.

Pulmonary events

Dyspnea, cough, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates have been associated with the administration of atezolizumab. Patients will be assessed for pulmonary signs and symptoms throughout the study and will have computed tomography (CT) scans of the chest performed at every tumor assessment.

All pulmonary events should be thoroughly evaluated for other commonly reported etiologies such as pneumonia or other infection, lymphangitic carcinomatosis, pulmonary embolism, heart failure, chronic obstructive pulmonary disease, or pulmonary hypertension. Management guidelines for pulmonary events are provided in the table below.

Event	Management
Pulmonary event, Grade 1	● Continue atezolizumab and monitor closely. ● Re-evaluate on serial imaging. ● Consider patient referral to pulmonary specialist.
Pulmonary event, Grade 2	● Withhold atezolizumab for up to 12 weeks after event onset. [a] ● Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL. ● Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. ● If event resolves to Grade 1 or better, resume atezolizumab. [b] ● If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. ● For recurrent events, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	● Permanently discontinue atezolizumab. ● Bronchoscopy or BAL is recommended. ● Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. ● If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. ● If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

BAL bronchoscopic alveolar lavage

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, 12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator and the Medical Monitor.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

Hepatic events

Immune-mediated hepatitis has been associated with the administration of atezolizumab. Eligible patients must have adequate liver function, as manifested by measurements of total bilirubin and hepatic transaminases, and liver function will be monitored throughout study treatment. Management guidelines for hepatic events are provided in the table below.

Patients with right upper-quadrant abdominal pain and/or unexplained nausea or vomiting should have liver function tests (LFTs) performed immediately and reviewed before administration of the next dose of study drug.

For patients with elevated LFTs, concurrent medication, viral hepatitis, and toxic or neoplastic etiologies should be considered and addressed, as appropriate.

Event	Management
Hepatic event, Grade 1	• Continue atezolizumab. • Monitor LFTs until values resolve to within normal limits or to baseline values.
Hepatic event, Grade 2	**All events:** • Monitor LFTs more frequently until return to baseline values. **Events of >5 days' duration:** • Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.
Hepatic event, Grade 3 or 4	• Permanently discontinue atezolizumab. • Consider patient referral to gastrointestinal specialist for evaluation and liver biopsy to establish etiology of hepatic injury. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

LFT = liver function test.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

Gastrointestinal events

Immune-mediated colitis has been associated with the administration of atezolizumab. Management guidelines for diarrhea or colitis are provided in the table below.

All events of diarrhea or colitis should be thoroughly evaluated for other more common etiologies. For events of significant duration or magnitude or associated with signs of systemic inflammation or acute-phase reactants (e.g., increased C-reactive protein, platelet count, or bandemia): Perform sigmoidoscopy (or colonoscopy, if appropriate) with colonic biopsy, with three to five specimens for standard paraffin block to check for inflammation and lymphocytic infiltrates to confirm colitis diagnosis.

Event	Management
Diarrhea or colitis, Grade 1	• Continue atezolizumab. • Initiate symptomatic treatment. • Endoscopy is recommended if symptoms persist for >7 days. • Monitor closely.

Event	Management
Diarrhea or colitis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Initiate symptomatic treatment. • Patient referral to GI specialist is recommended. • For recurrent events or events that persist >5 days, initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.
Diarrhea or colitis, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist for evaluation and confirmatory biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.
Diarrhea or colitis, Grade 4	• Permanently discontinue atezolizumab. • Refer patient to GI specialist for evaluation and confirmation biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

GI = gastrointestinal.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

Endocrine disorders

Thyroid disorders, adrenal insufficiency, diabetes mellitus, and pituitary disorders have been associated with the administration of atezolizumab. Management guidelines for endocrine events are provided in the table below.

Patients experiencing one or more unexplained AEs possibly indicative of endocrine dysfunction (including headache, fatigue, myalgias, impotence, mental status changes, and constipation) should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. The patient should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid stimulating hormone (TSH) and free T3 and T4 levels should be measured to determine whether thyroid abnormalities are present. Pituitary hormone levels and function tests [*e.g.*, TSH, growth hormone, luteinizing

hormone, follicle-stimulating hormone, testosterone, prolactin, adrenocorticotropic hormone (ACTH) levels, and ACTH stimulation test] and MRI of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency. The table below describes dose management guidelines for hyperthyroidism, hypothyroidism, symptomatic adrenal insufficiency, and hyperglycemia.

Event	Management
Asymptomatic hypothyroidism	• Continue atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly.
Symptomatic hypothyroidism	• Withhold atezolizumab. • Initiate treatment with thyroid replacement hormone. • Monitor TSH weekly. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving.
Asymptomatic hyperthyroidism	**TSH ≥0.1 mU/L and <0.5 mU/L:** • Continue atezolizumab. • Monitor TSH every 4 weeks. **TSH <0.1 mU/L:** • Follow guidelines for symptomatic hyperthyroidism.
Symptomatic hyperthyroidism	• Withhold atezolizumab. • Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. • Consider patient referral to endocrinologist. • Resume atezolizumab when symptoms are controlled and thyroid function is improving. • Permanently discontinue atezolizumab.
Symptomatic adrenal insufficiency, Grade 2–4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform appropriate imaging. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better and patient is stable on replacement therapy, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab, permanently discontinue atezolizumab.
Hyperglycemia, Grade 1 or 2	• Continue atezolizumab.

Event	Management
	• Investigate for diabetes. If patient has Type 1 diabetes, treat as a Grade 3 event. If patient does not have Type 1 diabetes, treat as per institutional guidelines. • Monitor for glucose control.
Hyperglycemia, Grade 3 or 4	• Withhold atezolizumab. • Initiate treatment with insulin. • Monitor for glucose control. • Consider referral to endocrinologist, particularly if patient is deemed to have atezolizumab-induced diabetes; if so, obtain C-peptide level paired with glucose, autoantibody levels (e.g. GAD65, islet cell autoantibodies), and hemoglobin A1C level. • If patient is found to have diabetic ketoacidosis or hyperglycemic hyperosmolar syndrome, treat as per institutional guidelines with appropriate management and laboratory values (*e.g.* anion gap, ketones, blood pH, *etc.*) reported. • Resume atezolizumab when symptoms resolve and glucose levels are stable.
Hypophysitis (pan-hypopituitarism), Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. • For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (pan-hypopituitarism), Grade 4	• Permanently discontinue atezolizumab. • Refer patient to endocrinologist. • Perform brain MRI (pituitary protocol). • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • Initiate hormone replacement if clinically indicated.

MRI = magnetic resonance imaging; TSH = thyroid-stimulating hormone.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

Ocular events

An ophthalmologist should evaluate visual complaints (e.g., uveitis, retinal events).

Management guidelines for ocular events are provided in the table below.

Event	Management
Ocular event, Grade 1	• Continue atezolizumab. • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If symptoms persist, treat as a Grade 2 event.
Ocular event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Patient referral to ophthalmologist is strongly recommended. • Initiate treatment with topical corticosteroid eye drops and topical immunosuppressive therapy. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.
Ocular event, Grade 3 or 4	• Permanently discontinue atezolizumab. • Refer patient to ophthalmologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

Immune-mediated Cardiac Events

Immune-mediated myocarditis and pericarditis have been associated with the administration of atezolizumab. Management guidelines for cardiac events are provided in the table below.

Immune-mediated Myocarditis

Immune-mediated myocarditis has been associated with the administration of atezolizumab. Immune-mediated myocarditis should be suspected in any patient presenting with signs or symptoms suggestive of myocarditis, including, but not limited to, laboratory (*e.g.*, B-NP [B-Natriuretic Peptide]) or cardiac imaging abnormalities, dyspnea, chest pain, palpitations, fatigue, decreased exercise tolerance, or syncope. Myocarditis may also be a clinical manifestation of myositis or associated with pericarditis (see section on pericardial disorders below) and should be managed accordingly.

Immune-mediated myocarditis needs to be distinguished from myocarditis resulting from infection (commonly viral, e.g., in a patient who reports a recent history of gastrointestinal illness), ischemic events, underlying arrhythmias, exacerbation of preexisting cardiac conditions, or progression of malignancy. All patients with possible

myocarditis should be urgently evaluated by performing cardiac enzyme assessment, an electrocardiogram (ECG), a chest X-ray, an echocardiogram, and a cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. An endomyocardial biopsy may be considered to enable a definitive diagnosis and appropriate treatment, if clinically indicated.

Patients with signs and symptoms of myocarditis, in the absence of an identified alternate etiology, should be treated according to the guidelines in the table below.

Event	Management
Immune-related myocarditis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset [a]. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Consider treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If symptoms resolve to below Grade 2 (*i.e.* patient is completely asymptomatic), resume atezolizumab. [b] • If symptoms do not resolve to below Grade 2 while withholding atezolizumab, permanently discontinue atezolizumab.
Immune-related myocarditis, Grade 3-4	• Permanently discontinue atezolizumab. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, or VAD as appropriate. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If symptoms resolve to below Grade 2, taper corticosteroids over ≥1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be documented by the investigator.

[b] If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

Immune-mediated Pericardial Disorders

Immune-mediated pericarditis should be suspected in any patient presenting with chest pain and may be associated with immune-mediated myocarditis (see section on myocarditis above).

Immune-mediated pericardial effusion and cardiac tamponade should be suspected in any patient presenting with chest pain associated with dyspnea or hemodynamic instability.

Patients should be evaluated for other causes of pericardial disorders such as infection (commonly viral), cancer related (metastatic disease or chest radiotherapy), cardiac injury related (post myocardial infarction or iatrogenic), and autoimmune disorders, and should be managed accordingly.

All patients with suspected pericardial disorders should be urgently evaluated by performing an ECG, chest X-ray, transthoracic echocardiogram, and cardiac MRI as appropriate per institutional guidelines. A cardiologist should be consulted. Pericardiocentesis should be considered for diagnostic or therapeutic purposes, if clinically indicated.

Patients with signs and symptoms of pericarditis, pericardial effusion, or cardiac tamponade, in the absence of an identified alternate etiology, should be treated according to the guidelines in the table below. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Event	Management
Immune-mediated myocarditis, Grade 2–4 Immune-mediated pericardial disorders, Grade 2–4	• Permanently discontinue atezolizumab. • Refer patient to cardiologist. • Initiate treatment as per institutional guidelines and consider antiarrhythmic drugs, temporary pacemaker, ECMO, VAD, or pericardiocentesis as appropriate. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

ECMO = extracorporeal membrane oxygenation; VAD = ventricular assist device.

Infusion-Related Reactions and Cytokine-Release Syndrome

No premedication is indicated for the administration of Cycle 1 of atezolizumab. However, patients who experience an infusion-related reaction (IRR) or cytokine-release syndrome (CRS) with atezolizumab may receive premedication with antihistamines, antipyretics, and/or analgesics (*e.g.*, acetaminophen) for subsequent infusions. Metamizole (dipyrone) is prohibited in treating atezolizumab-associated IRRs because of its potential for causing agranulocytosis.

IRRs are known to occur with the administration of monoclonal antibodies and have been reported with atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab administration and are generally mild to moderate in severity.

CRS is defined as a supraphysiologic response following administration of any immune therapy that results in activation or engagement of endogenous or infused T cells and/or other immune effector cells. Symptoms can be progressive, always include fever at the onset, and may include hypotension, capillary leak (hypoxia), and end-organ dysfunction (Lee *et al*., 2019). CRS has been well documented with chimeric antigen receptor T-cell therapies and bispecific T-cell engager antibody therapies but has also

been reported with immunotherapies that target PD-1 or PD-L1 (Rotz *et al*., 2017; Adashek and Feldman 2019) including atezolizumab.

There may be significant overlap in signs and symptoms of IRRs and CRS, and in recognition of the challenges in clinically distinguishing between the two, consolidated guidelines for medical management of IRRs and CRS are provided in the table below.

Management Guidelines for Infusion-Related Reactions and Cytokine-Release Syndrome

Event	Management
Grade 1[a] Fever[b] with or without constitutional symptoms	● Immediately interrupt infusion. ● Upon symptom resolution, wait 30 minutes and then restart infusion at half the rate being given at the time of event onset. ● If the infusion is tolerated at the reduced rate for 30 minutes, the infusion rate may be increased to the original rate. ● If symptoms recur, discontinue infusion of this dose. ● Administer symptomatic treatment,[c] including maintenance of IV fluids for hydration. ● In case of rapid decline or prolonged CRS (> 2 days) or in patients with significant symptoms and/or comorbidities, consider managing as per Grade 2. ● For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics, and monitor closely for IRRs and/or CRS.
Grade 2[a] Fever[b] with hypotension not requiring vasopressors **and/or** Hypoxia requiring low-flow oxygen[d] by nasal cannula or blow-by	● Immediately interrupt atezolizumab infusion. ● Upon symptom resolution, wait for 30 minutes and then restart infusion at half the rate being given at the time of event onset. ● If symptoms recur, discontinue infusion of this dose. ● Administer symptomatic treatment.[c] ● For hypotension, administer IV fluid bolus as needed. ● Monitor cardiopulmonary and other organ function closely (in the ICU, if appropriate). Administer IV fluids as clinically indicated and manage constitutional symptoms and organ toxicities as per institutional practice. ● Rule out other inflammatory conditions that can mimic CRS (*e.g*., sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. ● Consider IV corticosteroids (*e.g*., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). ● Consider anti-cytokine therapy.[e] ● Consider hospitalization until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 3, that is, hospitalize patient (monitoring in the ICU is recommended), permanently discontinue atezolizumab. ● If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, anti-pyretics, and/or analgesics and monitor closely for IRRs and/or CRS. ● If symptoms do not resolve to Grade 1 or better for 3 consecutive days, contact the Principal Investigator.
Grade 3[a] Fever[b] with	● Permanently discontinue atezolizumab. ● Administer symptomatic treatment.[c] ● For hypotension, administer IV fluid bolus and vasopressor as needed.

hypotension requiring a vasopressor (with or without vasopressin) **and/or** Hypoxia requiring high-flow oxygen[d] by nasal cannula, face mask, non-rebreather mask, or venturi mask	• Monitor cardiopulmonary and other organ function closely; monitoring in the ICU is recommended. Administer IV fluids as clinically indicated and manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (*e.g.*, sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (*e.g.*, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[e] • Hospitalize patient until complete resolution of symptoms. If no improvement within 24 hours, manage as per Grade 4, that is, admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed; for patients who are refractory to anti-cytokine therapy, experimental treatments may be considered at the discretion of the investigator.
Grade 4[a] Fever[b] with hypotension requiring multiple vasopressors (excluding vasopressin) and/or Hypoxia requiring oxygen by positive pressure (*e.g.*, CPAP, BiPAP, intubation and mechanical ventilation)	• Permanently discontinue atezolizumab. • Administer symptomatic treatment.[c] • Admit patient to ICU and initiate hemodynamic monitoring, mechanical ventilation, and/or IV fluids and vasopressors as needed. Monitor other organ function closely. Manage constitutional symptoms and organ toxicities as per institutional practice. • Rule out other inflammatory conditions that can mimic CRS (*e.g.*, sepsis). If no improvement within 24 hours, initiate workup and assess for signs and symptoms of HLH or MAS. • Administer IV corticosteroids (*e.g.*, methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). • Consider anti-cytokine therapy.[e] For patients who are refractory to anti-cytokine therapy, experimental treatments[f] may be considered at the discretion of the investigator. • Hospitalize patient until complete resolution of symptoms.

ASTCT= American Society for Transplantation and Cellular Therapy; BiPAP= bi-level positive airway pressure; CAR= chimeric antigen receptor; CPAP= continuous positive airway pressure; CRS= cytokine-release syndrome; HLH= hemophagocytic lymphohistiocytosis; IRR = infusion-related reaction; MAS= macrophage activation syndrome.

Note: The management guidelines have been adapted from NCCN guidelines for management of CAR T-cell-related toxicities (Version 2.2019).

a. Grading system for management guidelines is based on ASTCT consensus grading for CRS. NCI CTCAE (version as specified in the protocol) should be used when reporting severity of IRRs, CRS, or organ toxicities associated with CRS on the Adverse Event eCRF. Organ toxicities associated with CRS should not influence overall CRS grading.

b. Fever is defined as temperature ≥38°C not attributable to any other cause. In patients who develop CRS and then receive anti-pyretic, anti-cytokine, or corticosteroid therapy, fever is no longer required when subsequently determining event severity (grade). In this case, the grade is driven by the presence of hypotension and/or hypoxia.

c. Symptomatic treatment may include oral or IV antihistamines, anti-pyretics, analgesics, bronchodilators, and/or oxygen. For bronchospasm, urticaria, or dyspnea, additional treatment may be administered as per institutional practice.

d. Low flow is defined as oxygen delivered at ≤6 L/min, and high flow is defined as oxygen delivered at >6 L/min.

e. There are case reports where anti-cytokine therapy has been used for treatment of CRS with immune checkpoint inhibitors (Rotz et al. 2017; Adashek and Feldman 2019), but data are limited, and the role of such treatment in the setting of antibody-associated CRS has not been established.

f. Refer to Riegler et al. for information on experimental treatments for CRS.

Pancreatic events

Symptoms of abdominal pain associated with elevations of amylase and lipase, suggestive of pancreatitis, have been associated with the administration of atezolizumab. The differential diagnosis of acute abdominal pain should include pancreatitis. Appropriate workup should include an evaluation for ductal obstruction, as well as serum amylase and lipase tests. Management guidelines for pancreatic events, including pancreatitis, are provided in the table below.

Event	Management
Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase >1.5–2.0 × ULN:** • Continue atezolizumab. • Monitor amylase and lipase weekly. • For prolonged elevation (*e.g.*, >3 weeks), consider treatment with corticosteroids equivalent to 10 mg/day oral prednisone. **Asymptomatic with amylase and/or lipase >2.0–5.0 × ULN:** • Treat as a Grade 3 event.
Amylase and/or lipase elevation, Grade 3 or 4	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Monitor amylase and lipase every other day. • If no improvement, consider treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c] • For recurrent events, permanently discontinue atezolizumab.
Immune-related pancreatitis, Grade 2 or 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to GI specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. • For recurrent events, permanently discontinue atezolizumab.
Immune-related pancreatitis, Grade 4	• Permanently discontinue atezolizumab. • Refer patient to GI specialist.

Event	Management
	• Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator.

b If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

Dermatologic events

Treatment-emergent rash has been associated with atezolizumab. The majority of cases of rash were mild in severity and self-limited, with or without pruritus. A dermatologist should evaluate persistent and/or severe rash or pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A biopsy should be considered unless contraindicated. Management guidelines for dermatologic events are provided in the table below.

Event	Management
Dermatologic event, Grade 1	• Continue atezolizumab. • Consider treatment with topical corticosteroids and/or other symptomatic therapy (*e.g.*, antihistamines).
Dermatologic event, Grade 2	• Continue atezolizumab. • Consider patient referral to dermatologist for evaluation and if indicated, biopsy. • Initiate treatment with topical corticosteroids. • Consider treatment with higher-potency topical corticosteroids if event does not improve.
Dermatologic event, Grade 3	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to dermatologist for evaluation and if indicated, biopsy. • Initiate treatment with corticosteroids equivalent to 10 mg/day oral prednisone, increasing dose to 1-2 mg/kg/day if event does not improve within 48-72 hours. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.
Dermatologic event, Grade 4	• Permanently discontinue atezolizumab.

Event	Management
Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	**Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:** • Withhold atezolizumab for suspected Stevens-Johnson syndrome or toxic epidermal necrolysis. • Confirm diagnosis by referring patient to a specialist (dermatologist, ophthalmologist, or urologist as relevant) for evaluation and, if indicated, biopsy. • Follow the applicable treatment and management guidelines above. • If Stevens-Johnson syndrome or toxic epidermal necrolysis is confirmed, permanently discontinue atezolizumab.
[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator. b If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.	

Neurologic disorders

Myasthenia gravis and Guillain-Barré syndrome have been observed with single agent atezolizumab. Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic work-up is essential for an accurate characterization to differentiate between alternative etiologies. Management guidelines for neurologic disorders, and specific guidelines for myelitis, are provided in the table below.

Event	**Management**
Immune-mediated neuropathy, Grade 1	• Continue atezolizumab. • Investigate etiology. • Any cranial nerve disorder (including facial paresis) should be managed as per Grade 2 management guidelines below.

Immune-mediated neuropathy, including facial paresis, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a]
	• Investigate etiology and refer patient to neurologist.
	• Initiate treatment as per institutional guidelines.
	• For general immune-mediated neuropathy:
	  ○ If event resolves to Grade 1 or better, resume atezolizumab. [b]
	  ○ If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab. [c]
	• For facial paresis:
	  ○ If event resolves fully, resume atezolizumab. [b]
	  ○ If event does not resolve fully while withholding atezolizumab, permanently discontinue atezolizumab. [c]

Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	• Permanently discontinue atezolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines.

Event	Management
Myasthenia gravis and Guillain-Barré syndrome (any grade)	• Permanently discontinue atezolizumab. [c] • Refer patient to neurologist. • Initiate treatment as per institutional guidelines. • Consider initiation of corticosteroids equivalent to 1–2 mg/kg/day oral or IV prednisone.

[a] Atezolizumab may be withheld for a longer period of time (*i.e.*, >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be based on an assessment of benefit–risk by the investigator and in alignment with the protocol requirements for the duration of treatment and documented by the investigator.

b If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

c Resumption of atezolizumab may be considered in patients who are deriving benefit and have fully recovered from the immune-mediated event. The decision to re–challenge patients with atezolizumab should be based on investigator's assessment of benefit–risk and documented by the investigator (or an appropriate delegate).

Immune-Mediated Meningoencephalitis

Immune-mediated meningoencephalitis is an identified risk associated with the administration of atezolizumab. immune-mediated meningoencephalitis should be suspected in any patient presenting with signs or symptoms suggestive of meningitis or encephalitis, including, but not limited to, headache, neck pain, confusion, seizure, motor or sensory dysfunction, and altered or depressed level of consciousness. Encephalopathy from metabolic or electrolyte imbalances needs to be distinguished from potential meningoencephalitis resulting from infection (bacterial, viral, or fungal) or progression of malignancy, or secondary to a paraneoplastic process.

All patients being considered for meningoencephalitis should be urgently evaluated with a CT scan and/or MRI scan of the brain to evaluate for metastasis, inflammation, or edema. If deemed safe by the treating physician, a lumbar puncture should be performed, and a neurologist should be consulted.

Patients with signs and symptoms of meningoencephalitis, in the absence of an identified alternate etiology, should be treated according to the guidelines in the table below.

Event	Management
Immune-related meningoencephalitis, all grades	• Permanently discontinue atezolizumab. • Refer patient to neurologist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day IV methylprednisolone and convert to 1–2 mg/kg/day oral prednisone or equivalent upon improvement. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

Renal events

Immune-mediated nephritis has been associated with the administration of atezolizumab. Eligible patients must have adequate renal function. Renal function, including serum creatinine, should be monitored throughout study treatment. Patients with abnormal renal function should be evaluated and treated for other more common etiologies (including prerenal and postrenal causes, and concomitant medications such as non-steroidal anti-inflammatory drugs). Refer the patient to a renal specialist if clinically indicated. A renal biopsy may be required to enable a definitive diagnosis and appropriate treatment.

Patients with signs and symptoms of nephritis, in the absence of an identified alternate etiology, should be treated according to the guidelines in the table below.

Event	Management
Renal event, Grade 1	• Continue atezolizumab. • Monitor kidney function, including creatinine, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	• Withhold atezolizumab for up to 12 weeks after event onset. [a] • Refer patient to renal specialist. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event resolves to Grade 1 or better, resume atezolizumab. [b] • If event does not resolve to Grade 1 or better while withholding atezolizumab, permanently discontinue atezolizumab.
Renal event, Grade 3 or 4	• Permanently discontinue atezolizumab. • Refer patient to renal specialist and consider renal biopsy. • Initiate treatment with corticosteroids equivalent to 1–2 mg/kg/day oral prednisone. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

[a] Atezolizumab may be withheld for a longer period of time (i.e., >12 weeks after event onset) to allow for corticosteroids (if initiated) to be reduced to the equivalent of ≤10 mg/day oral prednisone. The acceptable length of the extended period of time must be determined by the investigator.

b If corticosteroids have been initiated, they must be tapered over ≥1 month to the equivalent of ≤10 mg/day oral prednisone before atezolizumab can be resumed.

Immune-Mediated Myositis

Immune-mediated myositis has been associated with the administration of atezolizumab. Myositis or inflammatory myopathies are a group of disorders sharing the common feature of inflammatory muscle injury; dermatomyositis and polymyositis are among the most common disorders. Initial diagnosis is based on clinical (muscle weakness, muscle pain, skin rash in dermatomyositis), biochemical (serum creatine kinase increase), and imaging (electromyography/MRI) features, and is confirmed with a muscle biopsy.

Patients with signs and symptoms of myositis, in the absence of an identified alternate etiology, should be treated according to the guidelines in table below.

Event	Management
Immune-mediated myelitis, Grade 1	• Continue atezolizumab unless symptoms worsen or do not improve. • Investigate etiology and refer patient to a neurologist.
Immune-mediated myelitis, Grade 2	• Permanently discontinue atezolizumab. • Investigate etiology and refer patient to a neurologist. • Rule out infection. • Initiate treatment with corticosteroids equivalent to 1-2 mg/kg/day oral prednisone.
Immune-mediated myelitis, Grade 3 or 4	• Permanently discontinue atezolizumab. • Refer patient to a neurologist. • Initiate treatment as per institutional guidelines.

Hemophagocytic Lymphohistiocytosis and Macrophage Activation Syndrome

Immune-mediated reactions may involve any organ system and may lead to hemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS).

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2017). A patient should be classified as having HLH if five of the following eight criteria are met:

- Fever ≥ 38.5°C
- Splenomegaly
- Peripheral blood cytopenia consisting of at least two of the following:
  - Hemoglobin < 90 g/L (9 g/dL) (<100 g/L [10 g/dL] for infants < 4 weeks old)
  - Platelet count < 100×10^9/L (100,000/mcL)
  - ANC < 1.0×10^9/L (1000/mcL)
- Fasting triglycerides >2.992 mmol/L (265 mg/dL) and/or fibrinogen <1.5 g/L (150 mg/dL)
- Hemophagocytosis in bone marrow, spleen, lymph node, or liver
- Low or absent natural killer cell activity
- Ferritin >500 mg/L (500 ng/mL)
- Soluble interleukin 2 (IL-2) receptor (soluble CD25) elevated ≥ 2 standard deviations above age-adjusted laboratory-specific norms

Patients with suspected MAS should be diagnosed according to published criteria for systemic juvenile idiopathic arthritis by Ravelli *et al*. (2016). A febrile patient should be classified as having MAS if the following criteria are met:

- Ferritin >684 mg/L (684 ng/mL)
- At least two of the following:
  - Platelet count ≤ 181×10^9/L (181,000/mcL)
  - AST ≥48 U/L
  - Triglycerides >1.761 mmol/L (156 mg/dL)
  - Fibrinogen ≤3.6 g/L (360 mg/dL)

Patients with suspected HLH or MAS should be treated according to the guidelines in below.

Event	Management
Suspected HLH or MAS	• Permanently discontinue atezolizumab and contact Medical Monitor. • Consider patient referral to hematologist. • Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. • Consider initiation of IV corticosteroids and/or an immunosuppressive agent. • If event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. • If event resolves to Grade 1 or better, taper corticosteroids over ≥1 month.

HLH=hemophagocytic lymphohistiocytosis; MAS=macrophage activation syndrome.

9.0 ADVERSE EVENTS

The prompt reporting of adverse events is the responsibility of each investigator engaged in clinical research, as required by Federal Regulations. Beginning April 1, 2018, adverse events must be described and graded using the terminology and grading categories defined in the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 5.0. The CTCAE is available at ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. Attribution to protocol treatment for each adverse event must be determined by the investigator and reported on the required forms. Please refer the NCI Guidelines: Adverse Event Reporting Requirements for further details on AE reporting procedures.

To complement CTCAE reporting, patients aged ≥ 18 years will self-report their side effects using the PRO-CTCAE. The specific PRO-CTCAE items for this protocol can be found in Appendix I. They can also be found at: http://healthcaredelivery.cancer.gov/pro-ctcae/instrument.html.

NOTE: PRO-CTCAE data should not be used for determining attribution, dose modifications, or reporting of serious adverse events.

9.1 Routine Adverse Event Reporting

Adverse event data collection and reporting, which are required as part of every clinical trial are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times according to the Study Calendar in Section 5.0. For this trial, the Form "Adverse Events" is used for routine AE reporting in Rave.

9.1.1 Rave-CTEP-AERS integration

The Rave Cancer Therapy Evaluation Program Adverse Event Reporting System (CTEP-AERS) integration enables evaluation of post-baseline Adverse Events (AE) entered in Rave to determine whether they require expedited reporting and facilitates entry in CTEP-AERS for those AEs requiring expedited reporting.

All AEs that occur after start of treatment are collected in Medidata Rave using the Adverse Event form, which is available for entry at each treatment course or reporting period, and used to collect AEs that start during the period or persist from the previous reporting period. AEs that occur 30 days after the last administration of the investigational agent/intervention are collected using the Late Adverse Event form.

The CRA will enter AEs that occur prior to the start of treatment on a baseline form that is not included in the Rave-CTEP-AERS integration. AEs that occur prior to enrollment must begin and end on the baseline Adverse Events form and should not be included on the standard Adverse Events form that is available at treatment unless there has been an increase in grade.

Prior to sending AEs through the rules evaluation process, site staff should verify the following on the Adverse Event form in Rave:

- The reporting period (course/cycle) is correct; and
- AEs are recorded and complete (no missing fields) and the form is query free.

The CRA reports AEs in Rave at the time the Investigator learns of the event. If the CRA modifies an AE, it must be re-submitted for rules evaluation.

Upon completion of AE entry in Medidata Rave, the CRA submits the AE for rules evaluation by completing the Expedited Reporting Evaluation form. Both NCI and protocol-specific reporting rules evaluate the AEs submitted for expedited reporting. A report is initiated in CTEP-AERS using information entered in Medidata Rave for AEs that meet reporting requirements. The CRA completes the report by accessing CTEP-AERS via a direct link on the Medidata Rave Expedited Reporting Evaluation form. Contact the CTSU Help Desk at 1-888-823-5923 or by email at ctsucontact@westat.com if you have any issues submitting an expedited report in CTEP-AERS.

In the rare occurrence that Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at 301-897-7497. Once Internet connectivity is restored, the 24-hour notification that was phoned in must be entered immediately into CTEP-AERS using the direct link from Medidata Rave.

Additional information about the CTEP-AERS integration is available on the CTSU website:

- Study specific documents: *Protocols > Documents> Protocol Related Documents> Adverse Event Reporting*; and
- Additional resources: *Resources > CTSU Operations Information> User Guides & Help Topics*.
- NCI requirements for SAE reporting are available on the CTEP website:
- NCI Guidelines for Investigators: Adverse Event Reporting Requirements is available at https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf

PRO-CTCAE paper booklets ordered from the CTSU website are to be administered by a nurse/CRA and completed by the patient at scheduled times according to the Study Calendar in Section 5.0 and entered into Rave.

9.1.2 Solicited Adverse Events

The following adverse events are considered "expected" and their presence/absence should be solicited, and severity graded, at baseline and for each cycle of treatment by CTCAE, PRO-CTCAE, or both.

NOTE: PRO-CTCAE data should not be used for determining attribution, dose modifications, or reporting of serious adverse events.

CTCAE v5.0 Term	PRO-CTCAE v1.0 Term	CTCAE v5.0 System Organ Class (SOC)
The following adverse events should be solicited at baseline and for each treatment cycle:		
Hypothyroidism		Endocrine disorders
Abdominal Pain	Pain in the abdomen (belly area)	Gastrointestinal disorders
Constipation	Constipation	Gastrointestinal disorders
Nausea	Nausea	Gastrointestinal disorders
Fatigue	Fatigue, tiredness, or lack of energy	General disorders and administration site conditions
Anorexia	Decreased appetite	Metabolism and nutrition disorders
Cough	Cough	Respiratory, thoracic, and mediastinal disorders
Dyspnea	Shortness of breath	Respiratory, thoracic, and mediastinal disorders
Fever		General disorders
Blood bilirubin increased		Investigations
Neutrophil count decreased		Investigations
Platelet count decreased		Investigations
	Loose or watery stools (diarrhea)	Gastrointestinal disorders
	Vomiting	Gastrointestinal disorders
	Numbness or tingling in your hands or feet	Nervous system disorders

CTCAE v5.0 Term	PRO-CTCAE v1.0 Term	CTCAE v5.0 System Organ Class (SOC)
	Heartburn	Gastrointestinal disorders
Palmar-plantar erythrodysesthesia syndrome	Hand-foot syndrome (a rash of the hands or feet that can cause cracking, peeling, redness, or pain)	Skin and subcutaneous tissue disorders
	Rash	Skin and subcutaneous tissue disorders
	Itchy skin	Skin and subcutaneous tissue disorders
	Mouth or throat sores	Gastrointestinal disorders
The following adverse events should be solicited as clinically indicated*:		
Alanine aminotransferase increased[1]		Investigations
Aspartate aminotransferase increased[1]		Investigations
Hepatitis		Infections and infestations
Encephalitis infection		Infections and infestations
Kidney infection		Infections and infestations
Infective myositis		Infections and infestations
Infections and infestations – Other, specify[2]		Infections and infestations
Pneumonitis		Respiratory, thoracic, and mediastinal disorders
Colitis		Gastrointestinal disorders
Pancreatitis		Gastrointestinal disorders
Hyperglycemia		Metabolism and nutrition disorders
Hyperthyroidism		Endocrine disorders

CTCAE v5.0 Term	PRO-CTCAE v1.0 Term	CTCAE v5.0 System Organ Class (SOC)
Adrenal insufficiency		Endocrine disorders
Hypophysitis		Endocrine disorders
Blood and lymphatic system disorders – Other, specify		Blood and lymphatic system disorders
Autoimmune disorder[3]		Immune system disorders
Cytokine release syndrome[4]		Immune system disorders
Immune system disorders – Other, specify[3, 4]		Immune system disorders
Flu like symptoms[4]		General disorders and administration site conditions
Uveitis		Eye disorders
Retinopathy		Eye disorders
Generalized muscle weakness[3]		Musculoskeletal and connective tissue disorders
Rhabdomyolysis		Musculoskeletal and connective tissue disorders
Musculoskeletal and connective tissue disorder – Other, specify[3]		Musculoskeletal and connective tissue disorders
Atrial fibrillation		Cardiac disorders
Myocarditis		Cardiac disorders
Pericarditis		Cardiac disorders
Vasculitis		Vascular disorders

* If the AE is not clinically indicated, then its presence/absence would not need to be solicited for that time point.

AEs of special interest have been incorporated above, please note the clarifications below:

1. Cases of potential drug-induced liver injury that include an elevated ALT or AST in combination with either an elevated bilirubin or clinical jaundice, as defined by Hy's Law and based on the following observations:

a. Treatment-emergent ALT or AST > 3 x baseline value in combination with total bilirubin > 2 x ULN (of which > 35% is direct bilirubin)
b. Treatment-emergent ALT or AST > 3 x baseline value in combination with clinical jaundice

2. Suspected transmission of an infectious agent by the study treatment, as defined below:
   a. Any organism, virus, or infectious particle (e.g. prion protein transmitting transmissible spongiform encephalopathy), pathogenic or non-pathogenic, is considered an infectious agent. A transmission of an infectious agent may be suspected from clinical symptoms or laboratory findings that indicate an infection in a patient exposed to a medicinal product. This term applies only when a contamination of study treatment is suspected.
3. Neurological Disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
4. Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, influenza-like illness, macrophage activation syndrome, hemophagocytic lymphohistiocytosis

9.2 CTCAE Routine Reporting Requirements

In addition to the solicited adverse events listed in Section 9.1, the following table outlines the combinations of time points, grades and attributions of AEs that require routine reporting to the Alliance Statistics and Data Center. Questions about routine reporting should be directed to the Data Manager.

NOTE: PRO-CTCAE data should not be used for determining attribution, dose modifications, or reporting of serious adverse events.

Combinations of CTCAE Grade & Attribution Required for Routine AE Data Submission on Case Report Forms (CRFs)

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated			a	a	a
Unlikely			a	a	a
Possible	a	a	a, b	a, b	a, b
Probable	a	a	a, b	a, b	a, b
Definite	a	a	a, b	a, b	a, b

a) Adverse Events CRF - Applies to AEs occurring between registration and within 30 days of the patient's last treatment date, or as part of the Clinical Follow-Up Phase.

b) Late Adverse Events CRF - Applies to AEs occurring greater than 30 days after the patient's last treatment date up to the end of the survival follow-up period.

9.3 Expedited Adverse Event Reporting (Rave-CTEP-AERS)

Investigators are required by Federal Regulations to report serious adverse events as defined in the table below. Alliance investigators are required to notify the Alliance Central Protocol Operations Program, the Study Chair, and their Institutional Review Board if a patient has a reportable serious adverse event. The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 will be utilized for AE

reporting. The CTCAE is identified and located on the CTEP website at: ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE. All reactions must first be reported in Rave on the "Adverse Events" Form and sent for rule evaluation at the time of the event. Adverse event data should not be entered in CTEP-AERS prior to entry in Rave for rules evaluation. Additional information about Rave-CTEP-AERS is available on the CTSU website (https://www.ctsu.org) under the "Resources" tab for each study.

In the rare occurrence when Internet connectivity is lost, a 24-hour notification is to be made to CTEP by telephone at (301) 897-7497. Once Internet connectivity is restored, the 24-hour notification phoned in must be entered electronically by the original submitter at the site.

For further information on the NCI requirements for SAE reporting, please refer to the 'NCI Guidelines for Investigators: Adverse Event Reporting Requirements' document published by the NCI.

NOTE: PRO-CTCAE data should not be used for determining attribution, dose modifications, or reporting serious adverse events.

Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

9.3.1 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies Under an IND/IDE ≤ 30 Days of the Last Administration of the Investigational Agent/Intervention [1]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** SAEs, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).

An AE is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening AE
3) An AE that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SAEs that meet the above criteria **MUST** be immediately reported to the NCI via CTEP-AERS within the timeframes detailed in the table below.

Grade 1-3 Timeframes	Grade 4-5 Timeframes
24-Hour notification, 10 Calendar Days	24-Hour notification, 5 Calendar Days

NOTE: Protocol-specific exceptions to expedited reporting of SAEs are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR.

Expedited AE reporting timeframes are defined as:

- "24-Hour notification, 5 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.

○ "24-Hour notification, 10 Calendar Days" - The SAE must initially be reported via CTEP-AERS within 24 hours of learning of the SAE, followed by a complete expedited report within 10 calendar days of the initial 24-hour report.
[1]SAEs that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows: **Expedited 24-Hour notifications are required for all SAEs followed by a complete report** • Within 5 calendar days for Grade 4-5 SAEs • Within 10 calendar days for Grade 1-3 SAEs [2]For studies using nuclear medicine or molecular imaging IND agents (NM, SPECT, or PET), the SAE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period. Effective Date: August 30, 2024

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Additional Instructions or Exclusions to CTEP-AERS Expedited Reporting Requirements for Phase 2 and 3 Trials Utilizing an Agent Under a CTEP IND or non-CTEP IND:

- All adverse events reported via CTEP-AERS (i.e. serious adverse events) should also be forwarded to your local IRB.
- Alliance A021502 uses a drug under a CTEP IND. The reporting requirements for investigational agents under a CTEP IND should be followed for all agents (any arm) in this trial.
- Grade 3 or 4 hematosuppression resulting in hospitalization does not require CTEP-AERS, but should be submitted as part of study results.
- All new malignancies must be reported via CTEP-AERS whether or not they are thought to be related to either previous or current treatment. All new malignancies should be reported, i.e. solid tumors (including non-melanoma skin malignancies), hematologic malignancies, myelodysplastic syndrome/acute myelogenous leukemia, and in situ tumors. In CTCAE version 5.0, the event(s) may be reported as one of the following: (1) Leukemia secondary to oncology chemotherapy, (2) Myelodysplastic syndrome, or (3) Treatment-related secondary malignancy. Whenever possible, the CTEP-AERS reports for new malignancies should include tumor pathology, history or prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics of the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome, if available. New primary malignancies should be reported using study Form Notice of New Primary.
- Grade 1-3 nausea or vomiting resulting in hospitalization does not require AERS reporting, but should be reported via routine AE reporting.
- Grade 3 or 4 nausea or vomiting not resulting in hospitalization does not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 oral mucositis resulting in hospitalization does not require AERS reporting, but should be reported via routine AE reporting
- Grade 3 or 4 oral mucositis not resulting in hospitalization does not require AERS reporting, but should be reported via routine AE reporting

- Grade 1-3 peripheral sensory neuropathy resulting in hospitalization does not require AERS reporting, but should be reported via routine AE reporting.
- Grade 3 peripheral sensory neuropathy not resulting in hospitalization does not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 hand foot syndrome resulting in hospitalization does not require AERS reporting, but should be reported via routine AE reporting
- Grade 3 hand foot syndrome not resulting in hospitalization does not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 hypersensitivity reaction resulting in hospitalization does not require AERS reporting, but should be reported via routine AE reporting.
- Grade 3 or 4 hypersensitivity reaction not resulting in hospitalization does not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 dehydration resulting in hospitalization does not require AERS reporting, but should be reported via routine AE reporting
- Grade 3 dehydration not resulting in hospitalization does not require AERS reporting, but should be reported via routine AE reporting
- Grade 1-3 fatigue resulting in hospitalization does not require AERS reporting, but should be reported via routine AE reporting.
- Grade 3 or 4 fatigue not resulting in hospitalization does not require AERS reporting, but should be reported via routine AE reporting
- Treatment expected adverse events include those listed in Section 10.0 and in the Comprehensive Adverse Events and Potential Risks list (CAEPR) below.
- CTEP-AERS reports should be submitted electronically.
- Pregnancy, as well as its outcome, must be reported as an AE in Rave and submitted for rules evaluation.
- Pregnancy loss
  - Pregnancy loss is defined in CTCAE as “Death in utero.”
  - Any Pregnancy loss should be reported expeditiously, as Grade 4 “Pregnancy loss” under the Pregnancy, puerperium and perinatal conditions SOC.
  - A Pregnancy loss should NOT be reported as a Grade 5 event under the Pregnancy, puerperium and perinatal conditions SOC, as currently CTEP-AERS recognizes this event as a patient death.
- A neonatal death should be reported expeditiously as Grade 4, “Death neonatal” under the General disorders and administration SOC.
- Death due to progressive disease should be reported as Grade 5 “Disease progression” under the system organ class (SOC) “General disorders and administration site conditions.” Evidence that the death was a manifestation of underlying disease (e.g. radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.
- Any death occurring within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.

- Any death occurring greater than 30 days after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.

9.4 Comprehensive Adverse Events and Potential Risks List (CAEPR) for Atezolizumab (MPDL3280A, NSC 783608)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 3097 patients*. Below is the CAEPR for Atezolizumab (MPDL3280A).

NOTE: PRO-CTCAE data should not be used for determining attribution, dose modifications, or reporting of serious adverse events.

NOTE: Report AEs on the SPEER ONLY IF they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		
CARDIAC DISORDERS			
		Heart failure[2]	
		Myocarditis[2]	
		Pericardial effusion[2]	
		Pericardial tamponade[2]	
		Pericarditis[2]	
ENDOCRINE DISORDERS			
		Adrenal insufficiency[2]	
		Endocrine disorders - Other (diabetes)[2]	
	Hyperthyroidism[2]		
		Hypophysitis[2]	
	Hypothyroidism[2]		
EYE DISORDERS			
		Eye disorders - Other (ocular inflammatory toxicity)[2]	
		Uveitis[2]	
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
		Colitis[2]	
	Diarrhea		***Diarrhea (Gr 2)***
	Dysphagia		
	Nausea		***Nausea (Gr 2)***
		Pancreatitis[2]	
	Vomiting		***Vomiting (Gr 2)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 2)***
	Fever[3]		
	Flu like symptoms[3]		
HEPATOBILIARY DISORDERS			
		Hepatic failure[2]	
		Hepatobiliary disorders - Other [immune related (hepatitis)][2]	
IMMUNE SYSTEM DISORDERS			
	Allergic reaction[3]		
		Anaphylaxis[3]	
		Cytokine release syndrome[3]	

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Immune system disorders - Other (hemophagocytic lymphohistiocytosis (HLH)/macrophage activation syndrome (MAS))[2]	
		Immune system disorders - Other (systemic immune activation)[2]	
INFECTIONS AND INFESTATIONS			
Infection[4]			
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[3]		
INVESTIGATIONS			
	Alanine aminotransferase increased[2] Alkaline phosphatase increased[2]		
	Aspartate aminotransferase increased[2]		
	Blood bilirubin increased[2]		
		Creatinine increased	
	GGT increased		
	Lipase increased*		
		Platelet count decreased	
	Serum amylase increased*		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 2)***
		Hyperglycemia[2]	
	Hypokalemia		
	Hyponatremia		
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia[2]		
	Back pain		
		Generalized muscle weakness	
	Myalgia		
		Myositis[2]	
NERVOUS SYSTEM DISORDERS			
		Ataxia[2]	
		Encephalopathy[2]	
		Guillain-Barre syndrome[2]	
		Myasthenia gravis[2]	
		Nervous system disorders - Other (meningitis non-infective)[2]	
		Nervous system disorders - Other (facial paresis)[2]	

Adverse Events with Possible Relationship to Atezolizumab (MPDL3280A) (CTCAE 5.0 Term) [n= 3097]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Nervous system disorders - Other (encephalitis non-infective)[2]	
		Nervous system disorders - Other (immune-mediated myelitis)[2]	
		Paresthesia[2]	
		Peripheral motor neuropathy[2]	
		Peripheral sensory neuropathy[2]	
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
		Renal and urinary disorders - Other (nephritis)[2]	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea Hypoxia		
	Nasal congestion		***Nasal congestion (Gr 2)***
		Pleural effusion[2]	
		Pneumonitis[2]	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Bullous dermatitis[2]	
		Erythema multiforme[2]	
	Pruritus		
	Rash acneiform		
	Rash maculo-papular		
		Skin and subcutaneous tissue disorders - Other (drug reaction with eosinophilia and systemic symptoms [DRESS]) [2]	
	Skin and subcutaneous tissue disorders - Other (lichen planus)[2]		
		Skin and subcutaneous tissue disorders - Other (exanthematous pustulosis)[2]	
		Stevens-Johnson syndrome[2]	
		Toxic epidermal necrolysis[2]	

*Denotes adverse events that are <3%.

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Atezolizumab, being a member of a class of agents involved in the inhibition of "immune checkpoints," may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. Immune-mediated adverse reactions have been reported in patients receiving atezolizumab. Adverse events potentially related to atezolizumab may be manifestations of immune-mediated adverse events. In clinical trials, most immune-mediated adverse reactions were reversible and managed with interruptions of atezolizumab, administration of corticosteroids and supportive care.

[3]Infusion reactions, including high-grade hypersensitivity reactions, anaphylaxis, and cytokine release syndrome, which have been observed following administration of atezolizumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of atezolizumab.

[4]Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

Adverse events reported on atezolizumab (MPDL3280A) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that atezolizumab (MPDL3280A) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (pancytopenia); Febrile neutropenia
CARDIAC DISORDERS - Cardiac arrest; Ventricular tachycardia
GASTROINTESTINAL DISORDERS - Constipation; Dry mouth; Ileus
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Multi-organ failure
HEPATOBILIARY DISORDERS - Portal vein thrombosis
INVESTIGATIONS - Lymphocyte count decreased; Neutrophil count decreased; Weight loss; White blood cell decreased
METABOLISM AND NUTRITION DISORDERS - Hypophosphatemia; Tumor lysis syndrome
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Bone pain; Muscle cramp: Pain in extremity
NERVOUS SYSTEM DISORDERS - Headache
PSYCHIATRIC DISORDERS - Confusion; Insomnia; Suicide attempt
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Breast pain
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchopulmonary hemorrhage; Pulmonary hypertension; Respiratory failure
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin[2]; Hyperhidrosis
VASCULAR DISORDERS - Hypertension; Hypotension; Thromboembolic event

Note: Atezolizumab (MPDL3280A) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

9.5 CDUS Monitoring

The assigned monitoring method for this protocol is CDUS-Abbreviated.

This study will be monitored by the Clinical Data Update System (CDUS) Version 3.0. Cumulative protocol- and patient-specific CDUS data will be submitted electronically to CTEP on a quarterly basis by FTP burst of data. Reports are due January 31, April 30, July 31, and October 31. Instructions for submitting data using the CDUS can be found on the CTEP website: (http://ctep.cancer.gov/reporting/cdus.html).

Note: If your study has been assigned to CDUS-Complete reporting, **all** adverse events (both routine and expedited) that have occurred on the study and meet the mandatory CDUS reporting

guidelines must be reported via the monitoring method identified above. If your study has been assigned to CDUS-Abbreviated reporting, no adverse event reporting (routine or expedited) is required to be reported via CDUS, but expedited adverse events are still required to be submitted via CTEP-AERS.

10.0 DRUG INFORMATION

10.1 General Considerations

Chemotherapy drug dosages need not be changed unless the calculated dose changes by ≥ 10%.

10.2 Fluorouracil (Adrucil®, 5FU)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Commercially available for injection 50 mg/mL (10 mL, 20 mL, 50 mL, and 100 mL).

Preparation, Storage and Stability

Store intact vials at room temperature and protect from light. A slight discoloration may occur with storage but usually does not denote decomposition. Dilute in 50 – 1000 mL of 0.9% NaCl or D5W. If exposed to cold, a precipitate may form; gentle heating to 60ºC will dissolve the precipitate without impairing the potency. Solutions in 50 – 1000 mL 0.9% NaCl or D5W or undiluted solutions in syringes are stable for 72 hours at room temperature. Fluorouracil should not be co-administered with either diazepam, doxorubicin, daunorubicin, idarubicin, cisplatin, or cytarabine. However, fluorouracil and leucovorin are compatible for 14 days at room temperature. Fluorouracil is compatible with vincristine, methotrexate, and cyclophosphamide.

Administration

Fluorouracil may be given IV bolus or IV infusion. Refer to the treatment section for specific administration instructions. Avoid extravasation, may be an irritant.

Drug Interactions

Fluorouracil may increase effects of warfarin. Avoid ethanol (due to GI irritation). Avoid black cohosh.

Pharmacokinetics

Distribution: V_d ~ 22% of total body water; penetrates extracellular fluid, CSF, and third space fluids (e.g. pleural effusions and ascitic fluid)

Metabolism: Hepatic (90%); via a dehydrogenase enzyme; Fluorouracil must be metabolized to be active.

Half-life Elimination: Biphasic: Initial: 6-20 minutes; two metabolites, FdUMP and FUTP, have prolonged half-lives depending on the type of tissue.

Excretion: Lung (large amounts as CO_2); urine (5% as unchanged drug) in 6 hours.

Adverse Events

Consult the package insert for the most current and complete information.

Common Known Potential Toxicities, > 10%:

Dermatologic: Dermatitis, pruritic maculopapular rash, alopecia.

Gastrointestinal (route and schedule dependent): Heartburn, nausea, vomiting, anorexia, stomatitis, esophagitis, anorexia, diarrhea. GI toxicity (anorexia, nausea, and vomiting) is generally more severe with continuous-infusion schedules.

Emetic Potential: <1000 mg: Moderately low (10% to 30%) ≥ 1000 mg: Moderate (30% to 60%)

Hematologic: Leukopenia; Myelosuppressive (tends to be more pronounced in patients receiving bolus dosing of FU). Decreased white blood cell count with increased risk of infection; decreased platelet count with increased risk of bleeding.

Local: Irritant chemotherapy.

Less Common Known Potential Toxicities, 1% - 10%:

Dermatologic: Dry skin

Gastrointestinal: GI ulceration

Rare Known Potential Toxicities, <1% (Limited to Important or Life-threatening):

Cardiac enzyme abnormalities, chest pain, coagulopathy, dyspnea, ECG changes similar to ischemic changes, hepatotoxicity; hyperpigmentation of nail beds, face, hands, and veins used in infusion; hypotension, palmar-plantar syndrome (hand-foot syndrome), photosensitization. Cerebellar ataxia, headache, somnolence, ataxia are seen primarily in intracarotid arterial infusions for head and neck tumors.

Nursing Guidelines

Monitor complete blood count and platelet count. Instruct patient to report signs and symptoms of infection, unusual bruising or bleeding to the physician.

Administer antiemetics as indicated.

Diarrhea may be dose–limiting; encourage fluids and treat symptomatically.

Assess for stomatitis; oral care measures as indicated. May try vitamin E oil dabbed on sore, six times daily. Cryotherapy recommended with IV push administration.

Monitor for neurologic symptoms (headache, ataxia).

Inform patient of potential alopecia.

Those patients on continuous infusion may need instruction regarding central intravenous catheters and portable intravenous or IA infusion devices.

5FU–induced conjunctivitis is a common problem. Advise patient to report any eye soreness or redness to the healthcare team.

Photosensitivity may occur. Instruct patients to wear sun block when outdoors.

10.3 Leucovorin Calcium

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler

Formulation

**Note: Levoleucovorin is a different from leucovorin.

Leucovorin is available as:

- Solution for Injection 100 mg/10mL (10mL, 30 mL)
- Lyophilized Powder for Injection 50 mg, 100 mg, 200 mg, 350 mg, 500 mg

Preparation, Storage and Stability

Powder for Injection: Store at room temperature of 25°C (77°F). Protect from light. Solutions reconstituted with bacteriostatic water for injection U.S.P., must be used within 7 days. Solutions reconstituted with SWFI must be used immediately. Parenteral admixture is stable for 24 hours stored at room temperature (25°C) and for 4 days when stored under refrigeration (4°C). Powder for injection: Reconstitute with SWFI or BWFI; dilute with D5W or NS for infusion. When doses > 10 mg/m^2 are required, reconstitute using sterile water for injection, not a solution containing benzyl alcohol.

Solution for Injection: Prior to dilution, store vials under refrigeration at 2°C to 8°C (36°F to 46°F). Protect from light. Dilute in D5W or NS for infusion.

Administration

Should be administered IV infusion (2 hours) and is not intended for intrathecal use.

Combination Therapy with Fluorouracil: Fluorouracil is usually given after, or at the midpoint, of the leucovorin infusion. Leucovorin is usually administered by IV infusion. Other administration schedules have been used; refer to individual protocols.

Drug Interactions

Capecitabine: Leucovorin Calcium-Levoleucovorin may enhance the adverse/toxic effect of Capecitabine. Risk C: Monitor therapy

Fluorouracil (Systemic): Leucovorin Calcium-Levoleucovorin may enhance the adverse/toxic effect of Fluorouracil (Systemic). This effect is associated with the ability of leucovorin or levoleucovorin to enhance the anticancer effects of fluorouracil. Risk C: Monitor therapy

Fluorouracil (Topical): Leucovorin Calcium-Levoleucovorin may enhance the adverse/toxic effect of Fluorouracil (Topical). Risk C: Monitor therapy

Fosphenytoin: Leucovorin Calcium-Levoleucovorin may decrease the serum concentration of Fosphenytoin. Risk C: Monitor therapy

Glucarpidase: May decrease serum concentrations of the active metabolite(s) of Leucovorin Calcium-Levoleucovorin. Specifically, 6S-5-methyltetrahydrofolateconcentrations may be reduced. Glucarpidase may decrease the serum concentration of Leucovorin Calcium-Levoleucovorin. Management: Avoid leucovorin administration within 2 hours of glucarpidase dosing. Continue to administer the pre-glucarpidase leucovorin dose for at least the first 48 hours after glucarpidase administration, and dose based on methotrexate concentration thereafter. Risk D: Consider therapy modification

PHENobarbital: Leucovorin Calcium-Levoleucovorin may decrease the serum concentration of PHENobarbital. Risk C: Monitor therapy

Phenytoin: Leucovorin Calcium-Levoleucovorin may decrease the serum concentration of Phenytoin. Risk C: Monitor therapy

Primidone: Leucovorin Calcium-Levoleucovorin may decrease the serum concentration of Primidone. Additionally, leucovorin/levoleucovorin may decrease concentrations of active metabolites of primidone (e.g. phenobarbital). Risk C: Monitor therapy

Raltitrexed: Leucovorin Calcium-Levoleucovorin may diminish the therapeutic effect of Raltitrexed. Risk X: Avoid combination

Tegafur: Leucovorin Calcium-Levoleucovorin may enhance the adverse/toxic effect of Tegafur. This effect is associated with the ability of leucovorin or levoleucovorin to enhance the anticancer effects of fluorouracil. Risk C: Monitor therapy

Trimethoprim: Leucovorin Calcium-Levoleucovorin may diminish the therapeutic effect of Trimethoprim. Management: Avoid concurrent use of leucovorin or levoleucovorin with trimethoprim (plus sulfamethoxazole) for Pneumocystis jiroveci pneumonia. If trimethoprim is used for another indication, monitor closely for reduced efficacy. Risk X: Avoid combination

Pharmacokinetics

Absorption: Oral, IM: Well absorbed

Metabolism: Intestinal mucosa and hepatically to 5-methyl-tetrahydrofolate (5MTHF; active)

Bioavailability: Saturable at oral doses >25 mg; 25 mg (97%), 50 mg (75%), 100 mg (37%)

Half-life Elimination: ~4-8 hours

Time to Peak: Oral: ~2 hours; IV: Total folates: 10 minutes; 5MTHF: ~1 hour

Excretion: Urine (primarily); feces

Adverse Events

Consult the package insert for the most current and complete information.

Dermatologic: Rash, pruritus, erythema, urticaria

Hematologic: Thrombocytosis

Respiratory: Wheezing

Miscellaneous: Allergic reactions, anaphylactoid reactions

Nursing Guidelines

Headache may occur. Advise patient that analgesics such as Tylenol may help. Instruct patient to report any headache that is unrelieved.

Observe for sensitization reaction (rash, hives, pruritus, facial flushing, and wheezing).

May potentiate the toxic effects of fluoropyrimidine (5-FU) therapy, resulting in increased hematologic and gastrointestinal (diarrhea, stomatitis) adverse effects. Monitor closely.

May cause mild nausea or upset stomach. Administer antiemetics if necessary and evaluate for their effectiveness.

10.4 Oxaliplatin (Eloxatin®, OXAL)

Procurement

Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

Formulation

Commercially Available for Injection as: Solution [preservative free]: 5 mg/mL (10 mL, 20 mL, and 40 mL)

Preparation, Storage and Stability

Refer to package insert for complete preparation and dispensing instructions. Store intact vials in original outer carton at room temperature and; do not freeze. According to the manufacturer, solutions diluted for infusion are stable up to 6 hours at room temperature or up to 24 hours under refrigeration. Oxaliplatin solution diluted with D_5W to a final concentration of 0.7 mg/mL (polyolefin container) has been shown to retain >90% of its original concentration for up to 30 days when stored at room temperature or refrigerated; artificial light did not affect the concentration (Andre, 2007). As this study did not examine sterility, refrigeration would be preferred to limit microbial growth. Do not prepare using a chloride-containing solution (e.g. NaCl). Dilution with D_5W (250 or 500 mL) is required prior to administration. Infusion solutions do not require protection from light.

Administration

Refer to the treatment section for specific administration instructions. Administer as I.V. infusion over 2 hours. Flush infusion line with D5W prior to administration of any concomitant medication. Patients should receive an antiemetic premedication regimen. Cold temperature may exacerbate acute neuropathy. Avoid mucositis prophylaxis with ice chips during oxaliplatin infusion.

Drug Interactions

Increased Effect/Toxicity: Nephrotoxic agents may increase Oxaliplatin toxicity.

When administered as sequential infusions, observational studies indicate a potential for increased toxicity when platinum derivatives (carboplatin, cisplatin, oxaliplatin) are administered before taxane derivatives (docetaxel, paclitaxel).

Decreased Effect: Oxaliplatin may decrease plasma levels of digoxin

Pharmacokinetics

Distribution: V_d: 440 L

Protein Binding: >90% primarily albumin and gamma globulin (irreversible binding to platinum)

Metabolism: Nonenzymatic (rapid and extensive), forms active and inactive derivative phase: 16.8 hours

Excretion: Primarily urine (~54%); feces (~2%)

Adverse Events

Consult the package insert for the most current and complete information. Percentages reported with monotherapy.

Common Known Potential Toxicities, > 10%:

Central nervous system: Fatigue, fever, pain, headache, insomnia

Gastrointestinal: Nausea, diarrhea, vomiting, abdominal pain, constipation, anorexia, stomatitis

Hematologic: Anemia, thrombocytopenia, leukopenia

Hepatic: Liver enzymes increased

Neuromuscular & skeletal: Back pain, peripheral neuropathy (may be dose limiting). The most commonly observed oxaliplatin-related toxicity is acute and cumulative neurotoxicity, observed in patients treated at doses above 100 mg/m^2/cycle. This neurotoxicity has included paresthesias and dysesthesias of the hands, feet, and perioral region as well as unusual laryngopharyngeal dysesthesias characterized by a loss of sensation of breathing without any objective evidence of respiratory distress (hypoxia, laryngospasm, or bronchospasm). OXAL neurotoxicity appears to be exacerbated by exposure to cold. Patients on this study will be counseled to avoid cold drinks and exposure to cold water or air. Should a patient develop laryngopharyngeal dysesthesia, their oxygen saturation should be evaluated via a pulse oximeter; if normal, an anxiolytic agent should be given and the patient observed in the clinic until the episode has resolved. Because this syndrome may be associated with the rapidity of OXAL infusion, subsequent doses of OXAL should be administered as a 6-hour infusion (instead of the normal 2-hour infusion).

Acute and cumulative neurotoxicities are dose limiting for OXAL. The acute neurotoxicity is characterized by paresthesias and dysesthesias that may be triggered or exacerbated by exposure to cold. These symptoms occur within hours of exposure and are usually reversible over the following hours or days. Cumulative doses of OXAL above 680 mg/m^2 may produce functional impairment characterized by difficulty performing activities requiring fine sensory-motor coordination; impairment is caused by sensory rather than motor changes.

The likelihood of experiencing neurotoxicity is directly related to the total cumulative dose of OXAL administered. The relative risk of developing neurotoxicity was 10%, 50%, and 75% in patients who received total cumulative OXAL doses of 780 mg/m^2, 1,170 mg/m^2, and 1,560 mg/m^2, respectively. Both acute and cumulative neurotoxicities due to OXAL have lessened in 82% of patients within 4 to 6 months, and have completely disappeared by 6 to 8 months in 41% of patients. In addition, the likelihood that neurologic symptoms will regress has been shown to correlate inversely with cumulative dose.

Respiratory: Dyspnea, cough

Less Common Known Potential Toxicities, 1% - 10%:

Cardiovascular: Edema, chest pain, peripheral edema, flushing, thromboembolism

Central nervous system: Dizziness

Dermatologic: Rash, alopecia, hand-foot syndrome

Endocrine & metabolic: Dehydration, hypokalemia

Gastrointestinal: Dyspepsia, taste perversion, flatulence, mucositis, gastroesophageal reflux, dysphagia

Genitourinary: Dysuria

Hematologic: Neutropenia

Local: Injection site reaction

Neuromuscular & skeletal: Rigors, arthralgia

Ocular: Abnormal lacrimation

Renal: Serum creatinine increased

Respiratory: URI, rhinitis, epistaxis, pharyngitis, pharyngolaryngeal dysesthesia

Miscellaneous: Allergic reactions, hypersensitivity (includes urticaria, pruritus, facial flushing, shortness of breath, bronchospasm, diaphoresis, hypotension, syncope, hiccup

Rare Known Potential Toxicities, <1% (Limited to Important or Life-threatening):

Gastrointestinal: Life threatening enteric sepsis secondary to neutropenia and diarrhea.

Hepatic: Veno-occlusive disease of the liver is a rare serious adverse event that has occurred in association with administration of oxaliplatin and fluorouracil.

Otic: Clinical ototoxicity occurs in less than 1% of patients following oxaliplatin administration, and severe ototoxicity has not been reported.

Nursing Guidelines

GI toxicity similar to cisplatin occurs with doses above 30 mg/m^2. It can be almost constant and frequently severe, but not always dose-limiting. Monitor for nausea and vomiting and treat accordingly.

Dose-limiting side effect can be paresthesias of hands, fingers, toes, pharynx, and occasionally cramps which develops with a dose-related frequency (>90 mg/m^2). Duration of symptoms tend to be brief (less than a week) with the first course, but longer with subsequent courses. Phase I patients have reported exacerbation of paresthesias by touching cold surfaces or exposure to cold. Advise patient of these possibilities and instruct patient to report these symptoms to the health care team. Also advise patient to refrain from operating dangerous machinery that requires fine sensory-motor coordination, if symptoms appear.

These sensory neuropathies developed after subsequent courses with increasing intensity (Grade 3 toxicity after the fourth course) and with increasing duration. In 63% of the patients tested in phase I at high doses (135-200 mg/m^2), neuropathies became long-term with slow reversal over several months. Disabling walking and handwriting difficulties, as well as mouth and throat dysesthesias and laryngospasms were seen. Instruct patient to report any swallowing difficulties or gait changes.

OXAL is incompatible with NS. Flush lines with D5W prior to and following OXAL infusion.

Low back pain is a common side effect, perhaps a form of hypersensitivity reaction. Instruct patient in good body mechanics, advise light massage, heat, etc.

Laryngopharyngeal dysesthesia (LPD) occurs in about 15% of patients and is acute, sporadic, and self-limited. It usually occurs within hours of infusion, is induced or exacerbated by

exposure to cold, and presents with dyspnea and dysphagia. The incidence and severity appear to be reduced by prolonging infusion time. Instruct patient to avoid ice and cold drinks the day of infusion.

Comparison of the Symptoms and Treatment of Laryngopharyngeal Dysesthesias and Platinum Hypersensitivity Reactions

Comparison of the Symptoms and Treatment of Laryngopharyngeal Dysesthesias and Platinum Hypersensitivity Reactions		
Clinical Symptoms	**Laryngopharyngeal Dysesthesias**	**Platinum Hypersensitivity**
Dyspnea	Present	Present
Bronchospasm	Absent	Present
Laryngospasm	Absent	Present
Anxiety	Present	Present
O_2 saturation	Normal	Decreased
Difficulty swallowing	Present (loss of sensation)	Absent
Pruritus	Absent	Present
Urticaria/Rash	Absent	Present
Cold-induced symptoms	Yes	No
BP	Normal or increased	Normal or decreased
Treatment	Anxiolytics, observation in a controlled clinical setting until symptoms abate or at the physicians' discretion	Oxygen, steroids, epinephrine, bronchodilators; fluids and vasopressors, if appropriate

Treatment anxiolytics, observation in a controlled clinical setting until symptoms abate or at the physicians' discretion oxygen, steroids, epinephrine, bronchodilators; fluids and vasopressors, if appropriate

Alopecia is rare with OXAL alone, but is seen with 5-FU-OXAL combination. Advise patient.

Mild-moderate diarrhea has been seen – usually of short duration. Treat accordingly. See Section 8.1 for ancillary treatment.

Respiratory problems (i.e. pulmonary fibrosis, cough, dyspnea, rales, pulmonary infiltrates, hypoxia, air hunger and tachypnea) have been observed in patients administered OXAL. In rare cases, death has occurred due to pulmonary fibrosis. Please monitor and instruct the patient to

report any respiratory difficulties and hold OXAL until interstitial lung disease is ruled out for cases of Grade ≥ 3. If patient is experiencing shortness of breath, a chest x-ray and assessment of oxygenation via either finger oximetry or arterial blood gas evaluation are required to confirm the absence or presence of pulmonary infiltrates and/or hypoxia (treat accordingly: no intervention, steroids, diuretics, oxygen, or assisted ventilation).

Veno-occlusive disease (VOD) is a rare but serious complication that has been reported in patients receiving oxaliplatin in combination with 5-FU. This condition can lead to hepatomegaly, splenomegaly, portal hypertension and/or esophageal varices. Instruct patients to report any jaundice, ascites, or hematemesis to the MD immediately as these could be a sign of VOD or other serious condition.

Acute vein irritation can occur with infusion. Apply heat to arm of infusion if you are using a peripheral line. However, extravasation of drug can cause severe pain, redness, soreness, and exfoliation of the skin in the affected area with loss of affected vein for a long period. If a patient has a problem with pain or sclerosis when chemotherapy is given by a peripheral line, then placement of a central line should be considered.

Hemolytic Uremic Syndrome (HUS) may result in kidney damage. Oxaliplatin is to be discontinued in cases where hematocrit is <25%, thrombocytopenia <100,000, and creatinine 1.6 mg/dL.

Patients may experience sleep disturbances, specifically insomnia. Encourage good sleep hygiene, and instruct patient to report any problems with sleep to the MD, to assess for the potential use of sleeping aids.

Cold-induced transient visual abnormalities can be experienced by patients while receiving OXAL, although the relationship to OXAL has not been completely determined. Instruct patient to report any problems with vision to the MD.

Extrapyramidal side effects and/or involuntary limb movement has been seen with OXAL administration. Patients may also experience restlessness. Instruct patient to report any of these side effects to the MD.

A bolus infusion of OXAL/CAPCIT may increase the risk of developing life-threatening enteric sepsis secondary to neutropenia and diarrhea. Patients with grade 4 ANC and grade 3 diarrhea should be closely monitored and condition reported to MD for possible hospitalization for appropriate hydration and treatment with antibiotics, appropriate for gram negative or anaerobic sepsis. Patients should be monitored closely and provided with aggressive supportive care until neutropenia and diarrhea resolve.

10.5 Atezolizumab (Supplied) (Tecentriq ™, MPDL3280A) IND # [redacted], IND Holder: NCI DCTD, NSC 783608

Investigators ordering and/or dispensing supplied agents at any time for study treatment must be currently registered with PMB, DCTD, NCI. A registered investigator must co-sign for other non-registered personnel prescribing the supplied agents.

Agent Ordering and Agent Accountability

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual

submission of FDA form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead participating investigator at that institution.

Submit agent requests through the PMB Online Agent Order Processing (OAOP) application. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Description

Atezolizumab is a humanized IgG1 monoclonal antibody consisting of two heavy chains (448 amino acids) and two light chains (214 amino acids). Atezolizumab targets human PD-L1 and inhibits its interaction with its receptor PD-1. Atezolizumab also blocks the binding of PD-L1 to B7.1, an interaction that is reported to provide additional inhibitory signals to T cells (Butte et al. 2007).

Formulation

Atezolizumab is provided by Genentech/F.Hoffmann-La Roche LTD and distributed by the Pharmaceutical Management Branch, CTEP, NCI. The agent is supplied in a single-use, 20-mL glass vial as a colorless-to-slightly-yellow, sterile, preservative-free clear liquid solution intended for IV administration. Each 20 mL vial contains 1200 mg of atezolizumab and is formulated in glacial acetic acid (16.5 mg), L-histidine (62mg) polysorbate 20 (8 mg), and sucrose (821.6 mg), with a pH of 5.8. The vial is designed to deliver 20 mL (1200 mg) of atezolizumab solution but may contain more than the stated volume to enable delivery of the entire 20 mL volume.

Storage

2°C-8°C (36°F-46°F). Vial contents should not be frozen or shaken and should be protected from direct sunlight.

If a storage temperature excursion is identified, promptly return atezolizumab to 2°C-8°C (36°F-46°F) and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability

Stability studies are ongoing.

CAUTION: No preservative is used in atezolizumab; therefore, the vial is intended for single use only. Discard any unused portion of drug remaining in a vial.

Preparation

The prescribed dose of atezolizumab should be diluted in 0.9% NaCl to a concentration between 3.2 mg/mL and 16.8 mg/mL and infused with or without a low-protein binding 0.2 or 0.22 micrometer in-line filter. The IV bag may be constructed of polyvinyl chloride (PVC), polyolefin (PO), polyethylene (PE). The prepared solution may be stored at 2°C-8°C for up to 24 hours or at ambient ≤ 25°C (77°F) for 6 hours from the time of preparation. If the dose

solution is stored at 2°C–8°C (36°F–46°F), it should be removed from refrigeration and allowed to reach room temperature prior to administration. These times include the storage and administration times for the infusion. Do not shake or freeze infusion bags containing the dose solution.

Route of Administration

IV infusion.

Method of Administration

Atezolizumab is administered as an intravenous infusion over 60 minutes. If the first infusion is tolerated, all subsequent infusions may be delivered over 30 minutes. Do not administer atezolizumab as an intravenous push or bolus. No premedication is indicated for administration of Cycle 1 of atezolizumab. Patients who experience an infusion related reaction with Cycle 1 of atezolizumab may receive premedication with subsequent infusions.

Potential Drug Interactions

Cytochrome P450 enzymes as well as conjugation/glucuronidation reactions are not involved in the metabolism of atezolizumab. No drug interaction studies for atezolizumab have been conducted or are planned. There are no known interactions with other medicinal products or other form of interactions.

Pharmacokinetics

Vdss: 6.9 L

Half-life Elimination: 27 days

Adverse Events

Consult the investigator's brochure and package insert for the most current and complete information.

Warnings and precautions include immune-related pneumonitis, hepatitis, colitis, endocrinopathies, myasthenic syndrome/Myasthenia Gravis, Guillain-Barre syndrome, meningoencephalitis, pancreatitis, ocular inflammatory toxicity, infection, infusion reaction, embryo-fetal toxicity.

<u>> 10%: All grades</u>

Gastrointestinal: Nausea, constipation, diarrhea, abdominal pain, vomiting

General Disorders and Administration: Fatigue, pyrexia, peripheral edema

Infection and Infestation: Urinary tract infection

Metabolism and Nutrition Disorders: Decreased appetite

Musculoskeletal and Connective Tissue Disorders: Back/Neck pain, arthralgia

Renal and urinary disorders: Hematuria

Respiratory, Thoracic, and Mediastinal Disorders: Dyspnea, cough

Skin and Subcutaneous Tissue Disorders: Rash, pruritus,

<u>< 1% to 10%: Grades 3-4</u>

Abdominal pain, acute kidney injury, anemia, dehydration, intestinal obstruction, liver enzyme increase, pneumonia, sepsis, urinary obstruction, and venous thromboembolism

Nursing Guidelines

Anti PD-L1 side effects vary greatly from those of traditional chemotherapy and can vary in severity from mild to life threatening. Instruct patients to report any side effects to the study team immediately. Side effects may be immediate or delayed up to months after discontinuation of therapy. Most side effects are reversible with prompt intervention of corticosteroids

Diarrhea can be common and can be very severe, leading to colonic perforation. Instruct patients to report ANY increase in the number of stools and/or change in baseline, blood in the stool, abdominal pain to the study team immediately.

Rash/pruritus/dermatitis is seen. Patients should report any rash to the study team. Treat per Section 8.0 and monitor for effectiveness.

Monitor LFT's closely as elevations in these levels could indicate early onset autoimmune hepatitis. Patients should also be instructed to report any jaundice, or right upper quadrant pain to the study team immediately.

Pneumonitis can be seen and may be mild (only seen on imaging) to severe. Patients should be instructed to report any SOB, dyspnea, cough, chest pain, etc. to the study team immediately. Patients reporting these symptoms should have a pulse ox checked and consider immediate imaging per the treating MD.

Endocrinopathies (including hypopituitarism, hypothyroidism, hypophysistis, and adrenal insufficiency) are a concern given the mechanism of action of this agent. Patients may present only with the vague sense of fatigue and "not feeling well." Additional symptoms may be that of nausea, sweating and decreased activity tolerance. Instruct patients to report these signs or symptoms immediately and obtain appropriate labs as ordered by MD.

Pancreatitis is possible with anti PD-L1 therapy based on mechanism of action. Instruct patients to report abdominal pain, nausea and vomiting to the study team.

Patients who are started on steroid therapy for any side effects of anti PD-L1 toxicity should be instructed to take the steroids as ordered, and not to discontinue abruptly as symptoms may return and be severe. Patients may be on steroid therapy for weeks. Instruct patients to report any increase or change in side effects with any dosage decrease as patients may need a slower taper.

Female patients of childbearing potential should utilize contraception and take active measures to avoid pregnancy while undergoing atezolizumab treatment and for at least 150 days after the last dose of atezolizumab.

Agent Inventory Records

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing, and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

Investigator Brochure Availability

The current versions of the IBs for the agents will be accessible to site investigators and research staff through the PMB OAOP application. Access to OAOP requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, and a "current" password and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

Useful Links and Contacts

- CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
- NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
- PMB Online Agent Order Processing (OAOP) application: https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx
- CTEP Identity and Access Management (IAM) account: https://ctepcore.nci.nih.gov/iam/
- CTEP Associate Registration and IAM Account Help: ctepreghelp@ctep.nci.nih.gov
- IB Coordinator: IBCoordinator@mail.nih.gov
- PMB email: PMBAfterHours@mail.nih.gov
- PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)

11.0 MEASUREMENT OF RECURRENCE

Relapse of disease will be evaluated in this study using CEA testing and radiographic imaging. **An elevated CEA level alone (without radiographic or pathologic evidence of disease) does not qualify as relapsed disease**. For patients who have signs or symptoms for which imaging is clinically indicated, the decision of timing of radiographic studies remains at the discretion of the treating clinician. However, for asymptomatic surveillance after the completion of FOLFOX, the timing of CEA testing and radiographic imaging has been standardized (see Section 5.0).

11.1 Schedule of Evaluations

For the purposes of this study, patients should be reevaluated for recurrence at the following intervals:

- Radiographic Imaging: every 6 months (+/- 1 month) for the first 2 years after registration, then yearly for an additional 3 years (i.e. years 3-5 after registration). Patients should follow the schedule outlined in the Study Calendar (Section 5.0).
- CEA Testing: 6 weeks after completion of FOLFOX, then every 6 months (+/- 1 month) for 3 years, then yearly (+/- 1 month) for an additional 2 years. Patients should follow the schedule outlined in the Study Calendar (Section 5.0). After the end of FOLFOX treatment, the timing of CEA should correspond with the timing of radiographic imaging, where possible, but more frequent testing is at provider discretion.

Supporting documentation of relapse should be submitted per Section 6.1.1.

11.2 Guidelines for Evaluation of Recurrence

11.2.1 Measurement Methods

All measurements should be recorded in metric notation (i.e. decimal fractions of centimeters) using a ruler or calipers.

The same method of assessment and the same technique should be used throughout the treatment and follow-up phases.

Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used at the same evaluation.

11.2.2 Acceptable Modalities for Measurable Disease

- **Conventional CT and MRI:** This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness.

  As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. The lesions should be measured on the same pulse sequence. Ideally, the same type of scanner should be used, and the image acquisition protocol should be followed as closely as possible to that used with prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

- **Chest X-ray:** Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT scans are preferable.

11.3 Definition of Relapsed Disease

11.3.1 Radiographic Recurrence

On radiologic assessment the following must be present: at least one new malignant lesion, which also includes any lymph node that was normal at baseline.

Whenever possible, radiographic relapsed disease should be confirmed by biopsy.

The use of cytology to confirm the neoplastic origin of any effusion that appears is mandatory to determine progressive disease.

Follow-up colonoscopies should be performed to monitor for relapse, with frequency at the discretion of the treating investigator. However, per current guidelines, follow-up colonoscopies should be performed either annually or every other year in patients with known or suspected Lynch Syndrome, as patients with Lynch Syndrome have increased rates of synchronous primary colon cancers. See Section 5.0 and Section 6.1 for additional details.

Elevated CEA level alone (without radiographic or pathologic evidence of disease) does not qualify as relapsed disease. An elevated CEA should trigger a diagnostic workup.

The primary endpoint of this study is disease-free survival (DFS), defined as the time from randomization to first documentation of disease recurrence (primary tumor relapse) 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 do not qualify as relapsed disease and will not be included as an event for the DFS endpoint**, which is consistent with the conduct of recent adjuvant phase III trials.

Recurrence can be defined as presence of primary tumor relapse.

Second primary can be defined as presence of a new secondary type of unrelated cancer.

A second primary colon cancer does not represent disease recurrence/relapse from the initially resected primary colon cancer. Recurrences typically occur in close proximity to the surgical anastomosis or at distant sites in the body. Second colon primaries do not involve the surgical anastomosis and can be diagnosed at colonoscopy and confirmed with biopsy. An extracolonic second primary cancer is a tumor that will typically present at a single site that is not believed to represent a recurrence or metastasis from the primary tumor. Both second primaries and extracolonic tumors are increased in patients with Lynch Syndrome, where the most common extracolonic cancer is endometrial cancer, although other potential sites include, but are not limited to, the small intestine and renal collecting system. **If an extracolonic cancer is suspected, biopsy is recommended whenever possible.** Based upon the medical literature, the risk of second primaries during the limited period of follow-up during this adjuvant trial is relatively low in the Lynch Syndrome population.

In the event that the local treating investigator determines that a disease recurrence is suspected, or a second primary or extracolonic malignancy is suspected, the protocol requires the following documentation to be submitted to Alliance for review by the Study Chair:

- Primary Tumor Relapse (DFS event): imaging report, pathology report (if applicable), colonoscopy report* (if applicable), operative report (if applicable)
- Suspected Second Primary or Extracolonic Malignancy (not DFS event): pathology report, colonoscopy report* (if applicable), imaging report (if applicable), and surgical report (if applicable)

  ***If recurrence is observed or suspected on imaging and it has colonic or rectal involvement that is not in close proximity to the surgical anastomosis, then a colonoscopy with biopsy is required to exclude a new primary malignancy in the colorectum.** Female patients with isolated recurrence that involves the uterus should undergo biopsy to exclude a primary endometrial carcinoma which is the most common extracolonic malignancy in patients with Lynch Syndrome.

Determination of a DFS event will be done by the local treating investigator. There will be no independent central review. Documentation of patient relapse/new primary will be reviewed by the Alliance Study Chair. Both the assessments of the local investigator and of the Alliance Study Chair will be recorded in the CRF. The primary analysis will be based on the assessment from the local treating investigator.

12.0 END OF TREATMENT

12.1 Duration of Treatment

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 in Section 5.0.

Disease Recurrence: Remove from protocol therapy any patient with disease recurrence. Document details, including tumor measurements, on data forms. (Patients will be followed for recurrence and survival every 6 months (+/- 1 month) for the first two years after registration, then survival every 6 months and recurrence once annually for years 3-5 after registration, and then survival every 6 months for years 5-8 after registration. Recurrence follow-up will continue per the schedule above for 5 years after registration or until evidence of relapse, whichever comes first. Survival follow-up will continue per the schedule above for 8 years after registration or until death, whichever comes first.)

Discontinuation of Study Agent: If the patient discontinues protocol therapy due to reasons other than recurrence, prior to the completion of planned therapy as per Section 7.0, patients should be followed for disease status and survival per the study calendar (Section 5.0).

Discontinuation of Specimen Submission: If the patient discontinues protocol therapy for any reason, specimens should continue to be collected and submitted after discontinuation of adjuvant therapy per Section 6.2.

12.2 Managing Ineligible Patients and Registered Patients Who Never Receive Protocol Intervention

Definition of ineligible patient:

A study participant who is registered to the trial but does not meet all of the eligibility criteria is deemed to be ineligible.

Follow-up for ineligible patients who continue with protocol treatment:

Patients who are deemed ineligible after registering may continue protocol treatment, provided the treating physician, study chair, and executive officer agree there are no safety concerns if the patient continues protocol treatment. All scans, tests, and data submission are to continue as if the patient were eligible. Notification of the local IRB may be necessary per local IRB policies.

Follow-up for ineligible patients who discontinue protocol treatment:

For patients who are deemed ineligible after registering to the trial, who start treatment, but then discontinue study treatment, the same data submission requirements are to be followed as for those patients who are eligible and who discontinue study treatment.

Follow-up for patients who are registered, but who never start study treatment:

For all study participants who are registered to the trial but who never receive study intervention (regardless of eligibility), the follow-up requirements are specified below.

Baseline, off-treatment, and post-treatment follow up (i.e. relapse, recurrence, and survival) data submission required. See the Data Submission Schedule accompanying the All Forms Packet.

12.3 Extraordinary Medical Circumstances

If at any time the constraints of this protocol are detrimental to the patient's health and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Document the reason(s) for discontinuation of therapy on data forms.
- Follow the patient for protocol endpoints as required by the Study Calendar.

12.4 Survival Follow-up

Patients will be followed for survival every 6 months (+/- 1 month) for 8 years after registration or until death, whichever comes first.

12.5 Lost to Follow-Up

A patient can be deemed lost to follow-up after two years and at least 3 unsuccessful documented attempts to contact the patient. The two-year period starts on the last successful contact of the patient. All attempted patient contacts must be documented in the patient's research record. The attempted contacts must be recorded in Rave as "no contact" and complete the Lost to Follow-up form after two years of no contact.

13.0 STATISTICAL CONSIDERATIONS

This study is a two-arm randomized phase III trial comparing the outcomes of patients with stage III colon cancer whose tumors have dMMR status treated with 1) mFOLFOX6 alone and 2) mFOLFOX6 with atezolizumab and its continuation as monotherapy. Patients will be randomized in 1:1 fashion to either mFOLFOX6 alone or mFOLFOX6 with atezolizumab. Efficacy analyses will be based on the intention to treat principle and all randomized patients (including adult and patients aged <18 years) will be included for the analysis i.e. patients will be assigned to the treatment group they were randomized to regardless of the actual treatment received. Analysis related to adverse events will be based on the safety population. All patients who were randomized and received any amount of protocol therapy will be considered evaluable for safety and patients will be assigned to the treatment group they actually received.

13.1 Study Endpoint

13.1.1 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.

13.1.2 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 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 (≥18 years of age) separately for these two periods.

13.2 Sample Size and Accrual

We anticipate randomizing a maximum of 700 adult patients (350 per arm) per statistical design. Patients aged 12 to <18 years old will be accrued and randomized, but they will not be counted toward the sample size of 700. If the study reaches full accrual of 700 adult patients, enrollment will be closed to both adult and patients aged 12 to <18 years at the same time.

When both NSABP C-08 and NCCTG N0147 adjuvant trials were simultaneously accruing patients, the NSABP C-08 trial accrued 110-130 patients/month and NCCTG N0147 concurrently accrued 20-30 patients/month. Of these 150 patients/month accrual capacity, we estimate that 12% of colon cancers will show dMMR which calculates to 18 patients/month or 216 patients/year.

One and a half years after trial opening, if the accrual rate exceeds the projection (e.g. >25 patients /month), we will consider amending the protocol to raise the accrual target and to allow the detection of a hazard ratio (HR) of > 0.6.

13.2.1 Pathology Considerations

We recognize that local/reference lab testing and central lab confirmatory testing may be performed using different antibodies and platforms for immunohistochemistry. Accordingly, and because of concerns over potential discrepant local/reference versus central testing results, central confirmation review will be performed retrospectively for all samples that had local or site-selected reference lab dMMR testing performed. We will examine the concordance rate after the first 100 samples have been tested and continue monitoring the rate every 100 samples thereafter. The discrepancy rate will be closely monitored for all reviewed samples by the A021502 Statisticians. If it is determined that the discrepancy rate of reviewed samples is high enough to impact the study power (e.g. decrease the study power to less than 85%), then an amendment to increase the sample size to account for this increased discrepancy rate may be considered.

13.3 Power Justification

The best historical data available on the outcome of patients with stage III colon cancer comes from Intergroup Study N0147, where the 3-year DFS in MSI-H stage III patients treated with mFOLFOX6 was 75% [40]. We assume an accrual period of 3.24 years, minimum follow-up on all patients of 2.05 years, exponential survival, and that a one-sided log-rank test for superiority will be conducted at level 0.025. Additionally, we assume a dropout rate of 1.25% per year. Based on these assumptions, a sample size of 350 adult patients per arm (700 adult patients in total) will result in 165 events which are required to provide 90% power to detect a hazard ratio (HR) of 0.6 between the two treatment arms. The 3-year DFS estimate for the atezolizumab arm corresponding to this HR is 84.147%.

13.4 Statistical Analysis Plan

13.4.1 Primary Endpoint

Treatment Efficacy Decision Rules

Interim Analysis: Two interim analyses will be performed to assess treatment futility and superiority. The first interim analysis, for both efficacy and futility, will be performed at the time at which 50% of the projected number of events have occurred. The second interim analysis is for efficacy only and will be performed at the time at which 75% of the projected number of events have occurred. The number of DFS events will be the total number of DFS events observed from both adult and patients aged <18 years. O'Brien-Fleming type stopping boundary will be used to control for overall alpha level. Gamma family spending function with parameter -5 will be used for futility boundary. The futility boundary will be considered non-binding. The specific hazard ratio and critical p-values for declaring superiority or futility at each analysis are specified in table below. Specifically, for example, at 1st interim analysis, if the hazard ratio of mFOLFOX6+atezo vs. mFOLFOX6 alone is greater or equal to 1.021 (equivalently, p-value ≥ 0.538), the mFOLFOX6+atezo regimen will be considered inefficacious; if the hazard ratio is less or equal to 0.523 (equivalently, p-value ≤0.002), the mFOLFOX6+atezo regimen will be deemed effective. When DFS crosses either futility of efficacy boundary, the accrual will be suspended (if still ongoing), the enrolled patients followed per protocol, and the data will be reported.

Final Analysis: The primary efficacy analysis will be performed at the time where 165 DFS events have occurred. The number of DFS events will be the total number of DFS events observed from both adult and patients aged <18 years. The specific hazard ratio and critical p-values for declaring superiority or futility at each analysis are specified in table below. Specifically, at the final analysis, if the hazard ratio is less or equal to 0.731 (equivalently, p-value ≤0.022), the mFOLFOX6+atezo regimen will be deemed effective; otherwise, mFOLFOX6+atezo regimen will be considered to have not met the criteria for efficacy.

Analysis time point (% events)	Number of events	Critical p-value for efficacy	HR for efficacy	Critical p-value for futility	HR for futility
50%	83	0.002	0.523	0.538	1.021
75%	124	0.009	0.655	NA	NA
100%	165	0.022	0.731	0.022	0.731

Operating Characteristics: The table below shows the operating characteristics assuming the DFS follows exponential survival functions. The table below includes the operating characteristics according to the monitoring plan outlined above. The proportion of times that 1) the study would stop early at 1st interim analysis due to futility of mFOLFOX6+atezo, 2) the study would stop early at 1st or 2nd interim analyses due to efficacy of mFOLFOX6+atezo, and 3) the study would conclude mFOLFOX6+atezo is superior to mFOLFOX6 alone at the final analysis, are tabulated by true 3-year rates and equivalent true hazard ratio for DFS by treatment groups.

True 3-year DFS rate†		True Hazard Ratio	%‡ of times the study will be stopped early for futility		%‡ of times the study will be stopped early for efficacy		%‡ of times that mFOLFOX6 + atezo is superior at the final analysis
mFOLFOX6 alone	mFOLFOX6 + atezo		1st interim analysis	2nd interim analysis	1st interim analysis	2nd interim analysis	
0.75	0.841	0.60	0.81	NA	24.96	42.59	89.26
0.75	0.829	0.65	2.07	NA	15.50	35.93	77.51
0.75	0.818	0.70	4.69	NA	13.49	27.14	59.37
0.75	0.794	0.8	13.17	NA	2.52	11.35	29.74
0.75	0.772	0.9	28.16	NA	0.6	3.51	5.84
0.75	0.75	1	46.12	NA	0.13	0.8	2.66

DFS: disease-free survival

† Although we use the 3-year rates to illustrate each scenario, the hypothesis testing is based on the entire survival curve.

‡ Proportions are based on 10,000 replicates in the simulation study.

Analysis Plan: DFS will be compared between treatment arms using the stratified log rank test at one-sided level 0.025. The stratification factors listed in Section 4.6, as collected at the time of randomization in OPEN, will be used for the analysis. If there are zero DFS events observed in any of the strata, unstratified log-rank test will be used. If zero DFS events are observed in a certain stratum at an interim analysis and unstratified log-rank is used, all subsequent analyses for DFS will use unstratified log-rank test. The HR for DFS will be estimated using a Cox proportional hazards model and the 95% CI for the HR will be provided. If a stratified log-rank test is used, stratified HR will be considered, and if an unstratified log-rank test is used, unstratified HR will be considered. Kaplan-Meier methodology will be used to estimate the median DFS for each treatment arm, and Kaplan-Meier curves will be produced. Brookmeyer-Crowley methodology will be used to construct the 95% CI for the median DFS for each treatment arm (Brookmeyer and Crowley 1982).

Sensitivity Analysis Plan:

1) One additional censoring rule will be added for missed disease assessments. For patients with a DFS event who missed one or more scheduled assessments immediately prior to the DFS event, the DFS event will be censored at the last tumor assessment prior to the missed disease assessment.

2) For patients with a DFS event who missed one or more scheduled disease assessments immediately prior to the DFS event, the DFS event will be dated on the earliest missed assessment (after the last known tumor assessment). This sensitivity analysis is aimed to assess the impact of missing disease assessment.

13.4.2 Secondary Endpoints

Overall Survival: The distribution of overall survival will be estimated using the method of Kaplan-Meier. Overall survival will be compared between treatment arms using the stratified log-rank test, only if DFS is statistically significant. The stratification factors listed in Section 4.6, as collected at the time of randomization in OPEN, will be used

for the analysis. If there are zero OS events observed in any of the strata, unstratified log-rank test will be used. If zero OS events are observed in a certain stratum at an interim analysis and unstratified log-rank is used, all subsequent analyses for OS will use unstratified log-rank test. The HR for OS will be estimated using a Cox proportional hazards model and the 95% CI for the HR will be provided. If a stratified log-rank test is used, stratified HR will be considered, and if an unstratified log-rank test is used, unstratified HR will be considered.

We assume an accrual period of 3.24 years, with accrual target of 700 patients, exponential survival, and that a one-sided log-rank test for superiority will be conducted at level 0.025. Five-year OS in MSI-H stage III patients treated with mFOLFOX6 was 78.3% (unpublished manuscript by Sinicrope et al.). Based on these assumptions, 163 events are required to provide 90% power to detect a hazard ratio (HR) of 0.6 between the two treatment arms. The 5-year OS estimate corresponding to this HR is 86.35%.

There will be one interim analysis for overall survival (OS) which will be carried out if DFS crosses an interim efficacy stopping boundary, or at the time of the final DFS analysis, if no interim DFS boundary is crossed. The interim analysis will be for efficacy only. One final OS analysis will be conducted after approximately 163 deaths are observed. The number of OS events will be the total number of OS events observed from both adult and patients aged <18 years. The O'Brien-Fleming type stopping boundary will be used to control for overall alpha level. The HR and critical p-values for declaring efficacy for OS are specified in the table below.

Analysis Time Point (% death events)	Expected Number of OS Events	Critical P-Value for Efficacy (1-sided)	HR for Efficacy
1st DFS IA (28%)[a]	46	0.00002	0.302
2nd DFS IA (42%)[a]	68	0.001	0.451
DFS PA (57%)[b]	93	0.003	0.563
100% (Final)	163	0.024	0.734

a. If DFS crosses efficacy stopping boundary at that analysis

b. If DFS was not crossed at either DFS interim analysis

IA = interim analysis; PA = primary analysis

The actual critical values used will be determined by the observed OS events at the time of the DFS analysis as well as that (those) at the previous DFS analysis (analyses) where applicable.

13.4.3 Adverse Events (AE)

AEs and the grade for each type of adverse event 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.

For CTCAE data, the frequency tables will be reviewed to determine the patterns. The overall adverse event rates will be compared between treatment groups using Chi-square test (or Fisher's exact test if the data in contingency table is sparse).

PRO-CTCAE data will, at minimum, be analyzed similarly to CTCAE data. Reasons for missed PRO-CTCAE assessments will be collected and we will describe the extent of missing data as well as its patterns and causes. The initial analysis of each PRO-CTCAE item will use all available scores in an analysis which mirrors the approach used for the CTCAE data. Supplemental analysis will use model-based multiple imputation incorporating baseline patient characteristics and physician-rated performance status (which is collected at each cycle). CTCAE data may be incorporated as axillary data into multiple imputation models for AEs which are captured by both PRO-CTCAE and CTCAE. Results from supplemental analysis will be descriptively compared to the results of the initial analysis to assess the robustness of results to missing data. Since a preferred or optimal statistical methodology for PRO-CTCAE data is yet to be determined, additional analyses of PRO-CTCAE data beyond those specified above may be undertaken based on the current state of the science at time of data maturity for this study.

13.5 Adverse Event Stopping Rule

The monitoring rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual, or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Death within 60 days is a tool that has proved useful in reviewing adverse event data as it removes any possible subjectivity. It has the caveat of including all deaths, from any cause, even those not related to therapy [41]. The following table provides a listing of the death rate seen in other large randomized trials in stage III or II/III colon cancer [8, 42-45]. Note: a consistent metric has not been used for all of these trials. Some studies have utilized a 'pure' 60-day all-cause mortality rate, whereas others have excluded deaths not felt to be due to treatment.

Trial	**Experimental Arm**		**Control Arm**	
	Regimen	Death Rate	Regimen	Death Rate
X-ACT	Capecitabine	0.80%	5FU/LV	1.03%
MOSAIC	FOLFOX	0.54%	LV5FU2	0.54%
NSABP C-07	FLOX	1.25%	5FU/LV	1.16%
NSABP C-08 (death within 60 days)	FOLFOX+bevacizumab	0.96%	FOLFOX	0.90%
N0147	FOLFOX+cetuximab	0.70%	FOLFOX	0.10%

(death within 60 days)				

Based on these experiences, we consider a rate of death within 60 days of 1.25% on the mFOLFOX6+atezo arm as the upper threshold of acceptability for this trial. We will monitor this rate continuously. If at any time the 80% two-sided confidence interval for the rate of death within the first 60 days after initiation of mFOLFOX6+atezo excludes 1.25% to the right (i.e. only includes values greater than 1.25%), the Alliance Data Safety Monitoring Board (DSMB) and CTEP will be immediately notified to discuss the possible need to enact a protocol amendment or to discontinue the trial.

This study will be monitored by the Alliance DSMB, an NCI-approved functioning body. Reports containing efficacy, adverse event, and administrative information will be provided to the DSMB every six months as per NCI guidelines.

13.6 Protocol-specific Monitoring Plan

This trial will utilize both central and on-site monitoring in order to ensure complete and consistent data collection.

Central Data Monitoring and Source Data Verification

Centralized data monitoring activities will be performed for the first three treatment cycles for the first two patient cases enrolled at each site (as identified by a unique CTEP Institution Code) and then for every fourth patient case enrolled thereafter at the site. The cases selected for central data monitoring will be reviewed for completeness and consistency via source data verification (SDV) with source documents compared to the data reported via the electronic Case Report Forms in Rave. Central data monitoring with SDV will be performed for all patients for key eligibility and response/disease outcomes.

A source document is a document in which data collected for a clinical trial is first recorded. This data is usually later entered in the Case Report Forms. The ICH-GCP guidelines define source documents as original documents, data, and records.

The following data and documents will be reviewed via centralized data monitoring and source documents should be uploaded within the two weeks after registration:

1) **Informed Consent:** Deidentified last page of the signed and dated informed consent document including any pages with responses indicated by patient for optional studies (patient's full signature should be redacted, but date should be retained).
2) **Key Eligibility Criteria:**
    a. Documentation of Disease: MMR laboratory report.
    b. Disease Status: Pathology report, operative report, imaging reports, and additional relevant source documents.
    c. Prior Treatment: Clinic notes and other relevant source documents.
    d. Comorbid Conditions: Pathology report, laboratory reports, clinic notes, and other relevant source documents.

    See the Data Submission Schedule, available on the Alliance and CTSU websites, for additional details regarding source data verification of key eligibility criteria.

3) **Treatment Verification/IP Administration:** Applicable drug administration and dosing records to document the first three cycles of treatment.

4) **Laboratory Test Results:** laboratory reports, clinic notes (if applicable)

5) **Disease Evaluations:** Applicable radiology, imaging assessment, and colonoscopy reports to document disease evaluations and primary endpoint.

Sites should ensure that patient identifiers have been removed from all pages that will be uploaded and add study-specific identifying information (i.e. Alliance Patient ID) and then scan and upload all documents to Rave. Please ensure that all pages are legible and correct.

In the event central monitoring or review of performance indicators (KPIs) identify deficiencies, then additional central monitoring, an unscheduled on-site monitoring visit, or an audit visit may be triggered. Deficiencies or KPIs that may elicit one of these responses include, but are not limited to:

- Accrual rate
- Eligibility
- Early termination
- Data submission timeliness
- Outstanding forms
- Outstanding queries
- Query responsiveness
- Protocol deviations

On-site Monitoring

Member networks that accrue less than five patients per year will not be monitored on site, unless other deficiencies have been identified, and thus indicate the need for a monitoring visit. Member networks that accrue five or more patients will be monitored approximately every 12 months. Member networks that accrue 10 or more patients per year will be monitored approximately every 6 months.

The first on-site monitoring visit will occur after the fifth patient has been enrolled and within 6 months after the fifth patient enrollment. Thereafter, on-site monitoring visits will occur at approximately 12-month intervals during the treatment phase of the study.

At the end of each on-site monitoring visit, the monitor will debrief the site study team and highlight areas that need improvement (if applicable). Any actions or findings will be documented in a visit follow-up letter, and on-site monitoring visit follow-up letters will be distributed to the Site Principal Investigator and Lead Clinical Research Professional within 4 weeks (30 days) of the last day of the on-site monitoring visit, but no later than 6 weeks (42 days).

All affiliate/component sites will be monitored at the main member site during scheduled on-site visits, unless a separate on-site visit is deemed necessary. All records from affiliate/component sites must be accessible to monitors.

Routine monitoring visits will be scheduled at approximately 6-12-month intervals, depending on accrual and other KPIs to ensure proper oversight of trial execution. On-site monitoring visits will only be conducted during the treatment phase. Central data monitoring will continue and sites will be audited per the Alliance auditing schedule during the follow-up phase.

Frequency of monitoring visits may be adjusted and will be determined based upon factors such as enrollment rate, data quality, protocol compliance, site performance, and the available amount of data to be monitored.

Inadequate attention to the protection of rights and safety of human patients, unreported or underreported safety information, or other non-compliance may result in an increase in the percentage of patient data monitored or monitoring visit frequency.

At selected sites, a minimum of 25% of patients will be selected for on-site SDV of the following:

- Primary endpoint
- Secondary endpoints

At selected sites, a minimum of 25% of patients will be selected for on-site SDV of the following:

- Eligibility

At selected sites, 100% of patients will be selected for on-site SDV of the following:

- Informed consent
- Expedited adverse events/serious adverse events
- Treatment administration
- Patient termination

On-site audits will be conducted according to the NCI Clinical Trials Monitoring Branch guidelines.

On-site monitoring will be conducted according to Alliance procedures.

13.7 Descriptive Factors

- Number of Lymph Nodes Resected and Examined: ≥ 12 vs. < 12
- Tumor Characteristics, Perforation: Yes vs. No
- Tumor Characteristics, Obstruction: Yes vs. No
- Tumor Characteristics, Adherence: Yes vs. No

13.8 Inclusion of Women and Minorities

DOMESTIC PLANNED ENROLLMENT REPORT					
Racial Categories	Ethnic Categories				Total
	Not Hispanic or Latino		Hispanic or Latino		
	Female	Male	Female	Male	
American Indian/ Alaska Native	2	2	1	1	6
Asian	21	22	2	1	46
Native Hawaiian or Other Pacific Islander	3	3	1	1	8
Black or African American	21	22	2	1	46
White	272	276	19	15	582
More Than One Race	5	5	1	1	12
Total	324	330	26	20	700

14.0 CORRELATIVE SCIENCE COMPANION STUDIES

14.1 Quality of Life Study in Alliance A021502: A021502-HO1

14.1.1 Background

Quality of life has been demonstrated to be a key outcome in colorectal cancer. We previously studied the quality of life of patients receiving mFOLFOX6 with or without cetuximab in the N0147 clinical trial (paper under review). Quality of life was measured using Linear Analog Self-Assessment (LASA) items measuring overall quality of life, physical well-being, mental well-being, and fatigue prior to randomization, after 6 cycles of treatment, and at end of treatment. The study concluded no disease-free survival benefits to adding cetuximab to adjuvant mFOLFOX6. In 1,422 patients completing questionnaires, patients receiving mFOLFOX6 with cetuximab reported significantly worse overall quality of life (3 points on a 0-100 scale, p=0.01), mental well-being (3 points on a 0-100 scale, p=0.05), and physical well-being (2 points on a 0-100 scale) at end of treatment than those patients who also received mFOLFOX6 alone. These results were consistent across sex and KRAS subgroups. Patients aged over 70 appeared to start and end the study will higher mental well-being (baseline: 4 points on a 0-100 scale, p=0.0001; end of treatment: 3 points on a 0-100 scale, p=0.03) than patients aged <70. However, the 70+ age group also started and ended the trial with higher levels of fatigue (baseline: 7 points on a 0-100 scale, p=0.01; end of treatment: 6 points on a 0-100 scale, p=0.08) than the <70 age group, though cetuximab did not appear to impact fatigue in either age group. These data support inclusion of elderly patients for studies in this population. Long-term quality of life was not assessed in this study.

There is also emerging data suggesting that immunotherapy could potentially reduce oxaliplatin-related peripheral neuropathy [46]. However, there are anecdotal reports that immune checkpoint inhibitors can cause polyneuropathy and most would regard this as a greater concern. Oxaliplatin typically causes a toxic neuropathy that may not have a major immune component. So the effect of atezolizumab on neuropathy when given in combination with mFOLFOX6 is unknown at this time (i.e. whether neuropathy will be non-inferior or perhaps even superior on the combination arm compared to mFOLFOX6 alone).

In addition, reported studies have not assessed the impact of atezolizumab using patient-reported outcomes. The purpose of this correlative study is to assess the impact of atezolizumab (both short-term during treatment as well as long-term at the 3-year post-registration time point) on patient-reported neuropathy, overall quality of life, and functioning. We will also assess health utilities and quality adjusted life years (QALYs) to fulfill Genentech requirements, and to combine PROs with overall survival data to complement the efficacy findings of the main protocol. Additionally, we intend to further investigate a methodological question about the relationship between bother from side effects and newly developed PRO-CTCAE items which are collected within the standard adverse event reporting of the main protocol.

14.1.2 Objectives

Primary: Compare peripheral neuropathy during the first six months of the study as assessed by the FACT/GOG-NTX (NTX subscale score – sensory items) between patients randomized to mFOLFOX6 + atezolizumab vs. mFOLFOX6. We hypothesize that patient-reported neuropathy will be non-inferior in the mFOLFOX6 + atezolizumab arm compared to the mFOLFOX6 arm.

Secondary: Compare health-related quality of life (HRQL) during the first six months of the study as assessed by the FACT-C Trial Outcome Index (TOI) between patients randomized to mFOLFOX6 + atezolizumab vs. mFOLFOX6. We hypothesize that HRQL will be non-inferior in the mFOLFOX6 + atezolizumab arm compared to the mFOLFOX6 arm.

Exploratory: Compare health utilities during the first six months of the study as assess by the EQ-5D-5L between patients randomized to mFOLFOX6 + atezolizumab vs. mFOLFOX6. We hypothesize that the health utilities will be non-inferior in the mFOLFOX6 + atezolizumab arm compared to the mFOLFOX6 arm.

Exploratory: Compare patient-reported neuropathy and HRQL at the 3-year long-term follow-up between patients randomized to mFOLFOX6 + atezolizumab vs. mFOLFOX6. We hypothesize that patient-reported neuropathy and HRQL of the mFOLFOX6 + atezolizumab arm will be non-inferior to that of the mFOLFOX6 alone arm.

Exploratory: Explore the relationship between patient-reported symptom bother using the single item from the FACT-C “I am bothered by side effects of treatment” and patient-reported symptomatic toxicity profile as measured by PRO-CTCAE (which is collected within the standard adverse event reporting of the main protocol).

14.1.3 Methods

The FACT-C quality of life questionnaire will be used to assess the quality of life of patients randomized to each treatment arm [12]. This questionnaire is comprised of 38 validated questions that can be used in assessing quality of life in the study population. The FACT-C will be completed by consented patients at registration and approximately 3 months, 6 months, 12 months, and 3 years after registration. Patient-reported neuropathy will also be assessed using the 11 additional questions of the FACT/GOG-NTX [47]. EQ-5D-5L is a short, 6-question, instrument which assesses a patient’s overall quality of life or health state [48]. The addition of the EQ-5D-5L will allow for

computation and comparison between arms of health utilities and QALYs and is needed in the current protocol to satisfy European Union reimbursement agency requirements.

For information regarding ordering and administering booklets, see Section 4.3 and Section 6.4. Booklets will be administered at the following time points in Arm 1: at registration, prior to treatment on Cycles 4, 7, and 13, at end of treatment, and 3 years after registration. In Arm 2, time points were designed to match those of Arm 1, though require post-treatment time points since treatment is only 6 months in duration on this arm. Thus time points in Arm 2 include: at registration, prior to treatment on cycles 4 and 7, at end of treatment, 12 months, and 3 years after registration. The booklet contains 55 questions and it is anticipated that the booklet will take approximately 10-15 minutes for the patient to complete at each administration time point. We anticipate having booklets available in English and Spanish. Patients who consent to participate in this quality of life study (A021502-HO1) may decline to complete a booklet at any time. The primary reason for each missed booklet will be collected on a case report form.

14.1.4 Statistical Considerations

All questionnaires will be scored according to published scoring algorithms. The primary analysis over the first six months of treatment will involve a single mixed model for the primary endpoint of FACT/GOG-NTX NTX sensory neuropathy subscale score (sum of NTX1-4). A mixed model will compare time points up to the 1 year time point between randomized arms. In addition to a randomized arm covariate, the model will include a randomized arm-by-time interaction term and will use the planned cycle of assessment as the categorical time value. Unstructured covariance will initially be used, though alternative covariance structures will be investigated with the final covariance structure selected based on minimization of the Akaike information criterion. A contrast will be used to compare mean change from baseline at 6 months between arms. If the two-sided 95% confidence interval excludes a difference of 1.9 endpoints (on the 0-16 point NTX sensory neuropathy scale) favoring the mFOLFOX6 arm, then non-inferiority will be concluded. The difference of 1.9 points represents 0.5 standard deviations, or a clinically meaningful effect based on the work of Normal et al [49], using the pooled standard deviation (computed as 3.8 points) of the sensory neuropathy scale as reported at the end of treatment in Cella et al [50]. For the secondary endpoint of HRQOL (measured by the FACT-C TOI), a similar analysis will be undertaken with a non-inferiority cutoff of 6 points (which is the minimally important difference for the FACT-C TOI [51] favoring mFOLFOX6. Group differences and confidence intervals will also be constructed using standard effect sizes (i.e. differences in terms of standard deviation units) to aid in interpretation. Supplemental analysis will include similar non-inferiority analyses for other scales of the FACT/GOG-NTX and FACT-C, including the constituent scales of the TOI, using published minimally important differences and/or standard effect sizes (i.e. 0.5 standard deviations) as cutoffs for non-inferiority at 6 months, and will include comparison of the mean changes from baseline at each of the remaining post-baseline time points. The change from 6 months to 1 year will also be compared between arms. In preliminary analyses, baseline patient characteristics will be compared between arms using t-tests for continuous variables and chi-squared tests for categorical variables in the cohort of patients who are evaluable for the primary analysis of this substudy. In the event that meaningful imbalances or other confounding factors are identified, supplemental analyses to the primary and secondary analyses will

incorporate baseline patient characteristics or other confounding factors as covariates in mixed models.

Primary patient-reported outcome analysis will be conducted at the time that all consented patients have completed the 1-year assessment visit (or are no longer being followed for QOL). The analysis of the 3-year time point will occur at the time that all consented patients have completed the 3-year assessment visit (or are no longer being followed for QOL). Timing of release of the data for presentation will be at the discretion of the DSMB. Patients will be analyzed according to the randomized treatment arm assignment. All randomized patients who consent for participation in the PRO component with a baseline endpoint value and at least one endpoint value post-registration will be included in the analysis for a given endpoint. In the primary analysis, all observations available will be used. See below for information regarding analyses to account for missing data.

Exploratory analysis will include similar mixed model comparisons of change from baseline in EQ-5D-5L health utility scores at 6 months with a non-inferiority margin of 0.06 points [52]. Patient QALYs will be computed using the area-under-the-curve approach (with and without discounting) and will include all data through the follow-up of the last consented patient (i.e. the earliest censored patient). A population-based approach will also be used such that the area-under-the-curve of a quality-adjusted survival curve (mean health utility multiplied by the proportion of patients surviving based on Kaplan-Meier estimates) is the mean quality-adjusted survival for the population. Mean quality-adjusted survival will then be compared between arms using a bootstrap approach. Exploratory analysis will also include comparison of the mean changes from baseline at the 3-year time point using a contrast from a mixed model (similar to the primary analysis, however including data through the 3-year time point). Finally, exploratory methodological analysis will include regression analyses at fixed time points to assess the relationship between patient-reported bother and PRO-CTCAE symptom profiles. The goal is to investigate what drives symptom bother – individual symptoms (e.g. worst symptom score) or cumulative symptom experience (e.g. average symptom score). Potential PRO-CTCAE cut-points may also be explored. Graphical procedures throughout analysis will include plots of average values over time by arm for each primary, secondary, and exploratory endpoint.

For all statistical analyses, two-sided 95% confidence intervals will be used (p-values <0.05 will be considered statistically significant for hypothesis testing). For interpreting the clinical significance of effects, 0.2, 0.5, and 0.8 standard deviation (SD) effects will be considered as small, moderate, and large based on Cohen [53] throughout. Minimally important differences for the FACT-C will also be used [51].

Missing data will be handled in a number of ways. Missing items within a summary or scale score will be handled according to each questionnaire's published scoring algorithms. Missing data at the summary or scale score level will be handled as follows. Baseline patient/disease characteristics will be compared between patients who do and do not provide data for the primary analysis. We will also graphically explore patterns of missing data. All analyses will be completed using all available data, followed by analyses completed using a range of imputation methods. Lastly, we will employ pattern mixture models for longitudinal analyses. Output from all analyses will be

tabulated and descriptively compared to assess the degree to which missing data impacts study results.

Power: Assuming that 490 patients are evaluable for the primary analysis (i.e. allowing up to 30% of patients to decline consent or be non-evaluable for the primary analysis), this QOL study has 91% power to exclude a 1.9 point difference (a moderate and clinically meaningful 0.5 standard deviation difference) in patient-reported neuropathy between arms using a two-sided alpha=0.05 test, assuming that the pooled standard deviation is 3.8 points and the true difference between the arms is 0.76 points (a small 0.2 standard deviation difference) favoring mFOLFOX6. If the true difference between arms is 0 points, this sample size would have 90% power to exclude a 1.14 point difference (a small to moderate 0.3 standard deviation difference) in patient-reported neuropathy between arms using a two-sided alpha=0.05 test, again assuming that the pooled standard deviation is 3.8 points. The secondary analysis has 98% power, if the true difference in HRQOL between arms is 2.12 points (a small 0.2 standard deviation difference) favoring mFOLFOX6 assuming that the non-inferiority margin of 6 points represents a 0.56 standard deviation difference (i.e. assuming the FACT-C TOI scale has a standard deviation of 10.6) [54].

14.2 Biomarker and Pharmacogenetic Studies in Alliance A021502: Mandatory Collection, A021502-PP1, and A021502-ST1

All blood specimens, other than those collected in ACD tubes (for immune cell biomarker studies), will be shipped to the Alliance Biorepository at Mayo Clinic, and the Biorepository will release samples upon request. TMA blocks will be constructed for future molecular and immunohistochemical studies, as the use of TMAs allows us to perform a high throughput screen of all available colon cancers in our study population. Construction will be conducted at the Alliance Biorepository at Mayo Clinic following their standard method. Two 2 mm tissue cores each from a tumor are placed in each TMA.

Note: Testing of banked samples will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

14.2.1 Mandatory Sample Collection Biomarker Studies

Mismatch Repair (MMR) Concordance Analysis

Since the methodology used for determining MMR status is not standardized among local testing or reference laboratory sites, tumor tissue will be used for retrospective central confirmation of dMMR status where the testing methodology can be standardized. We aim to ensure that all patients whose tumors were found to show deficient MMR at baseline do indeed show dMMR upon central testing, thus ensuring a uniform study population.

The retrospective central dMMR confirmation testing will be performed by a central laboratory agreed upon by the Alliance and the drug company supporting this study using the VENTANA MMR IHC panel. The name and shipping address for the central laboratory are included on the A021502 Requisition Form which can be found on the Alliance and CTSU websites. The first concordance analysis will be performed by the Alliance Statistics and Data Center after the first 100 samples have been tested.

While the local (or site-selected reference lab) testing must be MMR IHC per the eligibility section, the use of a specific testing protocol or strategy has not been required. The central laboratory will utilize the VENTANA MMR IHC panel which has been shown to produce a high rate of concordance with MSI testing by PCR using the Promega MSI Analysis system [ref in press]. The VENTANA MMR IHC panel tests all four MMR proteins associated with colorectal cancer: MLH1, MSH2, MSH6, and PMS2. A loss of expression of any one of these antibodies indicates dMMR, and therefore microsatellite instability (MSI-H). The VENTANA MMR IHC panel is currently FDA-approved for testing for Lynch Syndrome and for evaluating MMR proteins in solid tumors.

The required formalin-fixed, paraffin-embedded (FFPE) tumor tissues submitted directly to the central laboratory on Superfrost® Plus Micro Slides (or unstained, charged 5 micron slides) within 30 days of mounting to ensure sufficient antibody stability will be tested using the Ventana detection kits and a Ventana Roche BenchMark ULTRA automated slide-stainer.

The VENTANNA MMR IHC assay uses DAB immunoperoxidase (brown reaction product) as the reporter signal using a 3-step immunoperoxidase approach. Secondary reagents used for the 3-step assay are the OptiView DAB IHC Detection Kit and the OptiView Amplification Kit (PMS2 only).

In 2018, Ventana released an updated configuration to their MMR IHC panel class II device, replacing the reagent dispenser for the PMS2 primary antibody clone EPR3947 for clone A16-4. There was also an update to the platform from the Benchmark to the Ultra platform Prior to central laboratory adoption of the updated VENTANA MMR IHC panel, 279 ATOMIC study samples were evaluated with the discontinued PMS2 reagent. To evaluate MMR status in these cases with the FDA approved assay configuration, FFPE Tissue samples with sufficient tissue available for testing will have sections cut l to be resubmitted for central laboratory testing as described above.

Negative colon carcinoma controls will be run simultaneously alongside the locally-determined dMMR positive samples to reduce variability. Results of the retrospective central dMMR confirmation testing will not be reported back to the site; instead, the results will be recorded directly in Rave by lab personnel.

Mismatch Repair (MMR) interpretation is binary, intact or loss, thus there is no established threshold for this analysis. Assay testing results were collected on retrospective data sets (> 100) using separate training and validation sets, and results were validated using OPA, NPA, PPA, APA, and ANA. Standardization of testing conditions in order to minimize variance was achieved by using calibrators/controls and an automated slide-stainer, the Ventana BenchMark ULTRA. Either colorectal or normal tonsil tissue was used as controls and samples were stained as separate slides with slides. These controls were then included in each slide and stained as internal controls (for all slides, normal control cells [fibroblasts, lymphocytes, epithelial cells] act as internal positive controls) [55, 56].

Reproducibility of the Ventana assay has been previously assessed using colorectal tissue and determining whether the respective MMR protein was intact or loss. Replicates were done in duplicate, and all studies produced an intra-lab reproducibility (%CV) of great than 90% OPA, which met the primary endpoint. The pooled-analysis

results of the inter-lab reproducibility study are as follows: OPA of 99.4%, PPA of 99.8%, and NPA of 98.9%. For the inter-lab reproducibility study, each MMR antibody was tested on 3 intact and 3 loss colorectal cases for a total of 24 cases using 3 different labs. The assays were performed on whole colorectal tissue sections on 5 non-consecutive runs over the course of 21 days. Assay results were analyzed by two different readers at each side, and the agreement between readers was 99.5%, and differences were resolved using either a panel or arbitration [57-60].

An accuracy study was performed comparing the VENTANNA MMR IHC to molecular testing (NGS, MSI, MLHI promoter hypermethylation testing), and the results of the primary pooled-analysis results are as follows: OPA of 98.5%, PPA of 99.3%, and NPA of 89.7%. In the same study group, dMMR (loss) was compared to pMMR (intact) with the following results: OPA or 97.4%, PPA of 98.8%, and NPA of 94.6%. There were no staining artifacts noted during the accuracy study, however, staining and tissue artifacts would have been captured in the comments and then reflected in the interpretation guide.

14.2.2 Optional (A021502-PP1 and A021502-ST1) Sample Collection Biomarker Studies

Blood, tissue, and stool specimens will be collected and stored for future translational research for patients who consent to participate. Future studies may include: mutation analysis, immune cell biomarker studies, ctDNA, inflammation markers/cytokines, pharmacogenetic studies, future molecular and immunohistochemical studies, and microbiome profiling from stool samples. Testing of banked specimens will not occur until an amendment to this treatment protocol (or separate correlative science protocol) is reviewed and approved in accordance with National Clinical Trials Network (NCTN) policies.

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APPENDIX I QUALITY OF LIFE MEASURES

Registration Fatigue/Uniscale Assessments

At patient registration, this form is to be administered by a nurse/CRA, completed by the patient, and entered into Medidata Rave at the time of registration.

If needed, this appendix can be adapted to use as a source document. A booklet containing this assessment does not exist – please do not order this booklet.

How would you describe:

your level of fatigue, on the average in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
No Fatigue										Fatigue as bad as it can be

your overall quality of life in the past week including today?

0	1	2	3	4	5	6	7	8	9	10
As bad as it can be										As good as it can be

Patient Booklet

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' and the side effects you are experiencing as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet contains three sets of questions:

    a. FACT-C (38 questions)
    b. FACT/GOG-NTX (11 questions)
    c. EQ-5D-5L (6 questions)

2. Please follow the directions at the top of this questionnaire.

3. You may choose not to answer any questions that make you feel uncomfortable.

4. Please complete the booklet during your scheduled clinical visit and return it to your nurse, physician, or research coordinator.

Thank you for taking the time to help us.

FACT-C (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-C (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

English (Universal) 16 November 2007

FACT-C (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
C1	I have swelling or cramps in my stomach area	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
C4	I can digest my food well	0	1	2	3	4
C5	I have diarrhea (diarrhoea)	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
Q2	Do you have an ostomy appliance? (Mark one box)	☐ No		or	☐ Yes	
	If yes, please answer the next two items:					
C8	I am embarrassed by my ostomy appliance	0	1	2	3	4
C9	Caring for my ostomy appliance is difficult	0	1	2	3	4

English (Universal) 16 November 2007

FACT/GOG-NTX (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
NTX 1	I have numbness or tingling in my hands	0	1	2	3	4
NTX 2	I have numbness or tingling in my feet	0	1	2	3	4
NTX 3	I feel discomfort in my hands	0	1	2	3	4
NTX 4	I feel discomfort in my feet	0	1	2	3	4
NTX 5	I have joint pain or muscle cramps	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
NTX 6	I have trouble hearing	0	1	2	3	4
NTX 7	I get a ringing or buzzing in my ears	0	1	2	3	4
NTX 8	I have trouble buttoning buttons	0	1	2	3	4
NTX 9	I have trouble feeling the shape of small objects when they are in my hand	0	1	2	3	4
An6	I have trouble walking	0	1	2	3	4

16 November 2007

EQ-5D-5L

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

I have no problems walking ❑
I have slight problems walking ❑
I have moderate problems walking ❑
I have severe problems walking ❑
I am unable to walk ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

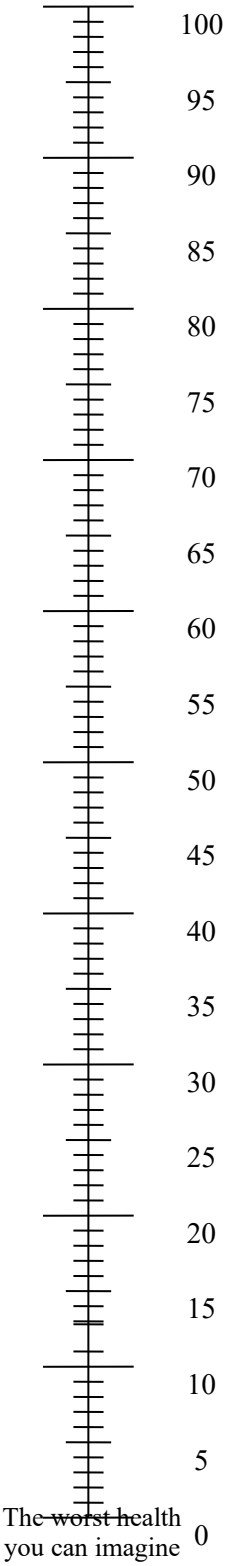
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



National Cancer Institute PRO-CTCAE

You have been given a booklet to complete for this study. The booklet contains some questions about your 'quality of life' and the side effects you are experiencing as a patient receiving treatment for cancer. Your answers will help us to better understand how the treatment you are receiving is affecting the way you feel.

1. This booklet contains one set of questions:
    a. National Cancer Institute PRO-CTCAE (20 questions)
2. Please follow the directions at the top of this questionnaire.
3. You may choose not to answer any questions that make you feel uncomfortable.
4. Please complete the booklet during your scheduled clinical visit and return it to your nurse, physician, or research coordinator.

Thank you for taking the time to help us.

NCI PRO-CTCAE™ Items - English

Item Library Version 1.0

As individuals go through treatment for their cancer they sometimes experience different symptoms and side effects. For each question, please check or mark an X in the one box that best describes your experiences over the past 7 days…

1.	In the last 7 days, what was the SEVERITY of your MOUTH OR THROAT SORES at their WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did MOUTH OR THROAT SORES INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

2.	In the last 7 days, what was the SEVERITY of your DECREASED APPETITE at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did DECREASED APPETITE INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

3.	In the last 7 days, how OFTEN did you have NAUSEA?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your NAUSEA at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

4.	In the last 7 days, how OFTEN did you have VOMITING?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your VOMITING at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

5.	In the last 7 days, how OFTEN did you have HEARTBURN?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your HEARTBURN at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

6.	In the last 7 days, what was the SEVERITY of your CONSTIPATION at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

7.	In the last 7 days, how OFTEN did you have LOOSE OR WATERY STOOLS (DIARRHEA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly

NCI PRO-CTCAE™ Items - English

Item Library Version 1.0

8.	In the last 7 days, how OFTEN did you have PAIN IN THE ABDOMEN (BELLY AREA)?				
	○ Never	○ Rarely	○ Occasionally	○ Frequently	○ Almost constantly
	In the last 7 days, what was the SEVERITY of your PAIN IN THE ABDOMEN (BELLY AREA) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did PAIN IN THE ABDOMEN (BELLY AREA) INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

9.	In the last 7 days, what was the SEVERITY of your SHORTNESS OF BREATH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did SHORTNESS OF BREATH INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

10.	In the last 7 days, what was the SEVERITY of your COUGH at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did COUGH INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

11.	In the last 7 days, did you have RASH?	
	○ Yes	○ No

12.	In the last 7 days, what was the SEVERITY of your ITCHY SKIN at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

13.	In the last 7 days, what was the SEVERITY of your HAND-FOOT SYNDROME (A RASH OF THE HANDS OR FEET THAT CAN CAUSE CRACKING, PEELING, REDNESS OR PAIN) at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

14.	In the last 7 days, what was the SEVERITY of your NUMBNESS OR TINGLING IN YOUR HANDS OR FEET at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did NUMBNESS OR TINGLING IN YOUR HANDS OR FEET INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

NCI PRO-CTCAE™ Items - English

Item Library Version 1.0

15.	In the last 7 days, what was the SEVERITY of your FATIGUE, TIREDNESS, OR LACK OF ENERGY at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
	In the last 7 days, how much did FATIGUE, TIREDNESS, OR LACK OF ENERGY INTERFERE with your usual or daily activities?				
	○ Not at all	○ A little bit	○ Somewhat	○ Quite a bit	○ Very much

Do you have any other symptoms that you wish to report?	
○ Yes	○ No

Please list any other symptoms:

1.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
2.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
3.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
4.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				
	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe
5.	In the last 7 days, what was the SEVERITY of this symptom at its WORST?				

	○ None	○ Mild	○ Moderate	○ Severe	○ Very severe

The PRO-CTCAE™ items and information herein were developed by the NATIONAL CANCER INSTITUTE at the NATIONAL INSTITUTES OF HEALTH, in Bethesda, Maryland, U.S.A. Use of the PRO-CTCAE™ is subject to NCI's Terms of Use.

APPENDIX II COLLABORATIVE AGREEMENTS PROVISIONS

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the Standards for Privacy of Individually Identifiable Health Information set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Email: ncicteppubs@mail.nih.gov

   The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

APPENDIX III STANDARD OF CARE FOLFOX PRIOR TO REGISTRATION CYCLE 1

Patients may receive one cycle of mFOLFOX6 prior to registration to the trial, in the event that they are still in screening or have not yet made a decision to enroll. Treatment must be administered at the institution that intends to register the patient should they meet all eligibility criteria and consent to participate (i.e. the registering institution). The doses received of Cycle 1 of mFOLFOX6 must be the following:

- 5-FU 400 mg/m^2 bolus followed by 2400 mg/m^2 over 2 days
- Leucovorin 400 mg/m^2 *
- Oxaliplatin 85 mg/m^2

  * Minor variations (<10%) in leucovorin dose for prior to registration Cycle 1 of mFOLFOX6 are permitted if needed to adhere to local institutional policy.

Infusion rates and length of infusion are per institutional standard. Prior to receiving Cycle 2 of mFOLFOX6 on study, the patient must meet all lab parameters as described in eligibility criteria, which must be verified in the OPEN eligibility checklist, in order to be registered and randomized.

Please note that Section 8.0 should be followed for Cycle 2 onward, based on the experienced toxicity with Cycle 1 and beyond.

APPENDIX IV AIO GROUP-SPECIFIC APPENDIX

ALLIANCE FOR CLINICAL TRIALS IN ONCOLOGY

AIO-Studien-gGmbH

AIO Group-specific Appendix

for

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)

Study codes:	AIO-KRK-0317 Alliance A021502 MO39901
EudraCT no.:	2019-003562-40
ClinicalTrials.gov Identifier:	NCT02912559
GSA version:	Final V3.0, 06-OCT-2023
Refers to protocol version:	Update #14, 23-MAY-2023
Investigational Product(s): Commercial Products(s):	Atezolizumab 5-Fluorouracil Oxaliplatin Calcium Folinate
Sponsor:	National Cancer Institute (NCI)
Legal Representative of the Sponsor in Europe:	AIO-Studien-gGmbH
Principal Investigator, Study Chair:	Dr. Frank A. Sinicrope, Rochester, MN, USA
National Coordinating Investigator, Germany & E.U. [redacted]:	Prof. Dr. [redacted], Bochum, Germany

Confidentiality

The contents of the protocol are confidential and may neither be communicated verbally nor in writing without the agreement of AIO-Studien-gGmbH.

PREFACE

The ATOMIC trial is a collaboration between:

- The Alliance for Clinical Trials in Oncology (Alliance), a National Cancer Institute (NCI)-funded National Clinical Trials Network (NCTN) Group of academic and community-oriented sites that conducts cancer research.
- The Arbeitsgemeinschaft Internistische Onkologie (AIO), a scientific non-profit organization under the umbrella of the German Cancer Society based in Berlin (DKG e.V.), Germany represented by its clinical trial branch AIO-Studien-gGmbH.
- Genentech Inc., a biotechnology company based in San Francisco, CA. Genentech is a member of the Roche Group.
- The National Cancer Institute - Cancer Therapy Evaluation Program (NCI/CTEP). The National Cancer Institute, hereinafter referred to as "NCI", is part of the National Institutes of Health, an agency of the United States Government. The NCI funds the National Clinical Trials Network (NCTN)

Alliance is the lead NCTN Group and is responsible for overall protocol development and study management of the trial. Alliance manages the participation of other participating organizations, including the international collaborating group and pharmaceutical partner.

AIO is the international collaborating group and the legal representative of the sponsor in Europe for the study and has been delegated certain tasks and responsibilities.

Roche/Genentech is the Marketing Authorization Holder for atezolizumab. NCI/CTEP is the US IND sponsor and overall study sponsor.

Sites in Germany must refer to the current approved study protocol for conducting the study. This AIO Group-specific Appendix (AIO-GSA) includes regulatory provisions, additional information and clarifications regarding study conduct in Germany. Some sections of the AIO-GSA take precedence over specific protocol sections and are marked as such.

Contact Addresses

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National Coordinating Investigator, Germany & E.U. [redacted]	Prof. Dr. [redacted] Abteilung für Hämatologie, Onkologie und Palliativmedizin Katholisches Klinikum Bochum Universitätsklinikum der Ruhr-Universität Bochum Gudrunstr. 56, 44791 Bochum, Germany [redacted]
E.U. Biomarker Collection and Laboratory	Institut für Pathologie Prof. Dr. [redacted] der Ruhruniversität Bochum an den BG-Kliniken Bergmannsheil Bürkle-de-la-Camp-Platz 1 44789 Bochum, German
European Central dMMR Confirmation Testing Laboratory	CellCarta (previously HistoGeneX) Belguim Sint-Bavostraat 78 2610 Antwerpen (Wilrijk) Belgium
Drug Supply	Roche (atezolizumab) F. Hoffmann-La Roche Ltd Grenzacherstrasse 124 CH-4070 Basel Switzerland kaiseraugst.gips-distribution@roche.com

APPROVAL OF THE AIO-GSA

„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

FINAL V3.0, 06-OCT-2023

Dr. [redacted] (Legal representative of the Sponsor in Europe)

Signature	Date (DD Month YYYY)

Investigator's agreement

I have read the attached protocol entitled

„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

Version **Update #14,** 23-MAY-2023

and the associated AIO **Group-specific Appendix** Version FINAL V3.0, 06OCT2023

and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonization Tripartite Guideline on Good Clinical Practice all applicable national regulations as well as the requirements of the appropriate Institutional Review Board/Independent Ethics Committee and any other institutional requirements.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the study sponsor.

I consent to report every serious clinical adverse event as well as any other adverse event as specified in the safety section of the protocol and this AIO-GSA and according §12 GCP-V within 24 hours after awareness, whether it is related to study medication or not.

Investigator Name (printed)

Signature

Date (DD Month YYYY)

Investigator's Institution

Table of contents

1. Patient selection, study locations and time frame

Additional to the protocol

1.1 Inclusion criteria

Precedence over protocol section 3.2

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. 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. Tumor(s) 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.] 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 R_0 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. [see also sec. 3.2.2. of the main protocol for guidance]

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). 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.
9. Absolute neutrophil count (ANC) ≥ 1500/mm^3
10. Platelet count ≥ 100,000/mm^3; platelets ≥ 75,000/mm^3 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

1.2 Exclusion criteria

Precedence over protocol section 3.2

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 Appendix III of the 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. HIV-positivity, unless all of the following are met:
    - 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. Contraindications against any of the chemotherapeutic agents of the mFOLFOX6 regimen including but not limited to known allergy to 5-fluorouracil, oxaliplatin, or folinic acid
13. Inability to provide consent because the patient does not understand the nature, significance, and/or implications of the clinical trial and therefore cannot form a rational intention in the light of the facts (e.g. patients with psychiatric illness).
14. 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.
15. A "currently active" second malignancy other than non-melanoma skin cancers or cervical carcinoma in situ. Guidance:
    - 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.
    - 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.

1.3 Withdrawal of subjects from study treatment

Additional to protocol section 12

Permanent discontinuation of study treatment

An individual subject will not receive any study treatment if any of the following occur in the subject in question:

1. Withdrawal of consent or lost to follow-up
2. Adverse event (AE) that, in the opinion of the investigator or the sponsor, contraindicates further dosing
3. Subject is determined to be ineligible with regard to inclusion and exclusion criteria for study participation at study entry and continuing protocol therapy might constitute a safety risk. Note: In this case, subject meets definition of ineligibility as given in protocol section 12.2. Refer to protocol section 12.2 for instructions on management of these subjects.
4. Pregnancy or intent to become pregnant
5. Any AE that meets criteria for discontinuation for the purpose of toxicity management (see protocol section 8.2.)

6. Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal; e.g., refusal to adhere to scheduled visits
7. Initiation of alternative anticancer therapy including another investigational agent
8. Confirmation of disease recurrence. Refer to protocol section 12.1 for instructions.

Subjects who are permanently discontinued from receiving protocol therapy will be followed for safety per AIO-GSA sections 3.1.3 and 3.1.4 unless consent is withdrawn or the subject is lost to follow-up.

Withdrawal of consent

If consent is fully withdrawn, the subject will not receive any further study treatment or further study observation. However, patients are requested and encouraged to at least perform an End-of-Treatment visit and to enter safety and survival follow-up. Data gathered until the day of full withdrawal will be used for future analyses. If patients only partially withdraw consent (e.g. refuse further treatment) but remain under study observation, all data recorded may be used without restriction.

In the event of withdrawal of consent for the participation of any of the optional substudies (i.e. translational research aspects) of this trial, all unprocessed samples and accompanying paperwork will be destroyed at study subjects' request. However, processed specimens and the research data generated from them will not be rescinded and may be used in study analyses.

1.4 Study sites

13 sites from Germany will participate in this trial.

1.5 Study time frame for Germany

Table 1: Study time line

FPI:	Q1/2021
LPI:	after approx. 14 months (Mar 2022)
LPLT:	after approx. 26 months (Feb 2023)
End of Follow up period after LPI:	after approx. 8 years (Mar 2030)
Study report:	after approx. 10 years

2 Study medication

2.1 Investigational Medicinal Product (IMP)

Atezolizumab is the investigational medicinal product (IMP) of interest.

Fluorouracil, oxaliplatin and calcium folinate are standard-of-care medication in this setting.

2.2 Drug supply

The experimental IMP atezolizumab will be supplied by Roche. The first site shipment will by generated automatically upon site initiation and activation. Subsequent shipments will be ordered by the site by email using the Consignment Request Form ('S-Form') provided by AIO-Studien-gGmbH in collaboration with Roche.

Chemotherapy drugs will be sourced locally by sites.

2.3 Fluorouracil

Precedence over protocol section 10.2

Fluorouracil will be used as commercially available and handled/prepared according to Summary of Product Characteristics (SmPC) and local guidelines.

Dosing will be according to protocol sections 7.1 and 7.2.

An example reference of the current SmPC is deposited in the ISF.

2.3.1 Fluorouracil – preparation

According to local standard and SmPC.

2.3.2 Fluorouracil – contraindications

Fluorouracil is contraindicated in seriously debilitated patients or those with bone marrow depression after radiotherapy or treatment with other antineoplastic agents.

Fluorouracil is strictly contraindicated in pregnant or breast feeding women.

Fluorouracil should not be used in the management of non-malignant disease.

Fluorouracil is contraindicated in patients who have had a serious hypersensitivity reaction to previous doses of fluorouracil or any of its constituents.

Fluorouracil must not be taken or used concomitantly with brivudin, sorivudine and analogues. Brivudin, sorivudine and analogues are potent inhibitors of the enzyme dihydropyrimidine dehydrogenase (DPD) which degrades fluorouracil (see also sections 4.4 and 4.5 of the SmPC).

Fluorouracil is contraindicated in patients with known complete absence of dihydropyrimidine dehydrogenase (DPD) activity (see section 4.4 of the SmPC).

2.3.3 Fluorouracil – special warnings and precautions

See section 4.4 of the SmPC.

Women of childbearing potential and men have to use effective contraception during and up to 6 months after treatment.

Dose modifications outlined in Section 8.2 of the protocol must be followed.

2.3.4 Fluorouracil – safety profile

Refer to the current version of the SmPC.

2.4 Calcium folinate

Supplements protocol section 10.3

Any authorized calcium folinate product may be used. This includes leucovorin and levoleucovorin. The medicinal product will be used as commercially available and handled/prepared according SmPC and local guidelines.

Dosing and administration will be according to protocol sections 7.1 and 7.2.

2.4.1 Calcium folinate – preparation

According to local standard and SmPC.

2.4.2 Calcium folinate – contraindications

Hypersensitivity to the active substance or to any of the excipients listed in the SmPC.

The combination of calcium folinate with fluorouracil is not indicated in existing contraindications against fluorouracil, in particular pregnancy and lactation.

2.4.3 Calcium folinate – special warnings and precautions

Calcium folinate may enhance the toxicity risk of 5-fluorouracil, particularly in elderly or debilitated patients. The most common manifestations are leucopenia, mucositis, stomatitis, and/or diarrhea, which may be dose limiting. Patients with diarrhea should be monitored with particular care until the diarrhoea has resolved, as rapid clinical deterioration leading to death can occur.

Toxicities observed under 5-fluorouracil/calcium folinate combination therapy require more stringent dose reductions of fluorouracil than toxicities observed under 5-fluorouracil monotherapy.

Dose modifications outlined in Section 8.2 of the protocol must be followed.

Because diarrhea may be a sign of gastrointestinal toxicity, patients presenting with diarrhea should be carefully monitored until the symptoms have disappeared completely, since a rapid clinical deterioration leading to death can occur. Especially the elderly and patients with a low physical performance due to their illness are prone to these toxicities. Therefore, particular care should be taken when treating these patients.

Calcium folinate must not be mixed with 5-fluorouracil in the same IV injection or infusion.

Calcium levels should be monitored in patients receiving combined 5-fluorouracil/calcium folinate treatment and calcium supplementation should be provided if calcium levels are low.

Interaction with other medicinal products and other forms of interaction

When calcium folinate is given in conjunction with a folic acid antagonist (e.g. cotrimoxazole, pyrimethamine) the efficacy of the folic acid antagonist may either be reduced or completely neutralized.

Calcium folinate may diminish the effect of anti-epileptic substances: phenobarbital, primidone, phenytoin and succinimides, and may increase the frequency of seizures.

(A decrease of plasma levels of enzymatic inductor anticonvulsant drugs may be observed due to an increase of hepatic metabolism, as folates are one of the cofactors.)

2.4.4 Calcium folinate – safety profile

Calcium folinate enhances the toxicity of 5-fluorouracil. Generally, the safety profile depends on the applied regimen of 5-fluorouracil due to enhancement of the 5-fluorouracil induced toxicities.

Please refer to the current version of the respective SmPC.

2.5 Oxaliplatin

Replaces protocol section 10.4

Oxaliplatin will be used as commercially available and handled/prepared according to SmPC and local guidelines.

Dosing and administration will be according to protocol sections 7.1 and 7.2.

An example reference of the current SmPC is deposited in the ISF.

2.5.1 Oxaliplatin – preparation

According to local standard and SmPC.

2.5.2 Oxaliplatin – contraindications

According to the SmPC, oxaliplatin is contraindicated in patients who:

- have a known history of hypersensitivity to oxaliplatin or to the excipient.
- are breastfeeding.
- have myelosuppression prior to starting first course, as evidenced by baseline neutrophils $<2x10^9$/L and/or platelet count of $<100x10^9$L
- have a peripheral sensitive neuropathy with functional impairment prior to first course
- have a severely impaired renal function (creatinine clearance less than 30 mL/min)

2.5.3 Oxaliplatin – special warnings and precautions

Please refer to the current version of the SmPC for full guidance on special warnings and precaution

Dose modifications outlined in Section 8.2 of the protocol must be followed.

2.5.4 Oxaliplatin – safety profile

The most frequent adverse events of oxaliplatin in combination with 5-fluorouracil/folinic acid (5-FU/FA) were gastrointestinal (diarrhea, nausea, vomiting, mucositis), haematological (neutropenia, thrombocytopenia) and neurological (acute and dose cumulative peripheral sensory neuropathy). Overall, these adverse events were more frequent and severe with oxaliplatin and 5-FU/FA combination than with 5-FU/FA alone.

For further details, please refer to the current version of the SmPC.

2.6 Storage and dispensing

The investigator should ensure that the IMP atezolizumab is stored in accordance with the environmental conditions (temperature, light, and humidity) as specified in protocol Section 10.5. If concerns regarding the quality or appearance of any IMP arise, the IMP should not be dispensed and *Roche and AIO-Studien-gGmbH* should be contacted immediately.

Upon arrival of IMP at the site, site personnel (local pharmacy) will check it for damage and verify its identity, quantity, integrity of seals and temperature conditions, and report any deviations or product complaints to *Roche and AIO-Studien-gGmbH* upon discovery.

2.7 Destruction

Any unused IMP may be disposed of at the study site under the following conditions:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the ISF or pharmacy file and a copy provided to the sponsor upon request.

If conditions for destruction cannot be met, please contact the *AIO-Studien-gGmbH*!

2.8 Documentation

The local investigator (PI) of the site is responsible to maintain records of IMP delivery and inventory at the site, of its storage, the use for each patient, and the destruction of unused IMP. Destruction records must allow for traceability of each container, including disposal date, quantity disposed of, and identification of the person disposing the containers. The method of disposal, i.e., incinerator, licensed sanitary landfill, or licensed waste disposal vendor, must be documented. Accountability and disposal records must be complete, up-to-date, and available for the sponsor to review throughout the clinical trial period as per the study agreement.

The investigator will also maintain records that adequately document that patients were administered the doses specified in the protocol. The date, time and amount will be documented in the drug accountability log by the investigator and his/her delegates.

3 Study procedures – alternative provisions for Germany

Supplements the protocol

3.1 Schedule of study procedures

The following section lists procedures which are mandatory for all patients. Additional procedures apply for patients participating in the optional substudies. See protocol sections 6.2 and 6.4 for assessment schedules.

3.1.1 Pre-Study testing (screening)

NOTE: Any routine procedure which is performed during the 28-day screening window may be used as a pre-study test (screening assessment) in this trial.

Any imaging used to confirm lack of evidence of definitive metastatic disease (pre-surgery scans are acceptable) must be completed ≤ 80 DAYS before registration.
Documentation of any screening procedure in the CRF can only be performed after informed consent of the patient. All patients will be screened and screening procedures performed within 28 days prior to registration include the following:

Mandatory procedures all arms:		
Procedure	*Instruction*	*pCRF (additional documentation required)*
Informed Consent		
dMMR testing	dMMR testing for the present tumor may be completed at any point prior to registration. Note that the patient can only be enrolled once positive dMMR test result is available. One cycle of mFOLFOX6 can be administered prior to enrollment.	Y
Demographics	age, sex	Y
Medical and colon cancer history	If hepatitis status is uncertain or undefined or unobtainable from medical records, HBV and HCV serologies should be obtained.	Y
Eligibility criteria	see AIO-GSA sections 1.1 and 1.2	
Vital signs	Blood pressure Heart rate	Y

Oxygen saturation	Oxygen saturation should be assessed at rest after 1 minute walk.	Y
Height		
Weight, BSA		
Full physical examination	incl. general appearance, skin, lymph nodes, respiratory, cardiovascular, abdominal, head and neck (including ears, eyes, nose and throat), musculo-skeletal (including spine and extremities), genital/rectal, neurological and thyroid function	Y
Cardiac function tests	QT interval monitoring acc. to local standards	Y
ECOG Performance Status		
Hematology	Hematocrit Hemoglobin Red blood cell count Platelet count Lymphocytes Basophils Eosinophils Monocytes Neutrophils Total white cell count	Y
Chemistry	Total protein Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Bicarbonate Calcium Chloride Serum Creatinine Glucose Potassium Sodium Magnesium Total bilirubin Blood urea nitrogen	Y
Urinalysis	acc. to local standards	Y
Thyroid function test	TSH Reflexive free T4, free T3 if TSH high	Y

Pregnancy test	Serum HCG or high sensitivity urine HCG for WOCBP must be performed within 7 days prior to registration.	Y
Dihydropyrimidine Dehydrogenase (DPD)	If DPD status is unknown, perform tests according to local standards.	Y
CD4 count & viral load	Only for HIV-positive patients	Y
CEA		
Toxicities/ adverse events	Document continuously using NCI-CTCAE v5.0	
Patient-reported outcomes	NCI PRO-CTCAE™	
Radiologic tumor assessment	Baseline abdominal/pelvic scans can include either: 1) a CT ABD/PELV, or 2) a MRI ABD/PELV. Chest imaging can be either chest CT or chest MRI. CT scans should be of diagnostic quality and performed with oral and IV contrast unless there is a medical contraindication. MRIs should be performed with IV contrast unless there is a medical contraindication.	Y

3.1.2 Treatment phase

The following procedures are to be performed on Day 1 (D1) +/- 2 business days of every 14-day cycle (Q2W) unless indicated otherwise:

Mandatory procedures all arms:		
Procedure	*Instruction*	*pCRF*
Vital signs	Blood pressure Heart rate See also protocol Section 7.0 regarding initial atezolizumab dose for Arm 1 patients.	Y
Weight, BSA		
Physical examination	targeted physical examination is to be performed according to clinical necessity including signs and symptoms of AEs	
Pregnancy test	Serum HCG or high sensitivity urine HCG for WOCBP must be performed **every other cycle [i.e. Q4W]**	Y

Cardiac function tests	QT interval monitoring acc. to local standards whenever clinically indicated	Y
ECOG Performance Status		
Hematology	Hematocrit Hemoglobin Red blood cell count Platelet count Lymphocytes Basophils Eosinophils Monocytes Neutrophils Total white cell count	Y
Chemistry	Total protein Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Bicarbonate Calcium Chloride Serum Creatinine Glucose Potassium Sodium Magnesium Total bilirubin Blood urea nitrogen	Y
Toxicities/ adverse events	Document continuously using NCI-CTCAE v5.0	
Patient-reported outcomes	NCI PRO-CTCAE™	

The following procedures are to be performed on Day 1 (D1) +/- 2 business days of every 14-day cycle (Q2W) unless indicated otherwise:

Arm 1 only:		
Procedure	*Instruction*	*pCRF*
Oxygen saturation	Oxygen saturation should be assessed at rest after 1 minute walk.	
Study treatment	Atezolizumab + mFOLFOX6 for 12 cycles, followed by atezolizumab alone for further 6 months	

	(see protocol section 7.1 for further details)	
CEA	6 weeks after end of FOLFOX	

Arm 1 only - Q4W		
Procedure	*Instruction*	*pCRF*
Urinalysis	acc. To local standard	Y

Arm 1 only – Q8W		
Procedure	*Instruction*	*pCRF*
Thyroid function test	TSH Reflexive free T4, free T3 if TSH high	Y

The following procedures are to be performed on Day 1 (D1) +/- 2 business days of every 14-day cycle (Q2W) unless indicated otherwise:

Arm 2 only:		
Procedure	*Instruction*	*pCRF*
Study treatment	mFOLFOX6 for 12 cycles (see protocol section 7.2 for further details)	

Mandatory procedures all arms - Every 6 months (+/- 1 month) for the first 2 years after registration:		
Procedure	*Instruction*	*pCRF*
Radiologic tumor assessment	The same imaging modality used at baseline must be used for all subsequent scans.	

3.1.3 End of Treatment (EoT)

EoT visit should be conducted 1 month (+/- 7 days) after the last day of the last treatment cycle. The following procedures will be performed during the EoT visit:

Mandatory procedures all arms:		
Procedure	*Instruction*	*pCRF*
Vital signs	Blood pressure	

	Heart rate	
Oxygen saturation	Oxygen saturation should be assessed at rest after 1 minute walk.	
Weight, BSA		
Full physical examination	incl. general appearance, skin, lymph nodes, respiratory, cardiovascular, abdominal, head and neck (including ears, eyes, nose and throat), musculo-skeletal (including spine and extremities), genital/rectal, neurological and thyroid function	
Cardiac function tests	QT interval monitoring acc. to local standards	Y
Pregnancy test	Serum HCG or high sensitivity urine HCG for WOCBP	Y
ECOG Performance Status		
Hematology	Hematocrit Hemoglobin Red blood cell count Platelet count Lymphocytes Basophils Eosinophils Monocytes Neutrophils Total white cell count	Y
Chemistry	Total protein Albumin Alkaline phosphatase Alanine aminotransferase Aspartate aminotransferase Bicarbonate Calcium Chloride Serum Creatinine Glucose Potassium Sodium Magnesium Total bilirubin Blood urea nitrogen	Y
Colonoscopy	Patients who did not receive a colonoscopy to the cecum prior to surgery are required to	

	have a full colonoscopy no later than 6 weeks after the completion of chemotherapy, but exact timing within the specified window is per treating physician discretion.	
Toxicities/ adverse events	Document using NCI-CTCAE v5.0	
Patient-reported outcomes	NCI PRO-CTCAE™	

Mandatory procedures all arms - Every 6 months (+/- 1 month) for the first 2 years after registration:		
Procedure	*Instruction*	*pCRF*
Radiologic tumor assessment	The same imaging modality used at baseline must be used for all subsequent scans.	Y

3.1.4 Follow-up assessments

Mandatory procedures all arms:		
Procedure	*Instruction*	*pCRF*
Weight		
Physical examination	targeted physical examination is to be performed according to clinical necessity including signs and symptoms of AEs	
ECOG Performance Status		
CEA	every 6 months (+/- 1 month) for 3 years, then every 12 months (+/- 1 month) for an additional 2 years, or until relapse.	Y
Toxicities/ adverse events	Document continuously using NCI-CTCAE v5.0	
Radiologic tumor assessment	Every 6 months (+/- 1 month) for first 2 years after registration, then annually for the next 3 years	Y
Survival	Every 6 months (+/- 1 month) for up to 8 years after registration	Y

3.2 Specimen collection and submission for dMMR status and other biomarkers

In addition to protocol section 6.2 and the Correlative Science Procedure Manual (CSM)

Tumor tissue: dMMR status can be determined either locally or by the central study lab in Bochum. Additional retrospective dMMR confirmation testing will be performed at CellCarta, Belgium, and the shipping address for this central laboratory is included on the A021502 Requisition Form-AIO which can be found on the Alliance and CTSU websites. An electronically completed A021502 Requisition Form-AIO is required to be included with the mandatory tissue submission to the central laboratory for retrospective dMMR confirmation testing. All tissue specimens for German patients must be accompanied by an electronically completed A021502 Pathology Form-AIO.

[Note: Surgical pathology tissue blocks should not be directly labeled in any manner. The institutional surgical pathology number (e.g. "S16-1234") and the individual block identifier (e.g. "A3") should be readable on the block. If tissue section slides are being submitted instead of the block, each tissue section slide should be labeled with the surgical pathology number and the block identifier. Please do NOT use sticky labels on slides.]

All other mandatory specimens will be submitted to the AIO pathology hub specified in the AIO-Appendix of the Correlative Science Procedure Manual where they will be collected, processed (if applicable) and later be shipped in batches to the Alliance Biorepository at Mayo Clinic.

Blood and stool samples for correlative science (planned):

Once translational research is implemented for the study in Germany optional specimens will be submitted either to the central AIO pathology hub or AIO central hub as specified in the AIO-Appendix of the *Correlative Science Procedure Manual* where they will be collected, processed (if applicable) and later be shipped in batches to the Alliance Biorepository at Mayo Clinic or Duke University.

Specimens for German patients should not be labeled with patient initials or full date of birth (full labeling instructions in the AIO-Appendix of the *Correlative Science Procedure Manual*).

3.3 Patient-reported outcomes

In addition to protocol appendix I

Patients in Germany will receive German language versions of the questionnaires for quality of life measurement and NCI PRO-CTCAE given in Appendix I of the study protocol, whereas the Registration Fatigue/Uniscale Assessment ist not applicable for German patients. These questionnaires will be provided by AIO to AIO sites in a printed format. The questionnaires will be handed over to patients, and patients must date each page of the questionnaire at every time point.

4 Assessment of safety

4.1 Safety recording and reporting requirements

Supplement to protocol section 9

AEs are to be recorded in the eCRF in Rave as detailed in protocol section 9.1. AE reports are to be printed from Rave and filed at the site. If applicable, additional AE information will be recorded in paper CRFs. For those adverse events that require immediate reporting (see AIO-GSA section), the Rave-CTEP-AERS integration for expedited event reporting will be used as described in study protocol section 9.3. **Reporting timelines given in the protocol will be replaced by those given in AIO-GSA section 4.2.1.**

AIO-Studien-gGmbH will be notified by CTEP (NCI) of events that require reporting to competent authorities, investigators and ethics committees in Europe, and act accordingly.

4.2 Sponsor obligations

In addition to protocol section 9

The legal representative of the sponsor in Europe for Germany (AIO-Studien-gGmbH) will ensure compliance with all regulatory reporting requirements, including the notification of the appropriate Ethics Committees, Competent Authority, and participating investigators of all serious adverse events occurring at the sites in accordance with national law, ICH Good Clinical Practice, and European / EMA requirements.

- An NCI Monitor (medical monitor) will medically review all SAE reports and perform the expectedness assessment.
- Every SAE assessed by either the investigator or the sponsor as suspected to be related to IMP and assessed as being either unexpected or unexpected with regard to outcome or severity of the event (i.e., every suspected unexpected serious adverse reaction, SUSAR) will be relayed by the sponsor to the AIO-Studien-gGmbH. The latter will then transmit SUSAR reports to the Competent Authority, responsible ethics committee of the trial according to national regulations (Medicinal Products Act [AMG] and § 13 GCP-V in Germany).
- Fatal or life-threatening SUSARs must be reported to authorities and ethics committee as soon as possible, but no later than 7 days after the sponsor received the initial information of their

occurrence. Additional important information on these cases may be reported as follow-up within additional 8 days. All others SUSARs have to be reported no later than 15 days after receiving the initial information.

- Also, all AEs which might change the risk-benefit evaluation of the study drugs or otherwise fulfil the criteria outlined in GCP-V §13 (4) have to be handled/reported as SUSARs.
- The NCI/Genentech assures to notify AIO-Studien-gGmbH of any SUSAR without delay in order to comply with these reporting timelines.

4.2.1 Reporting requirements and timelines for SAEs, AESIs, and other reportable events

Replaces protocol section 9.3.1

For each patient, the following events must be reported immediately, i.e. **within 24 hours** according to § 12 Abs. 4 GCP-V, of the investigator learning of the event:

- any adverse event or abnormal laboratory test value that is **serious**. This includes all events of special interest as incorporated into the listings of solicited adverse events as included in section 9.1 of the main protocol.

4.3 Handling of safety parameters

In addition to protocol section 9

4.3.1 Adverse events

The protocol (section 9.1) provides lists of AEs to be solicited. In addition, AEs may be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject.

NOTE: PRO-CTCAE data should not be used for determining attribution, dose modifications, or reporting of serious adverse events.

It will be left to the investigator's clinical judgment to determine whether an adverse event is related to study drug and of sufficient severity to require the subject's removal from treatment or from the study. A subject may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these situations arises, the subject should be strongly encouraged to undergo an end-of-treatment assessment and be under medical supervision until symptoms cease or the condition becomes stable.

4.3.2 Pregnancies and contraception

Supplement to protocol section 3.2.6.

Reproductive status:

For this trial, male subjects will be considered to be of non-reproductive potential if they have azoospermia (whether due to having had a vasectomy or due to an underlying medical condition).

Female subjects will be considered of non-reproductive potential if they are either:

(1) naturally postmenopausal (defined as at least 12 consecutive months with no menses) without an alternative medical cause;

OR

(2) have had a hysterectomy and/or bilateral oophorectomy.

Counseling of study subjects and partners:

Subjects should be informed that taking the study medication may involve unknown risks to the fetus if pregnancy were to occur during the study. In order to participate in the study, subjects of childbearing potential should adhere to the contraception requirements given below. If there is any question that a subject of childbearing potential will not reliably comply with the requirements for contraception, that subject should not be entered into the study.

- Maternal exposure: Female subjects of reproductive potential birth control should begin at least 28 days prior to the start of therapy should use appropriate method(s) of contraception during the study, for 5 months after the last dose of atezolizumab and for 6 months after the last dose of mFOLFOX6. A female patient must be instructed to immediately inform the investigator if she becomes pregnant during the study. Monitoring of the patient should continue until conclusion of the pregnancy.

- Paternal exposure: Men who are receiving study drug and are sexually active with females of reproductive potential must use any contraceptive method with a failure rate of less than 1% per year. For men, birth control should begin prior to registration and continue for 5 months after the last dose of atezolizumab or 6 months after the last dose of mFOLFOX6, whichever applies.

  Male subjects must refrain from donating sperm during the study and for 7 months after the last dose of investigational products. A male study subject must be instructed to immediately inform

the investigator if a pregnancy occurs in his partner during the study and up to 7 months after last dose of study drug.

Contraception

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Hormonal methods of contraception, including oral contraceptive pills* (combination of estrogen and progesterone), vaginal ring, injectables, implants and intrauterine devices (IUDs) ***NOTE: Due to the increased GI toxicity (nausea, vomiting, diarrhea) oral contraceptives must be combined with an additional method of contraception (e.g. a barrier method).**
- Nonhormonal IUDs, such as ParaGard®
- Bilateral tubal ligation
- Vasectomy
- Complete abstinence if it is the patient's preferred and usual lifestyle regardless of trial participation*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all IMPs. Subjects who choose complete abstinence are not required to use a second method of contraception. Acceptable alternate methods of highly effective contraception should be discussed in the event that the subject chooses to forego complete abstinence.

UNACCEPTABLE METHODS OF CONTRACEPTION

- Oral contraceptive pill alone
- Diaphragm with spermicide
- Cervical cap with spermicide
- Vaginal sponge
- Condom
- Withdrawal (coitus interruptus)
- Progestin only pills by WOCBP subject or male subject's WOCBP partner
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)

Pregnancies

Please also refer to section 9.3 of the protocol for special reporting requirements

Pregnancy of a subject or of a subject's partner is not regarded as an AE unless there is a suspicion that the investigational product under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities/birth defects and spontaneous miscarriages should be reported and handled as SAEs. Elective abortions without complications should not be handled as AEs.

For female subjects, the investigator will follow the pregnancy for outcome of both mother and child (including any premature terminations) and document in the patient's records. This applies to all pregnancies occurring between the date of the informed consent and 5 months after the last dose of atezolizumab and for 6 months after the last dose of mFOLFOX6. The investigator should counsel the pregnant subject, discuss the risks of continuing the pregnancy, and possible effects on the fetus.

For a pregnancy of a male subject's partner occurring between the date of the informed consent and 6 months after the last dose of mFOLFOX6, the outcome (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) of should, if possible, be followed up and documented in the patient records. The investigator should counsel the subject's partner, discuss the risks of continuing the pregnancy, and possible effects on the fetus. Where the information/suspicion/fact of pregnancy is received, prior to obtaining information about the pregnancy, the investigator must obtain the consent of the subject's partner and document as such in the patient records.

5 Ethical aspects

5.1 Risk-benefit assessment

Benefits:

The primary objective of this trial is to determine whether atezolizumab combined with FOLFOX and its continuation as monotherapy can significantly improve the time to disease recurrence (DFS) compared to FOLFOX alone in patients with stage III colon cancers and dMMR in an adjuvant setting. The corresponding statistical hypothesis test (a log-rank test for superiority) achieves a 90% power at a 0.025 one-sided significance level to detect a hazard ratio (HR) of 0.6 between the two treatments. This HR amounts to a clinically meaningful risk reduction of disease recurrence of 40 % [see protocol section 13.3] in the experimental arm. In terms of median DFS this translates to an increase of the 3-year DFS estimate form 70% to 84.147%.

The basic rationale for this trial is the promising efficacy of check-point inhibition (CPI) in metastatic colorectal cancer (CRC) with mismatch repair deficient tumors [Le DT et al., N Engl J Med 2015. 372(26)]. Since the initiation of the ATOMIC trial, substantially more data has come forth which supports the efficacy of CPI in advanced CRC and other tumor entities with deficient DNA repair mechanisms [Diaz L. A. JCO 2018 36(4); Overman MJ et. al. Lancet Oncol. 2017 Sep;18(9); Moehler M et. al, Ann. Onc. 2020, 31]. Even in early stages of CRC, complete pathological remissions could be demonstrated [Chalabi et al. Nat Med. 2020 Apr;26(4)].

Risks:

Potential risk of clinical significance	Mitigation strategy
Study intervention: atezolizumab + mFOLFOX6	
Lack of efficacy of the experimental treatment	Two interim analyses will be performed to assess treatment futility and superiority. The first interim analysis, for both efficacy and futility, will be performed at the time at which 50% of the projected number of events have occurred. For further details see protocol section 13.4.1.

Adverse drug reactions to atezolizumab, increased toxicity of the combination treatment and unknown/undiscovered AEs	• Safety assessment will be performed on a regular basis including assessment of relevant lab parameters to detect irAEs (e.g. thyroid function tests, liver function tests) [see protocol section 5.0 study calendar, and AIO-GSA section 3] • Comprehensive toxicity management guidelines are included in the protocol and the IB of atezolizumab. [see protocol section 8.2] • This study will be monitored by the Alliance DSMB, an NCI-approved functioning body. Reports containing efficacy, adverse event, and administrative information will be provided to the DSMB every six months as per NCI guidelines. [see protocol section 13.5] • Adverse event stopping rules are in place [see section 13.5 of the protocol]
Study-specific procedures	
Regular CT scans / exposure to ionizing radiation	• Type and frequency of radiographic imaging (every 6 months (+/- 1 month) for the first 2 years after registration, then yearly for an additional 3 years) is tailored toward the objective assessment of the primary endpoint disease-free survival. Radiographic imaging cannot be omitted or reduced further without compromising the validity of the trial results. • As per GERMAN legislation a notification (§ 32 Abs. 1 StrlSchG) to the Federal Office for Radiation Protection has been submitted.

Summary and conclusions:

The IMP atezolizumab is an approved drug for various cancer indications including a combination treatment with conventional chemotherapy in triple-negative breast cancer (SmPC Tecentriq®). Other comparable CPI (e.g. pembrolizumab) have demonstrated that combination with chemotherapy is feasible and efficacious (SmPC Keytruda®). The rationale for the clinical efficacy of CPI in mismatch-

repair deficient CRC is supported by robust data. In summary, the risk-benefit assessment strongly favors the conduct of this trial.

5.2 Declaration of Helsinki/Good Clinical Practice

Supplement to the protocol

This study will be conducted in accordance with the ICH E6 guideline for Good Clinical Practice and with the Declaration of Helsinki, as adopted by the 18th World Medical Assembly, Helsinki, Finland, June 1964 and most recently amended by the 64th WMA General Assembly, Fortaleza, Brazil, October 2013. The study will comply with the requirements of the ICH E2A guideline for *Clinical Safety Data Management: Definitions and Standards for Expedited Reporting.*

In Germany, the study will comply with the German Medicinal Products Act (Arzneimittelgesetz, AMG) and the GCP-Verordnung (Ordinance on the implementation of Good Clinical Practice in the conduct of clinical trials on medicinal products for use in humans, GCP-V). National law will be superseded by the European Trials Regulation (536/2014) as it comes into effect and as applicable to ongoing trials.

5.3 Independent ethics committees and regulatory authorities

Supplement to the protocol

5.3.1 Approval of the study by the regulatory authority and EC

It is the responsibility of the legal representative of the sponsor in Europe, AIO-Studien-gGmbH, to obtain and **maintain** independent approval from the applicable competent authorities and a positive opinion from the ethics committees to conduct the study in accordance with applicable local legal requirements, statutes, and the European Clinical Trials Directive.

Indemnity insurance will be contracted for the trial subjects in accordance with the applicable local law.

For Germany, the sponsor names the "Leiter der klinischen Prüfung" (LKP) who has to be a physician with at least 2 years of experience in the conduct of clinical trials of drugs according to § 4 (25) and § 40 (1) No. 5 AMG.

5.3.2 Notification about the study

The legal representative of the sponsor in Europe, AIO-Studien-gGmbH, is responsible to notify competent regional authority about the study and all investigators of the participating investigational sites, if applicable by local law.

5.3.3 Reporting and documentation obligations

Regarding study conduct in Europe, the sponsor, the legal representative of the sponsor in Europe, and the investigators are responsible to comply with the reporting and documentation obligations in accordance with local legal requirements, statutes and the European Clinical Trials Directive.

6 Study documentation, CRFs and record-keeping

6.1 Investigator's Files / Retention of documents

Supplement to the protocol

The Investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents should be classified into the two separate categories Investigator's Study File and subject/patient data.

The Investigator's Study File will contain all essential documents, including the protocol/amendments, the Investigator's Brochure for atezolizumab and sample SmPCs for fluorouracil, oxaliplatin and folinic acid, patient information and informed consent form, ethics committee and regulatory authority approval, notification of the federal regulatory authority and competent regional authorities, if applicable, drug records, staff curriculum vitae and authorization forms, and other appropriate documents/correspondence, etc.

Patient data include patient hospital/clinic records (e.g., NCI PRO-CTCAE assessments, quality of life questionnaires, medical reports, OP reports appointment book, medical records, pathology and laboratory reports, CT, MRI, etc.), signed informed consent forms and patient eligibility screening forms.

The investigator must keep these two categories of documents on file for at least 10 years (or longer if legally required) OR until 1) the study has been terminated by Alliance and 2) until two years after the New Drug Application (NDA) or Biologic License Application (BLA) has been approved or withdrawn; whichever is longer. Source documentation, including informed consent forms, should be retained indefinitely at the registering institution. The documents must be archived in a secure place and treated as confidential material.

6.2 Source documents and background data

Replaces protocol section 6.1.1

Source documents are original medical records kept in the subjects' medical files. They are supplemented by study-specific source documents, such as informed consent forms and quality of life questionnaires. In

the countries subject to this AIO-GSA, no remote source data verification will take place, and no source data will be systematically digitized and uploaded to eCRFs. Radiologic images will be submitted to IROC, USA, at the timepoints specified in protocol section 6.3, via a third-party in Germany.

The investigator will supply the sponsor upon request with any required background data from the study documentation or clinic records. This is particularly important when errors in data transcription are suspected. In case of special problems and/or governmental queries or requests for audit inspections, it is also necessary to have access to the complete study records, provided that patient confidentiality is protected. According to the standards of the data protection law, all data obtained in the course of a clinical study must be treated with discretion in order to guarantee the rights of the patient's privacy.

6.3 Audits and inspections

Each trial site in Germany will be audited according to CTMB guidelines. Audits will occur within 18-months of the first patient enrollment at each site.

To ensure quality of data, study integrity, and compliance with the protocol and the various applicable regulations and guidelines, the legal representative of the sponsor in Europe (AIO-Studien-gGmbH) may conduct site visits to institutions participating to protocols. The investigator, by accepting to participate to this protocol, agrees to co-operate fully with any quality assurance visit undertaken by third parties, including representatives of the sponsor, national regulatory authorities or the company supplying the product under investigation, as well as to allow direct access to documentation pertaining to the clinical trial (including eCRF, source documents, hospital subject charts and other study files) to these authorized individuals. The investigator must inform the legal representative of the sponsor in Europe – AIO-Studien-gGmbH- immediately in case a regulatory authority inspection is scheduled. If inspections will be performed in particular for this study by the competent authority, the competent authority/investigator has to send the inspection report to the Alliance within 5 working days.

6.4 Case Report Forms (CRF)

Supplement to the protocol

For each patient enrolled, a paper-based CRF and an eCRF (Medidata Rave®) must be completed by the principal investigator and/or authorized delegate of the study staff; the eCRF must be completed in English. This also applies to records for those patients who fail to complete the study. If a patient withdraws from the study, the reason must be noted in the pCRF and eCRF.

7 Monitoring the study

Replaces protocol section 13.6

On-site monitoring will be conducted according to Alliance and AIO procedures.

This trial will utilize both central and on-site monitoring in order to ensure complete and consistent data collection. In Germany centralized data monitoring activities, in particular the provision of supporting documents for such purposes will be restricted to trial documents that only contain the trial specific minimum of 'data concerning health' (according to article 4 GDPR) or does not contain any personal data of a trial subject [e.g. drug accountability log].

AIO-Studien-gGmbH will provide trained MONITORS for on-site monitoring to assist the investigator(s) in conducting the clinical study. Source data verification (SDV) will be carried out exclusively by on-site monitoring. In addition, the MONITOR has the responsibility to supplement site trainings provided by Alliance (online or remote) as well as familiarize the investigator(s) and the entire center staff involved in the study with all study procedures including the administration of IMP, to review the ongoing study with the investigator(s) to verify adherence to the protocol, and to deal with any problems that arise.

The monitor will visit each clinical study site at the following time points:

- before the first patient can be enrolled: site initiation visit (mandatory)
- after enrolment of the first patient, and thereafter at appropriate time points to conduct SDV, eligibility reviews, case evaluations, query resolution, additional site trainings etc.
- at study completion (close out visit).

Further details on monitoring of the study in the E.U., e.g., the extent of source data verification, and GDPR and GCP compliant eligibility review & case evaluations will be laid out in the APPENDIX of the A021502-Monitoring Plan.

At all times the MONITORS must maintain the confidentiality of the study documents.

The investigator (or his/her deputy) agrees to cooperate with the MONITOR to ensure that any problems detected in the course of these monitoring visits are resolved.

8 Confidentiality of trial documents and patient records

Additional to the protocol

The investigator and the sponsor (or designee) must assure that, as stipulated by the European and German data protection laws, all data obtained in the course of a clinical study are treated with discretion in order to guarantee the rights of the patients' privacy. Patient-related data must be submitted to the sponsor in a pseudonymous manner. The investigator must keep a patient identification log showing codes and names. The investigator will maintain documents not for submission to sponsor, e.g., patients' written consent forms, in strict confidence.

APPENDIX V AIO SITES AND INVESTIGATORS

Institution CTEP ID	Institution Name	Investigator CTEP ID	Investigator Name
76105	Saint Josef-Hospital Bochum	[redacted]	[redacted]
76108	Hamatologisch-Onkologische Praxis Eppendorf (HOPE)	[redacted]	[redacted]
76036	Medizinische Hochschule Hannover	[redacted]	[redacted]
76107	Kliniken Maria Hilf GmbH	[redacted]	[redacted]
76090	Universitätsklinikum Leipzig	[redacted]	[redacted]
76091	Technical University of Dresden	[redacted]	[redacted]
76061	Medizinische Klinik Iii	[redacted]	[redacted]
76106	Klinikum Esslingen GmbH	[redacted]	[redacted]
76034	University Hospital Ulm	[redacted]	[redacted]
76017	Medizinische Universitat	[redacted]	[redacted]
76056	Charite Humboldt - University Hospital	[redacted]	[redacted]
76104	Onkologie-Cologne	[redacted]	[redacted]
76097	University Hospital Wuerzburg	[redacted]	[redacted]

APPENDIX VI STOOL COLLECTION INSTRUCTIONS

Patient Stool Collection Instructions

NOTES:

- **Specimen should be collected Monday-Friday for this protocol.**
- **Patients, after the stool is collected it needs to be divided into the smaller containers, place the stool containers into a Ziplock bag and seal. Place the bag into your refrigerator freezer until you can take it frozen to your next appointment for the study.**
- **Sites Keep specimens frozen at -70/80°C until shipped.**

Set-up

1. Fill out the areas of the BioMS Form. Using a waterproof pen ensure that the following information is provided:
    - Patient Initials (last, first, middle); put in a dash (-) if the middle initial is missing
    - Patient ID #
    - Date of Birth
    - Stool Collection Date
    - Stool Collection Time

    NOTE: You will be contacted to obtain missing information.
2. Write the Study Number, Patient ID #, Patient Initials, Collection Date and Collection Time on a tube labels provided in the kit.
3. After the labels are affixed to the collection tubes, wrap clear scotch tape around the tube labels to ensure the labels will remain intact during shipping.

Specimen Collection:

Inside your collection kit you should have: A white plastic bowl collection device, a flat wooden blade, 3 tubes with "spoons" attached to cap, wypall pad, film, non-latex gloves and tongue blade.

To collect your stool specimen:

1. Place the holder under the seat of the toilet bowl towards the center back.
2. Lower the toilet seat onto the holder.

3. 

4. Have a bowel movement into the bowl taking care to not urinate into the bowl
5. Place Wypall pad on flat surface with the tubes, film and gloves.
6. Put on gloves
7. Place holder containing stool on Wypall pad to stabilize it.
8. Using the "spoons" attached to the caps, carefully place some of the bowel movement into the 3 tubes. If a "spoon" should break then use the flat wooden blade to transfer the stool.
9. Place the caps onto the tubes and wrap the film around the cap of the tubes to seal the tube closed.

Packaging Instructions:

1. Complete the BioMS packing list and confirm that the specimen is correctly labeled
2. Place the specimen into the Ziplock bag containing absorbent material.
3. Place the Ziplock bag into the plastic transport bag.
4. Place the completed original BioMS packing list into the outer pocket of the bag. Seal the bag
5. Keep the bag with the specimen Frozen while you make transportation arrangements.

Specimen Shipment:

Specimen will be shipped via FedEx®. Care must be taken to ensure that the specimen is properly shipped. **Specimen must be sent to BAP Monday – Friday**, for arrival at our labs Tuesday – Saturday.

Do NOT collect the specimen the day before, the day of, or the observed day of a United States federal holiday. Transportation services are frequently not available and the specimen may be compromised by delayed arrival at our labs. Call your local FedEx® office to determine service availability for pickups late in the day.

1. Specimen must be completely packaged in shipping containers prior to FedEx® pickup:

   FROZEN SPECIMENS

   Place the "frozen specimen" transport bag, along with 3 to 4 lb. (2kg) of commercially-prepared dry ice, into the "frozen" Styrofoam® container. Pellets or chunks no more than 8 cm on a side are preferred.

NOTE: It is your responsibility to obtain dry ice when shipping frozen specimens via FedEx®. Mayo does not provide dry ice. Businesses that may have dry ice for purchase include ice cream shops, research labs, hospital and commercial blood banks, or chemical supply companies.

2. Check that all of the required labels are clearly visible on the shipping boxes. Boxes will be delayed en route and specimen quality may be jeopardized if any of the required labels are missing, covered, or not filled out properly.
3. **US Sites Only -** The brown colored shipping boxes will have a pre-addressed return label affixed to them. This label replaces the need for an airbill. Ship the specimen to BAP Monday-Thursday only. NOTE: the shipping label should be the approximate size of 3x5 and will contain the FedEx tracking number. If the only label on the box starts with a tracking number of "BB" this shipping box will require an additional FedEx form. Contact the Biospecimens Resource Manager for further assistance.

   Canadian Sites Only - Complete a pre-printed FedEx® airbill. Request "Priority Overnight" service. Indicate "Deliver Saturday" on the airbill if you ship on Friday. Ship the specimen to BAP Monday-Thursday only.
4. Write your return address on the shipping container.
5. Call FedEx® at 1-800-238-5355 early for same-day service. Provide the following information:
   - Exact location of pick-up site
   - Number of boxes in shipment
6. Assist the FedEx® courier in finding the shipping box(es), if requested.

Instrucciones al paciente para recoger una muestra de heces

NOTAS:

- **Para este protocolo, hay que recoger las muestras entre lunes y viernes.**
- **Señores pacientes: una vez recogida la muestra, hay que dividirla en recipientes más pequeños y meterlos dentro de la bolsa plástica, congelada, que sirve para el transporte, contiene material absorbente y puede sellarse. Ponga la bolsa dentro del congelador hasta que pueda llevarla congelada a la siguiente cita del estudio.**
- **Los lugares del estudio mantienen las muestras congeladas a menos 70 u 80°C, hasta enviarlas.**

Preparación

1. Llene la información en el formulario BioMS con un bolígrafo a prueba de agua. Verifique que conste la siguiente información:
    - Iniciales del paciente (apellido, primer nombre, segundo nombre); ponga una raya (-) si falta la inicial del segundo nombre
    - Número de identificación del paciente
    - Fecha de nacimiento
    - Fecha en que se recoge la muestra
    - Hora en que se recoge la muestra

    NOTA: nos comunicaremos con usted para obtener cualquier información que falte.
2. En las etiquetas de los tubos que se envían con el kit, escriba el número del estudio, el número de identificación del paciente, las iniciales del paciente y la fecha en que se recogió la muestra.
3. Una vez pegadas las etiquetas a los frascos de las heces, envuelva con cinta adhesiva transparente las etiquetas de los tubos para garantizar que estas permanezcan intactas durante el envío.

Obtención de la muestra:

Dentro del kit para recoger la muestra, encontrará lo siguiente: un tazón blanco de plástico para recoger la muestra, 3 frascos con tapa café y «cucharas» pegadas a la tapa, una toalla Wypall, Parafilm, guantes sin látex y un palito de madera para usar en caso de que se rompa la cuchara.

Para recoger la muestra de heces:

1. Coloque el recipiente en el centro, por debajo del asiento del inodoro y hacia la parte posterior.
2. Baje el asiento del inodoro para sujetar el recipiente.

3. 

4. Defeque dentro del tazón, pero tenga cuidado de no orinar dentro del tazón. (Si desea orinar, hágalo antes de colocar el recipiente para recoger la muestra).
5. Extienda la toalla Wypall sobre una superficie plana, junto con los tubos, el Parafilm y los guantes.
6. Póngase los guantes.
7. Coloque el recipiente para recoger las heces sobre la toalla Wypall a fin de estabilizarlo.
8. Con las «cucharas» que están pegadas a las tapas, meta con cuidado las heces dentro de los 3 tubos. Si la «cuchara» se rompe, haga el traspaso de las heces con el palito de madera.
9. Tape los tubos y envuelva las tapas con la película plástica para que los tubos queden bien sellados. Verifique que las tapas estén bien cerradas en cada recipiente.

   (El **Parafilm** es una película plástica flexible que sirve para envíos). Desprenda el Parafilm del papel y úselo para envolver la parte superior de todos los recipientes. El Parafilm se quedará fijo, lo que garantizará que las muestras no contaminen otras cosas ni que se contaminen con sustancias externas.

Instrucciones para el empaque:

1. Llene la **lista de empaque de BioMS** y confirme que las muestras estén bien etiquetadas.
2. Meta las muestras dentro de la bolsa plástica, **congelada**, que contiene material absorbente y sirve para el transporte.
3. Meta la lista original de empaque de BioMS dentro del bolsillo exterior de la bolsa. Selle la bolsa.
4. Mantenga **congelada** la bolsa que contiene la muestra, mientras hace los arreglos para el transporte.

Envío de la muestra:

La muestra se enviará por FedEx®. Hay que prestar mucha atención para garantizar que la muestra se envíe correctamente. **Se puede enviar la muestra a BAP de lunes a viernes para que llegue a nuestros laboratorios entre el martes y el sábado**.

1. NO recoja la muestra el mismo día ni el día anterior a un feriado en los Estados Unidos, porque no suele haber servicio de transporte en esos días y la muestra puede comprometerse debido al retraso en llegar a nuestros laboratorios. Llame a la oficina local de FedEx® para averiguar si ofrecen servicio para recoger paquetes a última hora de la tarde.

   MUESTRAS CONGELADAS

Meta dentro del recipiente de poliestireno® la bolsa para transporte de «muestras congeladas» junto con 3 o 4 libras (2 kg) de hielo seco preparado comercialmente. Lo mejor es usar bolas o trozos que no excedan de 8 cm en un lado.

NOTA: usted tiene la responsabilidad de conseguir el hielo seco cuando envíe muestras congeladas por FedEx®. Mayo no le provee el hielo seco. Los lugares donde pueden vender hielo seco son las heladerías, los laboratorios de investigación, los hospitales, los bancos de sangre que funcionan a nivel comercial y las compañías de suministros químicos.

2. Verifique que todas las etiquetas necesarias estén claramente visibles en las cajas para el envío. Si alguna de las etiquetas faltara, estuviera cubierta o no se hubiese llenado bien, el transporte de las cajas se retrasaría y la calidad de la muestra podría estar en peligro.

3. **Solo para los sitios en Estados Unidos:** las cajas para envío que son de color café tienen pegada una etiqueta para enviarnos la muestra. Esa etiqueta evita la necesidad de una guía aérea. Envíe la muestra a BAP solamente de lunes a jueves. NOTA: la etiqueta para el envío debe tener un tamaño aproximado de 3 x 5 y mostrar el número de FedEx para rastreo. Si la única etiqueta de la caja muestra que el número de rastreo empieza por «BB», entonces esa caja para envíos requiere otro formulario para FedEx. Comuníquese con el gerente de recursos para muestras biológicas (Biospecimens Resource Manager) a fin de obtener más ayuda.
4. **Solo para los sitios en Canadá:** llene la guía aérea de FedEx® previamente impresa. Solicite el servicio «Priority Overnight» (entrega al siguiente día hábil). Si hace el envío en viernes, marque «Deliver Saturday» (entregar en sábado) en la guía aérea. Envíe la muestra a BAP solamente de lunes a jueves.
5. Escriba su dirección en el recipiente para el envío.
6. Llame a FedEx®, al 1-800-238-5355, temprano para que tenga el servicio ese mismo día. Brinde la siguiente información:
    - Ubicación exacta del lugar donde se debe recoger el envío.
    - Cantidad de cajas que envía.
7. Ayude a FedEx® a encontrar la(s) caja(s) del envío, en caso necesario.