A phase II trial of tiragolumab in combination with atezolizumab and bevacizumab in patients with previously treated, microsatellite stable, metastatic colorectal adenocarcinoma.

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National Clinical Trial

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PROTOCOL AMENDMENT HISTORY

Version	Date	Description of Change	Brief Rationale
Original (1)	08/14/2024		

1.1	05/09/2025	Addition of NCT number; clarification of Exclusion criteria for patients with positive Epstein-Barr virus (EBV) viral capsid antigen immunoglobulin M (IgM) test	Increase clarity of exclusion criteria to avoid unnecessary protocol deviations.

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STATEMENT OF COMPLIANCE

This is an investigator-initiated study. The principal investigator (PI), Hannah Robinson, is conducting the study and acting as the sponsor. As the sponsor-investigator, both the legal/ethical obligations of a PI and those of a sponsor will be followed.

The trial will be carried out in accordance with Good Clinical Practice (GCP) as required by applicable United States (US) laws and applications, including but not limited to United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812), as applicable.
The PI will assure that no changes to the protocol will take place without documented approval from the Institutional Review Board (IRB). All personnel involved in the conduct of this study have completed Human Subjects Protection Training.

I agree to ensure that all staff members involved in the conduct of this study are informed about their obligations in meeting the above commitments.

Sponsor-Principal Investigator: _____

Print/Type Name

Signature: _____ **Date:** _____

LIST OF ABBREVIATIONS

ACRONYM	DESCRIPTION
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine transaminase

ANC	Absolute neutrophil count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate transaminase
ASTCT	The American Society for Transplantation and Cellular Therapy
BP	Blood pressure
BUN	Blood urea nitrogen
C1D1 (CXDY)	Cycle 1, Day 1 (Cycle X, Day Y)
CA 19-9	Carbohydrate antigen 19-9
CA 125	Carbohydrate antigen 125
CBC	Complete blood count
CEA	Carcinoembryonic antigen
CI	Confidence Interval
CIT	Cancer Immunotherapy
CMP	Complete metabolic panel
CMP	Clinical Monitoring Plan
CNS	Central nervous system
COMIRB	Colorado Multiple Institutional Review Board
COPD	Chronic obstructive pulmonary disease
COVID-19	Corona virus disease-2019
CR	Complete response
CRC	Colorectal cancer

CRS	Cytokine-release syndrome
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor DNA
CTV	Case Transmission Verification
CTLA-4	Cytotoxic T-lymphocyte associated protein 4
DC	Dendritic cells
DCR	Disease control rate
DLT	Dose limiting toxicity
DOR	Duration of response
dMMR	Deficient mismatch repair
DNA	Deoxyribonucleic acid
DOR	Duration of response
DSMC	Data Safety and Monitoring Committee
EBV	Epstein Barr Virus
EC	Ethics committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EGFR	Epidermal growth factor receptor

EtM	Event to Monitor
Fc	Fragment crystallizable
FDA	Food and Drug Administration
GCP	Good Clinical Practices
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
HBcAb	Hepatitis B core antibody
HBsAb	Hepatitis B surface antibody
HBsAg	Hepatitis B surface antigen
HBV	Hepatitis B virus
HCC	Hepatocellular Carcinoma
HCV	Hepatitis C virus
HIMSR	Human Immune Monitoring Shared Resource
HIV	Human immunodeficiency virus

HLH	Hemophagocytic lymphohistiocytosis
HNSCC	Head and neck squamous cell carcinoma
HR	Hazard ratio
ICH	International Conference on Harmonization
ICI	Immune checkpoint inhibitor
IFN	interferon
Ig	Immunoglobulin
IL	Interleukin
IMP	Investigational medicinal product
IND	Investigational new drug
INR	International normalized ratio
IRB	Institutional Review Board
IRR	Infusion related reaction
ITT	Intention to treat
IV	Intravenous
kg	Kilogram
LFT	Liver function test
mAb	Monoclonal antibody
mCRC	Metastatic colorectal cancer
mg	Milligram

ml	Milliliter
MMR	Mismatch repair
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
MSI-H	Microsatellite instability high/ microsatellite unstable
MSS	Microsatellite Stable
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NK	Natural killer cell
NSCLC	Non-small cell lung cancer
ORR	Objective response rate
OS	Overall survival

OTC	Over the counter
PCR	Polymerase chain reaction
PD	Progressive disease
PD-1	Programmed death-1
PD-L1	Programmed death ligand-1
PFS	Progression free survival
PK	Pharmacokinetic
pMMR	Proficient mismatch repair

PO	Per Os
PR	Partial response
PT	Prothrombin time
PVR	Poliovirus Receptor
QC	Quality control
RBC	Red blood cell
RECIST	Response evaluation criteria in solid tumors
RNA	Ribonucleic Acid
SAE	Serious adverse event
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SBRT	Stereotactic body radiation therapy
SD	Stable disease
SITC	Society for Immunotherapy for Cancer
SOC	Standard of care
SOP	Standard operating procedure
TIGIT	T-cell immunoreceptor with Ig and ITIM domains
TIL	Tumor infiltrating lymphocyte
TMB	Tumor mutational burden
TME	Tumor microenvironment
TNF-α	Tumor necrosis factor-α
TPS	Tumor proportion score

TRAE	Treatment related adverse event
TSH	Thyroid-stimulating hormone
UA	Urinalysis
UAP	Unanticipated problems
UCCC	University of Colorado Cancer Center
ULN	Upper limit of normal
VCA	Viral capsid antigen
VEGF	Vascular endothelial growth factor
WBC	White blood cell
WOCBP	Women of childbearing potential

1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol Title: *A phase II trial of tiragolumab in combination with atezolizumab and bevacizumab in patients with previously treated, microsatellite stable, metastatic colorectal adenocarcinoma.*

Objectives:

- ***Primary Objective:*** ○ *To determine the objective response rate (ORR) to atezolizumab, bevacizumab, and tiragolumab therapy in patients with treatment refractory, microsatellite stable (MSS), metastatic colorectal cancer (mCRC), per RECIST v1.1.*

- ***Secondary Objectives:*** ○ *To determine the progression free survival (PFS) with atezolizumab, bevacizumab, and tiragolumab treatment in patients with treatment refractory, MSS mCRC.*
    - *To determine the overall survival (OS) with atezolizumab, bevacizumab, and tiragolumab treatment in patients with treatment refractory, MSS mCRC.*
    - *To evaluate the activity of atezolizumab, bevacizumab, and tiragolumab therapy in patients with active liver metastases compared to patients without active liver metastases.*
    - *To evaluate the safety of combined treatment with atezolizumab, bevacizumab, and tiragolumab in patients with treatment refractory, MSS mCRC.*

- ***Exploratory Objectives:*** ○ *To determine the disease control rate (DCR) with atezolizumab, bevacizumab, and tiragolumab therapy in patients with treatment refractory, MSS mCRC.*
    - ○ *To determine the duration of response (DOR) with atezolizumab, bevacizumab, and tiragolumab therapy in patients with treatment refractory, MSS mCRC.* ○ *To evaluate the relationship between pre-treatment tumor PVR and PD-L1 expression and response to atezolizumab, bevacizumab, and tiragolumab treatment.*

    - *To evaluate the relationship between pre-treatment T cell TIGIT and PD-1 expression and response to atezolizumab, bevacizumab, and tiragolumab treatment.*
    - *To evaluate the immune response to treatment with atezolizumab, bevacizumab, and tiragolumab by comparison of immune parameters, as assessed by mass cytometry, multispectral imaging, and mRNA expression panels, in pre-treatment versus on-treatment samples from the peripheral blood and tumor tissue.* ○ *To compare the immune response to atezolizumab, bevacizumab, and tiragolumab therapy in treatment responders versus treatment non-responders.*

- *To compare the immune response to atezolizumab, bevacizumab, and tiragolumab therapy in patients with versus without active liver metastases.*

Population:

- ***Gender*** *Male and Female*
- ***Age*** *≥ 18 years*
- ***Demographic group*** *treatment refractory MSS mCRC*
- ***Sample size*** *Maximum number of participants that will be enrolled is*
  54 (accounting for screen-fails, non-evaluable patients)
  Minimum number of participants to be enrolled is 16 (if stopped after interim futility analysis), or 44 (if proceeds past interim futility analysis)

Phase:	*II*
Participating Sites:	*University of Colorado*
Description of Study Intervention:	*Atezolizumab, bevacizumab, and tiragolumab*
Study Duration:	*Approximately 40 months (16 months for enrollment, 24 months for treatment and follow-up, including survival follow-up)*
Participant Duration:	*Approximately 12 months median (for treatment and follow-up, including survival follow-up). Participants with durable benefit may remain on study for longer durations.*

1.2 STUDY SCHEMA

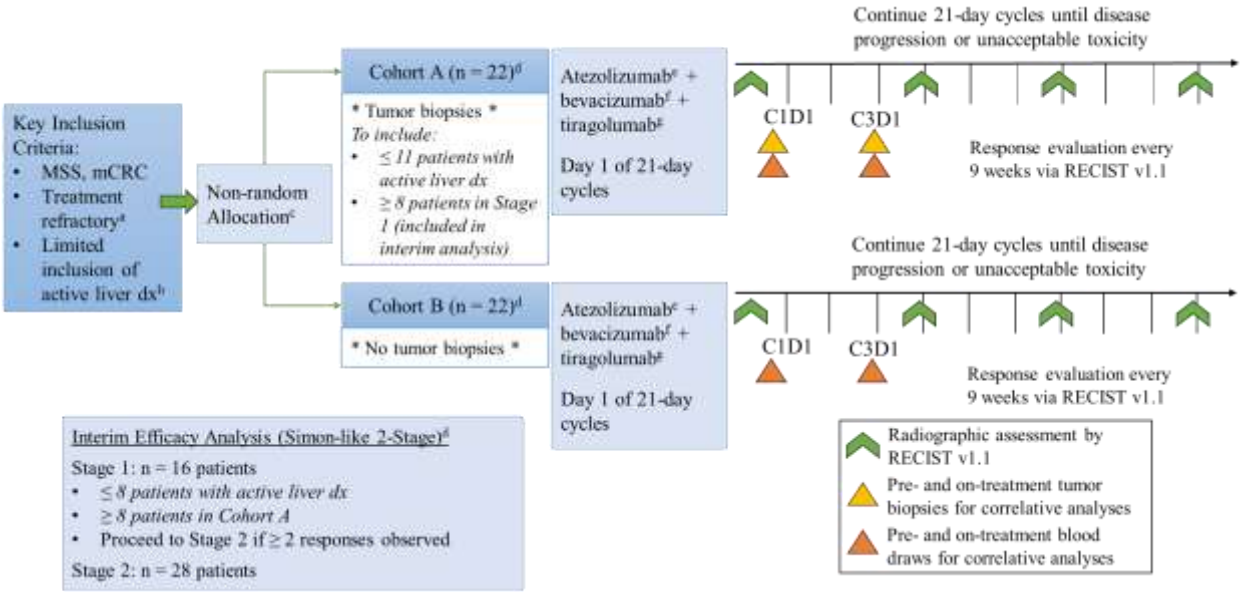


Figure 1 Study Schema

mCRC = metastatic colorectal cancer; MSS = microsatellite stable; dx = disease; C = cycle; D = day [a] Treatment refractory in this study is defined as refractory or intolerant to fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy. [b] A maximum of 22 patients with active liver metastases will be included; a maximum of 8 patients with liver metastases will be included in stage 1, and a maximum of 11 patients with liver metastases will be included in Cohort A. [c] Patients will be assigned to one of two cohorts: patients in Cohort A will undergo pre- and on-treatment

tumor biopsies for correlative analyses, patients in Cohort B will not. Otherwise, patients in Cohort A and Cohort B will receive identical treatment. Cohort allocation will not be randomized but will be based on patient and provider preference and slot availability.

[d] A Simon 2-stage design will be used. In stage 1, 16 patients will be treated and evaluated for response by RECIST v1.1. If ≤ 1 of 16 patients achieves a response (partial response or complete response), the trial will be stopped due to futility. If ≥ 2 patients respond, the trial will continue into stage 2, where an additional 28 patients will be enrolled and receive study treatment.

[e] Administered intravenously at a dose of 1200 mg on day 1 of each 21-day cycle. [f] Administered intravenously at a dose of 15 mg/kg mg on day 1 of each 21-day cycle. [g] Administered intravenously at a dose of 600 mg on day 1 of each 21-day cycle.

1.3 SCHEDULE OF EVENTS

Table 1 Schedule of Events

	Screening[a]	**Treatment Period (21-day cycles)**		**Final Study/ Treatment Discontinuation Visit[b,c]**	**Survival Follow-Up[d]**
		Cycle 1	**Cycle ≥ 2**		

Day (Window)	**-28 to -1**	**D1**	**D1 (± 2 days)**		**(± 14 days)**
Informed consent[e]	X				
Oncologic history	X				
Demographic data	X				
Medical history	X				
Concomitant treatments[f]	X	X	X	X	
ECOG performance status[g]	X	X	X	X	
Baseline signs and symptoms	X				
Adverse events[h]	X	X	X	X	
Vital signs[i, j]	X	X	X	X	
Weight	X	X	X	X	
Height	X				
Complete physical examination[k]	X				
Limited physical examination[l]		X	X	X	
12-lead ECG[m]	X	Perform as clinically indicated			
Hematology[n, o]	X	X	X	X	
Chemistry[n, p]	X	X	X	X	
Amylase, Lipase[q]		X	Perform as clinically indicated		
Thyroid Testing (TSH, free T3, free T4)[n]	X	X[r]	X[r] (every 4 cycles)		

Coagulation (INR and aPTT)[n]	X	X	X	X	
CEA[n,s]		X	X		
HIV[t], HBV[u], and HCV[v] serologies	X				
EBV serology[w]	X				
Pregnancy Test[n, x]	X	X	X	X	
Urinalysis[n, y]	X	X	X	X	
Atezolizumab dosing (every 3 weeks)		X	X		
Bevacizumab dosing (every 3 weeks)		X	X		
Tiragolumab dosing (every 3 weeks)		X	X		
Tumor assessments/RECIST 1.1[z]	X	Every 9 weeks (± 1 week)		X	
Research blood samples[aa]		X	X (C3D1)		
Research tumor biopsy[bb]	X		X (C3D1)		
Survival follow-up[d]				X	X

C = cycle; CEA = carcinoembryonic antigen; D = day; ECOG = Eastern Cooperative Oncology Group; HBV = hepatitis B virus; HCV = hepatitis C virus; HIV = human immunodeficiency virus; T3 = triiodothyronine; T4 = thyroxine; TSH = thyroid stimulating hormone; WOCBP = women of childbearing potential

Note: On treatment days, all assessments should be performed prior to dosing, unless otherwise specified.

[a] See Section 8.2.1 for additional details on screening assessments. Screening assessments are to be obtained within 28 days of C1D1. Results of standard of care testing performed prior to obtaining informed consent but within 28 days prior to C1D1 may be used and do not need to be repeated for screening. [b]

Patients who discontinue study treatment will return to the clinic for a Final Study/ Treatment Discontinuation Visit at least 30 days and no more than 35 days after treatment discontinuation. Laboratory assessments do not need to be repeated at this visit if they were already completed within the prior 7 days; tumor response assessments do not need to be repeated at this time if they were performed within the prior 42 days, or if a prior tumor response assessment has already confirmed progressive disease. See Sections 8.1.2 and 8.2.4 for more information. [c] Patients continuing to experience toxicity from serious adverse events (SAEs) at the Final Study/ Treatment Discontinuation Visit will be followed at least every 4 weeks until either (1) resolution of toxicity or (2) the determination, in the judgement of

the investigator, that no further improvement is expected. [d] Required follow-up information (survival assessment, documentation of subsequent anti-cancer therapies) will be collected via telephone calls and/or clinic visits every 3 months (±14 days), starting 3 months after the Final Study/Treatment Discontinuation Visit and continuing until death, withdrawal of consent, patient loss to follow-up, or study termination by the Sponsor-Investigator, whichever occurs first. See Section 8.2.5 for more information. [e] Informed consent must be obtained prior to undergoing any study-specific procedures, and within 28 days before C1D1.

[f] Concomitant treatments include any medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) and non-drug supportive treatments used by the patient in addition to protocol-mandated treatments. At screening, all concomitant treatments should be recorded in the eCRF. All concomitant treatments used during study participation will be recorded continuously in the eCRF starting at the screening visit and ending at the Final Study/ Treatment Discontinuation Visit. [g] ECOG performance status should be assessed per criteria in Section 8.2.1. [h] After informed consent has been obtained all adverse events will be reported until 30 days after the final dose of

study treatment, until study discontinuation/termination, or until the initiation of new systemic anti-cancer therapy, whichever occurs first. Patients experiencing ongoing toxicity related to SAEs at the Final Study/ Treatment Discontinuation Visit will be followed as outlined in footnote c. Instructions for reporting adverse events that occur during and after the adverse event reporting period are provided in Section 9. [i]

Includes heart rate, temperature, blood pressure, respiratory rate, and pulse oximetry, obtained while the patient is in the seated position. Record abnormalities observed at baseline in the eCRF. At subsequent visits, record new or worsened clinically significant abnormalities in the Adverse Event eCRF. [j] Vital signs should be obtained prior to, during, and after study infusions as outlined in Section 6.2. [k] A complete physical examination should be performed during screening. Abnormalities should be recorded

in the eCRF. [l] A limited, symptom-directed physical exam will be performed at other specified timepoints. New or worsened clinically significant abnormalities should be recorded as adverse events in the Adverse Event eCRF. [m] A single 12-lead electrocardiogram (ECG) will be obtained at screening; additional ECGs should be

obtained when clinically indicated. ECG recordings should be performed after the patient has been resting in a supine position for at least 10 minutes. See Section 8.2.1 for details. [n] Laboratory testing may be drawn up to 72 hours prior to treatment administration. [o] Hematology assessments include a CBC with differential, as described in Section 8.2.1 and Section 8.2.2.

[p] Chemistry assessments include a complete metabolic panel, magnesium, and phosphorous, as described in Section 8.2.1 and Section 8.2.2.

[q] Lipase and amylase should be collected on Day 1 of Cycle 1, and then as clinically indicated.

[r] TSH, free T3, and free T4 will be obtained on Day 1 of Cycle 1 and every 4 cycles thereafter (e.g., C5D1, C9D1, C13D1, etc) during the Treatment Period. [s] CEA should be drawn prior to each study treatment. Other tumor markers should be collected as clinically

indicated (e/g/ CA 19-9, CA-125). [t] HIV antigen/antibody combination test should be performed in all patients. Patients with a known history of HIV or positive HIV antigen/antibody testing should have HIV viral load and CD4 count obtained at screening. See Section 5 for details of relevant inclusion/exclusion criteria.

[u] HBV surface antigen (HBsAg), HBV surface antibody (HBsAb), and total HBV core antibody (HBcAb) should be performed in all patients. HBV DNA testing should be obtained for patients with negative HBsAg, negative HBsAb, and positive total HBcAb testing. Patients with a positive quantitative HBV DNA at screening (must be < 500 IU/mL per the eligibility criteria) will undergo additional HBV DNA tests every 3 months (± 7 days) during treatment, at treatment discontinuation (± 7 days), and at 3, 6, 9, and 12 months (± 14 days at each timepoint) after treatment discontinuation. Study treatment and procedures may proceed while HBV DNA is being processed, but results should be reviewed by the investigator as soon as they are available. If HBV DNA increases to > 500 IU/mL, consultation with a hepatologist or gastroenterologist with specialty in HBV is recommended. The Principal Investigator is available to advise as needed. [v] HCV antibody testing should be obtained in all patients; HCV RNA testing should be obtained for those with a positive HCV antibody test.

[w]EBV viral capsid antigen (VCA) IgM and EBV VCA IgG or nuclear antigen IgG testing should be obtained in all patients; EBV PCR should be obtained only in situations where there is clinical suspicion for active infection (ie positive EBV VCA IgM).

[x] For WOCBP, a serum pregnancy test should be performed during screening (within 28 days prior to treatment start), and urine pregnancy tests should be performed within 72 hours prior to each treatment. Positive urine pregnancy tests should be confirmed by serum tests. See Section 5.1 for definition of WOCBP. [y] Dipstick urinalysis may be performed, with microscopic examination as indicated. If protein is ≥ 2+, a 24-hour urine protein assessment should be performed. [z] Tumor assessments should be performed at baseline (within 28 days before C1D1), and every 9 weeks (± 1 week) following initiation of treatment (C1D1). The first post-treatment initiation scan should be performed prior to treatment on C4D1. Tumor assessments should be repeated at the Final Study/ Treatment Discontinuation Visit if not performed in the prior 42 days, and if disease progression on treatment has not yet been documented. At the investigator's discretion, tumor assessments may be repeated at any time if progressive disease is suspected. Tumor assessments must include computed tomography (CT) scans (with IV contrast; with or without oral contrast) or magnetic resonance imaging (MRI) scans (with IV contrast) of the chest, abdomen, and pelvis. A CT or MRI scan of the head with contrast should be performed at screening to evaluate for central nervous system (CNS) metastases in patients with a known history of CNS involvement, or if there is clinical concern for CNS disease. As only patients with treated and stable CNS involvement will be included in this study, subsequent imaging of the head is not required, but should be obtained if clinically indicated. Additional imaging (e.g., bone scans, CT scans of the neck) should be performed if clinically indicated at the discretion of the investigator. See Section 8.1 for further information regarding tumor assessments. [aa] Research blood samples will be obtained in all patients at (1) a pre-treatment timepoint, after completion of informed consent and confirmation of eligibility and prior to treatment on C1D1, and (2) an on-treatment timepoint, prior to treatment on C3D1 or following treatment discontinuation, whichever is earlier. If treatment discontinuation occurs prior to C3D1, research blood samples should be obtained at or before the time of the Final Study/ Treatment Discontinuation Visit, and no less than 14 days from the last study treatment. Prior to proceeding with pre-treatment blood draws for correlative research analyses, (1) patients must sign the Informed Consent Form, and (2) all other screening evaluations must be completed and reviewed by the treating clinician to confirm eligibility criteria are met. See Section 8.2 and Section 8.3.1 for additional information.

[bb] Research tumor tissue will be obtained by core biopsy or tissue resection in patients enrolled in Cohort A at (1) a pre-treatment timepoint, after completion of informed consent and confirmation of study eligibility and 3 days or more prior to treatment on C1D1, and (2) an on-treatment timepoint, at C3D1±3 days. Prior to proceeding with pretreatment biopsy, (1) patients must sign the Informed Consent Form, and (2) all other screening evaluations must be completed and reviewed by the treating clinician to confirm eligibility criteria are met. While the acceptable window for the on-treatment C3D1 biopsy is ±3 days, it is preferred that the biopsy occurs following all treatments on C3D1. For patients who discontinue treatment after cycle 2 but prior to cycle 3, an on-treatment biopsy should be obtained between C2D18 and C2D24 of treatment. For patients who discontinue treatment after cycle 1 but prior to cycle 2, an on-treatment biopsy should be obtained between C1D18 and C1D24 of treatment, if feasible. Archival tissue may not be used in place of a fresh pre-treatment biopsy. See Section 8.2 and Section 8.3.2 for additional information.

2 INTRODUCTION

2.1 STUDY RATIONALE

Colorectal cancer (CRC) is the second most common cause of cancer-related deaths in the United States, and 5-year survival for those diagnosed with metastatic disease is approximately 15%[1]. Initial treatment for metastatic CRC (mCRC) involves fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy, along with agents targeting Epidermal Growth Factor Receptor (EGFR) or Vascular Endothelial Growth Factor (VEGF), depending on *RAS* and *BRAF* status and left- versus right-sided primary tumor site. Following progression on these agents, available treatment options for mCRC have minimal activity[2]. Thus, new treatment options for mCRC refractory to fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy are badly needed.

Immunotherapy approaches, primarily those targeting the immune checkpoint receptor Programmed death-1 (PD-1) and its ligand Programmed Death Ligand-1 (PD-L1), have been a central focus of drug development and are now approved for use in several solid malignancies. Despite this success, the efficacy of anti-PD-1 and anti-PD-L1 therapies in microsatellite stable (MSS) mCRC has been largely disappointing[3-5]. Novel strategies to enhance the response to immunotherapy in MSS mCRC are therefore of particular interest.

Translational work supports an important role for both (1) the immune checkpoint inhibitor T cell immunoglobulin and ITIM domain (TIGIT) and (2) VEGF in maintaining an immunosuppressive tumor microenvironment (TME) in MSS CRC[6-8]. Preclinical CRC models demonstrate synergy of anti-PD-1/PD-L1 therapies with anti-TIGIT and anti-VEGF agents[6,9,10], and clinical trials evaluating anti-PD-1/PD-L1 agents with anti-TIGT and/or anti-VEGF therapies have shown promise in other cancer types including non-small cell lung cancer (NSCLC) and hepatocellular carcinoma (HCC)[11-14]. There is thus strong rationale for combination of anti-PD-1/PD-L1, antiTIGIT, and anti-VEGF agents in MSS mCRC.

This study will evaluate the combination of the anti-TIGIT monoclonal antibody (mAb) tiragolumab, the anti-PD-L1 mAb atezolizumab, and the anti-VEGF mAb bevacizumab, with the hypothesis that this regimen will promote an inflammatory TME able to overcome resistance previously observed to anti-PD-1/PD-L1 monotherapy in MSS mCRC.

A single-arm, Simon-like 2-stage design will be used to assess efficacy and safety of this treatment combination. The study will enroll patients with treatment refractory disease, in whom available therapeutic options have minimal activity. An interim analysis will be performed to assess futility, minimizing the number of patients enrolled if no early efficacy signal is observed. Correlative analyses are planned to explore mechanisms of response and/or resistance to therapy. Thus, this trial will provide information to help advance the field, regardless of whether significant efficacy of the study regimen is observed.

It is anticipated that the combination of tiragolumab, atezolizumab, and bevacizumab will be adequately tolerated, with a safety profile in line with that observed for anti-PD-L1 and anti-VEGF agents. This prediction is based on clinical trials and subsequent standard of care (SOC) use of atezolizumab plus bevacizumab[12,14], as well as results of clinical trials of atezolizumab plus tiragolumab[11,15] and atezolizumab, bevacizumab, and tiragolumab[13]. To mitigate risks, patients with conditions posing increased risk of toxicity with immunotherapy or anti-VEGF therapy will be excluded (see Section 5.2 and Appendix 7). Furthermore, specific guidelines for management of anticipated adverse events (AEs) as well as treatment discontinuation for unacceptable toxicity are outlined in this protocol (see Section 9 and Appendices 8-9).

2.2 Background

2.2.1 Background on Colorectal Cancer

Colorectal cancer (CRC) is the fourth most common cancer and the second most common cause of cancer-related deaths in the United States. Five-year survival for those diagnosed with metastatic disease is around 15%, and new treatments are badly needed[1]. The initial standard of care treatment for microsatellite-stable (MSS) metastatic CRC (mCRC) relies on fluoropyrimidine-based chemotherapy, either in combination with oxaliplatin (FOLFOX, CAPOX), irinotecan (FOLFIRI), or both (FOLFOXIRI, FOLFIRINOX). Current guidelines also recommend the addition of biologic agents to chemotherapy, targeting either EGFR with cetuximab or panitumumab or VEGF with bevacizumab, depending on tumor sidedness and *RAS* and *BRAF* mutational status. With this approach, median overall survival (OS) for mCRC is approximately 30 months, compared to less than a year in those with untreated disease[16].

Following progression on fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy, available treatment regimens offer only modest efficacy, and disease is considered to be treatment refractory. For instance, the combination of trifluridine/tipiracil plus bevacizumab in patients with refractory mCRC achieved an objective response rate (ORR) of 6% and a progression free survival (PFS) of 5.6 months in the phase III SUNLIGHT trial[2]. Other approved regimens including trifluridine/tipiracil monotherapy and regorafenib have demonstrated ORRs of less than 5% in this setting[17-20]. There is thus a pressing need for more effective therapies for MSS mCRC refractory to fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy.

2.2.2 Immunotherapy in Colorectal Cancer

Immunotherapy approaches, primarily those targeting the immune checkpoint PD-1 and its ligand PD-L1, have been a central focus of drug development in recent decades and are now approved for use in several solid malignancies. Despite this success, efficacy of immune checkpoint inhibitors (ICIs) is widely variable across cancer types and subgroups[11,22].

Approximately 5% of patients with mCRC have microsatellite instability-high (MSI-H) disease, as a result of dysfunctional or absent mismatch repair (MMR) proteins. Anti-PD-1 therapies including pembrolizumab and nivolumab have demonstrated impressive efficacy in this patient population, with response rates of approximately 50%[23,24]; they are now approved for use in frontline and subsequent-line settings for treatment of MSI-H mCRC. In the remaining 95% of patients with MSS mCRC, monotherapy with anti-PD-1/PD-L1 agents has been ineffective[3-5]. Resistance to ICI therapy is thought to be due to the immunologically "cold" or non-inflamed TME observed in MSS CRC, with characteristics including low tumor mutational burden (TMB) and reduced mutation-associated neoantigens, decreased numbers of tumor infiltrating lymphocytes (TILs), and high prevalence of immunosuppressive cells[25].

Growing evidence suggests that the presence of liver metastases, common in MSS mCRC, contributes to immunosuppression and decreased activity of ICI therapy. For instance, one study observed macrophage-mediated T cell elimination in liver metastases leading to systemic immunosuppression in mouse models[26]. Reduced efficacy of ICI therapy has been observed in patients with versus without liver metastases in several cancer types, including melanoma, NSCLC, and gastric cancer[27-29]. This has also been observed in MSS mCRC, with one retrospective cohort study reporting an ORR of 19.5% versus 0% in patients without versus with liver metastases, respectively, treated with anti-PD-1/PD-L1 therapy[30].

There is significant interest in developing novel strategies to overcome resistance to ICI therapy in MSS mCRC. Combined treatment of a fragment crystallizable (Fc)-enhanced anti-CTLA-4 antibody, botensilimab, with an anti-PD-1 antibody, balstilimab, demonstrated promising activity in a phase I trial, with an ORR of 22%[31]. Other efforts exploring combinations of ICI therapy with anti-VEGF agents have shown promise, albeit with mixed results[32-36]. Optimizing combinatorial therapies which act on distinct mechanisms of the tumor immune response may be key to achieving meaningful activity with cancer immunotherapy (CIT) in MSS mCRC.

[1] **.2.3.1 ATEZOLIZUMAB**

2.2.3 Background on Study Treatments

Atezolizumab is a humanized immunoglobulin (Ig) G1 mAb that targets PD-L1 and inhibits the interaction between PD-L1 and its receptors, PD-1 and B7-1 (also known as CD80), both of which function as inhibitory receptors expressed on T cells. Therapeutic blockade of PD-L1 binding by atezolizumab has been shown to enhance the magnitude and quality of tumor-specific T-cell responses, resulting in improved anti-tumor activity[37,38]. Atezolizumab has minimal binding to Fc receptors, thus eliminating detectable Fc-effector function and associated antibody-mediated clearance of activated effector T cells.

Atezolizumab has demonstrated antitumor activity in both nonclinical models and cancer patients and is being investigated as a potential therapy in a wide variety of malignancies. Atezolizumab is being studied as a single agent in the advanced cancer and adjuvant therapy settings, as well as in combination regimens with chemotherapy, targeted therapy, and other CITs.

Atezolizumab is approved for the treatment of several malignancies including NSCLC, small cell lung cancer, HCC, and melanoma.

Refer to the Atezolizumab Investigator's Brochure for details on nonclinical and clinical studies.

2.2.3.2 Bevacizumab

Bevacizumab is a recombinant humanized mAb that recognizes all isoforms of VEGF. Bevacizumab may exert a direct anti-angiogenic effect by binding to and clearing VEGF from the tumor microenvironment. Additional anti-tumor activity may be exerted on tumor vasculature, interstitial pressure, and blood vessel permeability, providing for enhanced drug delivery to tumor cells[39]. Bevacizumab may also enhance the anti-tumor immune response through inhibition of VEGF, as growing evidence supports an important role for VEGF in promoting an immunosuppressive TME. VEGF has been shown to inhibit dendritic cell (DC) maturation and antigen presentation, decrease T cell proliferation, trafficking, and tumor infiltration, and promote recruitment of immunosuppressive cells including regulatory T cells to the TME[40,41].

Bevacizumab is now approved in combination regimens for multiple indications, including in the first- and later-line treatment of mCRC; first-line treatment of advanced NSCLC, HCC, metastatic breast cancer, advanced renal cell carcinoma, and ovarian cancer; and treatment of recurrent glioblastoma. Bevacizumab is generally well tolerated, and adverse events have been manageable.

Refer to the current Bevacizumab Investigator's Brochure for additional details on nonclinical and clinical studies with bevacizumab.

2.2.3.3 TIRAGOLUMAB

Tiragolumab is a fully human IgG1/κ mAb that binds TIGIT, an immune inhibitory receptor that is expressed on the surface of activated T-cell and natural killer (NK)-cell subsets and interacts with high affinity with CD155 (also known as poliovirus receptor [PVR])[42]. Genetic ablation of TIGIT in T cells in mice results in exacerbated T-cell responses, demonstrating the role of TIGIT in inhibiting T-cell responses[9,43]. Therapeutic blockade of TIGIT by tiragolumab represents an attractive strategy for cancer therapy and is expected to enhance the magnitude and quality of tumor-specific T-cell responses, which may result in improved meaningful anti-tumor activity when tiragolumab is combined with other CIT. The available nonclinical and clinical data provide a strong rationale for evaluating the potential clinical benefit of tiragolumab in patients with cancer.

Refer to the Tiragolumab Investigator's Brochure for details on the nonclinical and clinical studies for tiragolumab.

2.2.4 BACKGROUND ON STUDY TREATMENT COMBINATIONS

Strong scientific rationale suggests that combined inhibition of PD-1/PD-L1, VEGF, and TIGIT may enhance anti-tumor activity and overcome resistance to ICI therapy in MSS mCRC. TIGIT has been shown to be co-expressed with PD-1 at high levels in MSS CRC[6], and combined therapy with anti-TIGIT and anti-PD-1/PD-L1 agents has demonstrated efficacy in preclinical MSS CRC models[9]. Meanwhile, VEGF inhibition has been shown to enhance antigen-presenting capacity of DCs and infiltration of tumor-rejecting CD8+ T cells[56,57], while reducing frequency of immune suppressor cells[58]. Thus, the immunomodulatory effects of bevacizumab are anticipated to increase CD8+ T-cell recruitment and diminish TME immunosuppression, thereby boosting the effects of immunotherapy.

Treatment regimens combining VEGF-targeting therapies and anti-PD-1/PD-L1 therapies are approved for use in indications other than MSS CRC. For instance, the combination of atezolizumab and bevacizumab is approved for use in HCC based on the IMbrave150 trial, and stands as a preferred frontline treatment in this setting. In this trial, treatment of patients with advanced HCC with atezolizumab plus bevacizumab resulted in improved efficacy compared to sorafenib, with a hazard ratio for death of 0.58 (95% confidence interval [CI], 0.42 to 0.79; $P<0.001$)[12].

Early-stage trials have evaluated the combination of anti-VEGF and anti-PD-1/PD-L1 therapies in MSS mCRC with variable results. For instance, a study evaluating the combination of regorafenib plus nivolumab in MSS CRC demonstrated an ORR of 7%, with an ORR of 22% in patients lacking liver metastases[33]. The phase II LEAP-005 trial evaluating lenvatinib plus pembrolizumab reported an ORR of 22% in MSS mCRC[36]; the phase II CAMILLA trial evaluating cabozantinib plus durvalumab demonstrated an ORR of 28%[52]. Meanwhile, trials evaluating the combination of regorafenib with pembrolizumab or regorafenib with avelumab demonstrated ORRs of 0%[32,53].

A phase II trial conducted at the University of Colorado evaluated the activity of pembrolizumab, binimetinib, and bevacizumab in previously treated, MSS mCRC (NCT03475004), based in part on evidence supporting a role for VEGF in maintaining an immunosuppressive TME[54]. Of 45 evaluable patients in this trial, 6 (13%) achieved a partial response (PR) and 29 (65%) achieved stable disease (SD) as best response, while 10 (22%) experienced disease progression. Of note, the KEYNOTE-651 trial evaluated the combination of pembrolizumab plus binimetinib without bevacizumab in previously treated, MSS mCRC, and observed no responses (NCT03374254)[55]. This suggests that bevacizumab provides synergistic activity in this regimen and may enhance response to immunotherapy in MSS mCRC.

Translational analyses were conducted to assess the immune response to treatment in this trial (NCT03475004). T cell expression of inhibitory receptors including PD-1 and TIGIT were evaluated on CD8+ T cells at both pre- and post-treatment timepoints. Notably, increased TIGIT expression was observed following treatment in patients who progressed on therapy, suggesting that TIGIT may mediate resistance to this treatment regimen and providing rationale for the combination of anti-PD-1/PD-L1, anti-VEGF, and anti-TIGIT therapy.

The addition of tiragolumab to atezolizumab plus bevacizumab has shown activity in advanced HCC in a cohort of the phase I/II MORPHEUS-Liver study (NCT04524871)[13]. Preliminary results from this trial demonstrate enhanced efficacy of the triplet regimen (atezolizumab, bevacizumab, and tiragolumab) versus the doublet regimen (atezolizumab and bevacizumab) among 58 patients, with a PFS of 11.1 versus 4.2 months (HR 0.42, 95% CI 0.22-0.82), respectively.

The combination of atezolizumab, bevacizumab, and tiragolumab is also under investigation for MSI-H mCRC in the phase I/Ib INTRINSIC trial (NCT04929223).

2.3 Risk/Benefit Assessment

2.3.1 Known Potential Risks

There has been substantial clinical experience with atezolizumab, bevacizumab, and tiragolumab to date, both as monotherapies, and in combination regimens including atezolizumab plus bevacizumab and atezolizumab plus tiragolumab. The triplet combination of atezolizumab, bevacizumab, and tiragolumab has also been evaluated in clinical trials, without new safety signals observed. Clinical risks and preliminary anti-tumor activity of the study drugs are described below.

2.3.1.1 ATEZOLIZUMAB

As with other anti-PD-1/PD-L1 therapies, severe and fatal immune-mediated AEs in any organ or tissue may occur with atezolizumab. These include immune-mediated pneumonitis, hepatitis, endocrinopathies, nephritis, colitis, and dermatologic AEs. However, most AEs observed with atezolizumab are low grade; rates of grade 3 or higher AEs have generally been low.

See the Investigator's Brochure for the most current risk profile for atezolizumab.

2.3.1.2 BEVACIZUMAB

The most serious adverse events identified in clinical trials with bevacizumab have been gastrointestinal perforations, hemorrhage (including tumor-associated bleeding and pulmonary hemorrhage/hemoptysis, more common in NSCLC patients), and arterial thromboembolic events. Other adverse events observed in patients treated with bevacizumab include fistulae, woundhealing complications, hypertension, arterial and venous thromboembolism, and proteinuria. In addition, congestive heart failure has been observed rarely. Analyses of the clinical safety data suggest that the occurrence of hypertension and proteinuria with bevacizumab is likely to be dose dependent.

The most frequently observed adverse events in patients who received bevacizumab have been hypertension, fatigue or asthenia, diarrhea, and abdominal pain. Increased rates of severe neutropenia, febrile neutropenia, or infection with severe neutropenia (including some fatalities) have been observed in patients treated with some myelotoxic chemotherapy regimens plus bevacizumab in comparison to chemotherapy alone. There have been rare reports in the postmarketing setting of the development of signs and symptoms that are consistent with posterior reversible encephalopathy syndrome (PRES) in bevacizumab-treated patients. Very rare cases of hypertensive encephalopathy have also been reported, some of which were fatal.

See the Investigator's Brochure for the most current risk profile for bevacizumab.

2.3.1.3 TIRAGOLUMAB (+/- ATEZOLIZUMAB)

Tiragolumab has been evaluated in several clinical trials to date, alone or in combination with other therapies, including atezolizumab[11,15,44]. Overall, tiragolumab as a single agent or in combination with atezolizumab has been well tolerated, and adverse events have been manageable,

Tiragolumab monotherapy and tiragolumab plus atezolizumab were evaluated in patients with locally advanced, recurrent, or metastatic tumors in a first-in-human, phase I, open-label, doseescalation and dose-expansion study. No maximum tolerated dose, dose related toxicities, or clear dose-related trends in the incidence or severity of AEs were identified for tiragolumab, alone or in combination with atezolizumab. Treatment related AEs (TRAEs) occurred in 67% of patients treated with monotherapy and 59% of patients treated with combination therapy, with grade ≥ 3 events occurring in 4% of patients in each treatment group[15]. Commonly reported AEs (in ≥ 10% of patients) among patients treated with atezolizumab and tiragolumab, regardless of relationship to tiragolumab, included pruritus, pyrexia, anemia, rash, malignant neoplasm progression, constipation, decreased appetite, diarrhea, cough, asthenia, arthralgia, and fatigue. Commonly reported AEs (in ≥ 10% of patients) related to tiragolumab and/or atezolizumab included pruritus and rash.

Tiragolumab was further evaluated in patients with PD-L1 selected advanced NSCLC (tumor proportion score [TPS] ≥ 1%) in the Phase II, global, randomized, double-blind, placebocontrolled CITYSCAPE study[11]. The safety profile in the primary analysis was similar between the tiragolumab combined with atezolizumab arm and the placebo combined with atezolizumab arm for Grade ≥ 3 AEs (48% vs 44%), SAEs (21% vs 18%), and AEs leading to study treatment withdrawal (15% vs 13%). Although immune mediated AEs were reported at a higher frequency for the atezolizumab plus tiragolumab arm compared to the atezolizumab plus placebo arm, they were generally mild, transient, and manageable in nature.

See the Investigator's Brochure for the most current risk profile for tiragolumab.

2.3.1.4 Atezolizumab, Bevacizumab, and Tiragolumab

The combination of atezolizumab, bevacizumab, and tiragolumab is under investigation for treatment of advanced HCC in a cohort of the phase I/II MORPHEUS-Liver study (NCT04524871)[13], and in MSI-H mCRC in the phase I/Ib INTRINSIC trial (NCT04929223).
The MORPHEUS-Liver trial is a Phase Ib/II study evaluating triplet therapy (atezolizumab, tiragolumab, and bevacizumab) versus doublet therapy (atezolizumab and bevacizumab) for

firstline treatment of patients with advanced HCC. Results from this study were presented at the American Society for Clinical Oncology (ASCO) Annual Meeting in 2023[13]. Triplet therapy was adequately tolerated compared to doublet therapy, with similar rates of grade 3-4 TRAEs (27.5% with triplet versus 33.3% with doublet), treatment-related SAEs (22.5% with triplet versus 27.8% with doublet), AEs leading to withdrawal of treatment (22.5% with triplet versus 22.2% with doublet), and AEs of special interest (AESI) requiring systemic corticosteroids (17.5% with triplet versus 16.7% with doublet). The most common AEs of any grade observed with triplet therapy were pruritus (45%), proteinuria (35%), fatigue (32.5%), hypertension (30%), arthralgias (27.5%), rash (27.5%), epistaxis (22.5%), abdominal pain (22.5%), decreased appetite (22.5%), constipation (20%), diarrhea (20%), and AST elevation (18.5%). The most common AESIs observed with triplet therapy included rash (47.5%), hepatitis (27.5%), infusion related reactions (IRRs, 12.5%), and hypothyroidism (10%).

2.3.1.5 TUMOR BIOPSIES

Patients in Cohort A will undergo a tumor biopsy at pre- and on-treatment timepoints for correlative analyses. Risks of biopsies include but are not limited to pain, bleeding, infection, and damage to nearby structures. Care will be taken to minimize risk to each patient by identifying the safest biopsy target. See Section 8.3.2 for additional information regarding tumor biopsies.

2.3.2 KNOWN POTENTIAL BENEFITS

2.3.2.1 ATEZOLIZUMAB, BEVACIZUMAB, AND TIRAGOLUMAB

Bevacizumab has demonstrated benefit in MSS mCRC as a part of several treatment regimens in first- and subsequent-line settings, including in fluoropyrimidine, oxaliplatin, and irinotecan refractory disease in combination with trifluridine/tipiracil[2].

While anti-PD-1/PD-L1 monotherapy has demonstrated disappointing activity in MSS mCRC, there is strong preclinical and clinical evidence to support rationale for combination of atezolizumab with bevacizumab and tiragolumab, as outlined in Section 2.2. This includes clinical trial results demonstrating increased efficacy with addition of tiragolumab to atezolizumab in NSCLC[11], established efficacy of atezolizumab and bevacizumab in advanced HCC[13], and preliminary trial results supporting increased efficacy of atezolizumab, bevacizumab, and tiragolumab versus atezolizumab plus bevacizumab in advanced HCC[13]. Preclinical and

translational work suggests that combined anti-PD-1/PD-L1, anti-VEGF, and anti-TIGIT therapy may be especially effective in MSS mCRC[6,9,45].

2.3.2.2 TUMOR BIOPSIES

Patients in Cohort A will undergo a tumor biopsy pre- and on-treatment. Since the advent of the targeted and immunotherapy treatment era, it has become clear that a better understanding of the intimate biological mechanisms that tailor cancer cell phenotypes would be translated into a better chance of disease control. However, this has been a difficult task due to the complex interaction between the tumor cell, tumor microenvironment, and immune response. Animal models do not accurately represent these intricate interactions, especially for the immune system[46]. Therefore, tumor biopsies during the clinical study present the best opportunity to increase understanding of the anti-tumor immune response and identify biomarkers predictive of response and resistance. See Section 8.3.2 for additional information regarding tumor biopsies.

2.3.3 ASSESSMENT OF POTENTIAL BENEFITS

Based on the potential benefits of the study regimen, the limitations of standard of care therapies for this patient population, and the well-defined, tolerable safety profile of each study agent alone and in combination, the Sponsor-Investigator believes that the potential benefits of this study outweigh its risks.

The risks to participants are reasonable in relation to the anticipated benefits to participants and/or society, and in relation to the importance of the knowledge that may reasonably be expected to result, thereby falling in favor of performing the study:

- To Participant: the benefit of possible short term and sustained disease response resulting in improvement in both quantity and quality of life.
- To Society: the knowledge gained regarding mechanisms of response and/or resistance to immunotherapy, and with this, the potential to guide research and treatment for other patients with mCRC; the potential to identify a novel therapy/ combination therapy with promise for other patients with mCRC.
- Justify the importance of the knowledge gained: the knowledge gained will help inform future directions of research and treatment in mCRC.

2.3.4 Risk/Benefit Considerations Specific to the COVID-19 Pandemic

In the setting of the coronavirus 2019 (COVID-19) pandemic, patients with comorbidities, including those with cancer, are considered a more vulnerable population, with the potential for more severe clinical outcomes from severe acute respiratory syndrome coronavirus 2 (SARSCoV2) infection. However, it is unclear whether or how systemic cancer therapies, such as chemotherapy, targeted therapy, or immunotherapy, impact the incidence or severity of SARSCoV-2 infection.

A possible consequence of inhibiting the PD-1/PD-L1 pathway may be the modulation of the host immune response to acute infection, which may result in immunopathology or dysregulated immune system defenses. In nonclinical models, PD-1/PD-L1 blockade appears to be associated with serious exacerbation of inflammation in the setting of acute (as opposed to chronic) viral infection with lymphocytic choriomeningitis virus (Clone 13)[47]. However, there are insufficient and inconsistent clinical data to assess if outcome from SARS-CoV-2 infection is altered by cancer immunotherapy.

Severe SARS-CoV-2 infection appears to be associated with a cytokine release syndrome (CRS) involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and interferon (IFN)-γ[48]. While it is not known, there may be a potential for an increased risk of an enhanced inflammatory response if a patient develops SARS-CoV-2 infection while receiving atezolizumab. At this time, there is insufficient evidence for causal association between atezolizumab and an increased risk of severe outcomes from SARS-CoV-2 infection.

There may be potential synergy or overlap in clinical and radiologic features for immune mediated pulmonary toxicity with atezolizumab and clinical and radiologic features for SARS-CoV2−related interstitial pneumonia. Thus, investigators should use their clinical judgment when evaluating and managing patients with pulmonary symptoms.

There are limited data concerning the possible interactions between cancer immunotherapy treatment and COVID-19 vaccination, and it is recognized that human immune responses are highly regulated and that immune modifying therapies may positively or negatively impact the efficacy and safety of COVID-19 vaccination (Society for Immunotherapy for Cancer [SITC] 2020).

Per recommendations of the National Comprehensive Cancer Network (NCCN) COVID-19 Vaccination Advisory Committee, COVID-19 vaccination is recommended for all patients with

cancer receiving active therapy (including immune checkpoint inhibitors), with the understanding that there are limited safety and efficacy data in such patients. Given the lack of clinical data, currently no recommendations can be made regarding the optimal sequence of COVID-19 vaccination in patients who are receiving cancer immunotherapy. For patients enrolling in this study and receiving atezolizumab treatment, a decision to administer the vaccine to a patient should be made on an individual basis by the investigator in consultation with the patient.

In alignment with clinical practice procedures, factors to consider when making the individualized decision for patients receiving atezolizumab treatment to receive COVID-19 vaccination include the following: the risk of SARS-CoV-2 infection and potential benefit from the vaccine, the general condition of the patient and potential complications associated with SARS-CoV-2 infection, underlying disease, and the severity of COVID-19 outbreak in a given area or region.

SITC and NCCN recommendations along with institutional guidelines should be used by the investigator when deciding on administering COVID-19 vaccines. When administered, COVID19 vaccines must be given in accordance with the approved or authorized vaccine label. Receipt of the COVID-19 vaccine is considered a concomitant medication and should be documented as such.

3 OBJECTIVES AND ENDPOINTS

3.1 STUDY OBJECTIVES

2.1.34 PRIMARY OBJECTIVE

To determine the objective response rate (ORR) to atezolizumab, bevacizumab, and 1. tiragolumab therapy in patients with treatment refractory, MSS mCRC using RECIST v1.1.

3. To evaluate the activity of atezolizumab, bevacizumab, and tiragolumab therapy in patients with active liver metastases compared to patients without active liver metastases.

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[2] **.1.2 SECONDARY OBJECTIVES**

[3] . To determine the progression free survival (PFS) with atezolizumab, bevacizumab, and tiragolumab treatment in patients with treatment refractory, MSS mCRC.

[4] . To determine the overall survival (OS) with atezolizumab, bevacizumab, and tiragolumab treatment in patients with treatment refractory, MSS mCRC.

4. To evaluate the safety of combined treatment with atezolizumab, bevacizumab, and tiragolumab in patients with treatment refractory, MSS mCRC.

3.1.3 Exploratory Objectives

1. To determine the disease control rate (DCR) with atezolizumab, bevacizumab, and tiragolumab therapy in patients with treatment refractory, MSS mCRC.
2. To determine the duration of response (DOR) with atezolizumab, bevacizumab, and tiragolumab therapy in patients with treatment refractory, MSS mCRC.
3. To evaluate the relationship between pre-treatment tumor PVR and PD-L1 expression and response to atezolizumab, bevacizumab, and tiragolumab treatment.
4. To evaluate the relationship between pre-treatment T cell TIGIT and PD-1 expression and response to atezolizumab, bevacizumab, and tiragolumab treatment.
5. To evaluate the immune response to treatment with atezolizumab, bevacizumab, and tiragolumab by comparison of immune parameters, as assessed by mass cytometry, multispectral imaging, and messenger ribonucleic acid (mRNA) expression panels, in pretreatment versus on-treatment samples from the peripheral blood and tumor tissue.
6. To compare the immune response to atezolizumab, bevacizumab, and tiragolumab therapy in treatment responders versus treatment non-responders.
7. To compare the immune response to atezolizumab, bevacizumab, and tiragolumab therapy in patients with versus without active liver metastases.

3.2 Study Endpoints

3.2.1 Primary Endpoint

1. Objective response rate (ORR) per RECIST v1.1, defined as complete response (CR) or partial response (PR) to treatment.

3.2.2 Secondary Endpoints

1. Progression free survival (PFS), defined as the time from enrollment to the first observation of progression per RECIST v1.1 or death from any cause.
2. Overall survival (OS), defined as the time from enrollment to death from any cause.
3. ORR, PFS, and OS as defined above, according to the presence or absence of active liver metastases.

4. Incidence, type, and severity of adverse events as defined by the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) v5.0, including serious adverse events and adverse events of special interest.

3.2.3 Exploratory Endpoints

1. Disease control rate (DCR) per RECIST v1.1, defined as stable disease (SD), partial response (PR), or complete response (CR) to treatment.
2. Duration of response (DOR), defined as the time from response (CR or PR) to progression or death from any cause, per RECIST v1.1.
3. Objective response rate (ORR) per RECIST v1.1, according to pre-treatment tumor PVR and PD-L1 expression.
4. Objective response rate (ORR) per RECIST v1.1, according to pre-treatment T cell TIGIT and PD-1 expression.
5. Change in pre-treatment to on-treatment immune parameters, as assessed by mass cytometry and multispectral imaging immune profiling and mRNA expression patterns of immune-related genes.
6. On-treatment immune parameters, as assessed by mass cytometry and multispectral imaging immune profiling and mRNA expression patterns of immune-related genes, according to treatment response (treatment responders versus treatment non-responders).
7. On-treatment immune parameters, as assessed by mass cytometry and multispectral imaging immune profiling and mRNA expression patterns of immune-related genes, according to the presence or absence of active liver metastases.

4 STUDY DESIGN

4.1 Overall Design

4.1.1 Study Overview

This is an open-label, single-arm, phase II trial utilizing a Simon-like 2-stage design to evaluate the combination of tiragolumab with atezolizumab and bevacizumab in patients with MSS mCRC refractory to fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy. Patients with *RAS/BRAF* wildtype, left-sided disease must also have received prior anti-EGFR therapy. A graphical representation of the study design is shown in Section 1.2; a detailed schedule of activities is shown in Section 1.3.

All enrolled patients will receive treatment with atezolizumab (1200 mg every 3 weeks), bevacizumab (15 mg/kg every 3 weeks), and tiragolumab (600 mg every 3 weeks), administered on day 1 of 21-day treatment cycles. Tumor response assessments will be performed at screening and every 9 weeks following day 1 of cycle 1 with imaging of the chest, abdomen, and pelvis and assessment via RECIST v1.1. See Section 8.1 for more information about response assessments. Safety assessments will be conducted prior to each treatment cycle with reporting and grading of adverse events (AEs) according to CTCAE version 5.0. See Section 9 for more information about safety grading and reporting.

Patients enrolled in the trial will be divided into 2 cohorts by non-randomized allocation based on slot availability and patient and provider preference: Cohort A (n = 22) and Cohort B (n = 22). Patients in Cohort A will undergo pre-treatment and on-treatment biopsies for correlative analyses, with on-treatment biopsies obtained at cycle 3, day 1 (C3D1) +/- 3 days of treatment. In Cohort B, no study-related biopsies will be obtained. Outside of pre- and on-treatment biopsies, patients in Cohort A and Cohort B will receive identical treatments and assessments. All patients will undergo peripheral blood testing for correlative analysis at pre-treatment and on-treatment timepoints, with on-treatment samples collected prior to cycle 3. See Sections 4.1.2 and 8.3.2 for additional information regarding biopsies and cohort allocation.

A Simon-like 2-stage design will be used to assess futility. An interim response assessment will be conducted after enrollment of 16 evaluable patients. If 1 or less partial response (PR) or complete response (CR) is observed among 16 evaluable patients, then study enrollment will be stopped. If 2 or more PRs or CRs are observed, then the study will proceed, and an additional 28 patients will be enrolled. See Section 10.4.6 for further description of the interim analysis.

A maximum of 22 patients with active liver metastases will be included in this study, with a maximum of 11 patients with active liver metastases included in Cohort A. A maximum of 8 patients with active liver metastases may be included in the interim response analysis.

Patients will continue to receive study therapy until disease progression as determined by RECIST v1.1, unacceptable toxicity, death, decision by the patient and/or treating physician to withdraw from the study, pregnancy, or study termination, whichever occurs first. Patients with ongoing clinical stability/benefit on treatment may be eligible to continue therapy beyond radiographic progression; criteria for continuation of treatment beyond RECIST v1.1-defined progression is listed in Section 4.1.3.

At least 30 days and no more than 35 days after discontinuation of treatment, patients will return for a Final Study/Treatment Discontinuation Visit and will undergo assessments listed in the Schedule of Events (Section 1.3). Patients continuing to experience toxicity related to SAEs at this visit will be followed at least every 4 weeks until either (1) resolution of toxicity or (2) the determination, in the clinical judgment of the investigator, that no further improvement is expected.

Overall survival information will be collected via telephone calls and/or clinic visits every 3 months ±14 days, starting 3 months after the Final Study/Treatment Discontinuation Visit and continuing until patient death, patient withdrawal of consent, patient loss to follow-up, or study termination by the Sponsor-Investigator.

The time from first patient enrollment until the end of follow-up is expected to take approximately 40 months (16 months for enrollment, 24 months for follow-up, including survival follow-up).

4.1.2 COHORT ALLOCATION AND STUDY BIOPSIES

Allocation into Cohorts A and B will not be randomized or sequential, but will be based on patient and provider preference and slot availability. Among the initial 16 patients enrolled for inclusion in the initial interim response analysis, a minimum of 8 patients must be enrolled into Cohort A (study biopsy cohort). This will ensure that correlative analyses can be performed on tissue samples even if the trial is stopped early due to futility to explore mechanisms of resistance. The remainder of the initial 16 patients enrolled will be assigned to Cohort B (no study biopsies).

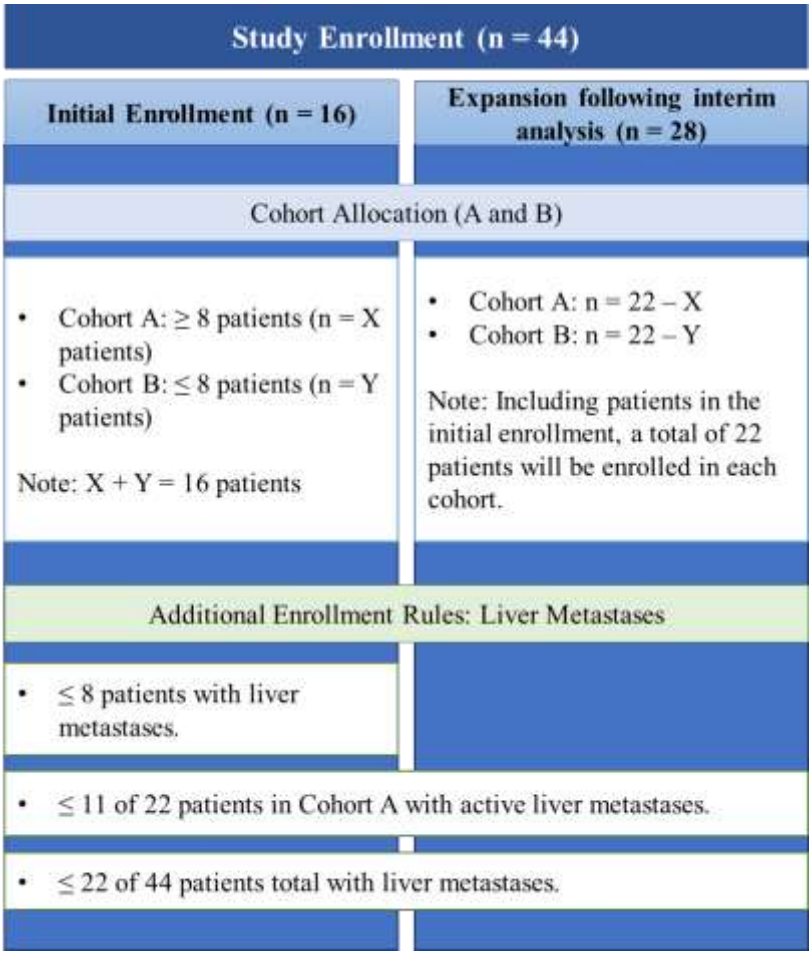
If the study continues beyond the initial interim analysis, an additional 28 patients will be enrolled in the expansion stage for a total of 44 patients. In the expansion stage, patients will be enrolled in Cohort A and Cohort B such that there are 22 patients total in each cohort (including patients from the initial enrollment stage).

As discussed in Section 4.1.1, the study will limit the number of patients with active liver metastases as follows:

- No more than 8 of the initial 16 patients enrolled may have active liver metastases.
- Among the 22 patients enrolled in Cohort A, no more than 11 may have active liver metastases.
- Among the 44 patients enrolled if the trial continues beyond the initial interim analysis (Cohort A plus Cohort B), no more than 22 may have active liver metastases.

The figure below summarizes rules for cohort allocation and enrollment of patients with versus without liver involvement.

Patient Cohort Allocation and Enrollment



Patients in Cohort A will provide a fresh pre-treatment biopsy and an on-treatment biopsy at cycle 3, day 1 (C3D1, ±3 days). Prior to the pre-treatment biopsy, patients must sign the Informed Consent Form, and all other described screening evaluations must be completed and reviewed by the treating clinician to confirm that all eligibility criteria are met. The pre-treatment biopsy should be performed at least 3 days prior to C1D1 of treatment. While the acceptable window for the C3D1 biopsy is ±3 days, it is preferred that the biopsy occurs following all treatments on C3D1. Study treatment may be continued around the time of on-treatment biopsies. The date and time of the biopsies will be documented. Archival tissue may not be used in place of a fresh pre-treatment biopsy for Cohort A. Additional details for handling of biopsy samples including processing,

storage, and shipment can be found in Section 8.3.2, and will be provided in the Laboratory Manual.

If the investigator determines that the risk of a biopsy is unacceptable (for example, due to complications incurred during a previous procedure, use of blood thinning medications, or inaccessible tumor), or if the patient refuses, the patient should not be enrolled in Cohort A. If a patient enrolled in Cohort A is not able to proceed with the on-treatment biopsy due to unacceptable risk, the patient will be allowed to remain on-study and will be included in Cohort B of the study.

If a patient discontinues treatment after cycle 2 but prior to cycle 3, an on-treatment biopsy should be obtained between C2D18 and C2D24 of treatment. If a patient discontinues treatment after cycle 1 but prior to cycle 2, an on-treatment biopsy should be obtained between C1D18 and C1D24, if feasible.

If a patient initially assigned to Cohort A does not obtain both pre- and on-treatment biopsies and the study is still enrolling, the patient will be moved to Cohort B and an additional patient may be enrolled to Cohort A, with the goal to achieve 22 patients with both pre- and on-treatment biopsies. If a patient initially assigned to Cohort A does not obtain both pre- and on-treatment biopsies and the study is no longer enrolling, no additional patients will be enrolled.

4.1.3 Criteria for Continuation of Treatment Beyond RECIST v1.1-Defined Progression

At the time of RECIST v1.1-defined progression, treatment is permitted to continue until the next assessment (at least 4 weeks but no longer than 10 weeks later) if the following criteria are met:

1. The patient is clinically stable. An assignment of clinical stability requires that no worsening of performance status has occurred, that no clinically relevant increase in disease-related symptoms such as pain or dyspnea occur that are thought to be associated with disease progression (these symptoms are generally understood to mean a requirement for increased palliative intervention), and that no requirement for intensified management of disease-related symptoms exists, including increased analgesia, radiotherapy, or other palliative care.
2. There is no progression at critical anatomical sites (e.g., leptomeningeal disease) that cannot be managed by protocol-allowed medical interventions.
3. The patient and investigator agree to continue treatment.
4. The patient signs the Treatment Beyond Progression Informed Consent Form.

If the subsequent scan continues to show progression, or if the above criteria are no longer met, study treatment will be discontinued. At this point, the patient will proceed with the Final Study/ Treatment Discontinuation Visit, additional visits as indicated for ongoing toxicities, and survival follow-up visits. See Sections 8.2.4 and 8.2.5 for details of procedures following treatment discontinuation.

4.2 End of Study and Study Length

A patient is defined to have completed the study following the completion of survival follow-up, which will continue until patient death, patient withdrawal of consent, patient loss to follow-up, or study termination by the Sponsor-Investigator, whichever comes first. The end of study is defined as the date that the last patient completes the study.

Enrollment is anticipated to take approximately 16 months, with an estimated enrollment of 3-4 patients per month. The end of study is expected to occur 24 months after the last patient is enrolled. In addition, the investigator may decide to terminate the study at any time. The total length of study, from screening of the first patient to the end of the study, is therefore expected to take approximately 40 months.

4.3 Scientific Rationale for Study Design

4.3.1 Rationale for Patient Population

This study will enroll patients with MSS mCRC, refractory or intolerant to therapy with fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy, as well as anti-EGFR therapy for those with left-sided, *RAS/BRAF* wildtype disease.

There is significant unmet need for new treatment options for this patient population, where activity of approved treatment regimens is marginal with observed ORRs of 6% or less[2,18,19]. Meanwhile, compelling translational and clinical evidence supports the rationale for combined treatment of atezolizumab, bevacizumab, and tiragolumab in MSS mCRC; see Section 2 for more details.

Evidence from early-stage trials suggests that MSS mCRC patients with active liver metastases are less likely to respond to immunotherapy-based regimens compared to patients without liver involvement, as discussed in Section 2.2.2. However, this evidence remains limited, and it is not known how the presence of liver metastases will impact response to treatment with atezolizumab,

bevacizumab, and tiragolumab. Liver metastases are common in mCRC and portend a poor prognosis, and there is a significant need for new therapies for this subset of patients. Accordingly, this trial will permit enrollment of a limited number of patients with liver involvement, and incorporate secondary and exploratory objectives to investigate activity and immune response in these patients.

4.3.2 Rationale for Treatment Doses and Dosing Schedule

Atezolizumab, bevacizumab, and tiragolumab will each be administered every 3 weeks on day 1 of 21-day treatment cycles.

Atezolizumab will be administered at a fixed dose of 1200 mg intravenously every 3 weeks. This is an approved dosage for atezolizumab, as outlined in the prescribing information. Anti-tumor activity has been observed across doses ranging from 1 mg/kg to 20 mg/kg Q3W. In Study GO27381 (NCT01375842), the maximum tolerated dose of atezolizumab was not reached, and no dose limiting toxicities (DLTs) were observed at any dose[49]. The fixed dose of 1200 mg Q3W (equivalent to an average body weight-based dose of 15 mg/kg Q3W) was selected on the basis of both nonclinical studies and available clinical pharmacokinetic (PK), efficacy, and safety data [50]. Refer to the Atezolizumab Investigator's Brochure for details.

Tiragolumab will be administered at a fixed dose of 600 mg intravenously every 3 weeks. This dose was selected on the basis of available clinical PK, efficacy, and safety data from Study GO30103, in which patients received single agent tiragolumab or tiragolumab plus atezolizumab[15]. In Study GO30103, the maximum tolerated dose was not reached, and no DLTs were observed with tiragolumab monotherapy or in combination with atezolizumab 1200 mg Q3W (tiragolumab dose range of 2-1200 mg Q3W). Complete occupancy of peripheral TIGIT receptors on CD4+, CD8+, and NK cells was observed beginning at tiragolumab dose level of 30 mg Q3W and remained sustained at all higher doses. Anti-tumor activity (as assessed by radiographic response) was observed for tiragolumab at a dose range of 30-600 mg Q3W when given in combination with atezolizumab 1200 mg Q3W.

In the Phase II CITYSCAPE trial, all patients enrolled in the atezolizumab plus tiragolumab arm received 600 mg tiragolumab every 3 weeks[11]. Treatment was adequately tolerated and the combination of atezolizumab plus tiragolumab resulted in a clinically meaningful improvement in PFS compared with placebo in combination with atezolizumab. Given the favorable benefit risk ratio observed at 600 mg, this same dose of tiragolumab will be used for this study. For further details, refer to the Tiragolumab Investigator's Brochure.

Bevacizumab will be administered at a dose of 15 mg/kg intravenously every 3 weeks. This is an approved dosage for bevacizumab, and is the approved dose of bevacizumab when combined with atezolizumab for treatment of HCC. See the Bevacizumab Investigator's Brochure for additional details.

4.3.3 Rationale for Allowing Patients to Continue Treatment Beyond Disease Progression

Conventional response criteria may not adequately assess the activity of immunotherapeutic agents because progressive disease (by initial radiographic evaluation) may not necessarily reflect therapeutic failure. Because of the potential for pseudo-progression and/or tumor immune infiltration, this study will allow enrolled patients to continue to receive study treatment after apparent radiographic progression, provided the benefit risk ratio is judged to be favorable (see Section 4.1.3). Patients should still discontinue therapy for unacceptable toxicity or symptomatic deterioration attributed to disease progression, as determined by the investigator after an integrated assessment of radiographic data, biopsy results (if available), and clinical status.

4.3.4 Rationale for Biomarker and Correlative Assessments

A better understanding of the intimate biological mechanisms that tailor cancer cell phenotypes is crucial for identifying strategic therapy combinations and patient populations who will benefit from them. However, this has been challenging to obtain due to the complexities of tumor cell signaling, the tumor microenvironment, and the tumor immune response, which animal models are not able to accurately recapitulate[21,46]. Correlative analyses using tumor biopsies and blood samples from pre- and on-treatment timepoints in clinical studies are therefore crucial.

This study requires tumor biopsies at pre- and on-treatment timepoints for patients enrolled in Cohort A, as well as pre- and on-treatment blood samples for all patients. These samples will be used for correlative analyses to explore potential predictive biomarkers for treatment response as well as immune mechanisms of response or resistance to therapy. The former may help to identify patients who will derive the most benefit from this and/or other immunotherapy regimens; the latter may guide future strategies for overcoming immunotherapy resistance.

Blood and tumor tissue obtained in this trial will be used to evaluate the association between PD1, PD-L1, TIGIT, and PVR expression and tumor response, and to characterize immune cell frequency, phenotype, and function at pre- and on-treatment timepoints. Testing methods may

include mass cytometry, multispectral imaging, and messenger RNA (mRNA) expression panels. See Section 8.3 for additional information about planned correlative analyses.

5 STUDY POPULATION

5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Provision to sign and date the consent form.
2. Stated willingness and ability to comply with all study procedures and be available for the duration of the study.
3. Age ≥ 18 years at the time of signing the informed consent.
4. Histologically confirmed, unresectable, metastatic colorectal adenocarcinoma.
5. Measurable disease, as assessed by the investigator per RECIST v1.1 (see Appendix 6). Previously irradiated lesions are not considered measurable unless progression has been unequivocally documented in the lesion after the time of radiation. Lesions intended to be biopsied should not be target lesions.
6. If in Cohort A, (1) the patient must state willingness to undergo pre- and on-treatment biopsies, and (2) the patient's disease must be amenable to biopsy without exposing the patient to substantially increased risks of complications, per the Investigator's judgment.
7. Eastern Cooperative Oncology Group (ECOG) performance status of 0-2.
8. Documented microsatellite stable (MSS) and/or proficient mismatch repair (pMMR) status. Only one of these criteria is required to be eligible (e.g. either MSI or MMR testing completed with results consistent with MSS or pMMR disease). However, in the unusual case of discordant results if both MSI and MMR testing is completed, consultation with the Principal Investigator and pathology review will be required to determine eligibility.
9. Documented testing for *KRAS*, *NRAS*, and *BRAF* V600E mutation status. Patients with *BRAF* V600E mutation will be excluded. Patients with *KRAS* or *NRAS* mutation will be included.
10. Progression on or intolerance to prior therapy for unresectable, metastatic CRC including at least (1) fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy AND (2) EGFR inhibitor therapy for patients with *KRAS/NRAS/BRAF* wild-type, left-sided disease. Prior EGFR inhibitor therapy is not required for patients with right-sided disease and/or *KRAS/NRAS* mutations.

- Chemotherapy given with curative intent may be considered as a prior therapy for this eligibility criteria if it was administered within 6 months of diagnosis of unresectable, metastatic CRC.
- Fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy may have been given in any combination (e.g., FOLFOX, FOLFIRI, FOLFOXIRI), as long as all 3 agents were used in a prior line of therapy.
- Prior therapy with bevacizumab is permitted.

11. Adequate hematologic and end organ function, defined by laboratory results obtained within 28 days prior to the first dose of study treatment:
    - ANC ≥ 1.2 × 10^9/L, without granulocyte colony-stimulating factor support in the prior 4 weeks.
    - Lymphocyte count ≥ 0.5 x 10^9/L (500/μL) ○ Platelet count ≥ 100 × 10^9/L, without transfusion in the prior week. ○ Hemoglobin ≥ 9 g/dL; patients may be transfused to meet this criterion.
    - Serum total bilirubin ≤ 1.5 x the upper limit of normal (ULN); patients with known Gilbert's disease may have a bilirubin ≤ 3.0 × ULN.
    - Aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP) ≤ 2.5 × ULN with the following exceptions:
        - For patients with documented liver metastases, AST and/or ALT ≤ 5 × ULN.
        - For patients with documented liver or bone metastases, ALP ≤ 5 × ULN. ○ Serum albumin ≥ 25 g/L (2.5 g/dL) ○ Creatinine clearance ≥ 45 mL/min as calculated using the Cockcroft-Gault formula or measured using a 24-hour urine collection.
    - For patients not receiving therapeutic anticoagulation, international normalized ratio (INR) and activated partial thromboplastin time (aPTT) ≤ 1.5 × ULN.
12. Patients receiving therapeutic anticoagulation must be on a stable regimen, with INR and aPTT within the expected therapeutic range of intended use of the anticoagulant.
13. Negative HIV testing at screening, or, for those with known history of HIV, documented control of infection on anti-retroviral therapy with evidence of undetectable viral load and CD4 count of >500 cells/microL for a least 6 months prior to enrollment.
14. Negative hepatitis B surface antigen (HBsAg) test at screening.
15. Positive hepatitis B surface antibody (HBsAb) test at screening, or negative HBsAb test at screening accompanied by either of the following:
    ○ Negative total hepatitis B core antibody (HBcAb) ○ Positive total HBcAb test followed by quantitative hepatitis B virus (HBV) DNA < 500 IU/mL. The HBV DNA test will be performed only for patients who have a negative HBsAg test, a negative HBsAb test, and a positive total HBcAb test.

16. Negative hepatitis C virus (HCV) antibody test at screening, or positive HCV antibody test followed by a negative HCV RNA test at screening.
    - The HCV RNA test will be performed only for patients who have a positive HCV antibody test.
17. For women of childbearing potential (WOCBP): agreement to refrain from heterosexual intercourse or use contraception as defined below:
    - A woman is considered to be of childbearing potential if she is postmenarchal, has not reached a postmenopausal state (≥ 12 continuous months of amenorrhea with no identified cause other than menopause), has not undergone surgical sterilization (i.e., removal of ovaries, fallopian tubes, and/or uterus), and does not have another cause of permanent sterilization or infertility as determined by the investigator (e.g., Müllerian agenesis). Per this definition, a woman with a tubal ligation is considered to be of childbearing potential.
    - WOCBP must refrain from heterosexual intercourse or use contraceptive methods with a failure rate of < 1% per year during the treatment period and for 5 months after the final dose of atezolizumab, 6 months after the final dose of bevacizumab, and 90 days after the final dose of tiragolumab.
    - Examples of contraceptive methods with a failure rate of < 1% per year include bilateral tubal ligation, male sterilization, hormonal contraceptives that inhibit ovulation, hormone-releasing intrauterine devices, and copper intrauterine devices.
      - The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.
18. Women who would like to become pregnant after study treatment discontinuation should seek advice on oocyte cryopreservation prior to initiation of study treatment because of the possibility of increased risk of ovarian failure with bevacizumab, noting that ovarian function has been shown to recover in the majority of women after treatment discontinuation.
19. For men: agreement to refrain from heterosexual intercourse or use a condom, and agreement to refrain from donating sperm, as defined below:
    - With a female partner of childbearing potential or a pregnant female partner, men must remain abstinent or use a condom during the treatment period and for 6 months after the final dose of bevacizumab and 90 days after the final dose of tiragolumab to avoid exposing the embryo. Men must refrain from donating sperm during this same period.

- The reliability of sexual abstinence should be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, or postovulation methods) and withdrawal are not adequate methods of contraception.

5.2 EXCLUSION CRITERIA

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Illness or condition that may interfere with a patient's capacity to understand, follow, and/or comply with study procedures.
2. Known microsatellite instability-high (MSI-H) or deficient mismatch repair (dMMR) status, or unknown status for both MSI and MMR.
3. Prior testing documenting a *BRAF* V600E mutation, or unknown testing results for *KRAS*, *NRAS*, and *BRAF*.
4. A limited number of patients with active liver metastases will be permitted in this trial (see Sections 1.2 and 4.1). Additional patients with active liver metastases will be excluded. In this study, active liver metastases are defined as the presence of metastatic disease in the liver per CT and/or MRI imaging.
    - Those with a history of definitively treated liver metastases (e.g., with surgical resection or stereotactic body radiation therapy [SBRT]) with treatment occurring at least 6 months prior to enrollment with no evidence of metastatic disease in the liver on subsequent imaging may be eligible to enroll as a patient without active liver disease.
5. Known symptomatic, untreated, or actively progressing central nervous system (CNS) metastases. Asymptomatic patients with treated CNS lesions are eligible, provided that all of the following criteria are met:
    - Measurable disease, per RECIST v1.1, must be present outside of the CNS.
    - The patient has no history of intracranial hemorrhage or spinal cord hemorrhage related to metastatic disease.
    - Any treatment received for CNS disease, including radiation therapy or surgery, was completed at least 28 days prior to initiation of study treatment.
    - The patient has no ongoing requirement for corticosteroids as therapy for CNS disease. Anti-convulsant therapy at a stable dose is permitted.
    - There is no evidence of interim progression between completion of CNS-directed therapy and initiation of study treatment. Imaging to confirm stability of CNS disease must be performed during screening for patients with known history of CNS involvement.

6. History of leptomeningeal disease or carcinomatous meningitis.
7. Spinal cord compression not definitively treated with surgery and/or radiation.
8. Uncontrolled tumor-related pain. Patients requiring pain medication must be on a stable regimen at study entry.
    - Symptomatic lesions (e.g., bone metastases or metastases causing nerve impingement) amenable to palliative radiotherapy should be treated prior to enrollment. Radiation should be completed at least 14 days prior to initiation of study treatment, and patients should be recovered from the effects of radiation prior to enrollment.
    - Asymptomatic metastatic lesions that would likely cause functional deficits or intractable pain with further growth (e.g., epidural metastasis that is not currently associated with spinal cord compression) should be considered for loco-regional therapy if appropriate prior to enrollment.
9. Uncontrolled pleural effusion, pericardial effusion, or ascites requiring recurrent drainage procedures (once monthly or more frequently).
10. History of malignancy other than colorectal cancer within 3 years prior to screening, with the exception of malignancies with a negligible risk of metastasis or death (e.g., 5-year OS rate > 90%), such as adequately treated carcinoma *in situ* of the cervix, basal or squamous cell skin cancer, localized prostate cancer, or ductal carcinoma *in situ*.
11. Active autoimmune disease, history of autoimmune disease requiring treatment with corticosteroids, disease modifying agents, and/or immunosuppressive therapy, or immune deficiency including, but not limited to, myasthenia gravis, myositis, autoimmune hepatitis, systemic lupus erythematosus, rheumatoid arthritis, inflammatory bowel disease, antiphospholipid antibody syndrome, Wegener granulomatosis, Sjögren syndrome, Guillain-Barré syndrome, or multiple sclerosis (see Appendix 7 for a more comprehensive list of autoimmune diseases and immune deficiencies), with the exceptions listed below: ○ Patients with a history of autoimmune-related hypothyroidism who are on thyroid replacement hormone are eligible for the study.
    - Patients with controlled Type 1 diabetes mellitus who are on an insulin regimen are eligible for the study.
    - Patients with eczema, psoriasis, lichen simplex chronicus, or vitiligo with dermatologic manifestations only (e.g., patients with psoriatic arthritis are excluded) are eligible for the study provided all of following conditions are met:
        - Rash must cover < 10% of body surface area.
        - Disease is well controlled at baseline and requires only low-potency topical corticosteroids.

- There has been no occurrence of acute exacerbations of the underlying condition requiring psoralen plus ultraviolet A radiation, methotrexate, retinoids, biologic agents, oral calcineurin inhibitors, or high potency or oral corticosteroids within the previous 12 months.

12. Prior allogeneic stem cell or solid organ transplantation.
13. History of idiopathic pulmonary fibrosis, organizing pneumonia (e.g., bronchiolitis obliterans), drug-induced pneumonitis, or idiopathic pneumonitis, or evidence of active pneumonitis on screening chest CT scan.
14. Known history of tuberculosis and/or active tuberculosis.
15. Active bowel inflammation on imaging at the time of enrollment (including diverticulitis).
16. History of abdominal fistula, gastrointestinal (GI) perforation, or intra-abdominal abscess.
17. Clinical signs or symptoms of GI obstruction or requirement for routine parenteral hydration, parenteral nutrition, or tube feeding.
18. Evidence of abdominal free air not explained by paracentesis or recent surgical procedure.
19. History of or active clinically significant cardiovascular dysfunction, including the following:
    - History of stroke or transient ischemic attack within 6 months prior to first dose of study treatment.
    - History of myocardial infarction within 6 months prior to first dose of study treatment.
    - Heart failure with New York Heart Association Class II or higher symptoms within 3 months prior to initiation of study treatment.
    - Unstable arrhythmia.
    - Coronary heart disease that is symptomatic or unstable angina.
20. Inadequately controlled hypertension (defined as systolic blood pressure > 150 mmHg and/or diastolic blood pressure > 100 mmHg and based on an average of ≥ 3 blood pressure readings on ≥ 2 sessions). Anti-hypertensive therapy to achieve these parameters is allowed.
21. History of hypertensive crisis or hypertensive encephalopathy.
22. Grade ≥ 2 proteinuria, as demonstrated by ≥ 2+ protein on dipstick urinalysis and ≥ 1.0 g of protein in a 24-hour urine collection.
    - All patients with ≥ 2+ protein on dipstick urinalysis at screening must undergo a 24-hour urine collection for protein. Patients with < 2+ protein on dipstick urinalysis are eligible for the study and do not require 24-hour urine collection.
23. Significant vascular disease (e.g., aortic aneurysm requiring surgical repair or recent arterial thrombosis) within 6 months prior to initiation of study treatment.
24. History of Grade 4 venous thromboembolism.

25. History of Grade ≥ 2 hemoptysis (defined as ≥ 2.5 mL of bright red blood per episode), or other serious hemorrhage or bleeding risk, within 1 month prior to screening.
26. History or evidence of inherited bleeding diathesis or significant coagulopathy at risk of bleeding (e.g. in the absence of therapeutic anticoagulation).
27. Major surgical procedure, or significant traumatic injury, within 4 weeks prior to initiation of study treatment, or anticipation of need for a major surgical procedure during the study.
    - Study-related biopsies are not considered major surgical procedures in this study.
28. Minor surgical procedures, including placement of a vascular access device, within 7 days prior to initiation of study treatment, with the following exceptions:
    - Study-related biopsies are NOT considered as surgical procedures under the exclusion criteria. Pre-treatment study biopsies should be performed at least 3 days prior to study treatment initiation.
    - Patients must have sufficiently recovered from any prior surgery, including adequate wound healing.
29. Serious, non-healing wound, active ulcer, or untreated bone fracture.
30. Severe infection within 4 weeks prior to initiation of study treatment, including, but not limited to, hospitalization for complications of infection, bacteremia, or severe pneumonia, or any active infection that could impact patient safety.

31. Positive Epstein-Barr virus (EBV) viral capsid antigen immunoglobulin M (IgM) test at screening. An EBV polymerase chain reaction (PCR) test should be performed as clinically indicated to screen for acute infection or suspected chronic
    active infection in cases where there is a clinical suspicion for active infection (ie positive EBV viral capsid antigen IgM). Patients with a positive EBV PCR test and clinical presentation consistent with acute or chronic active EBV infection are excluded.

32. Current or recent (< 10 days prior to initiation of study treatment) use of aspirin (> 325 mg/day), or clopidogrel (> 75 mg/day), or recent (< 21 days prior to initiation of study treatment) use of therapeutic thrombolytic agents.
33. Recent (< 21 days prior to initiation of study treatment) initiation of full-dose oral or parenteral anticoagulants. The use of full-dose oral or parenteral anticoagulants is permitted as long as the following criteria are met:
    - The INR and/or aPTT are within therapeutic limits (according to the medical standard of the enrolling institution).
    - The patient has been on a stable dose of anticoagulants for at least 21 days prior to initiation of study therapy.

- There is no evidence of or clinical concern for new or worsening thromboembolism within 21 days prior to initiation of study treatment. ○ The patient has no history of serious hemorrhage or bleeding risk, as per exclusion criteria 25.
- The patient has no persisting bleeding diathesis or anatomic or pathologic condition that significantly increases the risk of hemorrhage.

34. Treatment with therapeutic oral or IV antibiotics within 2 weeks prior to initiation of study treatment.
    - Patients receiving prophylactic antibiotics (e.g., to prevent a urinary tract infection or chronic obstructive pulmonary disease exacerbation) are eligible for the study.
35. Treatment with a live, attenuated vaccine within 4 weeks prior to initiation of study treatment, or anticipation of need for such a vaccine during study treatment, within 90 days after the final dose of tiragolumab, or within 5 months after the final dose of atezolizumab.
36. Current treatment with anti-viral therapy for HBV.
37. Treatment with any systemic anti-cancer therapy within 21 days or 5 half-lives of starting study treatment, whichever is shorter.
38. Treatment with an investigational therapy within 42 days of initiation of study treatment.
39. Prior treatment with CD137 agonists or investigational immune checkpoint blockade therapies, including anti-LAG3, anti-CTLA-4, anti-PD-1, anti-PD-L1, or anti-TIGIT agents.
40. Prior radiation therapy within 14 days of Cycle 1, Day 1 of study treatment, and/or persistence of radiation-related adverse effects. Participants must have recovered from all radiation-related toxicities, not require corticosteroids, and not have had radiation pneumonitis prior to study treatment start. Palliative radiation therapy (as long as it does not involve target lesions) is permitted on the study.
41. Treatment with systemic immunostimulatory agents, including, but not limited to, interferon and IL-2, within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment.
42. Treatment with systemic immunosuppressive medication (including, but not limited to, corticosteroids, cyclophosphamide, azathioprine, methotrexate, thalidomide, and antitumor necrosis factor-α [TNF- α] agents) within 2 weeks prior to initiation of study treatment, or anticipation of need for systemic immunosuppressive medication during study treatment, with the following exceptions:
    - Patients who received acute, low-dose systemic immunosuppressant medication or a one-time pulse dose of systemic immunosuppressant medication (e.g., 48 hours of corticosteroids for a contrast allergy) are eligible for the study.
    - Patients who received mineralocorticoids (e.g., fludrocortisone), corticosteroids for chronic obstructive pulmonary disease (COPD) or asthma, or low-dose

corticosteroids (< 10 mg prednisone per day or an equivalent dose of an alternative corticosteroid) for orthostatic hypotension or adrenal insufficiency are eligible for the study.

- Patients requiring chronic use of ≥ 10 mg prednisone per day or equivalent dose of other anti-inflammatory corticosteroids are excluded.

43. Requirement for treatment with any medicinal product that contraindicates the use of any of the study treatments, may interfere with the planned treatment, impact patient compliance, or puts the patient at higher risk for treatment-related complications.
44. History of severe allergic anaphylactic reactions to chimeric or humanized antibodies or fusion proteins.
45. Known hypersensitivity to Chinese hamster ovary cell products or to any component of the atezolizumab, bevacizumab, or tiragolumab formulations.
46. Pregnancy or breastfeeding, or intention of becoming pregnant during study treatment, within 90 days after the final dose of tiragolumab, 5 months after the final dose of atezolizumab, or 6 months after the final dose of bevacizumab. Women of childbearing potential must have a negative serum pregnancy test result within 28 days prior to initiation of study treatment, and a negative urine pregnancy test within 72 hours of each study treatment.
47. Any other disease, metabolic dysfunction, physical examination finding, or clinical laboratory finding that contraindicates the use of an investigational drug, may affect the interpretation of the results, or may render the patient at high risk from treatment complications.

5.3 Lifestyle Considerations

There are no lifestyle considerations other than those pertaining to abstinence/contraception and avoidance of breastfeeding as outlined in Section 5.1.

5.4 Screen Failures

Subjects may be re-screened for eligibility after a prior screen failure, if (1) the investigator feels there is a reasonable chance that the patient will meet inclusion/exclusion criteria at a time following a screen failure, and (2) documented approval from the Sponsor-Investigator is obtained.

5.5 Strategies for Recruitment and Retention

Potential subjects will be identified and recruited from the University of Colorado Cancer Center (UCCC) Medical Oncology and Multidisciplinary Clinics. Advertisements approved by ethics committees, investigator databases, and UCHealth may be used as recruitment procedures. Patients

will be recruited without regard to sex, race, or ethnicity. Study-related documents will be translated into Spanish, the most common primary language of underrepresented populations treated in our clinics.

The consent process will be conducted in a private room. Potential subjects will be given a copy of the consent form to take home with them before making a final decision to participate.

In order to achieve a total sample size of 44 patients, we estimate up to 54 patients will need to be screened. This accounts for patients who fail screening or are not evaluable for assessment. It is anticipated that approximately 3-4 patients will be enrolled per month; the enrollment period is therefore expected to take approximately 16 months.

6 STUDY INTERVENTION

6.1 PREPARATION/ HANDLING/ STORAGE / ACCOUNTABILITY OF STUDY DRUG

6.1.1 STUDY INTERVENTION DESCRIPTION

The study agents for this trial are atezolizumab, bevacizumab, and tiragolumab.

Packaging of study agents will be overseen by Genentech and will bear a label with identification required by local law. The packaging and labeling of the study drugs will be in accordance with the manufacturer's standards and local regulations.

Upon delivery of the investigational products to the site, site personnel should check for damage and verify proper identity, quality, integrity of seals and temperature conditions. Site personnel should report any deviations or product complaints to the study monitor and/or Genentech upon discovery.

Atezolizumab, bevacizumab, and tiragolumab will be stored at the clinical site under the required storage conditions as indicated on the study drug labels.

6.1.2 ACQUISITION AND ACCOUNTABILITY

Atezolizumab, bevacizumab, and tiragolumab will be provided by Genentech, from investigational supply.

6.1.3 Formulation, Appearance, Packaging, and Labeling

6.1.3.1 Atezolizumab

Atezolizumab will be supplied by Genentech, as a sterile liquid in a single-use, 20 mL glass vial. The vial contains approximately 20 mL (1200 mg) of atezolizumab solution.

For information on the atezolizumab formulation, see the Atezolizumab Investigator's Brochure.

6.1.3.2 Bevacizumab

Bevacizumab will be supplied by Genentech, as a sterile solution in a single-use, 16-mL, preservative-free glass vial. The 16-mL vial contains 400 mg of bevacizumab (25 mg/mL).

For information on the formulation and handling of bevacizumab, refer to t the Bevacizumab Investigator's Brochure.

6.1.3.3 Tiragolumab

Tiragolumab will be supplied by Genentech, as a sterile liquid in a single-use, 15 mL glass vial. Vials contain approximately 10 mL (600 mg) of tiragolumab for the 600-mg Q3W dosing.

For further information on the tiragolumab formulation, refer to the Tiragolumab Investigator's Brochure.

6.1.4 Product Storage and Stability

Specific storage and stability instructions for atezolizumab, bevacizumab, and tiragolumab are provided in theirrespective Investigator's Brochures.

6.1.5 Preparation

Specific preparation and dispensing instructions for atezolizumab, bevacizumab, and tiragolumab are provided in their respective Investigator's Brochures.

6.2 DOSAGE AND ADMINISTRATION

All patients enrolled in this study will receive treatment with atezolizumab, bevacizumab, and tiragolumab on day 1 (±2 days) of 21-day cycles, as outlined in Section 6.2, Table 1. Study treatments will be given on an outpatient basis, in a monitored setting where there is immediate access to trained personnel and adequate equipment and medicine to manage potentially serious reactions.

Patients will be monitored for acute hypersensitivity reactions after the end of the study drug administration per Section 6.2, Table 2. Epinephrine and parenteral diphenhydramine must be readily available for immediate use if required to treat a hypersensitivity reaction; site personnel must be able to detect and treat such reactions. Patients with severe hypersensitivity reactions (e.g., stridor, angioedema, life threatening change in vital signs) must be withdrawn from study treatment. All adverse events of systemic hypersensitivity reactions or anaphylactoid or anaphylaxis reactions must be reported within 24 hours to the Sponsor.

Patients will continue therapy until disease progression as determined by RECIST v1.1, unacceptable toxicity, death, decision by the patient and/or treating physician to withdraw from the study, pregnancy, or study termination, whichever occurs first. There is no maximum duration for therapy in this trial.

Table 1 Treatment Regimen Overview

Cycle Length	Dose, Route, and Regimen (drugs listed in order of administration)
21 days	● Atezolizumab 1200 mg by IV infusion on Day 1 ● Bevacizumab 15 mg/kg IV infusion on Day 1[a] ● Tiragolumab 600 mg by IV infusion on Day 1[b, c]

[a] On Day 1 of each cycle, bevacizumab will be administered at least 5 minutes after completion of the atezolizumab infusion.

[b] On Day 1 of Cycle 1, tiragolumab will be administered at least 60 minutes after completion of the bevacizumab infusion. The interval between subsequent infusions will be a least 30 minutes if the previous bevacizumab infusion was given without premedication and tolerated without an infusion-related reaction (IRR), or at least 60 minutes if the patient experienced an IRR or required premedication with the previous bevacizumab infusion.

[c] Patients will be observed for at least 60 minutes following completion of tiragolumab on Day 1 of Cycle 1. For subsequent cycles, this observation period may be reduced to 30 minutes if the prior infusion was tolerated without an IRR.

Note: See Section 6.2, Table 2 for further dosing instructions, vital sign collection, and treatment administration windows.

6.2.1 ATEZOLIZUMAB

Atezolizumab will be administered by IV infusion at a fixed dose of 1200 mg on Day 1 of each 21-day cycle. The dose of atezolizumab is fixed and is not dependent on body weight. Dose reductions are not allowed.

Atezolizumab infusions will be administered as outlined in Section 6.2, Table 2. For anaphylaxis precautions, see Appendix 5. Guidelines for treatment interruption or discontinuation are provided in Section 9.1.3 and the Atezolizumab Investigator's Brochure. Guidelines for study drug administration in the context of management of specific adverse events are provided in Appendix 8.

6.2.2 BEVACIZUMAB

Bevacizumab will be administered by IV infusion at a dose of 15 mg/kg of body weight on Day 1 of each 21-day cycle, at least 5 minutes after completion of the atezolizumab infusion.

Body weight at baseline should be used to calculate the required dose of bevacizumab. If a weight change of > 10% from baseline is observed, the treatment dosage should be modified accordingly (e.g., this becomes the new weight for dose calculation). A rounding up or down of the dose is acceptable to allow practical ease of administration. Rounding of the dose is optional, and if the treating physician decides to round the total dose of bevacizumab, it should be rounded to the nearest 5 mg. No dose reductions are allowed, with the exception of dose rounding as outlined above.

Bevacizumab infusions will be administered as outlined in Section 6.2, Table 2. For anaphylaxis precautions, see Appendix 5. Guidelines for treatment interruption or discontinuation are provided in Section 9.1.3, and in the Bevacizumab Investigator's Brochure. Guidelines for study drug administration in the context of management of specific adverse events are provided in Appendix 9.

6.2.3 TIRAGOLUMAB

Tiragolumab will be administered by IV infusion at a fixed dose of 600 mg on Day 1 of each 21day cycle, following administration of atezolizumab and bevacizumab as above. No dose reductions are permitted.
On Day 1 of Cycle 1, tiragolumab will be administered at least 60 minutes after completion of the bevacizumab infusion. The interval between subsequent infusions will be at least 30 minutes if the previous bevacizumab infusion was given without premedication and tolerated without an infusion related reaction (IRR), or at least 60 minutes if the patient experienced an IRR and/or required premedication with the previous bevacizumab infusion.

Following completion of tiragolumab infusion, patients will be monitored for a minimum of 60 minutes on Day 1 of Cycle 1. With subsequent cycles, the observation period may be reduced to 30 minutes if the prior infusion was tolerated well without an IRR; otherwise, it should remain 60 minutes.

Tiragolumab infusions will be administered as outlined in Section 6.2, Table 2. For anaphylaxis precautions, see Appendix 5. Guidelines for treatment interruption or discontinuation are provided in Section 9.1.3, and the Tiragolumab Investigator's Brochure. Guidelines for study drug administration in the context of management of specific adverse events are provided in Appendix 8.

Table 2 Administration of First and Subsequent Infusions of Study Drugs

Study Drug	First Infusion	Subsequent Infusions
Infusion of atezolizumab	● No premedication is permitted prior to the atezolizumab infusion. ● Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. ● Atezolizumab should be infused over 60 (± 15) minutes. ● If clinically indicated, vital signs should be recorded every 15 (± 5) minutes during the infusion.	● If the patient experienced an IRR with any previous infusion of atezolizumab, premedication with an antihistamine and/or antipyretic medication may be administered for subsequent doses at the discretion of the investigator. ● Vital signs should be recorded within 60 minutes prior to the infusion. ● Atezolizumab should be infused over 30 (± 10) minutes if the previous infusion was tolerated without an IRR, or 60 (± 15) minutes if the patient experienced an IRR with the previous infusion. ● If the patient experienced an IRR with the previous infusion or if otherwise clinically indicated, vital signs should be recorded during the infusion (every 15 minutes, ±5 minutes).

After infusion of atezolizumab	● Bevacizumab infusion should not be initiated until at least 5 minutes after completion of atezolizumab. ● Vital signs should be recorded at 30 (± 10) minutes after the infusion of atezolizumab; this may occur during infusion of bevacizumab. ● Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study team if they develop such symptoms.	● Bevacizumab infusion should not be initiated until at least 5 minutes after completion of atezolizumab. ● If the patient experienced an IRR with the previous infusion or if otherwise clinically indicated, vital signs should be recorded at 30 (± 10) minutes after the infusion of atezolizumab.

Study Drug	First Infusion	Subsequent Infusions
Infusion of bevacizumab	● No premedication is permitted prior to the bevacizumab infusion. ● Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. ● The initial infusion of bevacizumab should be given over 90 (± 10) minutes.	● If the patient experienced an IRR with any previous infusion of bevacizumab, premedication with an antihistamine and/or antipyretic medication may be administered for subsequent doses at the discretion of the investigator. ● Vital signs should be recorded within 60 minutes prior to the infusion. ● Bevacizumab should be infused over 60 (±10) minutes if the previous 90-minute infusion was tolerated without an IRR, or 90 (±10) minutes if the patient experienced an IRR with the previous infusion. If the 60-minute infusion is well tolerated, bevacizumab may be infused over 30 (±5) minutes thereafter. ● If the patient experienced an IRR with the previous infusion of bevacizumab, the infusion time may not be decreased for that infusion. If the next infusion is well tolerated with premedication, the subsequent infusion time may then be decreased by 30 (±10) minutes as long as the patient continues to be premedicated. If a patient experiences an IRR with the 60-minute infusion despite premedication, all subsequent doses should be delivered over 90 (±10) minutes. Similarly, if a patient experiences an IRR with the 30-minute infusion despite premedication, all subsequent doses should be delivered over 60 (±10) minutes.

After infusion of bevacizumab	● Tiragolumab infusion should not be initiated until at least 60 minutes (or longer) after completion of bevacizumab. ● Vital signs should be recorded at 30 (± 10) minutes and 2 (± 1) hours after completion of the infusion. ● Patients should be informed about the possibility of delayed post-infusion symptoms and instructed to contact their study team if they develop such symptoms.	● Tiragolumab infusion should not be initiated until at least 30 minutes after completion of bevacizumab, if bevacizumab was given without premedication and tolerated without an IRR. Otherwise, tiragolumab infusion should not be initiated until at least 60 minutes (or longer) after completion of bevacizumab. ● Vital signs should be recorded at 30 (± 10) minutes after completion of the infusion.
Study Drug	**First Infusion**	**Subsequent Infusions**
Infusion of tiragolumab	● No premedication is permitted prior to the tiragolumab infusion. ● Vital signs (pulse rate, respiratory rate, blood pressure, and temperature) should be recorded within 60 minutes prior to the infusion. ● Tiragolumab should be infused over 60 (± 10) minutes. ● Vital signs should be recorded every 15 (± 5) minutes during the infusion.	● If the patient experienced an IRR during any previous infusion of tiragolumab, premedication with an antihistamine and/or antipyretic may be administered for subsequent doses, at the discretion of the investigator. ● Vital signs should be recorded within 60 minutes prior to the tiragolumab infusion. ● Tiragolumab should be infused over 30 (± 10) minutes if the previous infusion was tolerated without an IRR, or 60 (± 10) minutes if the patient experienced an IRR with the previous infusion. ● If the patient experienced an IRR with the previous infusion or if otherwise clinically indicated, vital signs should be recorded during the infusion.

After infusion of tiragolumab	● After the infusion of tiragolumab, the patient begins a 60-minute observation period. ● Vital signs should be recorded at 30 (± 10) minutes after the infusion of tiragolumab. ● Patients should be informed about the possibility of delayed post-infusion symptoms and will be instructed to contact their study team if they develop such symptoms.	● If the patient tolerated the previous infusion of tiragolumab well without an IRR, the observation period may be reduced to 30 minutes. ● If the patient experienced an IRR with the previous infusion, the observation period should be 60 minutes. ● If the patient experienced an IRR with the previous infusion or if otherwise clinically indicated, vital signs should be recorded at 30 (± 10) minutes after completion of infusion.

IRR = infusion-related reaction.

6.2.4 DOSE DELAYS

Every effort should be made to administer study products on the planned dose and schedule. In the event of significant toxicity dosing may be delayed or discontinued as described in Section 9.1.3. In the event of multiple toxicities, dose interruption or discontinuation should be based on the worst toxicity observed. Patients are to be instructed to notify investigators at the first occurrence of any adverse symptom.

The following rules apply to dose delays as long as neither atezolizumab, bevacizumab, nor tiragolumab has been permanently discontinued:

- Treatment cycles will normally begin with dosing of atezolizumab, bevacizumab, and tiragolumab on Day 1 of each 21-day cycle.
- If either atezolizumab or tiragolumab is delayed for a related toxicity, it is recommended that both drugs are delayed since the safety profiles for atezolizumab and tiragolumab are similar. Bevacizumab may be continued in this case as long as clinically appropriate.
- If bevacizumab dosing is delayed for a related toxicity, atezolizumab and tiragolumab may be continued as long as clinically appropriate. In this case, atezolizumab should be administered first as outlined in Table 2. Tiragolumab may be administered starting at least 5 minutes after completion of atezolizumab infusion.

- In case of delays in dosing of one study drug for drug-related toxicity while other study drug(s) are given as planned, it is recommended that the study drug being delayed will be administered at the next scheduled infusion (e.g., at the next scheduled 21-day cycle), if criteria to resume treatment is met at that time.
- If atezolizumab and/or tiragolumab are held for more than 12 weeks, the patient should be discontinued from atezolizumab and/or tiragolumab. Similarly, if bevacizumab is held for more than 42 days, the patient should be discontinued from bevacizumab. Exceptions may be made if, in the judgment of the Principal Investigator, the patient is likely to derive clinical benefit from resuming therapy after a hold greater than 12 weeks (for atezolizumab and/or tiragolumab) or 42 days (for bevacizumab). See Section 9.1.3 for additional information about treatment discontinuation.

See Appendices 8-9 for additional details regarding management for specific treatment-related toxicities.

6.2.5 Medication Errors

Medication errors include the administration of drug to the wrong patient, at the wrong time, or at the wrong dosage strength, or the administration of the wrong drug. Such medication errors occurring to a study participant are to be captured on the medication error electronic case report form (eCRF) which is a specific version of the adverse event (AE) page, and on the serious AE (SAE) form when appropriate. In the event of a medication dosing error, the Sponsor-Investigator should be notified immediately.

Medication errors are reportable irrespective of the presence of an associated AE/SAE, including:

- Medication errors involving patient exposure to atezolizumab, bevacizumab, and/or tiragolumab.
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the participating subject.

Whether or not the medication error is accompanied by an AE, as determined by the Investigator, the medication error should be captured on the drug administration eCRF and, if applicable, any associated AE should be captured on an AE eCRF page.

6.3 Measures to Minimize Bias: Treatment Assignment, Randomization, and Blinding

All patients in this study will receive the same treatment, and there is no randomization or blinding in this single-arm trial. There will be 2 cohorts (Cohort A, Cohort B) that differ only by requirement to undergo pre- and on-treatment tumor biopsy. Allocation into these cohorts will not be randomized, but will be performed based on patient and provider preferences and slot availability (see Section 4.1.2).

6.4 Study Intervention Compliance

All study drugs are given intravenously; therefore, a drug diary is not needed. All patients will be given a study calendar detailing study activities. Subject retention and compliance with the protocol will be reported using:

- A CONSORT diagram illustrating the subject flow through the trial.
- Tables summarizing retention and compliance.
- Listings showing retention and compliance results at the individual subject level.

6.5 Concomitant Therapy

Concomitant therapy consists of any medication (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) used by a patient in addition to protocol-mandated study treatment, starting from the screening visit and ending at the Final Study/Treatment Discontinuation Visit. All such medications should be reported to the investigator and recorded on the Concomitant Medications eCRF. For this protocol, a prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician.

6.5.1 Permitted Therapy

Examples of permitted concomitant therapies include but are not limited to:

- Oral contraceptives with a failure rate of < 1% per year (see Section 5.1) ● Hormone-replacement therapy
- Prophylactic anticoagulation therapy (such as warfarin at a stable dose or lowmolecularweight heparin).
- Vaccinations (such as influenza, COVID-19) ○ Live, attenuated vaccines are not permitted.
- Megestrol acetate administered as an appetite stimulant
- Mineralocorticoids (e.g., fludrocortisone)
- Inhaled corticosteroids administered for COPD or asthma

- Low-dose corticosteroids administered for orthostatic hypotension or adrenocortical insufficiency (< 10 mg prednisone per day or the equivalent)

Premedication & Rescue Medications

Premedication with antihistamines, antipyretics, and/or analgesics may be administered for the second and subsequent infusions only, at the discretion of the investigator.

In general, investigators should manage a patient's care (including preexisting conditions) with supportive therapies other than those defined as cautionary or prohibited therapies (see Sections 6.5.2 and 6.5.3) as clinically indicated, per local standard practice. Patients who experience infusion-associated symptoms may be treated symptomatically with acetaminophen, ibuprofen, diphenhydramine, and/or H_2−receptor antagonists (e.g., famotidine, cimetidine), or equivalent medications per local standard practice. Serious infusion associated events manifested by dyspnea, hypotension, wheezing, bronchospasm, tachycardia, reduced oxygen saturation, or respiratory distress should be managed with supportive therapies as clinically indicated (e.g., supplemental oxygen and β_2-adrenergic agonists).

Anti-emetics and anti-diarrheal medications should not be administered prophylactically before initial treatment with study drugs. At the discretion of the investigator, prophylactic anti-emetic and anti-diarrheal medication(s) may be used per standard clinical practice before subsequent doses of study drugs.

Hematopoietic growth factors should not be administered prophylactically before initial treatment with study drugs. Hematopoietic growth factors and transfusions may be administered according to local guidelines if indicated during the study.

Guidelines for management of known toxicities of study agents are provided in Appendices 8-9. All medications must be recorded on the Concomitant Medications eCRF.

Radiation

Palliative radiotherapy (e.g., treatment of painful bony metastases) to sites outside of the CNS on study is permitted, provided (1) the lesions were known at the time of study entry and the investigator clearly indicates that the need for palliative radiotherapy is not indicative of disease progression, and (2) the treated lesions are not target lesions.

Treatment with atezolizumab and tiragolumab may be continued during palliative radiotherapy. Treatment with bevacizumab should be suspended at least 7 days prior to palliative radiotherapy. Upon completion of radiotherapy, bevacizumab may be resumed starting 7 days after radiotherapy,

and when felt to be safe by the investigator. The Sponsor-Investigator is available to advise as needed.

The intensities, number, and dates of doses received for allowed palliative radiotherapy should be recorded on the appropriate eCRFs.

6.5.2 CAUTIONARY THERAPY

Corticosteroids, Immunosuppressive Medications, and TNF-α Inhibitors

Systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may attenuate potential beneficial immunologic effects of treatment with immunotherapy. Therefore, in situations in which systemic corticosteroids, immunosuppressive medications, or TNF-α inhibitors would be routinely administered (for indications other than immune-related AEs), alternatives, including antihistamines, should be considered. If the alternatives are not feasible, systemic corticosteroids, immunosuppressive medications, and TNF-α inhibitors may be administered at the discretion of the investigator.

Systemic corticosteroids or immunosuppressive medications are recommended, at the discretion of the investigator, for the treatment of specific adverse events when associated with atezolizumab and/or tiragolumab therapy (refer to Appendix 8 for details).

Herbal Therapies

Concomitant use of herbal therapies is not recommended because their pharmacokinetics, safety profiles, and potential drug-drug interactions are generally unknown. However, herbal therapies not intended for the treatment of cancer may be used during the study at the discretion of the investigator.

6.5.3 PROHIBITED THERAPY

Use of the following concomitant therapies is prohibited as described below:

- Concomitant therapy intended for the treatment of cancer (including, but not limited to, chemotherapy, hormonal therapy, immunotherapy, radiotherapy, and herbal therapy), whether health authority approved or experimental, is prohibited for various time periods prior to starting study treatment, depending on the therapy (see Section 5), and during study

treatment, until the patient has discontinued study treatment. Palliative radiation may be permitted for symptomatic disease per criteria in Section 6.5.1.

- Investigational therapy within 42 days prior to initiation of study treatment and during study treatment.
- Live, attenuated vaccines are prohibited within 4 weeks prior to initiation of study treatment, during study treatment, for 90 days after the final dose of tiragolumab, and for 5 months after the final dose of atezolizumab.
- Systemic immunostimulatory agents (including, but not limited to, interferons and IL-2) are prohibited within 4 weeks or 5 drug-elimination half-lives (whichever is longer) prior to initiation of study treatment and during study treatment because these agents could potentially increase the risk for autoimmune conditions when given in combination with atezolizumab and tiragolumab.
- Use of thrombolytic therapy at therapeutic doses.
- Use of aspirin at doses > 325 mg per day, or clopidogrel at doses of >75 mg/day.
- Use of therapeutic anticoagulation (e.g. anticoagulation initiated for an acute thromboembolic event) is permitted only if the following criteria are met:
    - The patient is on a stable dose of anticoagulant for at least 21 days prior to bevacizumab treatment.
    - There is no evidence of or clinical concern for new or worsening thromboembolism within 21 days of subsequent study treatment.
    - The INR and/or aPTT are within therapeutic limits prior to study treatment (according to the medical standard of the enrolling institution).
    - The patient does not have history of recent clinically significant hemorrhage, or additional risk factors for hemorrhage (e.g., tumor invading major vessels).
- Chronic, daily use of non-steroidal anti-inflammatory drugs (NSAIDs) is not permitted, with the exception of daily low-dose aspirin. However, for the symptomatic relief of medical conditions (e.g., headache, fever) intermittent or short-term intake of oral NSAIDs is allowed, when co-administered with proton pump inhibitors to reduce potential GI damage.

The above lists of medications are not necessarily comprehensive. Thus, the investigator should consult the prescribing information for any concomitant medication as well as online drug interaction resources. In addition, the investigator should contact the Sponsor-Investigator if questions arise regarding medications not listed above.

7 PATIENT AND STUDY INTERVENTION DISCONTINUATION

7.1 Discontinuation of Study Intervention (Stopping Rules)

The Sponsor-Investigator has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- The incidence or severity of adverse events in this or other studies indicates a potential health hazard to patients.
- Patient enrollment is unsatisfactory.

The Sponsor-Investigator will notify Genentech if they decide to discontinue the study.

7.2 Participant Discontinuation/Withdrawal From Study

Participants are free to withdraw from participation in the study at any time upon request. In addition, the investigator has the right to withdraw a patient from the study at any time. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time.
- Any medical condition that the Sponsor-Investigator determines may jeopardize the patient's safety if he or she continues in the study.
- The Sponsor-Investigator determines it is in the best interest of the patient.
- Patient non-compliance.

Patients must discontinue study treatment if they experience any of the following:

- Disease progression. Patients are allowed to receive study treatment beyond RECIST v1.1defined disease progression if certain conditions are met, outlined in Section 4.1.3.
- Symptomatic deterioration attributed to disease progression as determined by the investigator after integrated assessment of radiographic data, biopsy results, and clinical status.
- Intolerable toxicity related to atezolizumab, bevacizumab, and/or tiragolumab, including the development of an immune mediated adverse event determined by the Investigator to be unacceptable given the individual patient's potential response to therapy and severity of the event.
    - Atezolizumab and tiragolumab may be continued if bevacizumab is discontinued, provided that (1) there are no contraindications for continuation of therapy, and (2)

the patient is likely to derive clinical benefit, as determined by the investigator. ○ Bevacizumab and atezolizumab may be continued if tiragolumab is discontinued, provided that (1) there are no contraindications for continuation of therapy, and (2) the patient is likely to derive clinical benefit, as determined by the investigator. Of note, immune mediated adverse events should generally be attributed to both tiragolumab and atezolizumab, and in most circumstances, atezolizumab should be discontinued with tiragolumab. ○ Bevacizumab should be discontinued if atezolizumab or atezolizumab and tiragolumab are discontinued.

  - See Section 9.1.3 for additional details.
- Any medical condition that the Sponsor-Investigator determines may jeopardize the patient's safety if he or she continues in the study.
- Use of another non-protocol specified anti-cancer therapy.
- Pregnancy.

The primary reason for study treatment discontinuation should be documented on the appropriate eCRF.

Every effort should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate eCRF. If a patient requests to be withdrawn from the study, this request must be documented in the source documents and signed by the investigator. Patients who withdraw from the study/ discontinue treatment prematurely due to reasons other than progression or treatment-related toxicity may be replaced. Patients who withdraw from the study during the survival follow-up period will not be replaced. If a patient withdraws from the study, the study staff may use a public information source (e.g., county records) to obtain information about survival status.

7.3 LOST TO FOLLOW-UP

A subject will be considered lost to follow-up if he or she fails to return for 3 scheduled visits and is unable to be contacted by the study staff.

The following actions must be taken if a subject fails to return to the clinic for a required study visit:

- The site will attempt to contact the subject and reschedule the missed visit and advise the subject on the importance of maintaining the assigned visit schedule.
- Before a subject is deemed lost to follow-up, the investigator will make three documented attempts to regain contact with the subject. These contact attempts must be documented in the subject's medical record or study file.

- Should the subject continue to be unreachable, he or she will be considered to have withdrawn from the study.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 EFFICACY ASSESSMENTS

8.1.1 BASELINE TUMOR ASSESSMENTS

Baseline tumor assessments should be performed ≤ 28 days before Cycle 1 Day 1, and all measurable and/or evaluable lesions should be assessed and documented according to RECIST v1.1 (Appendix 6). Tumor assessments performed as standard of care (SOC) prior to obtaining informed consent and within 28 days prior to initiation of study treatment do not have to be repeated at screening.

Screening assessments must include computed tomography (CT) scans (with IV contrast; with or without oral contrast) or magnetic resonance imaging (MRI) scans (with IV contrast) of the chest, abdomen, and pelvis. If a CT scan with contrast is contraindicated (e.g., in patients with contrast allergy or impaired renal clearance), a non-contrast CT scan of the chest may be performed and MRI scans (with IV contrast, if feasible) of the abdomen and pelvis should be performed. If a CT scan for tumor assessment is performed in a positron emission tomography/CT scanner, the CT acquisition must be consistent with the standards for a full-contrast diagnostic CT scan.

A CT or MRI scan of the head with contrast should be performed at screening to evaluate CNS metastases in patients with a known history of CNS involvement, or if there is clinical concern for CNS involvement. If iodinated contrast is contraindicated, this assessment must be done by MRI. Brain metastases identified at baseline that have been treated with radiotherapy or surgery will not be considered measurable or evaluable unless there is suspected disease progression in the brain (e.g., the patient becomes symptomatic). Thus, subsequent head scans are not required unless clinically indicated.

Bone scans and CT scans of the neck should also be performed if clinically indicated. At the investigator's discretion, other methods of assessment of measurable disease as per RECIST v1.1 may also be used (See Appendix 6).

8.1.2 EFFICACY ASSESSMENTS ON TREATMENT

Evaluation of tumor response conforming to RECIST v1.1 must be documented every 9 weeks ± 1 week following start of treatment, until investigator-determined disease progression according to RECIST v1.1, loss of clinical benefit (for those who continue treatment beyond radiographic progression), withdrawal of consent, death, or study termination by the Sponsor-Investigator, whichever occurs first. Schedule of tumor assessments are independent of any changes to the study treatment administration schedule (e.g., dose delay) and may occur mid-cycle depending on length of cycle. If a tumor assessment has to be performed early or late, subsequent assessments should be conducted according to the original schedule based on the date of first study drug administration (C1D1). The first efficacy tumor assessment should be performed prior to treatment on C4D1. Confirmation of response (partial response [PR] or complete response [CR]) will be done no earlier than 28 days from study entry. In the case of stable disease [SD], measurements must have met the SD criteria at least once after study entry at a minimum interval not less than 6 weeks.

Patients who discontinue study treatment for any reason other than disease progression (e.g., treatment toxicity) will continue to undergo tumor response evaluations until progressive disease, according to the schedule above. Rising tumor markers (e.g., CEA) in the absence of radiographic evidence of progression is not considered progressive disease.

Patients who continue to experience clinical benefit, despite evidence of radiographic progression as defined by RECIST v1.1, may continue treatment per conditions outlined in Section 4.1.3. In this setting, tumor assessments should be continued according to the schedule above until treatment is discontinued due to confirmed progression and/or loss of clinical benefit.

All measurable and/or evaluable lesions identified at baseline should be re-assessed at subsequent tumor evaluations according to the schedule described above. The same radiographic procedures used to assess disease sites at screening should be used for subsequent tumor assessments (e.g., the same contrast protocol for CT scans). As above, CT or MRI scans of the chest, abdomen, and pelvis are required at each assessment; additional imaging should be performed based on baseline tumor involvement and clinical concerns, at the discretion of the investigator. As above, CNS imaging is not required at efficacy assessments unless there is clinical concern for new involvement or progression of previously-treated lesions.

Overall response at a given timepoint will be assessed by the investigator using RECIST v1.1 (see Appendix 6). Assessments should be performed by the same evaluator, if possible, to ensure internal consistency across visits. Available results must be reviewed by the investigator before further dose administration.

8.2 Other Study Assessments

8.2.1 Screening

Screening evaluations are to be performed within 28 days prior to the treatment start date (e.g. prior to C1D1). Written informed consent must be obtained prior to undergoing study specific procedures, including screening evaluations. Results of SOC tests or examinations performed prior to obtaining informed consent and within specified time windows from C1D1 may be used (see the Schedule of Activities, Section 1.3).

Screening Assessments to Determine Eligibility

The following assessments will be conducted to determine eligibility. All of these investigations must be completed, reviewed, and recorded as part of the screening process. The investigator will maintain a screening log to record details of all patients screened irrespective of eligibility. Any pre-existing baseline abnormalities must be graded as per NCI CTCAE v5.0, and recorded in the General Medical History and Baseline Conditions eCRF.

Oncologic History: CRC history should be recorded including stage, date of first diagnosis, site of primary disease, previous biopsies (including dates and sites of biopsies), location of metastases, previous treatments administered including all surgeries and radiation therapy, previous clinical trials especially details of any previous use of immunotherapies, ECOG performance status, MMR/MSI status, and mutational testing including *KRAS*, *NRAS*, and *BRAF*.

Demographic Data: Demographic data will be recorded including age, sex, and self-reported ethnicity.

Medical History: Medical history will be recorded including detailed history of any non-CRC cancers, past medical and surgical history, reproductive status, allergies, social history (including alcohol, tobacco, and recreational drug use), and family history (including malignancy history).

Concomitant Treatments: All medications and Non-Drug Supportive Interventions used by the patients within 7 days of study entry (e.g., C1D1) should be recorded in the eCRF. All concomitant medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) taken during study will be recorded continuously on the eCRF starting at the screening visit and ending at the Final Study/Treatment Discontinuation Visit.

Vital Signs: Vital signs will be measured at screening including blood pressure, heart rate, respiratory rate, pulse oximetry, and temperature, while the patient is in a seated position. Height and weight will also be recorded. Any abnormalities should be recorded in the eCRF.

Physical Exam: A complete physical exam will be performed at screening. Any abnormalities should be recorded in the eCRF.

Performance Status: Performance status will be recorded according to Eastern Cooperative Oncology Group (ECOG) performance status criteria, outlined below.

ECOG Performance Status Criteria

Grade	ECOG Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework or office work.
2	Ambulatory and capable of all self-care but unable to carry out work activities; up and about more than 50% of waking hours.
3	Capable of limited self-care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on any self-care; totally confined to bed or chair.

ECOG = Eastern Cooperative Oncology Group

Baseline Signs and Symptoms/ Adverse Event (AE) Assessments: Any baseline/ pre-existing symptoms must be recorded and graded at screening, using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Adverse events will be documented and recorded continuously throughout the study, starting at the screening visit. Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. See Sections 9.2 and 9.3 for additional information about AE assessment and recording.

Electrocardiogram: A single 12-lead electrocardiogram (ECG) is required at screening; additional ECGs should be obtained when clinically indicated. ECG recordings should be performed after the patient has been resting in a supine position for at least 10 minutes. For safety monitoring purposes, the investigator must review, sign, and date all ECG tracings. Paper copies of ECG tracings will be kept as part of the patient's permanent study file at the site. Digital recordings will be stored at

the site. Any morphologic waveform changes or other ECG abnormalities must be documented on the eCRF.

Laboratory Assessments: Samples for the following laboratory tests will be collected and sent to the study site's laboratory for analysis. Screening laboratory tests should be performed within 28 days prior to initiation of study treatment. Laboratory testing does not need to be repeated at C1D1 of treatment if already obtained within 72 hours of treatment.

- **Hematology:** Complete blood count (CBC) including red blood cell (RBC) count, hemoglobin, hematocrit, platelet count, white blood cell (WBC) count, and differential counts (neutrophils, lymphocytes, monocytes, eosinophils, and basophils).
- **Chemistry: Complete metabolic panel** (CMP) including bicarbonate or total carbon dioxide, sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, calcium, total and direct bilirubin, ALP, ALT, and AST; **phosphate, and magnesium.**
- **Thyroid function testing:** TSH, free T3, and free T4.
- **Coagulation:** INR and aPTT.
- **HIV serology:** HIV antigen/antibody combination test. Patients with a known history of HIV should also have HIV viral load and CD4 count obtained at screening.
- **Hepatitis B virus (HBV) serology:** Hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (HBsAb), and total hepatitis B core antibody (HBcAb) for all patients. HBV DNA testing should be obtained for patients with negative HBsAg, negative HBsAb, and positive total HBcAb testing. Patients with a positive quantitative HBV DNA at screening (must be < 500 IU/mL per the eligibility criteria) will undergo additional HBV DNA tests every 3 months (± 7 days) during treatment, at treatment discontinuation (± 7 days), and at 3, 6, 9, and 12 months (± 14 days at each timepoint) after treatment discontinuation. Study treatment and procedures may proceed while HBV DNA is being processed, but results should be reviewed by the investigator as soon as they are available. If HBV DNA increases to > 500 IU/mL, consultation with a hepatologist or gastroenterologist with specialty in HBV is recommended. The Sponsor-Investigator is available to advise as needed.
- **Hepatitis C virus (HCV) serology:** HCV antibody testing in all patients; HCV RNA testing for those with a positive HCV antibody test.
- **Ebstein Barr Virus (EBV) serology:** EBV viral capsid antigen (VCA) IgM and EBV VCA IgG or nuclear antigen IgG testing should be obtained in all patients. EBV PCR testing should be obtained as clinically indicated to screen for suspected active infections.

- **Pregnancy test:** All women of childbearing potential (WOCBP) will have a serum pregnancy test performed at screening. See Section 5.1 for definition of WOCBP.
- **Urinalysis panel:** Including pH, specific gravity, glucose, protein, ketones, and blood. Dipstick testing is acceptable. Microscopic examination including sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria should be performed if dipstick is abnormal. If protein is ≥2+ on dipstick, a 24-hour urine protein assessment should be performed.

Baseline Tumor Assessments: Baseline tumor assessments should be performed ≤ 28 days before C1D1, as described in Section 8.1.1.

Pre-treatment Testing to be Performed After Confirming Eligibility

Prior to proceeding with pre-treatment tissue biopsies and blood draws for correlative research analyses, (1) patients must sign the Informed Consent Form, and (2) all other screening evaluations must be completed and reviewed by the treating clinician to confirm eligibility criteria are met.

Research Tumor Tissue Samples: Tumor tissue samples will be collected for correlative analyses from patients enrolled in Cohort A at pre-treatment and on-treatment timepoints. Pre-treatment samples should be obtained after confirmation of study eligibility and providing written informed consent, and at least 3 days prior to C1D1 of treatment. See Section 8.3.2 and the Laboratory Manual for further information about collection, handling, and storage of samples.

8.2.2 TREATMENT PERIOD

On-treatment study assessments and procedures will be performed as outlined by the Schedule of Events (Section 1.3), starting from the time of treatment initiation (C1D1), until treatment discontinuation.

On-treatment assessments include:

Concomitant Treatments: Concomitant Treatments assessments will be performed at the time points indicated in Schedule of Events (Section 1.3) and recorded continuously. All concomitant medications (e.g., prescription drugs, over-the-counter drugs, vaccines, herbal or homeopathic remedies, nutritional supplements) and Non-Drug Supportive Interventions should be recorded in the eCRF until the Final Study/Treatment Discontinuation Visit.

Vital Signs: Vital signs will be measured at time points indicated in the Schedule of Events (Section 1.3) and as clinically indicated, including blood pressure, heart rate, respiratory rate, pulse

oximetry, and temperature, while the patient is in a seated position. Weight will be collected on Day 1 of each cycle. New or worsened clinically significant abnormalities should be recorded on the Adverse Event eCRF.

Vital signs should be assessed before, during, and after administration of study treatments as outlined in Section 6.2, Table 2.

Physical Exam: Symptom-directed physical exams will be conducted at the time points indicated in Schedule of Events (Section 1.3), and as clinically indicated. Changes from baseline abnormalities should be recorded in patient notes. New or worsened clinically significant abnormalities should be recorded as adverse events in the Adverse Event eCRF.

Performance Status: Performance status will be recorded at the time points indicated in Schedule of Events (Section 1.3), using ECOG performance status criteria (Section 8.2.1).

Adverse Events (AE) Assessments: Adverse Event (AE) assessments will be done at the time points indicated in Schedule of Events (Section 1.3) and recorded continuously. Adverse events should be documented and recorded at each visit using the NCI CTCAE version 5.0. See Sections 9.2 and 9.3 for additional details regarding AE assessments and recording.

Laboratory Assessments: Laboratory tests will be collected at the timepoints indicated in the Schedule of Events (Section 1.3). These tests include:

- **Hematology:** Complete blood count (CBC) including RBC count, hemoglobin, hematocrit, platelet count, WBC count, and differential counts (neutrophils, lymphocytes, monocytes, eosinophils, and basophils).
- **Chemistry: Complete metabolic panel** (CMP) including bicarbonate or total carbon dioxide, sodium, potassium, chloride, glucose, BUN or urea, creatinine, total protein, albumin, calcium, total and direct bilirubin, ALP, ALT, and AST; **phosphate,** and **magnesium**.
- **Amylase & Lipase:** Collected prior to C1D1, and then as clinically indicated.
- **Thyroid function testing:** TSH, free T3, and free T4, collected at baseline and then every 4 cycles of therapy.
- **Coagulation:** INR and aPTT.
- **Tumor Markers: Carcinoembryonic antigen (CEA**), other tumor markers as clinically indicated (e.g. Carbohydrate antigen 19-9 [CA 19-9], Carbohydrate antigen 125 [CA 125]).

- **Pregnancy test:** All women of childbearing potential (WOCBP) will have a urine pregnancy test performed at pre-treatment visits. If a urine pregnancy test is positive, it should be confirmed with a serum pregnancy test. See Section 5.1 for definition of WOCBP.
- **Urinalysis panel:** Including pH, specific gravity, glucose, protein, ketones, and blood. Dipstick testing is acceptable. Microscopic examination including sediment, RBCs, WBCs, casts, crystals, epithelial cells, and bacteria should be performed if dipstick is abnormal. If protein is ≥2+ on dipstick, a 24-hour urine protein assessment should be performed.

Additional laboratory tests should be completed as clinically indicated.

Research Blood Samples: Blood samples will be collected for correlative analyses from all patients at pre-treatment and on-treatment timepoints. Pre-treatment samples will be collected prior to treatment on C1D1. On-treatment collections should be obtained prior to treatment on C3D1, or at the time of treatment discontinuation, whichever occurs first. If treatment discontinuation occurs prior to C3D1, research blood samples should be obtained at or before the time of the Final Study/ Treatment Discontinuation Visit, and no less than 14 days from the last study treatment. See Section 8.3.1 and the Laboratory Manual for further information about collection, handling, and storage of samples.

Research Tumor Tissue Samples: Tumor tissue samples will be collected for correlative analyses from patients enrolled in Cohort A at pre-treatment and on-treatment timepoints. On-treatment samples should be obtained at C3D1, ±3 days; it is preferred that the biopsy is collected following all treatments on C3D1, if possible. The date and time of all biopsies will be documented. For patients who discontinue treatment after cycle 2 but prior to cycle 3, an on-treatment biopsy should be obtained between C2D18 and C2D24 of treatment. If a patient discontinues treatment prior to C2D1, an on-treatment biopsy should be obtained between C1D18 and C1D24 if feasible.
Ontreatment study biopsies are permitted without additional holds/delays of bevacizumab therapy. See Section 8.3.2 and the Laboratory Manual for further information about collection, handling, and storage of samples.

Tumor Response Assessments: Tumor response assessments with radiographic imaging of the chest, abdomen, and pelvis should be performed every 9 weeks (+/- 1 week) from the time of treatment initiation until disease progression or loss of clinical benefit in those who remain on treatment after progression, as outlined in the Schedule of Events in Section 1.3 and described in Section 8.1.2. The first treatment assessment should be performed prior to treatment on C4D1.

8.2.3 UNSCHEDULED VISITS

Patients should be evaluated at visits outside of the scheduled study visits as needed if medical concerns arise. The investigator will assess the patient per standard of care and document pertinent information as described in Section 8.2.2.

8.2.4 FINAL STUDY/ TREATMENT DISCONTINUATION VISIT

All patients will be assessed at a final study visit following treatment discontinuation (Final Study/ Treatment Discontinuation Visit), regardless of the reason for treatment discontinuation. See Sections 7.2 and 9.1.3 for details regarding rules for treatment discontinuation.

The Final Study/Treatment Discontinuation visit will occur at least 30 days and no more than 35 days after discontinuation of treatment, and will include the activities listed in Schedule of Events (Section 1.3). Laboratory assessments do not need to be repeated at this visit if they were already completed within the prior week; tumor response assessments do not need to be repeated if they were performed within the prior 6 weeks, and/or disease progression was documented on the prior scan.

Patients continuing to experience toxicity related to SAEs at the Final Study/ Treatment Discontinuation Visit will be followed with additional visits at least every 4 weeks until either (1) resolution of toxicity or (2) the determination, in the clinical judgment of the investigator, that no further improvement is expected. Assessments at these visits will be identical to those performed at the Final Study/ Treatment Discontinuation Visit, with the exception that response assessments do not need to be repeated.

8.2.5 SURVIVAL FOLLOW-UP

After treatment discontinuation, survival follow-up information will be collected via telephone calls and/or clinic visits every 3 months ±14 days, starting 3 months after the Final Study/ Treatment Discontinuation Visit and continuing until patient death, patient withdrawal of consent, patient loss to follow-up, or study termination by the Sponsor-Investigator. Information regarding subsequent anti-cancer therapies will also be collected during these follow-ups.

8.3 RESEARCH ASSESSMENTS

8.3.1 Blood Specimens for Research

Blood Sample Acquisition & Processing

Site staff will collect blood samples for research, as well as for clinical testing as outlined above. The University of Colorado Pathology Shared Resource will coordinate the collection of blood samples for research-related testing from study site laboratories. A Laboratory Manual and supply kits will be provided for all central laboratory assessments including those listed in this section. For sampling procedures, storage conditions, and shipment instructions, please see the Laboratory Manual.

Blood Sample Analyses

Blood samples will be obtained for correlative/ research evaluation from all enrolled patients at pre-treatment and on-treatment timepoints per Section 8.2. Anticipated analyses are described here. However, additional/alternative assays may be performed depending on innovation and scientific progress in the field. Blood sample analysis will be coordinated by the GI Translational Research Laboratory/ Pitts Laboratory at the University of Colorado.

Tumor biopsies are not always readily available and biomarkers of response to treatment in the peripheral blood may be more clinically impactful; this testing may thus provide important insight into markers and mechanisms of response or resistance to therapy.

Mass Cytometry

The phenotype and function (activation makers, signaling molecules, and cytokines) of peripheral immune cells will be compared before and after treatment in all patients using CyTOF® mass cytometry, through collaboration with the Human Immune Monitoring Shared Resource (HIMSR) at the University of Colorado School of Medicine. Mass cytometry is a variant of flow cytometry that allows single cell analysis of up to 45 antibody specificities. Samples will be labeled with a unique barcode and stained with a large panel of antibodies designed to detect the phenotype and activation of myeloid and lymphoid immune cells, as well as signaling molecules and cytokines. These antibodies are labeled with heavy metal ion tags rather than fluorochromes. The metal barcodes allow up to 20 samples to be stained and analyzed simultaneously, increasing high throughput capability, and decreasing technical variability of the assay. The signal intensities will be normalized across samples using polystyrene beads that are acquired simultaneously with every sample. Data will then be analyzed using the University of Colorado Denver's CytoBank software premium account, utilizing the unsupervised clustering tool ViSNE, the population visualization tool SPADE, and the two-sample comparison tool Citrus.

Immune cell phenotype and function at pre-treatment and on-treatment timepoints will be compared to evaluate for changes following treatment. These parameters will be assessed according to clinical treatment response, and will be compared in patients with versus without liver involvement.

Additional Testing

Peripheral blood may also be analyzed using a circulating tumor DNA (ctDNA) platform to assess oncogenic mutations and mutational loads (TMB). Exploratory analyses may be performed correlating response to treatment with molecular findings, including the use of serial ctDNA levels.

Samples remaining post-analysis may be stored for future testing with the University of Colorado Pathology Shared Resource Biorepository, provided consent for banking has been obtained. See Section 11.1.4 for further details.

8.3.2 TUMOR TISSUE SPECIMENS FOR RESEARCH

Tumor Biopsy Acquisition & Processing

The University of Colorado Pathology Shared Resource will coordinate the collection of tumor tissue samples for research-related testing. A Laboratory Manual and supply kits will be provided for all central laboratory assessments including those listed in this section. For sampling procedures, storage conditions, and shipment instructions, please see the Laboratory Manual.

Fresh tumor samples will be obtained by biopsy from patients enrolled in Cohort A at pre-treatment and on-treatment timepoints as outlined in Sections 8.2.1 and 8.2.2. Acceptable samples include core needle biopsies for deep tumor tissue or tumor tissue resection. Fine-needle aspiration, brushings, cell pellets from pleural effusion, and lavage samples are not acceptable. Biopsies should be obtained from sites deemed safe and feasible to biopsy.

If non-evaluable tumor tissue is collected from the on-study biopsy procedures, (e.g., necrotic or fibrotic tissue, or the procedure is interrupted because of a complication), the patient will still be eligible to continue treatment. Tissue will not be assessed or analyzed in real-time, so patients will not be moved to a different cohort if tissue is found to be non-evaluable at the time of analysis.

See the Laboratory Manual for more information.

Tumor Biopsy Sample Analyses

Tumor tissue will be analyzed from pre- and on-treatment timepoints. Anticipated analyses are described here. However, additional/alternative assays may be performed depending on innovation and scientific progress in the field. Tumor biopsy sample analysis will be coordinated by the GI Translational Research Laboratory/ Pitts Laboratory at the University of Colorado.

Mass Cytometry

The phenotype and function (activation makers, signaling molecules, and cytokines) of tumor immune cells will be compared before and after treatment in all patients using CyTOF® mass cytometry, through collaboration with the Human Immune Monitoring Shared Resource (HIMSR) at the University of Colorado School of Medicine. Data will then be analyzed using the University of Colorado Denver's CytoBank software premium account, utilizing the unsupervised clustering tool ViSNE, the population visualization tool SPADE, and the two-sample comparison tool Citrus.

Immune cell phenotype and function at pre-treatment and on-treatment timepoints will be compared to evaluate for changes following treatment. These parameters will be assessed according to clinical treatment response, and will be compared in patients with versus without liver involvement.

Nine-color Multispectral Imaging

The frequency and activation status of infiltrating immune cells in the tumor microenvironment will be compared before and during treatment using 9-color multispectral imaging. Through our collaboration with the Human Immune Monitoring Shared Resource (HIMSR) at the University of Colorado School of Medicine, we will phenotype, quantify, and determine the spatial relationship of immune infiltrate in formalin-fixed paraffin-embedded biopsies. We will determine the presence and activation status of myeloid and lymphoid cells in the tumor microenvironment and determine the level of inhibitory markers on tumors by staining slides from untreated and treated biopsy specimens with antibodies.

The frequency of each immune cell subset, the activation status of those subsets, the expression of inhibitory molecules, and their location relative to tumor regions in on-treatment biopsies will be compared to the baseline biopsy in each patient to determine whether treatment with atezolizumab, bevacizumab, and tiragolumab reprograms the tumor microenvironment. The pre- and ontreatment biopsies will also be compared between patients who respond to treatment and patients who are refractory to treatment, and between patients with and without liver metastases.

mRNA Expression

Pre-treatment and on-treatment mRNA expression will be measured using the NanoString PanCancer IO 360 Gene Expression Panel. This panel analyzes 770 genes and will be used to characterize mRNA expression in the tumor, tumor microenvironment, and immune response. Changes in gene expression signatures will be compared between pre- and on-treatment samples to determine how treatment with atezolizumab, bevacizumab, and tiragolumab reprograms the tumor microenvironment. The pre- and on-treatment biopsies will also be compared between patients who respond to treatment versus patients who are refractory to treatment, and between patients with versus without liver involvement. Additionally, baseline gene expression signatures will be correlated to response to treatment as a possible predictive biomarker.

Samples remaining post-analysis may be stored for future testing with the University of Colorado Pathology Shared Resource Biorepository, provided consent for banking has been obtained. See Section 11.1.4 for further details.

9 SAFETY MONITORING & PROCEDURES

9.1 POTENTIAL OVERLAPPING TOXICITIES

9.1.1 IMMUNE MEDIATED ADVERSE EVENTS

Based on nonclinical and/or clinical studies with atezolizumab or tiragolumab as a single agent, clinical data from studies with atezolizumab and tiragolumab as a combination therapy, and data from molecules with similar mechanisms of action, there is a potential for overlapping toxicity in patients treated with atezolizumab plus tiragolumab. Because the expected pharmacologic activity of these two molecules is to increase adaptive T cell immune responses, there is the possibility of heightened immune responses. The following adverse events are potential overlapping toxicities associated with combination use of atezolizumab plus tiragolumab: immune mediated pulmonary, hepatic, gastrointestinal, renal, endocrine, ocular, pancreatic, dermatologic, and neurologic adverse events, as well as immune mediated myocarditis, meningoencephalitis, and myositis.

Refer to the Tiragolumab Investigator's Brochure for a list of identified risks associated with tiragolumab in combination with atezolizumab. Based on the mechanism of action of atezolizumab and tiragolumab, additional immune mediated adverse events are possible with the combination use of tiragolumab plus atezolizumab.

Based on the clinical experience to date, it is anticipated that immune mediated adverse events following treatment with atezolizumab plus tiragolumab will be amenable to monitoring and manageable in the setting of this combination study. The extensive experience with ICIs to date has been incorporated into the design and safety management plan in order to reduce the potential risks to participating patients. Patients with a history of autoimmune disease will be excluded from this study (see Section 5.2). Owing to the risks of active viral infection and viral reactivation, patients with active infection (including, but not limited to, HBV, HCV, or tuberculosis) and/or patients with recent severe infections will also be excluded from this study (see Section 5.2).

Toxicities should initially be managed according to the recommendations in Appendix 8, with dose holds applied to the component(s) of the treatment judged to be the primary cause. Prompt symptomatic management is appropriate for mild immune mediated adverse events. In severe cases, immune mediated toxicities may be acutely managed with systemic corticosteroids, TNF-α inhibitors, or other appropriate immunosuppressive agents. These cases should be discussed with the Principal Investigator.

9.1.2 Infusion Related Reactions

Guidelines for management of infusion relate reactions (IRR) associated with atezolizumab, bevacizumab, and tiragolumab are outlined in Appendices 8-9.

Because tiragolumab is a therapeutic mAb and targets immune cells, IRRs associated with hypersensitivity reactions, target-mediated cytokine release, and/or emergent anti-drug antibodies (ADAs) may occur. Clinical signs and symptoms of such reactions may include rigors, chills, wheezing, pruritus, flushing, rash, hypotension, hypoxemia, and fever.

IRRs have been reported in patients treated with tiragolumab, with or without atezolizumab. The majority of events were mild to moderate and manageable. To minimize the risk and sequelae of IRRs, the initial dose of tiragolumab will be administered over 60 minutes followed by a 60-minute observation period as outlined in Section 6.2.

9.1.3 Treatment Modification, Interruption, and Discontinuation

Study treatment may be temporarily suspended and/or discontinued as appropriate for management of toxicity. See Appendices 8-9 for details regarding management of specific adverse events related to study medications. See Appendix 5 for precautions for anaphylaxis.

Treatment Dose Modification

There will be no dose modifications, including dose reductions, for atezolizumab, bevacizumab, or tiragolumab in this study, with the exception of dose changes for bevacizumab due to a >10% change in weight from baseline.

Treatment Interruptions/ Dose Delays

If atezolizumab, bevacizumab, or tiragolumab are interrupted, then the other study drugs can be continued if (1) there are no clear contraindications to continuing the other drugs, and (2), the patient is likely to derive clinical benefit, as determined by the investigator per medical judgment. Note, given overlapping/related toxicities of atezolizumab and tiragolumab, if either atezolizumab or tiragolumab are held due to an immune-related AE, it is generally recommended that both medications are held. See Sections 6.2.4, 9.1.3.1, and 9.3.1.2 for details about dose delays.

Treatment Discontinuation

If a patient discontinues atezolizumab or both atezolizumab and tiragolumab, then the other study treatment(s) will also be discontinued.

As immune mediated AEs should generally be attributed to both tiragolumab and atezolizumab, if tiragolumab is discontinued due to an immune mediated toxicity it is generally recommended that atezolizumab be discontinued as well. However, if a patient discontinues tiragolumab, treatment with atezolizumab and bevacizumab may be continued provided that (1) there is no contraindication for continuation of therapy, and (2) the patient is likely to derive clinical benefit, as determined by the investigator.

If a patient discontinues bevacizumab, atezolizumab and tiragolumab may be continued provided that (1) there is no clear contraindication for continuation of therapy, (2) the patient is likely to derive clinical benefit, as determined by the investigator.

Following discontinuation of all study treatments, patients should be monitored for safety and efficacy as described in Sections 8.1, 8.2.4, and 8.2.5.

9.1.3.1 ATEZOLIZUMAB AND TIRAGOLUMAB

On the basis of the available characterization of mechanism of action, tiragolumab may cause adverse events similar to but independent of atezolizumab, may exacerbate the frequency or severity of atezolizumab related adverse events, or may have non-overlapping toxicities with atezolizumab. Because these scenarios may not be distinguished from one another in the clinical

setting, immune mediated adverse events should generally be attributed to both study drugs, and dose interruptions or treatment discontinuation in response to immune mediated adverse events should be applied to both atezolizumab and tiragolumab.

Atezolizumab and/or tiragolumab treatment may be temporarily suspended in patients experiencing toxicity considered to be related to study treatment. If corticosteroids are initiated for treatment of the toxicity, they must be tapered over ≥ 1 month to ≤ 10 mg/day oral prednisone or equivalent before atezolizumab and tiragolumab can be resumed. See Appendix 8 for guidance on management of atezolizumab- and tiragolumab-specific AEs, including recommendations for dose interruptions and discontinuation.

If atezolizumab and/or tiragolumab are held for > 12 weeks, the patient should be discontinued from atezolizumab and/or tiragolumab. An exception may be made to this if, in the judgment of the principal investigator, the patient is likely to derive clinical benefit from resuming atezolizumab and/or tiragolumab after a hold of > 12 weeks. The decision to re-challenge patients with atezolizumab and/or tiragolumab should be based on the investigator's benefit risk assessment and documented by the investigator. The Sponsor-Investigator is available to advise as needed.

Dose interruptions for reason(s) other than toxicity may be allowed with Sponsor-Investigator approval.

9.1.3.2 BEVACIZUMAB

Bevacizumab treatment may be temporarily interrupted in patients due to toxicity considered to be related to study treatment. If bevacizumab is withheld for > 42 days, the patient will be discontinued from bevacizumab. An exception to this may be made if, in the opinion of the investigator, the patient is likely to derive clinical benefit from resuming bevacizumab after > 42 days. The decision to re-challenge patients with bevacizumab should be based on investigator's assessment of benefit/ risk and documented by the investigator. See Appendix 9 for guidance on management of bevacizumab-specific AEs. The Sponsor-Investigator is available to advise as needed.

Bevacizumab treatment may be interrupted for reasons other than toxicity (e.g., surgical procedures). The acceptable length of treatment interruption 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. The Sponsor-Investigator is available to advise as needed.

The appropriate interval between the last dose of bevacizumab and major surgery is unknown. Because bevacizumab has a half-life of approximately 21 days, elective surgery should be delayed whenever possible, but if necessary, bevacizumab should be withheld for ≥ 28 days prior to the procedure. Re-initiation of bevacizumab following surgery should not occur for ≥ 28 days and until wounds have fully healed. The acceptable length of treatment interruption 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. The Sponsor-Investigator is available to advise as needed.

9.2 Safety and Other Assessments

9.2.1 Adverse Events

Safety assessments will consist of monitoring and reporting adverse events (AEs) and serious adverse events (SAEs) per protocol. This includes all events of death and any study-specific issue of concern.

The investigator is responsible for ensuring that all AEs and SAEs that are observed or reported during the study, are collected and reported to the U.S. Food and Drug Administration (FDA), appropriate IRB(s), and Genentech, Inc. in accordance with CFR 312.32 (IND Safety Reports).

An AE is any unfavorable and unintended sign, (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational medicinal product (IMP) or other protocol−imposed intervention, regardless of attribution.

This includes the following:

- AEs not previously observed in the subject that emerge during the protocol-specified AE reporting period, including signs or symptoms associated with metastatic colorectal adenocarcinoma that were not present prior to the AE reporting period
- Complications that occur as a result of protocol-mandated interventions (e.g., invasive procedures such as cardiac catheterizations)
- If applicable, AEs that occur prior to assignment of study treatment associated with medication washout, no treatment run-in, or other protocol-mandated intervention
- Preexisting medical conditions (other than the condition being studied) judged by the investigator to have worsened in severity or frequency or changed in character during the protocol-specified AE reporting period

9.2.2 DEFINITION OF SERIOUS ADVERSE EVENTS

Serious adverse event or serious suspected adverse reaction.

An AE or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse event
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- It results in congenital anomaly/ birth defect
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate 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. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

9.2.3 ADVERSE EVENTS OF SPECIAL INTEREST

Adverse events of special interest (AESIs) are a subset of Events to Monitor (EtMs) of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor-Investigator and Genentech is required. Such an event might require further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the trial Sponsor to other parties (e.g., Regulatory Authorities) may also be warranted.

AESIs for this study are as follows:

- 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: ○ Treatment-emergent ALT or AST > 3 x ULN in combination with total bilirubin > 2 x

ULN ○ Treatment-emergent ALT or AST > 3 x ULN in combination with clinical jaundice.

- Suspected transmission of an infectious agent by the study drug (STIAMP), as defined below: 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 the study drug is suspected.

The Atezolizumab and Tiragolumab Adverse Events of Special Interest (AESI) are:

- Pneumonitis
- Colitis
- Endocrinopathies: diabetes mellitus, pancreatitis, adrenal insufficiency, hyperthyroidism, and hypophysitis
- Hepatitis, including AST or ALT > 10 x ULN
- Neurological disorders: Guillain-Barré syndrome, myasthenic syndrome or myasthenia gravis, and meningoencephalitis
- Systemic lupus erythematosus
- Events suggestive of hypersensitivity, infusion-related reactions, cytokine release syndrome, hemophagocytic lymphohistiocytosis (HLH), macrophage activation syndrome (MAS)
- Nephritis
- Ocular toxicities (e.g., uveitis, retinitis, optic neuritis)
- Myositis
- Myopathies, including rhabdomyolysis ● Grade ≥ 2 cardiac disorders
- Vasculitis
- Autoimmune hemolytic anemia
- Severe cutaneous reactions (e.g., Stevens-Johnson syndrome, dermatitis bullous, toxic epidermal necrolysis)
- Myelitis
- Facial paresis

9.2.4 Classification of an Adverse Event

9.2.4.1 Severity of Event

The adverse event severity grading scale for the NCI CTCAE (v5.0) will be used for assessing adverse event severity. The following table will be used for assessing severity for adverse events that are not specifically listed in the NCI CTCAE (v5.0).

Grade	Severity
1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; or intervention not indicated
2	Moderate; minimal, local, or non-invasive intervention indicated; or limiting age-appropriate instrumental activities of daily living [a]
3	Severe or medically significant, but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; or limiting self-care activities of daily living [b, c]
4	Life-threatening consequences or urgent intervention indicated [d]
5	Death related to adverse event [d]

NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events.
Note: Based on the most recent version of NCI CTCAE (v5.0) which can be found at:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

a. Instrumental activities of daily living refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
b. Examples of self-care activities of daily living include bathing, dressing and undressing, feeding oneself, using the toilet, and taking medications, as performed by patients who are not bedridden.
c. If an event is assessed as a "significant medical event," it must be reported as a serious adverse event
d. Grade 4 and 5 events must be reported as serious adverse events

9.2.4.2 RELATIONSHIP TO STUDY INTERVENTION

For all collected AEs, the clinician who examines and evaluates the participant will determine the AE's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below.

- **Definitely Related** – There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- **Probably Related** – There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within

a reasonable time after administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.

- **Possibly Related** – There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, other factors may have contributed to the event (e.g., the participant's clinical condition, other concomitant events). Although an AE may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- **Unlikely to be Related** – A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the participant's clinical condition, other concomitant treatments).
- **Not Related** – The AE is completely independent of study drug administration, and/ or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

9.2.4.3 EXPECTEDNESS

Expectedness will only be documented for SAEs. The study investigator will be responsible for determining whether an SAE is expected or unexpected. An SAE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study agent.

9.2.4.4 SPECIFIC INSTRUCTIONS FOR RECORDING ADVERSE EVENTS

Investigators should use correct medical terminology/concepts when reporting AEs or SAEs. Avoid colloquialisms and abbreviations.

9.2.4.5 DIAGNOSIS VERSUS SIGNS AND SYMPTOMS

If known at the time of reporting, a diagnosis should be reported rather than individual signs and symptoms (e.g., record only liver failure or hepatitis rather than jaundice, asterixis, and elevated

transaminases). However, if a constellation of signs and/or symptoms cannot be medically characterized as a single diagnosis or syndrome at the time of reporting, it is acceptable to report the information that is currently available. If a diagnosis is subsequently established, it should be reported as follow-up information.

9.2.4.6 DEATHS

All deaths that occur during the protocol-specified AE reporting period (see Section 9.2.4.9), regardless of attribution, will be reported to the appropriate parties. When recording a death, the event or condition that caused or contributed to the fatal outcome should be reported as the single medical concept. If the cause of death is unknown and cannot be ascertained at the time of reporting, report "Unexplained Death".

9.2.4.7 PREEXISTING MEDICAL CONDITIONS

A preexisting medical condition is one that is present at the start of the study. Such conditions should be reported as medical and surgical history. A preexisting medical condition should be reassessed throughout the trial and reported as an AE or SAE only if the frequency, severity, or character of the condition worsens during the study. When reporting such events, it is important to convey the concept that the preexisting condition has changed by including applicable descriptors (e.g., "more frequent headaches").

9.2.4.8 HOSPITALIZATIONS FOR MEDICAL OR SURGICAL PROCEDURES

Any AE that results in hospitalization or prolonged hospitalization should be documented and reported as an SAE. If a subject is hospitalized to undergo a medical or surgical procedure as a result of an AE, the event responsible for the procedure, not the procedure itself, should be reported as the SAE. For example, if a subject is hospitalized to undergo coronary bypass surgery, record the heart condition that necessitated the bypass as the SAE.

Hospitalizations for the following reasons do not require reporting:

- Hospitalization or prolonged hospitalization for diagnostic or elective surgical procedures for preexisting conditions.
- Hospitalization or prolonged hospitalization required to allow efficacy measurement for the study.

- Hospitalization or prolonged hospitalization for scheduled therapy of the target disease of the study.

9.2.4.9 Time Period and Frequency for Event Assessment and Follow-up

The occurrence of an AE or SAE may come to the attention of study personnel during study visits and interviews of a study participant presenting for medical care, or upon review by a study monitor. All AEs including local and systemic reactions not meeting the criteria for SAEs will be captured on the appropriate CRF. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study product (assessed only by those with the training and authority to make a diagnosis), and time of resolution/ stabilization of the event. All AEs occurring while on study must be documented appropriately regardless of relationship. All AEs will be followed to adequate resolution (grade 1 or lower).

Any medical condition that is present at the time that the participant is screened will be considered as baseline and not reported as an AE. However, if the study participant's condition deteriorates at any time during the study, it will be recorded as an AE. UAPs will be recorded in the data collection system throughout the study.

Changes in the severity of an AE will be documented to allow an assessment of the duration of the event at each level of severity to be performed. AE's characterized as intermittent may be recorded as one event unless there is a change in frequency or intensity (i.e. the highest grade is captured and the AE indicated as ongoing unless it resolves or increases).

The investigator will record all reportable events with start dates occurring any time after informed consent is obtained until 30 days following the last administration of study treatment, until study discontinuation/termination, or until the initiation of new systemic anti-cancer therapy, whichever is earlier. After this period, investigators should only report SAEs that are attributed to the prior study treatment through the final follow-up visit. AESI, however, will be recorded at any time they happen throughout the final follow up as needed. SAEs will be followed until resolution or stabilization. At each study visit, the investigator will inquire about the occurrence of AE/ SAEs since the last visit.

9.2.5 Adverse Event Reporting

The investigator must record non-serious adverse events and report to DSMC and IRB according to timeline for reporting specified in Section 11.1.5. A quarterly line-listing for non-serious adverse events will be provided to Genentech as detailed under Appendix 4.

9.2.6 SERIOUS ADVERSE EVENT REPORTING

The investigator must record all serious adverse events and report to DSMC and IRB according to timeline for reporting specified in Section 11.1.5.

SAEs will be submitted using the MedWatch 3500A (Mandatory Reporting) form which is available at *https://www.fda.gov/media/69876/download* .

The study clinician will complete an SAE Form within the following timelines:

SAEs, regardless of relationship, pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation reports, AESIs and Product Complaints with/without an AE where the patient has been exposed to the Product will be submitted to the Genentech within 24 hours of site awareness. Similarly, all deaths and immediately lifethreatening events, whether related or unrelated, will be recorded on the SAE Form and submitted to Genentech within 24 hours of site awareness.

To submit an SAE, email as follows within 24 hours of becoming aware of the event:

To: *hannah.r.robinson@cuanschutz.edu*
cpdm.iit@cuanschutz.edu usds_aereporting-d@gene.com

Subject: 24-0547 SAE Report Form

Attach: SAE form completed and signed by the Investigator

The fax cover sheet for safety reporting can be found in Appendix 1.

Per institutional policy, all serious adverse events occurring at UCCC/UCHealth will be entered into OnCore according to timeline for reporting specified in Section 11.1.5.

Follow-up of unresolved serious adverse events

Any SAEs that are unresolved at the time of the initial report submission should be followed up by the investigator for as long as medically indicated, and an updated SAE report submitted at the time new information regarding the event becomes available.

Post-Study Adverse Events

The investigator should expeditiously report any SAE occurring after a subject has completed or discontinued study treatment if attributed to prior study drug exposure (i.e. exposure to atezolizumab, tiragolumab, bevacizumab) through the end of their study participation. If the investigator should become aware of the development of cancer or a congenital anomaly in a subsequently conceived offspring of a female subject who participated in the study, this should be reported as an SAE adequately to Genentech Patient Safety during the follow-up period.

As this study involves collection of survival data and extended follow up period, at the end of the adverse event reporting period, the investigator should report all deaths (regardless of cause), in addition to SAEs attributed to the study drug exposure and pregnancy reports. During this extended follow-up period, Case Transmission Verification will be performed by both parties during this extended follow-up period on a half-yearly basis to ensure successful transmission of single case reports.

9.2.6.1 Special Situations Reporting

University of Colorado Cancer Center will be responsible for collecting and reporting all protocoldefined Adverse Events (AEs)/Serious Adverse Events (SAEs), pregnancy reports (including pregnancy occurring in the partner of a male study subject), other Special Situation reports, AESIs and Product Complaints with an AE where the patient has been exposed to the Product.

9.2.6.2 Reporting of Pregnancy

Although pregnancy and lactation are not considered adverse events, it is the responsibility of investigators or their designees to report any pregnancy or lactation in a subject (spontaneously reported to them) that occurs during the trial.

Pregnancies and lactations that occur after the informed consent form is signed but before treatment initiation must be reported by the investigator.

If a female subject becomes pregnant while receiving the study drug or within 90 days after the final dose of tiragolumab, 5 months after the final dose of atezolizumab, or 6 months after the final dose of bevacizumab; or if the female partner of a male study subject becomes pregnant while the study subject is within 90 days after the final dose of tiragolumab, 5 months after the final dose of atezolizumab, or 6 months after the final dose of bevacizumab, a report should be completed and expeditiously submitted to Genentech, Inc. Any pregnancy that occurs during the time period above, or any lactations that occur any time after starting the study therapy and within 120 days following the cessation of study drug, or 30 days following cessation of study drug if the subject initiates a new cancer therapy, whichever is earlier, must be reported by the investigator.

Pregnancies and lactations will be reported as an SAE on a MedWatch Form3500A and submitted within 24 hours from first becoming aware. Please follow the instructions for Serious Adverse Event Reporting specified in Section 9.2.6.

All reported pregnancies must be followed to the completion/termination of the pregnancy. Pregnancy outcomes of abortion, benign hydatidiform mole, blighted ovum, fetal death, intrauterine death, miscarriage, and stillbirth must be reported as serious events (Important Medical Events). Abortion, whether accidental, therapeutic, or spontaneous, should always be classified as serious, and expeditiously reported as an SAE. Similarly, any congenital anomaly/birth defect in a child born to a female subject exposed to the study drug should be reported as an SAE. If the pregnancy continues to term, the outcome (health of infant) must also be reported.

9.2.6.3 Adverse Events of Special Interest (AESI) Reporting

All Adverse Events of Special Interest as described within section 9.2.3 will be reported using the FDA 3500A Mandatory MedWatch report. The reporting form can be found at:
http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

To submit an AESI, email as follows within 24 hours of becoming aware of the event:

To: *hannah.r.robinson@cuanschutz.edu*
cpdm.iit@cuanschutz.edu usds_aereporting-d@gene.com

Subject: 24-0547 AESI Report Form

Attach: MedWatch form completed and signed by the Investigator

9.2.6.4 OTHER SPECIAL SITUATION REPORTS

The following other Special Situations Reports should be collected and transmitted to Genentech even in the absence of an Adverse Event within 30 days:

- Data related to product usage during breastfeeding.
- Data related to overdose, abuse, misuse or medication error (including potentially exposed or intercepted medication errors). In addition, reasonable attempts should be made to obtain and submit the age or age group of the patient, in order to be able to identify potential safety signals specific to a particular population.

9.2.6.5 PRODUCT COMPLAINTS

A Product Complaint is defined as any written or oral information received from a complainant that alleges deficiencies related to identity, quality, safety, strength, purity, reliability, durability, effectiveness, or performance of a product after it has been released and distributed to the commercial market or clinical trial.

All Product Complaints (with or without an AE) reports (initial and follow-up) shall be forwarded to Genentech within 30 calendar days of the awareness date.

All Product Complaints without an AE should be called into the phone number below, in order to be able to identify potential safety signals specific to a particular patient population:

Phone: 800-334-0290 (M-F: 5 am to 5 pm PST)

9.2.6.6 EXCHANGE OF SINGLE CASE REPORTS WITH GENENTECH:

The University of Colorado Cancer Center will be responsible for collecting all protocol-defined Adverse Events (AEs)/Serious Adverse Events (SAEs) (related and not related to the product), pregnancy reports, Special Situation Reports even in the absence of an AE (including all pregnancy reports and pregnancy occurring in the partner of a male study subject), other Special Situation reports, non-serious AESIs, Product Complaints (with or without an AE) where the patient has been exposed to the Genentech Product.

It is understood and agreed that the University of Colorado Cancer Center will perform adequate due diligence with regard to obtaining follow-up information on incomplete case safety reports.

In addition, reasonable attempts must be made to obtain and submit the age or age group of the patient in order to be able to identify potential safety signals specific to a particular population.

The University of Colorado Cancer Center agrees to allow requests for follow-up information from Genentech, for instance, in order to fulfill regulatory obligations, or where the requested information is not already routinely covered by standard follow-up activities (e.g., clarification of data discrepancies, or to request typical confirmatory laboratory data or batch numbers for biologics and other advanced therapies). Genentech will not contact the reporter directly for such data, but will route all such requests for follow-up to the provided University of Colorado Cancer Center contact. It is understood and agreed that University of Colorado Cancer Center will be responsible for the evaluation of all the case safety reports originating from the study.

Transmission of these reports (initial and follow-up) will be either electronically via email or by fax to the following email address/fax number:

Fax: 650-238-6067
Email: usds_aereporting-d@gene.com

The completed MedWatch form should be sent to the Genentech contact specified above to report applicable events (applicable events include all SAEs, serious and non-serious AESIs, all Special Situation reports including pregnancies and all Product Complaints). A quarterly line-listing for non-serious adverse events will be provided to Genentech. The non-serious line-listing must include all fields as detailed in Appendix 4.

Batch ID/lot ID for biologics associated with AE/Special Situation/Scenario/PC/AESI must be included.

Transmission of the applicable reports (initial and follow-up) will be sent within the timelines specified below:

Type of Report	**Timelines**
Serious Adverse Events deemed related to the product	Fifteen (15) Calendar Days

Serious Adverse Events deemed not related to the product	30 calendar days from awareness date
Special Situation Reports (with or without AE and pregnancy)	
Product Complaints (with or without AE)	
AESI	
Non-Serious Adverse Events	Quarterly Line Listing that must include all fields as detailed in Appendix 4

University of Colorado Cancer Center will send quarterly non-serious Line-Listing (per Appendix 4), quarterly line-listings for CTV (per Appendix 3) and Cumulative CTV originating from the study to Genentech at ctvistsa@gene.com.

9.2.7 RECONCILIATION (CASE TRANSMISSION VERIFICATION)

The Investigator agrees to conduct case-level reconciliation as instructed by Genentech to confirm receipt of all reports from the investigator. Genentech and the Investigator agree to verify that all single case reports have been adequately received by Genentech via the exchange of quarterly line listings of cases that includes all fields detailed in Appendix 3 and 4, unless otherwise agreed by Genentech in writing. The quarterly line listings will be exchanges within seven (7) Calendar days of the end of the agreed period. Following Case Transmission Verification (CTV), single case reports which have not been received by Genentech shall be forwarded by University of Colorado Cancer Center to Genentech within five (5) calendar days from request by Genentech.

If discrepancies are identified, the Investigator and Genentech will cooperate in resolving the discrepancies. The responsible individuals for each party shall handle the matter on a case-bycase basis until satisfactory resolution.

At the end of the study, a final cumulative Case Transmission Verification (FCTV) report will be sent to Genentech.

Quarterly line-listing for non-serious events, quarterly CTV line-listing and cumulative/final CTV should be sent to ctvistsa@gene.com (please see Appendix 3 and Appendix 4 for "Content required in the line-listing used for CTV" and "Content required in the line-listing used for exchange of non-serious events", respectively).

9.2.8 MEDWATCH 3500A REPORTING GUIDELINES

In addition to completing appropriate patient demographic (Section A) and suspect medication information (Section C and D), the report should include the following information within the Event Description (Section B.5) of the MedWatch 3500A form:

- Protocol number and title description
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics (Section B.6)
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

9.2.9 FOLLOW-UP INFORMATION

Additional information may be added to a previously submitted report by any of the following methods:

- Adding to the original MedWatch 3500A report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original MedWatch 3500A form
- Summarizing new information and faxing it with a cover letter including patient identifiers (i.e., D.O.B. initial, patient number), protocol description and number, if assigned, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

9.2.10 Reporting to Regulatory Authorities, Ethics Committees, and Investigators

University of Colorado Cancer Center, as the Sponsor of the Study, will be responsible for the reporting of safety reports originating from the Study to the EMA through Eudravigilance Clinical Trial Module (EVCTM), where applicable.

University of Colorado Cancer Center will be responsible for the reporting of safety reports originating from the Study to the Ethics Committees and Institutional Review Boards (IRB), where applicable.

The Sponsor-Investigator will be responsible for the distribution of safety information to its own investigators, where relevant, in accordance with local regulations.

And to the site IRB:

Colorado Multiple Institutional Review Board (COMIRB)

Phone: 303-724-1055

Email: *comirb@ucdenver.edu*

All materials will be submitted to COMIRB via the InfoEd eRA website.

For Investigator-Initiated IND studies, some additional reporting requirements for the FDA apply in accordance with the guidance set forth in 21 CFR § 312.32.

Events meeting the following criteria need to be submitted to the FDA as expedited IND Safety Reports according to the following guidance and timelines:

7 Calendar Day Telephone or Fax Report
The Investigator is required to notify the FDA of any fatal or life-threatening adverse event that is unexpected and assessed by the Investigator to be possibly related to the use of study drug. An unexpected adverse event is one that is not already described in the study drug Investigator's Brochure. Such reports are to be emailed to the FDA and Genentech within 7 calendar days of first learning of the event.

15 Calendar Day Written Report

The Investigator is also required to notify the FDA and all participating investigators, in a written IND Safety Report, of any serious, unexpected AE that is considered reasonably or possibly related to the use of study drug. An unexpected adverse event is one that is not already described in the study drug Investigator's Brochure.

Written IND Safety Reports should include an Analysis of Similar Events in accordance with regulation 21 CFR § 312.32. All safety reports previously filed by the investigator with the IND concerning similar events should be analyzed and the significance of the new report in light of the previous, similar reports commented on.

Written IND Safety Reports with Analysis of Similar Events are to be submitted to the FDA, Genentech, and all participating investigators within 15 calendar days of first learning of the event. The FDA prefers these reports on a MedWatch 3500 form, but alternative formats are acceptable (e.g., summary letter).

All written IND Safety Reports submitted to the FDA by the investigator must also be emailed to Genentech Patient Safety:

Email: usds_aereporting-d@gene.com

For questions related to safety reporting, please contact Genentech Drug Safety:

Tel: (888) 835-2555

Fax: (650) 225-4682 or (650) 225-4630

9.3 AGGREGATE REPORTS

University of Colorado Cancer Center will forward a copy of the Final Study Report to Genentech upon completion of the Study.

All summary reports submitted by the Sponsor-investigator to any health authority should also be sent to Genentech. Copies of such reports as described below should be emailed to Genentech at: ctvistsa@gene.com.

The parties agree that aggregate reporting obligations for the study in accordance to the applicable laws and regulations in the concerned countries will reside with University of Colorado Cancer Center as the sponsor of the study.

9.4 STUDY CLOSE-OUT

Any study report submitted to the FDA by the Sponsor-Investigator should be copied to Genentech. This includes all IND annual reports and the Clinical Study Report (final study report). Additionally, any literature articles that are a result of the study should be sent to Genentech. Copies of such reports should be mailed to the assigned Clinical Operations contact for the study: *tiragolumab-gsur-d@gene.com*

And to Genentech Patient Safety CTV oversight mailbox at: *ctvistsa@gene.com*

9.4.1 QUERIES

Queries related to the study will be answered by the Sponsor-Investigator. However, responses to all safety queries from Regulatory Authorities, Ethics Committees and Institutional Review Board or for publications will be discussed and coordinated between the Parties. The Parties agree that Genentech shall have the final say and control over safety queries relating to the Product. The Sponsor-Investigator agrees that it shall not answer such queries from regulatory authorities and other sources relating to the Product independently but shall redirect such queries to Genentech.

Both Parties will use all reasonable effort to ensure that deadlines for responses to urgent requests from Regulatory Authorities and/or IRB/IEC for information or review of data are met. The Parties

will clearly indicate on the request the reason for urgency and the date by which a response is required.

9.4.2 Signal Management and Risk Management

Genentech is responsible for safety signal management (signal detection and/or evaluation) for their own Product. However, it is agreed that the Sponsor-Investigator, as Sponsor of the study, will be primarily responsible for assessment of the benefit-risk balance of the study.

If the Sponsor-Investigator issues a safety communication relevant for Genentech (i.e., a safety issue that notably impacts the benefit-risk balance of the study and / or triggers any changes to the study) this will be sent to Genentech within five (5) business days of its internal approval.

As needed, Genentech will reasonably assist the Sponsor-Investigator with signal and risk management activities related to the Product within the study.

Genentech will also provide the Sponsor-Investigator with any new relevant information that may modify, or supplement known data regarding the Product (e.g., relevant Dear Investigator Letter).

9.4.3 Compliance with Pharmacovigilance Agreement/ Audit

The Parties shall follow their own procedures for adherence to single case reporting timelines.

Each Party shall monitor and, as applicable, request feedback from the other Party regarding single case report timeliness in accordance with its own procedures. The Parties agree to provide written responses in a timely manner to inquiries from the other Party regarding single case reports received outside the agreed upon Agreement timelines. If there is any detection of trends of increasing or persistent non-compliance to transmission timelines stipulated in this Agreement, both Parties agree to conduct ad hoc or institute regular joint meeting to address the issue.

In case of concerns related to non-compliance of processes, other than exchange timelines, with this Agreement, the Parties will jointly discuss and collaborate on clarifying and resolving the issues causing non-compliance. Every effort will be made by the non-compliant Party to solve the non-compliance issues and inform the other Party of the corrective and preventative actions taken.

Upon justified request, given sufficient notice of no less than sixty (60) calendar days, an audit under the provisions of this Agreement can be requested by either Party. The Parties will then

discuss and agree in good faith upon the audit scope, agenda, and execution of the audit. The requesting Party will bear the cost of the audit.

9.5 Unanticipated Problems

9.5.1 Definition of Unanticipated Problems (UAP)

This study will use the COMIRB definition of UAP. An unanticipated problem is any event or information that was unforeseen and indicates that the research procedures caused harm (including physical, psychological, economic, or social harm) to participants or others or indicates that participants or others are at increased risk of harm than was previously known or recognized.

9.5.2 Reporting of Unanticipated Problems

This study will follow COMIRB's guidance for UAP reporting and the DSMC's requirements (discussed below). AEs, noncompliance, and protocol violations will be recorded and reported as required either promptly or at the time of the study's continuing review.

It is the responsibility of the Principal Investigator to report incidents or events that meet the criteria for UAPs reporting to their IRB using the IRB's standard UAP form. The PI is also responsible for reporting the UAP to the UCCC DSMC.

10 STATISTICAL CONSIDERATIONS

10.1 Statistical Hypotheses

Primary Hypothesis:

1. Treatment with atezolizumab, bevacizumab, and tiragolumab will result in an improved objective response rate (ORR, per RECIST v1.1) compared to historical controls. ● Primary Efficacy Endpoint: ORR, per RECIST v1.1

Secondary Hypotheses:

1. Treatment with atezolizumab, bevacizumab, and tiragolumab will result in improved progression free survival (PFS) compared to historical controls.

- Secondary Endpoint: PFS; defined as the time from enrollment to the first observation of progression per RECIST v1.1 or death from any cause.

2. Treatment with atezolizumab, bevacizumab, and tiragolumab will result in improved overall survival (OS) compared to historical controls.
    - Secondary Endpoint: OS; defined as the time from enrollment to death from any cause.
3. Patients without active liver metastases will demonstrate superior response to treatment with atezolizumab, bevacizumab, and tiragolumab compared to patients with active liver metastases.
    - Secondary Endpoints: ORR, PFS, and OS as defined above, according to the presence or absence of active liver metastases.
4. Combined treatment with atezolizumab, bevacizumab, and tiragolumab will be safe and adequately tolerated.
    - Secondary Endpoints: Incidence, type, and severity of adverse events (AEs) as defined by CTCAE v5.0, including serious AEs (SAEs) and AEs of special interest (AESIs).

10.2 Sample Size Determination

This trial will utilize a phase II, single-arm, Simon 2-stage design to evaluate the combination of tiragolumab with atezolizumab and bevacizumab in patients with previously treated, MSS mCRC. Sixteen patients will be enrolled in the first stage, after which an interim analysis will be performed to assess futility. If the study proceeds to the second stage, an additional 28 patients will be enrolled for a total of 44 patients.

The sample size calculation was determined based on the primary endpoint, ORR (best response). The ORR selected for hypothesis testing was 6%, based on historical data from clinical trials of approved treatments for MSS mCRC refractory to fluoropyrimidine, oxaliplatin, and irinotecan chemotherapy[2,17-20]. In this setting, the highest ORR achieved to date is 6%, per the phase III SUNLIGHT trial evaluating combined treatment with trifluridine-tipiracil and bevacizumab[2]. We predict an ORR of 20% in this study, which would represent a clinically meaningful improvement from standard of care as well as from responses observed with pembrolizumab, binimetinib, and bevacizumab in our investigator-initiated phase II trial (NCT03475004)[45].

Sample size calculations were performed using the following parameters:

- H0: ORR ≤ 0.06

- H1: ORR ≥ 0.20
- Type 1 error rate of ≤ 0.05
- Power of ≥ 0.80

Using a 2-stage single-arm design, a total of 44 patients will be enrolled if the trial continues into its second stage, for a type I error rate of 0.035 and a power of 0.81 (H0: ORR ≤ 0.06 versus H1: ORR ≥ 0.2). In the first stage, 16 subjects will be needed, with an additional 28 subjects in the second stage, if necessary. The expected (average) sample size of this design is 22.97, with a probability of stopping after Stage 1 of 0.75105. With 16 subjects at the first stage, the trial should be discontinued if 1 or fewer respond to the treatment.

The sample sizes and critical values were based on the primary endpoint and hypothesis to achieve desired operating characteristics, and were computed using PASS 2022, version 22.0.2.

10.3 Population for Analyses

Efficacy and safety analyses will be conducted using the safety-evaluable population, defined as all patients who receive any amount of study drug. Exploratory analyses will also be conducted using the efficacy-evaluable population, defined as patients who received at least 1 cycle of therapy and have had their disease re-evaluated for response.

Exploratory analyses based on correlative/ biomarker testing of peripheral blood and tumor tissue samples will be conducted in patients with available pre- and on-treatment samples.

In order to achieve a total sample size of 44 patients, it is estimated that approximately 54 patients will need to be screened, although additional patients may be screened as needed. This accounts for patients who fail screening or are not evaluable for assessment.

10.4 Statistical Analyses

10.4.1 General Approach

The primary analysis will be based on patient data collected through study discontinuation or end of study. Efficacy and safety analyses will be conducted using the safety-evaluable population, defined as all patients who receive any amount of study drug. Exploratory analyses of efficacy endpoints may also be performed using the efficacy-evaluable population. Exploratory analyses

based on correlative/ biomarker testing of peripheral blood and tumor tissue samples will be conducted in patients with available paired pre- and on-treatment samples.

Summary descriptive statistics will be calculated and presented for all primary, secondary, and exploratory outcomes for all patients, and for stratifications defined by participants demographic characteristics. The demographic characteristics of patients will be presented with descriptive statistics also. The means, medians and the 95% confidence intervals will be calculated for continuous variables; the frequencies, estimated rates, and the exact 95% confidence intervals will be calculated for the binary and categorical variables.

The safety, tolerability, and clinical activity atezolizumab, bevacizumab, and tiragolumab will be described and summarized, as warranted by sample size. That is, listings may be used in lieu of tables in the event of small sample size. Analysis of the primary and secondary efficacy endpoints will be performed as described in Section 10.4.2 and Section 10.4.3, respectively. Safety analyses will be performed as described in Section 10.4.4; exploratory endpoints will be analyzed as described in Section 10.4.8.

10.4.2 Analysis of the Primary Efficacy Endpoint and Stopping Criteria

A one-sided proportion test will be conducted to test the observed ORR (best response) against the null hypothesis that ORR ≤ 0.06, with a significance level of 0.05. See Section 10.2 for rationale behind selection of the null hypothesis. The cumulative frequency, estimated proportion, and the exact 95% confidence intervals will be reported.

As described in Section 10.2, a sample size of 44 achieves a power of 0.81 if the observed ORR is 20%, using a one-sided exact test with a significance level of 0.035.

Using a Simon 2-stage design, ORR will be determined based on the first 16 evaluable patients. If there are ≤ 1 responses (partial response or complete response as defined in the protocol) among 16 patients, study enrollment will be stopped for futility. If there are ≥ 2 responses among the first 16 evaluable patients, then full study enrollment will proceed as planned.

If the study proceeds, 44 patients will be enrolled. In this case, the upper critical value is 6 (e.g., if 6 or more patients respond to treatment, the null hypothesis will be rejected).

10.4.3 Analysis of the Secondary Efficacy Endpoints

Secondary efficacy endpoints in this trial are progression free survival (PFS), overall survival (OS), and frequency and types of adverse events (AEs) among the total evaluable study population. ORR, PFS, and OS will also be assessed in patients with versus without liver metastases.

Efficacy Among the Evaluable Study Population

For PFS and OS, the survival probability (Kaplan-Meier survival curve) at 6 months will be calculated by the Kaplan-Meier method. The survival curve and the median survival time for PFS and OS will be reported with the corresponding 2-sided 95% Brookmeyer-Crowley's CI, if feasible. PFS and OS will be compared to historical controls if sample size allows. Results from the SUNLIGHT trial (bevacizumab plus trifluridine–tipiracil in treatment refractory mCRC) will be used as historical controls, unless there are interim changes in standard of care, where median PFS and OS were 5.6 and 10.6 months, respectively[2].

Efficacy According to the Presence of Absence of Liver Metastases

The efficacy endpoints of ORR, PFS, and OS will be assessed in and compared between evaluable patients with versus without active liver metastases. A chi-squared test will be conducted to assess for difference in the ORR in patients with versus without liver metastases. Two-sided, log-rank tests will be conducted to assess for differences in PFS and OS in patients with versus without liver metastases.

10.4.4 Safety Analyses

Safety will be assessed through summaries of adverse events. Adverse events will include changes in symptoms, changes in medical conditions, changes in vital signs, and changes in laboratory values (see Section 9). Additionally, separate summaries will be created which will include only serious adverse events (SAEs). When subjects experience multiple events of varying severity, the highest grade will be used in the subject-level summaries.

Toxicity will be summarized and tabulated based on organ and severity.

10.4.5 Baseline Descriptive Statistics

The demographic characteristics of the participants will be presented with descriptive statistics. The means, medians, and 95% confidence intervals will be calculated for continuous variables; the frequencies, estimated rates, and the exact 95% confidence intervals will be calculated for binary and categorical variables.

10.4.6 Planned Interim Analyses

A planned interim efficacy analysis will be performed based on the first 16 evaluable patients as detailed in Section 10.4.2. The study will be stopped due to futility if less than 2 of 16 patients respond to study treatment.

10.4.7 Tabulation of Individual Participant Data

Tabulation data sets will be created which provide a tabular listing of subject data for all domains (e.g. demographics, outcomes, adverse events, etc).

10.4.8 Exploratory Analyses

Efficacy Endpoints
Exploratory efficacy endpoints in this study will be:

1. Disease control rate (DCR), defined as stable disease (SD), partial response (PR), or complete response (CR) to treatment, per RECIST v1.1.
2. Duration of response (DOR), defined as the time from response (CR or PR) to progression or death from any cause, per RECIST v1.1.

For DCR, the cumulative frequency and estimated DCR with 95% confidence intervals will be reported. For DOR, the survival curve and the median survival time will be reported with the corresponding 2-sided 95% Brookmeyer-Crowley's CI, if feasible. Observed DCR and DOR will be compared to historical controls, if feasible.

Correlative Endpoints
Exploratory analyses will be conducted in evaluable patients who have available pre- and ontreatment blood samples and/or tumor tissue samples to explore potential predictive biomarkers and mechanisms of treatment response and resistance. Planned correlative testing includes immune profiling by mass cytometry and multispectral imaging, as well as assessment of mRNA expression of immune-related genes, per Sections 8.3.1 and 8.3.2.

Exploratory endpoints in this study involving correlative analyses will include:

1. Objective response rate (ORR) per RECIST v1.1, according to pre-treatment tumor PVR and PD-L1 expression (by mass cytometry and multispectral imaging).
2. Objective response rate (ORR) per RECIST v1.1, according to pre-treatment T cell TIGIT and PD-L1 expression (by mass cytometry and multispectral imaging).
3. Change in pre-treatment to on-treatment immune parameters by mass cytometry and multispectral imaging immune profiling and mRNA expression patterns of immune-related genes.
4. On-treatment immune parameters by mass cytometry and multispectral imaging immune profiling and mRNA expression patterns of immune-related genes according to treatment response (patients with treatment response versus patients with progressive disease).
5. On-treatment immune parameters by mass cytometry and multispectral imaging immune profiling and mRNA expression patterns of immune-related genes according to the presence or absence of liver metastases.

Pre-treatment expression of PD-1 and TIGIT on T cells in the peripheral blood and tumor tissue and expression of PD-L1 and PVR on tumor cells are of interest as potential biomarkers for response, as these are the receptor-ligand pairs targeted by atezolizumab and tiragolumab, respectively. Patients will be classified as "low" or "high" expressors of PD-1, TIGIT, PD-1/TIGIT (dual expression), PD-L1, PVR, and PD-L1/PVR (dual expression). ORR according to level of expression will be determined and compared between "low" and "high" expressors, using a chisquared test.

For evaluable patients with available paired pre- and on-treatment samples, changes in immune parameters will be evaluated between pre- and on-treatment timepoints using linear mixed model. The change parameters of immune activation between pre- and on-treatment timepoints will be compared in on-treatment samples between treatment responders versus treatment non-responders, and between patients with versus without liver metastases using linear mixed model. The immune parameters may be log transformed for model validation. Multiple comparisons will be adjusted using the Benjamini-Hochberg procedure.

11 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

11.1 Regulatory, Ethical, and Study Oversight Considerations

11.1.1 Informed Consent Process

11.1.1.1 Consent/Assent and Other Informational Documents Provided to Participants

Consent forms describing in detail the study agent, study procedures, and risks are given to the participant and written documentation of informed consent is required prior to starting intervention/ administering study product.

11.1.1.2 Consent Procedures and Documentation

Informed consent process will be initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Extensive discussion of risks and possible benefits of participation will be provided to the participants and their families.

Consent forms will be IRB-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the participant and answer any questions that may arise. All participants will receive a verbal explanation in terms suited to their comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants will have the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. The participant will sign the informed consent document prior to any procedures being done specifically for the study.

The participants may withdraw consent at any time throughout the course of the trial. A copy of the informed consent document will be given to the participants for their records. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

The study allows the inclusion of non-English speaking and non-reading participants. Witnesses to these consent processes will be individuals not associated with the trial and will not have a conflict of interest.

11.1.2 Study Discontinuation and Closure

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending, or terminating party to the study partners including the Sponsor-Investigator, Genentech, and regulatory authorities. If the study is prematurely terminated or suspended, the Sponsor-Investigator will promptly inform the IRB providing the reason(s) for the termination or suspension.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants.
- Demonstration of efficacy that would warrant stopping.
- Insufficient compliance to protocol requirements.
- Data that are not sufficiently complete and/ or evaluable.
- Determination of futility.

The study may resume once concerns about safety, protocol compliance, and data quality are addressed and satisfy the IRB, the DSMC, and/or the FDA.

11.1.3 Confidentiality and Privacy

Participant confidentiality is strictly held in trust by the participating investigators, their staff, and the Sponsor-Investigator(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the Sponsor-Investigator.

The study monitor, other authorized representatives of the Sponsor-Investigator, representatives of the IRB or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the Investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study. The clinical study site will permit access to such records.

The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by local IRB and Institutional regulations.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Colorado Cancer Center (UCCC). This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the UCCC research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the UCCC.

11.1.4 Banking and Future Use of Stored Specimens and/or Data

The following refer to specimens obtained during this study:

- **Intended Use:** Samples and data collected under this protocol may be used to study tumorassociated immune cells and the tumor microenvironment, peripheral blood immune cells, ctDNA, and biomarkers related to CRC and immunotherapy to investigate patterns of response or resistance to treatment in the future. No germline genetic testing will be performed.
- **Storage:** During the study, blood and tissue samples will be stored at the University of Colorado Cancer Center. Access to stored samples will be limited to research personnel only. Samples and data will be stored using codes assigned by the investigators. Data will be kept in password-protected computers. Only investigators will have access to the samples and data. The following information obtained from the subject's medical record may be recorded and may be provided to research collaborators when specimens are made available:

- Diagnosis
- Collection time in relation to study treatment
- Clinical outcome
- Demographic data

These samples could be used for research into the causes of immunotherapy resistance, response, and/or toxicity, and other conditions for which individuals with CRC and those receiving immunotherapy are at increased risk, and to improve treatment. University of Colorado Pathology Shared Resource will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the masking of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. If future use is denied or withdrawn by the participant, best efforts will be made to stop any additional studies and to destroy the specimens. However, withdrawal of consent with regard to bio- sample storage will not be possible after the study is completed.

The University of Colorado Pathology Shared Resource will coordinate the collection of blood samples for research-related testing from study site laboratories. The GI Translational Research Laboratory/ Pitts Laboratory will lead study correlative assessments.

When the study is completed, access to study data and/ or samples will be provided through the University of Colorado Pathology Shared Resource.

At the time of study completion, remaining samples not used must be transferred to a COMIRB approved tissue bank/data repository protocol designed specifically for secondary research.

11.1.5 SAFETY OVERSIGHT

Monitoring and Oversight

The Sponsor-Investigator will be responsible for monitoring the trial per the trial monitoring plan, in addition to overseeing the safety and efficacy of the trial including any specimens collected, executing the data and safety monitoring (DSM) plan, and complying with all reporting requirements to local and federal authorities. This oversight will be accomplished through additional oversight from the Data and Safety Monitoring Committee (DSMC) at the University of Colorado Cancer Center (UCCC). The DSMC is responsible for ensuring data quality and study participant safety for all clinical studies at the UCCC, which is the coordinating institution of this trial. A summary of the DSMC's activities is as follows:

- Conduct of internal audits
- Ongoing review of all serious adverse events (SAEs) and unanticipated problems (UAPs)
- May submit recommendations for corrective actions to the CU Cancer Center's Executive Committee

Per the UCCC Institutional DSM Plan, SAEs and UAPs are reported to the DSMC, IRB, and the Sponsor -Investigator per protocol. All SAEs and UAPs are to be reported to the DSMC within 7 (for fatal or life-threatening events) or 15 (non-life-threatening events) calendar days of the Sponsor -Investigator receiving notification of the occurrence.

Each subject's treatment outcomes will be discussed by the site PI and appropriate staff at weekly meetings. Data regarding number of subjects, significant toxicities, dose modifications, and treatment responses will be discussed and documented in the meeting's minutes.

The Sponsor-Investigator will provide a DSM progress report to the UCCC DSMC on a recurring basis (either every six or twelve months based on DSMC vote). The DSM report will include a

protocol summary, current enrollment numbers, summary of toxicity data to include specific SAEs, UAPs and AEs, any dose modifications, all protocol deviations, and protocol amendments. The DSM progress report submitted to the DSMC will also include, if applicable, the results of any efficacy data analysis conducted. Results and recommendations from the review of this progress report by the DSMC will then be provided to the Sponsor Investigator in a DSMC review letter. The Sponsor Investigator is then responsible for ensuring this letter is submitted to the site's IRB of record at the time of IRB continuing review.

11.1.6 Clinical Monitoring

Clinical site monitoring will be conducted to ensure that the rights and well-being of human participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/ amendment(s), with Good Clinical Practice (GCP), and with applicable regulatory requirement(s).

Monitoring for this study will be performed by a UCCC Clinical Monitor in accordance with the clinical monitoring plan (CMP), incorporated herein by reference. The CMP describes in detail who will conduct the monitoring, at what frequency monitoring will be done, at what level of detail monitoring will be performed, and the distribution of the monitoring reports.

11.1.7 Quality Assurance and Quality Control

Quality Control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/ resolution.

Following written Standard Operating Procedures (SOPs), the study monitor will verify that the clinical trial is conducted and data are generated, documented (recorded), and reported in compliance with the protocol, GCP, and the applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial-related sites, source data/ documents, and reports for the purpose of monitoring and auditing by the DSMC audit team, and inspection by local and regulatory authorities.

Site monitoring visits will be performed by the sponsor investigator's authorized representative on a regular basis, pursuant to the Monitoring Plan. During these visits, information recorded on the CRFs will be verified against source documents. Additional computer programs that identify selected protocol deviations, out-of-range data, and other data errors within the electronic data entry may also be used to help monitor the study. As necessary, requests for data clarification or correction will be sent to the appropriate site PI. Independent auditors from the sponsor investigator's authorized representative will be allowed by the site's PI to audit. In addition, audits may be conducted at any time by appropriate regulatory authorities and/or the IRB.

11.1.8 Data Handling and Record Keeping

11.1.8.1 Data Collection and Management Responsibilities

Data collection is the responsibility of the clinical trial staff at the site under the supervision of the site PI. The PI is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported.

All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data. When making changes or corrections, cross out the original entry with a single line, and initial and date the change. DO NOT ERASE, OVERWRITE, OR USE CORRECTION FLUID OR TAPE ON THE ORIGINAL.

Copies of the electronic CRF (eCRF) will be provided for use as source documents and maintained for recording data for each participant enrolled in the study. Data reported in the eCRF derived from source documents should be consistent with the source documents or the discrepancies should be explained and captured in a progress note and maintained in the participant's official electronic study record.

Clinical data (including AEs, concomitant medications, and expected adverse reactions data) and clinical laboratory data will be entered into a 21 CFR Part 11-compliant data capture system provided by UCCC. The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate. Clinical data will be entered directly from the source documents.

11.1.8.2 Study Records Retention

FDA regulations (21 CFR §312.62[c]) and the International Conference on Harmonization (ICH) Guideline for GCP (see Section 4.9 of the guideline) require that records and documents pertaining to the conduct of clinical trials and the distribution of investigational drug, patient records, consent forms, laboratory test results, and medication inventory records, must be retained for 2 years after the last marketing application approval in an ICH region or after at least 2 years have elapsed since formal discontinuation of clinical development of the investigational product. All state and local laws for retention of records also apply. Study documents should be retained for a longer period, however, if required by local regulations or institutional policies. No records will be destroyed without the written consent of the Sponsor, if applicable.

11.1.9 Protocol Deviations

A protocol deviation is any noncompliance with the clinical trial protocol, GCP, or SOP requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. These practices are consistent with ICH E6, sections:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3.
- 5.1 Quality Assurance and Quality Control, section 5.1.1.
- 5.20 Noncompliance, sections 5.20.1 and 5.20.2.

It is the responsibility of the study team to use continuous vigilance to identify and report deviations. All deviations must be addressed in study source documents, reported as required by the DSMC, COMIRB, and Genentech. Protocol deviations must be sent to the local IRB per institutional guidelines. The site PI/ study staff is responsible for knowing and adhering to their IRB requirements. Further details about the handling of protocol deviations will be included in the SOP.

11.1.10 Publication and Data Sharing Policy

This study will ensure that the public has access to the published results of this research.

As required, either for publication (the ICMJE or other publication policy), or according to U.S. regulations (Section 801 of the Food and Drug Administration Amendments Act of 2007) this clinical trial will be registered in a public trials registry including ClinicalTrials.gov, which is

sponsored by the National Library of Medicine, and the NCI CTRP Registry for cancer clinical trials.

11.1.11 CONFLICT OF INTEREST POLICY

Independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed.by the University of Colorado Denver's (UCD) Office of Regulatory Compliance Conflict of Interest and Commitment Management (COIC) program. Persons with a perceived conflict of interest will have such conflicts managed in a way that is appropriate to their participation in the trial. Conflict of Interest management plans are project-specific and are reviewed at least annually. UCD has integrated the institutional conflict of interest management program with its existing program.

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13 APPENDICES

13.1 APPENDIX 1: SAFETY REPORTING FAX COVER SHEET

Genentech
A Member of the Roche Group

SAFETY REPORTING FAX COVER SHEET

GENENTECH SUPPORTED RESEARCH

AE / SAE FAX No: (650) 238-6067

Genentech Study Number	
Principal Investigator	
Site Name	
Reporter name	
Reporter Telephone #	
Reporter Fax #	

Initial Report Date	[DD] / [MON] / [YY]
Follow-up Report Date	[DD] / [MON] / [YY]

Subject Initials (Enter a dash if patient has no middle name)	[ ] - [ ] - [ ]

SAE or Safety Reporting questions, contact Genentech Drug Safety: (888) 835-2555

PLEASE PLACE MEDWATCH REPORT or SAFETY REPORT BEHIND THIS COVER SHEET

13.2 Appendix 2: MedWatch 3500A Form

The MedWatch form can be accessed from the following link:
http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

13.3 Appendix 3: Content Required In The Line Listing Used For CTV (Case Transmission Verification)

Upon enrollment of patients for the study, a line listing is required to be provided on a quarterly basis to Genentech to perform reconciliation of Single Case Reports. Please send these listings directly to ctvistsa@gene.com.

The line listing should include the following information:

- CTV Period
- Product name / Study drug(s) received
- Protocol/Program number (if applicable)
- Patient number/other identifier
- Sponsor reference number of case
- Submission date to Genentech
- Patient initials, as applicable
- Event Term
- Seriousness
- Outcome
- Causality

13.4 Appendix 4: Content Required In The Line Listing Used For Exchange of Non-Serious Adverse Events (Non-Serious AEs)

A line listing is required to be provided on a quarterly basis to Genentech to perform reconciliation of nonserious events. Please send these listings directly to ctvistsa@gene.com.

The following fields must be populated in the Quarterly Line Listing for non-serious events:

- Protocol number
- Patient number
- Patient gender
- Date of birth
- Patient initials, as applicable
- AE term and/or Medical Dictionary for Regulatory Activities (MedDRA) term
- Seriousness of event and seriousness criteria
- Medical History and concomitant medications
- Onset date and end date (if applicable) of event
- Death date and cause (if applicable)
- Study drugs received
- First and last dose dates, dosage, frequency and indication of the suspected drug
- Cause(s) of event - Genentech/Roche Medicinal Product
- Cause(s) of event - other study drugs attribution (to be specified) and other attributions (to be • specified)
- AE Event description
- AE Event outcome
- Action taken
- Batch Lot number for each biologic product

13.5 Appendix 5: Anaphylaxis Precautions

Anaphylaxis Precautions

EQUIPMENT NEEDED

- Monitoring devices: ECG monitor, blood pressure monitor, oxygen saturation monitor, and thermometer
- Oxygen
- Epinephrine for intravenous, intramuscular, and endotracheal administration in accordance with institutional guidelines
- Antihistamines

- Corticosteroids
- Intravenous infusion solutions, tubing, catheters, and tape

PROCEDURES

In the event of a suspected anaphylactic reaction during study treatment infusion, the following procedures should be performed:

- Stop the study treatment infusion.
- Call for additional medical assistance.
- Maintain an adequate airway.
- Ensure that appropriate monitoring is in place, with continuous ECG and pulse oximetry monitoring, if possible.
- Administer antihistamines, epinephrine, or other medications as required by participant status and as directed by the physician in charge.
- Transfer patient/ escalate to a higher level of care as appropriate.
- Continue to observe the participant and document observations.

13.6 APPENDIX 6: RESPONSE EVALUATION CRITERIA IN SOLID TUMORS

Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1)

Selected sections from the Response Evaluation Criteria in Solid Tumors, Version 1.1 (RECIST v1.1), (Eisenhauer et al. 2009) are presented below, with slight modifications from the original publication and the addition of explanatory text as needed for clarity.[5]

TUMOR MEASURABILITY

At baseline, tumor lesions/lymph nodes will be categorized as measurable or non-measurable as described below. All measurable and non-measurable lesions should be assessed at screening and at subsequent protocol-specified tumor assessment timepoints. Additional assessments may be performed as clinically indicated for suspicion of progression.

[5] For clarity and for consistency within this document, the section numbers and cross-references to other sections within the article have been deleted and minor changes have been made.

DEFINITION OF MEASURABLE LESIONS

Tumor Lesions

Tumor lesions must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size as follows:

- 10 mm by computed tomography (CT) or magnetic resonance imaging (MRI) scan (CT/MRI scan slice thickness/interval ≤ 5 mm)
- 10-mm caliper measurement by clinical examination (lesions that cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

Malignant Lymph Nodes

To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in the short axis when assessed by CT scan (CT scan slice thickness recommended to be ≤ 5 mm). At baseline and followup, only the short axis will be measured and followed. Additional information on lymph node measurement is provided below (see "Identification of Target and Non-Target Lesions" and "Calculation of Sum of Diameters").

DEFINITION OF NON-MEASURABLE LESIONS

Non-measurable tumor lesions encompass small lesions (longest diameter < 10 mm or pathological lymph nodes with short axis ≥ 10 mm but < 15 mm) as well as truly non−measurable lesions. Lesions considered truly non-measurable include leptomeningeal disease, ascites, pleural or pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, peritoneal spread, and abdominal mass/abdominal organomegaly- identified by physical examination that is not measurable by reproducible imaging techniques.

SPECIAL CONSIDERATIONS REGARDING LESION MEASURABILITY

Bone lesions, cystic lesions, and lesions previously treated with local therapy require particular comment, as outlined below.

Bone Lesions:

- Technetium-99m bone scans, sodium fluoride positron emission tomography scans, and plain films are not considered adequate imaging techniques for measuring bone lesions. However, these techniques can be used to confirm the presence or disappearance of bone lesions.
- Lytic bone lesions or mixed lytic-blastic lesions with identifiable soft tissue components that can be evaluated by cross-sectional imaging techniques such as CT or MRI can be considered

measurable lesions if the soft tissue component meets the definition of measurability described above.

- Blastic bone lesions are non-measurable.

Cystic Lesions:

- Lesions that meet the criteria for radiographically defined simple cysts should not be considered malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.
- Cystic lesions thought to represent cystic metastases can be considered measurable lesions if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

Lesions with Prior Local Treatment:

- Tumor lesions situated in a previously irradiated area or in an area subjected to other loco-regional therapy are usually not considered measurable unless there has been demonstrated progression in the lesion.

METHODS FOR ASSESSING LESIONS

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during the study. Imaging-based evaluation should always be the preferred option.

CLINICAL LESIONS

Clinical lesions will only be considered measurable when they are superficial and ≥ 10 mm in diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is suggested.

CHEST X-RAY

Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT AND MRI SCANS

CT is the best currently available and reproducible method to measure lesions selected for response assessment. In this guideline, the definition of measurability of lesions on CT scan is based on the

assumption that CT slice thickness is ≤ 5 mm. When CT scans have slice thickness of > 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable.

If prior to enrollment it is known that a patient is unable to undergo CT scans with IV contrast because of allergy or renal insufficiency, the decision as to whether a non-contrast CT or MRI (without IV contrast) will be used to evaluate the patient at baseline and during the study should be guided by the tumor type under investigation and the anatomic location of the disease. For patients who develop contraindications to contrast after baseline contrast CT is done, the decision as to whether non-contrast CT or MRI (enhanced or non-enhanced) will be performed should also be based on the tumor type and the anatomic location of the disease, and should be optimized to allow for comparison with the prior studies if possible. Each case should be discussed with the radiologist to determine if substitution of these other approaches is possible and, if not, the patient should be considered not evaluable from that point forward. Care must be taken in measurement of target lesions and interpretation of non-target disease or new lesions on a different modality, since the same lesion may appear to have a different size using a new modality.

ENDOSCOPY, LAPAROSCOPY, ULTRASOUND, TUMOR MARKERS, CYTOLOGY, HISTOLOGY

Endoscopy, laparoscopy, ultrasound, tumor markers, cytology, and histology cannot be used for objective tumor evaluation.

ASSESSMENT OF TUMOR BURDEN

To assess objective response or future progression, it is necessary to estimate the overall tumor burden at baseline and use this as a comparator for subsequent measurements.

IDENTIFICATION OF TARGET AND NON-TARGET LESIONS

When more than one measurable lesion is present at baseline, all lesions up to a maximum of five lesions total (and a maximum of two lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline. This means that, for instances in which patients have only one or two organ sites involved, a maximum of two lesions (one site) and four lesions (two sites), respectively, will be recorded. Other lesions (albeit measurable) in those organs will be considered non-target lesions.

Target lesions should be selected on the basis of their size (lesions with the longest diameter) and should be representative of all involved organs, but in addition should lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement, in which circumstance the next largest lesion that can be measured reproducibly should be selected.

Lymph nodes merit special mention since they are normal anatomical structures that may be visible by imaging even if not involved by tumor. As noted above, pathological nodes that are defined as measurable and may be identified as target lesions must meet the criterion of a short axis of ≥ 15 mm by CT scan. Only the short axis of these nodes will contribute to the baseline sum. The short axis of the node is the diameter

normally used by radiologists to judge if a node is involved by solid tumor. Lymph node size is normally reported as two dimensions in the plane in which the image is obtained (for CT, this is almost always the axial plane; for MRI, the plane of acquisition may be axial, sagittal, or coronal). The smaller of these measures is the short axis. For example, an abdominal node that is reported as being 20 mm × 30 mm has a short axis of 20 mm and qualifies as a malignant, measurable node. In this example, 20 mm should be recorded as the node measurement. All other pathological nodes (those with short axis ≥ 10 mm but < 15 mm) should be considered non-target lesions. Nodes that have a short axis of < 10 mm are considered nonpathological and should not be recorded or followed.

All lesions (or sites of disease) not selected as target lesions (measurable or non-measurable), including pathological lymph nodes, should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required. It is possible to record multiple nontarget lesions involving the same organ as a single item on the Case Report Form (CRF) (e.g., "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

CALCULATION OF SUM OF DIAMETERS

A sum of the diameters (longest diameter for non-lymph node lesions, short axis for lymph node lesions) will be calculated for all target lesions at baseline and at each subsequent tumor assessment as a measure of tumor burden.

Measuring Lymph Nodes

Lymph nodes identified as target lesions should always have the actual short axis measurement recorded (measured in the same anatomical plane as the baseline examination), even if the node regresses to < 10 mm during the study. Thus, when lymph nodes are included as target lesions, the sum of diameters may not be zero even if complete response criteria are met, since a normal lymph node is defined as having a short axis of < 10 mm.

Measuring Lesions That Become Too Small to Measure

During the study, all target lesions (lymph node and non-lymph node) recorded at baseline should have their actual measurements recorded at each subsequent evaluation, even when very small (e.g., 2 mm). However, sometimes lesions or lymph nodes that are recorded as target lesions at baseline become so faint on CT scan that the radiologist may not feel comfortable assigning an exact measurement and may report them as being too small to measure. When this occurs, it is important that a value be recorded on the CRF, as follows:

- If it is the opinion of the radiologist that the lesion has likely disappeared, the measurement should be recorded as 0 mm.
- If the lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned and "too small to measure" should be ticked. (Note: It is less likely that this rule will be used for lymph nodes since they usually have a definable size when normal and are frequently surrounded by fat such as in the retroperitoneum; however, if a lymph node is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned in this circumstance as well and "too small to measure" should also be ticked).

To reiterate, however, if the radiologist is able to provide an actual measurement, that should be recorded, even if it is < 5 mm, and in that case "too small to measure" should not be ticked.

Measuring Lesions That Split or Coalesce on Treatment

When non−lymph node lesions fragment, the longest diameters of the fragmented portions should be added together to calculate the sum of diameters. Similarly, as lesions coalesce, a plane between them may be maintained that would aid in obtaining maximal diameter measurements of each individual lesion. If the lesions have truly coalesced such that they are no longer separable, the vector of the longest diameter in this instance should be the maximum longest diameter for the coalesced lesion.

EVALUATION OF NON-TARGET LESIONS

Measurements are not required for non-target lesions, except that malignant lymph node non-target lesions should be monitored for reduction to < 10 mm in short axis. Non-target lesions should be noted at baseline and should be identified as "present" or "absent" and (in rare cases) may be noted as "indicative of progression" at subsequent evaluations. In addition, if a lymph node lesion shrinks to a non-malignant size (short axis < 10 mm), this should be captured on the CRF as part of the assessment of non-target lesions.

RESPONSE CRITERIA

CRITERIA FOR TARGET LESIONS

Definitions of the criteria used to determine objective tumor response for target lesions are provided below:

- Complete response (CR): Disappearance of all target lesions

  Any pathological lymph nodes must have reduction in short axis to < 10 mm.
- Partial response (PR): At least a 30% decrease in the sum of diameters of all target lesions, taking as reference the baseline sum of diameters, in the absence of CR
- Progressive disease (PD): At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum of diameters at prior timepoints (including baseline)

  In addition to the relative increase of 20%, the sum of diameters must also demonstrate an absolute increase of ≥ 5 mm.
- Stable disease (SD): Neither sufficient shrinkage to qualify for CR or PR nor sufficient increase to qualify for PD

CRITERIA FOR NON-TARGET LESIONS

Definitions of the criteria used to determine the tumor response for the group of non-target lesions are provided below. While some non-target lesions may actually be measurable, they need not be measured and instead should be assessed only qualitatively at the timepoints specified in the schedule of activities.

- CR: Disappearance of all non-target lesions and (if applicable) normalization of tumor marker level
  All lymph nodes must be non-pathological in size (< 10 mm short axis).

- Non-CR/Non-PD: Persistence of one or more non-target lesions and/or (if applicable) maintenance of tumor marker level above the normal limits

- PD: Unequivocal progression of existing non-target lesions

SPECIAL NOTES ON ASSESSMENT OF PROGRESSION OF NON-TARGET LESIONS

Patients with Measurable and Non-Measurable Disease

For patients with both measurable and non-measurable disease to achieve unequivocal progression on the basis of the non-target lesions, there must be an overall level of substantial worsening in non-target lesions in a magnitude that, even in the presence of SD or PR in target lesions, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. A modest increase in the size of one or more nontarget lesions is usually not sufficient to qualify for unequivocal progression status. The designation of overall progression solely on the basis of change in non-target lesions in the face of SD or PR in target lesions will therefore be extremely rare.

Patients with Non-Measurable Disease Only

For patients with non-measurable disease only, the same general concepts apply as noted above. However, in this instance there is no measurable disease assessment to factor into the interpretation of an increase in non-measurable disease burden. Because worsening in non-measurable disease cannot be easily quantified (by definition, if all lesions are truly non-measurable), a useful test that can be applied when assessing patients for unequivocal progression is to consider if the increase in overall disease burden based on the change in non-measurable disease is comparable in magnitude to the increase that would be required to declare PD for measurable disease, that is, an increase in tumor burden representing an additional 73% increase in volume (which is equivalent to a 20% increase in diameter in a measurable lesion). Examples include an increase in a pleural effusion from "trace" to "large" or an increase in lymphangitic disease from localized to widespread. If unequivocal progression is seen, the patient should be considered to have had overall PD at that point. While it would be ideal to have objective criteria to apply to non-measurable disease, the very nature of that disease makes it impossible to do so; therefore, the increase must be substantial.

NEW LESIONS

The appearance of new malignant lesions denotes disease progression; therefore, some comments on detection of new lesions are important. There are no specific criteria for the identification of new radiographic lesions; however, the finding of a new lesion should be unequivocal, that is, not attributable to differences in scanning technique, change in imaging modality, or findings thought to represent something other than tumor (for example, some "new" bone lesions may be simply healing or flare of preexisting lesions). This is particularly important when the patient's baseline lesions show PR or CR. For example, necrosis of a liver lesion may be reported on a CT scan report as a "new" cystic lesion, which it is not.

A lesion identified during the study in an anatomical location that was not scanned at baseline is considered a new lesion and will indicate disease progression.

If a new lesion is equivocal, for example because of its small size, continued therapy and follow-up evaluation will clarify if it represents truly new disease. If repeat scans confirm there is definitely a new lesion, progression should be declared using the date of the initial scan.

CRITERIA FOR OVERALL RESPONSE AT A SINGLE TIMEPOINT

Table 1 provides a summary of the overall response status calculation at each response assessment timepoint for patients who have measurable disease at baseline.

Table 1 Criteria for Overall Response at a Single Timepoint: Patients with Target Lesions (with or without Non-Target Lesions)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/non-PD	No	PR
CR	Not all evaluated	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or no	PD
Any	PD	Yes or no	PD
Any	Any	Yes	PD

CR = complete response; NE = not evaluable; PD = progressive disease; PR = partial response; SD = stable disease.

MISSING ASSESSMENTS AND NOT-EVALUABLE DESIGNATION

When no imaging/measurement is done at all at a particular timepoint, the patient is not evaluable at that timepoint. If measurements are made on only a subset of target lesions at a timepoint, usually the case is also considered not evaluable at that timepoint, unless a convincing argument can be made that the contribution of the individual missing lesions would not change the assigned timepoint response. This would be most likely to happen in the case of PD. For example, if a patient had a baseline sum of 50 mm with three measured lesions and during the study only two lesions were assessed, but those gave a sum of 80 mm, the patient will have achieved PD status, regardless of the contribution of the missing lesion.

SPECIAL NOTES ON RESPONSE ASSESSMENT

Patients with a global deterioration in health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "symptomatic deterioration." Every effort should be made to document objective progression even after discontinuation of treatment. Symptomatic deterioration is not a descriptor of an objective response; it is a reason for stopping study therapy. The objective response status of such patients is to be determined by evaluation of target and nontarget lesions as shown in Table 1.

For equivocal findings of progression (e.g., very small and uncertain new lesions; cystic changes or necrosis in existing lesions), treatment may continue until the next scheduled assessment. If at the next scheduled assessment, progression is confirmed, the date of progression should be the earlier date when progression was suspected.

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13.7 Appendix 7: Preexisting Autoimmune Diseases and Immune Deficiencies

Preexisting Autoimmune Diseases and Immune Deficiencies

Patients should be carefully questioned regarding their history of acquired or congenital immune deficiencies or autoimmune disease. Patients with any history of immune deficiencies or autoimmune disease listed in the table below are excluded from participating in the study. Possible exceptions to this exclusion could be patients with a medical history of such entities as atopic disease or childhood arthralgias where the clinical suspicion of autoimmune disease is low. Patients with a history of autoimmune-related hypothyroidism on a stable dose of thyroid replacement hormone or patients with controlled Type 1 diabetes mellitus who are on an insulin regimen may be eligible for this study. In addition, transient autoimmune manifestations of an acute infectious disease that resolved upon treatment of the infectious agent are not excluded (e.g., acute Lyme arthritis). Caution should be used when considering atezolizumab and tiragolumab for patients who have previously experienced a severe or life-threatening skin adverse reaction or pericardial disorder while receiving another immunostimulatory anti-cancer agent.

Autoimmune Diseases and Immune Deficiencies

● Acute disseminated encephalomyelitis ● Addison disease ● Ankylosing spondylitis ● Antiphospholipid antibody syndrome ● Aplastic anemia ● Autoimmune hemolytic anemia ● Autoimmune hepatitis ● Autoimmune hypoparathyroidism ● Autoimmune hypophysitis ● Autoimmune myelitis ● Autoimmune myocarditis ● Autoimmune oophoritis ● Autoimmune orchitis ● Autoimmune thrombocytopenic purpura ● Behçet disease ● Bullous pemphigoid ● Chronic fatigue syndrome ● Chronic inflammatory demyelinating polyneuropathy ● Churg-Strauss syndrome ● Crohn disease	● Dermatomyositis ● Diabetes mellitus type 1 ● Dysautonomia ● Epidermolysis bullosa acquisita ● Gestational pemphigoid ● Giant cell arteritis ● Goodpasture syndrome ● Granulomatosis with polyangiitis ● Graves disease ● Guillain-Barré syndrome ● Hashimoto disease ● IgA nephropathy ● Inflammatory bowel disease ● Interstitial cystitis ● Kawasaki disease ● Lambert-Eaton myasthenia syndrome ● Lupus erythematosus ● Lyme disease, chronic ● Meniere syndrome ● Mooren ulcer ● Morphea ● Multiple sclerosis ● Myasthenia gravis	● Neuromyotonia ● Opsoclonus myoclonus syndrome ● Optic neuritis ● Ord thyroiditis ● Pemphigus ● Pernicious anemia ● Polyarteritis nodosa ● Polyarthritis ● Polyglandular autoimmune syndrome ● Primary biliary cholangitis ● Psoriasis ● Reiter syndrome ● Rheumatoid arthritis ● Sarcoidosis ● Scleroderma ● Sjögren syndrome ● Stiff-Person syndrome ● Takayasu arteritis ● Ulcerative colitis ● Vitiligo ● Vogt-Koyanagi-Harada disease

13.8 APPENDIX 8: GUIDELINES FOR ADVERSE EVENTS ASSOCIATED WITH ATEZOLIZUMAB AND TIRAGOLUMAB

Risks Associated with Atezolizumab and/or Tiragolumab and Guidelines for Management of Adverse Events Associated with Atezolizumab and/or Tiragolumab

Toxicities associated or possibly associated with atezolizumab and/or tiragolumab treatment should be managed according to standard medical practice. Additional tests, such as autoimmune serology or biopsies, should be used to evaluate for a possible immunogenic etiology, when clinically indicated.

Although most immune-mediated adverse events observed with immunomodulatory agents have been mild and self-limiting, such events should be recognized early and treated promptly to avoid potential major complications. Discontinuation of atezolizumab and/or tiragolumab may not have an immediate therapeutic

effect, and in severe cases, immune-mediated toxicities may require acute management with topical corticosteroids, systemic corticosteroids, or other immunosuppressive agents.

The following are general recommendations for management of any other adverse events that may occur and are not specifically listed in the following subsections:

- Patients and family caregivers should receive timely and up-to-date information about immunotherapies, their mechanism of action, and the clinical profile of possible immune-related adverse events prior to initiating therapy and throughout treatment and survival follow-up. There should be a high level of suspicion that new symptoms are treatment related.
- In general, atezolizumab and tiragolumab therapy should be continued with close monitoring for Grade 1 toxicities, with the exception of some neurologic toxicities.
- Consider holding atezolizumab and tiragolumab for most Grade 2 toxicities and resume when symptoms and/or laboratory values resolve to Grade 1 or better. Corticosteroids (initial dose of 0.51 mg/kg/day of prednisone or equivalent) may be administered.
- For Grade 2 recurrent or persistent (lasting for more than 5 days) events, treat as a Grade 3 event.
- Hold atezolizumab and tiragolumab for Grade 3 toxicities and initiate treatment with high-dose corticosteroids (1-2 mg/kg/day prednisone or equivalent). Corticosteroids should be tapered over 1 month to 10 mg/day oral prednisone or equivalent, before atezolizumab and tiragolumab can be resumed. If symptoms do not improve within 48 to 72 hours of high-dose corticosteroid use, other immunosuppressants may be offered for some toxicities.
- In general, Grade 4 toxicities warrant permanent discontinuation of atezolizumab and tiragolumab treatment, with the exception of endocrinopathies that are controlled by hormone-replacement therapy.
- The investigator should consider the benefit-risk balance for a given patient prior to further administration of atezolizumab and/or tiragolumab. Resumption of atezolizumab and/or tiragolumab 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 and/or tiragolumab should be based on the investigator's assessment of the benefits and risks and documented by the investigator.

MANAGEMENT GUIDELINES

Suspected immune-related toxicities should be managed according to standard of care practices and per the investigator's discretion. Alternative etiologies should be evaluated as appropriate (e.g., consider etiologies related to infection, malignancy, or pulmonary embolism in addition to an immune-related event for pulmonary presentations).

For suspected immune-related adverse events, management of bevacizumab therapy should be determined per the investigator's discretion, with consideration of possible overlapping AEs and risks, potential need

for invasive procedures/ surgeries, and overall fitness for systemic therapy. The Sponsor-Investigator is available for questions as needed.

PULMONARY EVENTS

Pulmonary events may present as new or worsening cough, chest pain, fever, dyspnea, fatigue, hypoxia, pneumonitis, and pulmonary infiltrates. Patients will be assessed for pulmonary signs and symptoms throughout the study.

Table 1 Management Guidelines for Pulmonary Events, Including Pneumonitis

Event	Management
Pulmonary event, Grade 1	● Continue atezolizumab and tiragolumab and monitor closely. ● Re-evaluate on serial imaging. ● Consider patient referral to pulmonary specialist. ● For Grade 1 pneumonitis, consider withholding atezolizumab and tiragolumab.
Pulmonary event, Grade 2	● Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset. [a] ● Refer patient to pulmonary and infectious disease specialists and consider bronchoscopy or BAL with or without transbronchial biopsy. ● Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day oral prednisone. ● If event resolves to Grade 1 or better, resume atezolizumab and tiragolumab. [b] ● If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. [c, d] ● For recurrent events or events with no improvement after 48−72 hours of corticosteroids, treat as a Grade 3 or 4 event.
Pulmonary event, Grade 3 or 4	● Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. [c, d] ● Oral or IV broad-spectrum antibiotics should be administered in parallel to the immunosuppressive treatment. ● Bronchoscopy or BAL with or without transbronchial biopsy is recommended. ● Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day IV methylprednisolone. ● 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 and tiragolumab 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 the investigator's benefit-risk assessment 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 and tiragolumab can be resumed. [c] Resumption of atezolizumab and tiragolumab 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 and/or tiragolumab should be based on the investigator's benefit-risk assessment and documented by the investigator. [d] In case of pneumonitis, atezolizumab should not be resumed after permanent discontinuation.

HEPATIC EVENTS

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

Table 2 Management Guidelines for Hepatic Events

Event	Management
Guidelines for patients <u>without</u> hepatocellular carcinoma	
Hepatic event, Grade 1	● Continue atezolizumab and tiragolumab. ● 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 and tiragolumab 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 and tiragolumab. [b] ● If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. [c]
Hepatic event, Grade 3 or 4	● Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. [c] ● 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 and tiragolumab 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 the investigator's benefit-risk assessment 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 and tiragolumab can be resumed. [c] Resumption of atezolizumab and tiragolumab 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 and/or tiragolumab should be based on the investigator's benefit-risk assessment and documented by the investigator.

GASTROINTESTINAL EVENTS

Management guidelines for diarrhea or colitis are provided in Table 3.

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.

Table 3 Management Guidelines for Gastrointestinal Events (Diarrhea or Colitis)

Event	Management
Diarrhea or colitis, Grade 1	● Continue atezolizumab and tiragolumab. ● Initiate symptomatic treatment. ● Endoscopy is recommended if symptoms persist for > 7 days. ● Monitor closely.
Diarrhea or colitis, Grade 2	● Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset.[a] ● Initiate symptomatic treatment. ● If strong clinical suspicion for immune-mediated colitis, start empiric IV steroids while waiting for definitive diagnosis. ● 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 the event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. ● If event resolves to Grade 1 or better, resume atezolizumab and tiragolumab.[b] ● If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact the principal investigator.[c]

Diarrhea or colitis, Grade 3	● Withhold atezolizumab and tiragolumab 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 does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. ● If event resolves to Grade 1 or better, resume atezolizumab and tiragolumab. [b] ● If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. [c]
Diarrhea or colitis, Grade 4	● Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. [c] ● 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 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 and tiragolumab 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 the investigator's benefit-risk assessment 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 and tiragolumab can be resumed. [c] Resumption of atezolizumab and tiragolumab 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 and/or tiragolumab should be based on the investigator's benefit-risk assessment and documented by the investigator.

ENDOCRINE EVENTS

Patients with unexplained symptoms such as headache, fatigue, myalgias, impotence, constipation, or mental status changes should be investigated for the presence of thyroid, pituitary, or adrenal endocrinopathies. Patients should be referred to an endocrinologist if an endocrinopathy is suspected. Thyroid-stimulating hormone (TSH) and free triiodothyronine and thyroxine 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 magnetic resonance imaging (MRI) of the brain (with detailed pituitary sections) may help to differentiate primary pituitary insufficiency from primary adrenal insufficiency.

Table 4 Management Guidelines for Endocrine Events

Event	Management
Grade 1 hypothyroidism	● Continue atezolizumab and tiragolumab. ● Initiate treatment with thyroid replacement hormone. ● Monitor TSH closely.
Grade 2 hypothyroidism	● Consider withholding atezolizumab and tiragolumab. ● Initiate treatment with thyroid replacement hormone. ● Monitor TSH closely. ● Consider patient referral to endocrinologist. ● Resume atezolizumab and tiragolumab when symptoms are controlled, and thyroid function is improving.
Grade 3 and 4 hypothyroidism	● Withhold atezolizumab and tiragolumab. ● Initiate treatment with thyroid replacement hormone. ● Monitor TSH closely. ● Refer to an endocrinologist. ● Admit patient to the hospital for developing myxedema (bradycardia, hypothermia, and altered mental status). ● Resume atezolizumab and tiragolumab when symptoms are controlled, and thyroid function is improving. ● Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator for life-threatening immune-mediated hypothyroidism. [c]
Grade 1 hyperthyroidism	**TSH ≥ 0.1 mU/L and < 0.5 mU/L:** ● Continue atezolizumab and tiragolumab. ● Monitor TSH every 4 weeks. ● Consider patient referral to endocrinologist. **TSH < 0.1 mU/L:** ● Follow guidelines for Grade 2 hyperthyroidism. ● Consider patient referral to endocrinologist.

Event	Management
Grade 2 hyperthyroidism	● Consider withholding atezolizumab and tiragolumab. ● Initiate treatment with anti-thyroid drug such as methimazole or carbimazole as needed. ● Consider patient referral to endocrinologist. ● Resume atezolizumab and tiragolumab when symptoms are controlled, and thyroid function is improving.
Grade 3 and 4 hyperthyroidism	● Withhold atezolizumab and tiragolumab. ● Initiate treatment with anti-thyroid drugs such as methimazole or carbimazole as needed. ● Refer to an endocrinologist. ● Resume atezolizumab and tiragolumab when symptoms are controlled, and thyroid function is improving. ● Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator for life-threatening immune-mediated hyperthyroidism. [c]
Symptomatic adrenal insufficiency, Grade 2−4	● Withhold atezolizumab and tiragolumab 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 and tiragolumab. [b] ● If event does not resolve to Grade 1 or better or patient is not stable on replacement therapy while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. [c]
Hyperglycemia, Grade 1 or 2	● Continue atezolizumab and tiragolumab. ● 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 and tiragolumab. ● Initiate treatment with insulin. ● Evaluate for diabetic ketoacidosis and manage as per institutional guidelines. ● Monitor for glucose control. ● Resume atezolizumab and tiragolumab when symptoms resolve, and glucose levels are stable.
Event	Management
Hypophysitis (panhypopituitarism), Grade 2 or 3	● Withhold atezolizumab and tiragolumab 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 and tiragolumab. [b] ● If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. [c] ● For recurrent hypophysitis, treat as a Grade 4 event.
Hypophysitis (panhypopituitarism), Grade 4	● Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. [c] ● 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 and tiragolumab 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 the investigator's benefit-risk assessment 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 and tiragolumab can be resumed. [c] Resumption of atezolizumab and tiragolumab 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 and/or tiragolumab should be based on the investigator's benefit-risk assessment and documented by the investigator.

OCULAR EVENTS

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

Table 5 Management Guidelines for Ocular Events

Event	Management
Ocular event, Grade 1	● Continue atezolizumab and tiragolumab. ● 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 and tiragolumab 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 and tiragolumab. [b] ● If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. [c]
Ocular event, Grade 3 or 4	● Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. [c] ● 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 and tiragolumab 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

the investigator's benefit-risk assessment 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 and tiragolumab can be resumed.

[c] Resumption of atezolizumab and tiragolumab 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 and/or tiragolumab should be based on the investigator's benefit-risk assessment and documented by the investigator.

IMMUNE-MEDIATED CARDIAC EVENTS

IMMUNE-MEDIATED MYOCARDITIS

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-type 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 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.

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. Withhold treatment with atezolizumab for Grade 1 pericarditis and conduct a detailed cardiac evaluation to determine the etiology and manage accordingly.

Table 6 Management Guidelines for Immune-Mediated Cardiac Events

Event	Management
Immune-mediated myocarditis, Grades 2−4 Immune-mediated pericardial disorders, Grades 2-4	● Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. ● 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

No premedication is indicated for the administration of Cycle 1 of atezolizumab or tiragolumab. However, patients who experience an infusion-related reaction (IRR) with the Day 1, Cycle 1 infusion of tiragolumab or atezolizumab may receive premedication with antihistamines, antipyretic medications, 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 tiragolumab and atezolizumab. These reactions, which are thought to be due to release of cytokines and/or other chemical mediators, occur within 24 hours of atezolizumab or tiragolumab administration and are generally mild to moderate in severity. Guidelines for the medical management of IRRs during Cycle 1 are provided below. For subsequent cycles, IRRs should be managed according to institutional guidelines.

Table 7 Management Guidelines for Infusion-Related Reactions

Event	Management
IRR, Grade 1	● Reduce infusion rate to half the rate being given at the time of event onset. ● After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. ● If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.
IRR, Grade 2	● Interrupt infusion. ● Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids). ● After symptoms have resolved to baseline, resume infusion at half the rate being given at the time of event onset. ● For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic medications, and/or analgesics and monitor closely for IRRs.
IRR, Grade 3 or 4	● Stop infusion. ● Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids). ● Permanently discontinue atezolizumab or tiragolumab and contact the principal investigator. [a]

IRR = infusion-related reaction.

[a] Resumption of atezolizumab or tiragolumab may be considered in patients who are deriving benefit and have fully recovered from the event. The decision to re-challenge patients with atezolizumab and/or tiragolumab should be based on the investigator's benefit-risk assessment and documented by the investigator.

CYTOKINE-RELEASE SYNDROME

No premedication is indicated for the administration of Cycle 1 of atezolizumab or tiragolumab. However, patients who experience CRS with atezolizumab or tiragolumab may receive premedication with antihistamines, antipyretic medications, and/or analgesics (e.g., acetaminophen) for subsequent infusions.

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.

Severe SARS-CoV-2 infection appears to be associated with a CRS involving the inflammatory cytokines interleukin (IL)-6, IL-10, IL-2, and IFN-γ (Merad and Martin 2020). If a patient develops suspected CRS during the study, a differential diagnosis should include SARS-CoV-2 infection, which should be confirmed or refuted through assessment of exposure history, appropriate laboratory testing, and clinical or radiologic evaluations per investigator's judgment. If a diagnosis of SARS-CoV-2 infection is confirmed, the disease should be managed as per local or institutional guidelines.

Table 8 Management Guidelines for Cytokine-Release Syndrome

Event	Management

Grade 1 [a] Fever [b] with or without constitutional symptoms	● Immediately interrupt 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 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, antipyretic medications, and/or analgesics, and monitor closely for CRS.
Grade 2 [a] Fever [b] with at least one of the following: ● Hypotension not requiring vasopressors	● Immediately interrupt 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]

● Hypoxia requiring lowflow oxygen [d] by nasal cannula or blow-by	● 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 as described in this appendix. ● Consider IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). ● Consider anti-cytokine therapy. ● 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 or tiragolumab and contact the principal investigator. ● If symptoms resolve to Grade 1 or better for 3 consecutive days, the next dose of atezolizumab or tiragolumab may be administered. For subsequent infusions, consider administration of oral premedication with antihistamines, antipyretic medications, and/or analgesics and monitor closely for 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 at least one of the following: ● Hypotension requiring a vasopressor (with or without vasopressin) ● Hypoxia requiring highflow oxygen [d] by nasal cannula, face mask, nonrebreather mask, or Venturi mask	● Permanently discontinue atezolizumab or tiragolumab and contact the principal investigator. [e] ● Administer symptomatic treatment. [c] ● For hypotension, administer IV fluid bolus and vasopressor as needed. ● 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 as described in this appendix. ● Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). ● Consider anti-cytokine therapy. ● 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 at least one of the following: ● Hypotension requiring multiple vasopressors (excluding vasopressin)	● Permanently discontinue atezolizumab or tiragolumab and contact the principal investigator. [e] ● Administer symptomatic treatment. [c]
● Hypoxia requiring oxygen by positive pressure (e.g., CPAP, BiPAP, intubation and mechanical ventilation)	● 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 as described in this appendix. ● Administer IV corticosteroids (e.g., methylprednisolone 2 mg/kg/day or dexamethasone 10 mg every 6 hours). ● Consider anti-cytokine therapy. For patients who are refractory to anticytokine 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 = cytokinerelease syndrome; CTCAE = Common Terminology Criteria for Adverse Events; eCRF = electronic

Case Report Form; HLH = hemophagocytic lymphohistiocytosis; ICU = intensive care unit; MAS = macrophage activation syndrome; NCCN = National Cancer Comprehensive Network; NCI = National Cancer Institute.

The management guidelines have been adapted from the NCCN guidelines for the management of CAR Tcell−related toxicities (Version 2.2019).

[a] Grading system for management guidelines is based on the ASTCT CRS Consensus Grading Scale. NCI CTCAE v5.0 and the ASTCT CRS Consensus Grading Scale should be used when reporting severity of CRS on the Adverse Event eCRF. NCI CTCAE v5.0 should be used when reporting severity of organ toxicities associated with CRS on the dedicated Cytokine Release Syndrome 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, antipyretic medications, 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] Resumption of atezolizumab or tiragolumab may be considered in patients who are deriving benefit and have fully recovered from the event. The decision to re-challenge patients with atezolizumab or tiragolumab should be based on the investigator's benefit-risk assessment and documented by the investigator. For subsequent infusions, administer oral premedication with antihistamines, antipyretic medications, and/or analgesics, and monitor closely for CRS. Premedication with corticosteroids and extending the infusion time may also be considered after assessing the benefit-risk ratio. [f] Refer to Riegler et al. (2019) for information on experimental treatments for CRS.

PANCREATIC EVENTS

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.

Table 9 Management Guidelines for Pancreatic Events, Including Pancreatitis

Event	Management

Amylase and/or lipase elevation, Grade 2	**Amylase and/or lipase > 1.5−2.0 × ULN:** ● Continue atezolizumab and tiragolumab. ● 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 and tiragolumab 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 and tiragolumab. [b] ● If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. [c] ● For recurrent events, permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. [c]
Immune-mediated pancreatitis, Grade 2 or 3	● Withhold atezolizumab and tiragolumab 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 and tiragolumab. [b] ● If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. [c] ● For recurrent events, permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. [c]
Immune-mediated pancreatitis, Grade 4	● Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. [c] ● 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.
Event	Management

	● 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 and tiragolumab 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 the investigator's benefit-risk assessment 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 and tiragolumab can be resumed. [c] Resumption of atezolizumab and tiragolumab 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

and/or tiragolumab should be based on the investigator's benefit-risk assessment and documented by the investigator.

DERMATOLOGIC EVENTS

The majority of cases of rash reported with the use of atezolizumab and/or tiragolumab were mild in severity and self-limiting, with or without pruritus. Although uncommon, cases of severe cutaneous adverse reactions such as Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported with atezolizumab. A dermatologist should evaluate persistent and/or severe rash or pruritus. A biopsy should be considered unless contraindicated.

Table 10 Management Guidelines for Dermatologic Events

Event	Management
Dermatologic event, Grade 1	● Continue atezolizumab and tiragolumab. ● Consider treatment with topical corticosteroids and/or other symptomatic therapy (e.g., antihistamines).
Dermatologic event, Grade 2	● Continue atezolizumab and tiragolumab. ● 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. ● If unresponsive to topical corticosteroids, consider oral prednisone 0.5 mg/kg/day.
Dermatologic event, Grade 3	● Withhold atezolizumab and tiragolumab 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 and tiragolumab. [b] ● If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. [c]
Dermatologic event, Grade 4	● Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. [c]

Stevens-Johnson syndrome or toxic epidermal necrolysis (any grade)	**Additional guidance for Stevens-Johnson syndrome or toxic epidermal necrolysis:** ● Withhold atezolizumab and tiragolumab 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, permanently discontinue atezolizumab and tiragolumab.

[a] Atezolizumab and tiragolumab 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 the investigator's benefit-risk assessment 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 and tiragolumab can be resumed. [c] Resumption of atezolizumab and tiragolumab 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 and/or tiragolumab should be based on the investigator's benefit-risk assessment and documented by the investigator.

NEUROLOGIC DISORDERS

Patients may present with signs and symptoms of sensory and/or motor neuropathy. Diagnostic workup is essential for an accurate characterization to differentiate between alternative etiologies.

Table 11 Management Guidelines for Neurologic Disorders

Event	Management
Immune-mediated neuropathy, Grade 1	● Continue atezolizumab and tiragolumab. ● 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 and tiragolumab 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 and tiragolumab. [b] ○ If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. [c] ● For facial paresis: ○ If event resolves fully, resume atezolizumab and tiragolumab [b] ● If event does not resolve fully while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. [c]
Immune-mediated neuropathy, including facial paresis, Grade 3 or 4	● Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. [c] ● Refer patient to neurologist. ● Initiate treatment as per institutional guidelines.
Myasthenia gravis and Guillain-Barré syndrome (any grade)	● Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. ● 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 and tiragolumab 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 the investigator's benefit-risk assessment 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 and tiragolumab can be resumed.

[c] Resumption of atezolizumab and tiragolumab 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 and/or tiragolumab should be based on the investigator's benefit-risk assessment and documented by the investigator.

Table 12 Management Guidelines for Immune-Mediated Myelitis

Event	Management
Immune-mediated myelitis, Grade 1	● Continue atezolizumab and tiragolumab unless symptoms worsen or do not improve. ● Investigate etiology and refer patient to a neurologist.
Immune-mediated myelitis, Grade 2	● Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. ● 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 and tiragolumab and contact the principal investigator. ● Refer patient to a neurologist. ● Initiate treatment as per institutional guidelines.

IMMUNE-MEDIATED MENINGOENCEPHALITIS

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 Table 13.

Table 13 Management Guidelines for Immune-Mediated Meningoencephalitis

Event	Management
Immune-mediated meningoencephalitis, all grades	● Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. ● Withold bevacizumab. ● 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

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 nonsteroidal 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 Table 14.

Table 14 Management Guidelines for Renal Events

Event	Management
Renal event, Grade 1	● Continue atezolizumab and tiragolumab. ● Monitor kidney function, including creatinine and urine protein, closely until values resolve to within normal limits or to baseline values.
Renal event, Grade 2	● Withhold atezolizumab and tiragolumab 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 and tiragolumab. [b] ● If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. [c]
Renal event, Grade 3 or 4	● Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. ● 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 and tiragolumab 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 the investigator's benefit-risk assessment 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 and tiragolumab can be resumed. [c] Resumption of atezolizumab and tiragolumab 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 and/or tiragolumab should be based on the investigator's benefit-risk assessment and documented by the investigator.

IMMUNE-MEDIATED MYOSITIS

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 possible myositis should be referred to a rheumatologist or neurologist. Patients with possible myositis should be monitored for signs of myocarditis.

Table 15 Management Guidelines for Immune-Mediated Myositis

Event	Management
Immune-mediated myositis, Grade 1	● Continue atezolizumab and tiragolumab. ● Refer patient to rheumatologist or neurologist. ● Initiate treatment as per institutional guidelines.
Immune-mediated myositis, Grade 2	● Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset [a] and contact the principal investigator. ● Refer patient to rheumatologist or neurologist. ● Initiate treatment as per institutional guidelines. ● 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 corticosteroids are initiated and event does not improve within 48 hours after initiating corticosteroids, consider adding an immunosuppressive agent. ● If event resolves to Grade 1 or better, resume atezolizumab and tiragolumab. [b] ● If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. [c]

Immune-mediated myositis, Grade 3	● Withhold atezolizumab and tiragolumab for up to 12 weeks after event onset [a] and contact the principal investigator. ● Refer patient to rheumatologist or neurologist. ● Initiate treatment as per institutional guidelines. ● Respiratory support may be required in more severe cases. ● Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); 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, resume atezolizumab and tiragolumab. [b]
Event	Management
	● If event does not resolve to Grade 1 or better while withholding atezolizumab and tiragolumab, permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. [c] ● For recurrent events, treat as a Grade 4 event. Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. [c]
Immune-mediated myositis, Grade 4	● Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. [c] ● Refer patient to rheumatologist or neurologist. ● Initiate treatment as per institutional guidelines. ● Respiratory support may be required in more severe cases. ● Initiate treatment with corticosteroids equivalent to 1−2 mg/kg/day IV methylprednisolone, or higher-dose bolus if patient is severely compromised (e.g., cardiac or respiratory symptoms, dysphagia, or weakness that severely limits mobility); 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 and tiragolumab 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 the investigator's benefit-risk assessment 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 and tiragolumab can be resumed. [c] Resumption of atezolizumab and tiragolumab 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 and/or tiragolumab should be based on the investigator's benefit-risk assessment and documented by the investigator.

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).

Clinical and laboratory features of severe CRS overlap with HLH, and HLH should be considered when CRS presentation is atypical or prolonged.

Patients with suspected HLH should be diagnosed according to published criteria by McClain and Eckstein (2014). 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/µL) ○ ANC < 1.0×10^9/L (1000/µL)
- 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 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/µL) ○ 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 Table 16.

Table 16 Management Guidelines for Suspected Hemophagocytic Lymphohistiocytosis or Macrophage Activation Syndrome

Event	Management
Suspected HLH or MAS	● Permanently discontinue atezolizumab and tiragolumab and contact the principal investigator. ● Consider patient referral to hematologist. ● Initiate supportive care, including intensive care monitoring if indicated per institutional guidelines. ● Consider initiation of IV corticosteroids, an immunosuppressive agent, and/or anti-cytokine therapy. ● If event does not respond to treatment within 24 hours, contact the principal investigator and initiate treatment as appropriate according to published guidelines (La Rosée 2015; Schram and Berliner 2015; La Rosée et al. 2019). ● If event resolves to Grade 1 or better, taper corticosteroids over ≥ 1 month.

HLH = hemophagocytic lymphohistiocytosis; MAS = macrophage activation syndrome.

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13.9 APPENDIX 9: GUIDELINES FOR ADVERSE EVENTS ASSOCIATED WITH BEVACIZUMAB

Suspected bevacizumab-related toxicities should be managed according to standard of care practices and per the investigator's discretion. Alternative etiologies should be evaluated as appropriate. These guidelines are intended to inform rather than supersede an investigator's clinical judgement and assessment of the benefit-risk balance when managing individual cases.

For suspected bevacizumab-related adverse events, atezolizumab and tiragolumab therapy should be determined per the investigator's discretion, with consideration of possible overlapping AEs and risks, as well as fitness for systemic therapy. The Sponsor-Investigator is available for questions as needed.

Table 1 Management Guidelines for Infusion-Related Reactions

No premedication is indicated for the administration of Cycle 1 of bevacizumab. However, patients who experience an infusion-related reaction (IRR) with the Day 1, Cycle 1 infusion of bevacizumab may receive premedication with antihistamines, antipyretic medications, and/or analgesics (e.g., acetaminophen) for subsequent infusions.

Event	Management
IRR, Grade 1	● Reduce infusion rate to ≤ 50%. ● After the event has resolved, the investigator should wait for 30 minutes while delivering the infusion at the reduced rate. ● If the infusion is tolerated at the reduced rate for 30 minutes after symptoms have resolved, the infusion rate may be increased to the original rate.
IRR, Grade 2	● Reduce the infusion rate to ≤ 50% or interrupt infusion at the discretion of the investigator per medical judgement. ● Administer symptomatic treatment (e.g., oral or IV antihistamine, antipyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids) per the clinician's discretion. ● If the infusion is interrupted, it may be resumed at ≤ 50% of the rate prior to the reaction after the patient's symptoms have adequately resolved and increased in 50% increments up to the full rate if well tolerated.
IRR, Grade 3 or 4	● Stop infusion. ● Administer aggressive symptomatic treatment (e.g., oral or IV antihistamine, antipyretic medication, glucocorticoids, epinephrine, bronchodilators, oxygen, IV fluids). ● Permanently discontinue bevacizumab and contact the principal investigator. [a]

IRR = infusion-related reaction. [a] Resumption of bevacizumab may be considered in patients who are deriving benefit and have fully recovered from the event. The decision to re-challenge patients with bevacizumab should be based on the investigator's benefit-risk assessment and documented by the investigator.

Table 2 Management Guidelines for Thromboembolic Events

Event	Management

Venous thromboembolic event, grade 3	● nab. If the planned duration of full-dose anticoagulation is < 2 umab should be held until the full-dose anticoagulation period is over. ● may be resum luration of full-dose anticoagulation is > 2 weeks, bevacizumab met: ○ d during full-dose anticoagulation IF all of the criteria below are The patient must not have pathological conditions that carry high risk of bleeding (e.g., tumor involving major vessels or other conditions). ○ The patient must not have had hemorrhagic events Grade > 2 while in the study. ○ The patient must be on stable dose of anticoagulation for at least 3 weeks prior to resumption of bevacizumab therapy. ● If thromboemboli worsen/recur upon resumption of study therapy, discontinue bevacizumab.
Venous thromboembolic event, grade 4	● Discontinue bevacizumab.
Arterial thromboembolic event, any grade	● Discontinue bevacizumab

Table 3 Management Guidelines for Hypertension

Event	Management
General Guidance	● Treat with anti-hypertensive medication as needed. The goal BP control should be consistent with general medical practice.
Grade 1 (SBP 120-139 mmHg or DBP 80-89 mmHg)	● Consider increased BP monitoring; consider starting anti-hypertensive medication as appropriate.
Grade 2 (SBP 140-159 mmHg or DBP 90-99 mmHg)	● Begin (or modify baseline) anti-hypertensive therapy and continue bevacizumab if asymptomatic.
Grade 3 (SBP ≥ 160 mmHg or DBP 100 mmHg)	● Begin or modify baseline anti-hypertensive therapy (increase dose or and/or add additional anti-hypertensive therapy). ● Hold bevacizumab until any symptoms resolve AND BP < 160/90 mmHg.
Grade 4 (e.g. hypertensive crisis or malignant hypertension)	● Discontinue bevacizumab.

BP = blood pressure; SBP = systolic blood pressure; DBP = diastolic blood pressure

Table 4 Management Guidelines for Congestive Heart Failure

Event	Management
Grade 3	● Discontinue bevacizumab.
Grade 4	● Discontinue bevacizumab.

Table 5 Management Guidelines for Proteinuria

Event	Management

Grade 1, 1+ proteinuria (≥ ULN - < 1.0 g/24 hrs)	● Continue bevacizumab.
Grade 2, 2+ and 3+ proteinuria 1.0 - < 3.5 g/24 hrs)	● 2+ - administer bevacizumab and obtain a 24-hour urine protein before the next administration. ● 3+ - obtain a 24-hour urine protein and administer bevacizumab if < 2.0 g/24 hrs. If urine protein is ≥ 2.0 g/24 hrs, hold bevacizumab. ● If bevacizumab is held and urine protein improves to < 2.0 g/24 hrs within 42 days, resume bevacizumab. If not, discontinue bevacizumab.
Grade 3, 4+ proteinuria (≥ 3.5 g/24 hrs) with no diagnosis of nephrotic syndrome	● Hold bevacizumab. ● If a 24-hour urine protein shows < 2.0 g/24 hrs within 42 days from event onset, resume bevacizumab. If not, discontinue bevacizumab.
Nephrotic syndrome, grade 3 or 4	● Discontinue bevacizumab.

ULN = upper limit of normal; g = gram; hrs = hours

Table 6 Management Guidelines for Hemorrhage

Event	Management
CNS hemorrhage (any grade)	● Discontinue bevacizumab.
Hemoptysis, grade 2-4 (≥ 2.5 mL bright red blood per episode)	● Discontinue bevacizumab.

Hemorrhage, other, grade 3	In patients who are receiving full-dose anti-coagulation: ● Discontinue bevacizumab In patients not on full-dose anti-coagulation: ● Hold bevacizumab until all of the following criteria are met: ○ The bleeding has resolved and hemoglobin is stable. ○ No persisting bleeding diathesis exists that increases risk of therapy. ○ No anatomic or pathologic condition significantly increases the risk of hemorrhage recurrence. ● If the patient experiences another grade 3 or higher hemorrhagic event after resumption, discontinue bevacizumab.
Hemorrhage, other, grade 4	● Discontinue bevacizumab.

CNS = central nervous system; mL = milliliter

Table 7 Management Guidelines for Gastrointestinal Toxicities

Event	Management
Bowel obstruction, grade 2	● Withold bevacizumab for partial obstruction requiring medical intervention. ● Hold bevacizumab until complete resolution of obstruction.
Bowel obstruction, grade 3-4	● Hold bevacizumab until complete resolution. ● Patient may restart bevacizumab after full recovery and >28 days from surgery, and at investigator's discretion.
GI perforation, any grade	● Discontinue bevacizumab. ● Initiate treatment per institutional guidelines. ● If the event improves, atezolizumab and tiragolumab may be resumed at the discretion of the investigator. If not, permanently discontinue atezolizumab and tiragolumab.

Table 8 Management Guidelines for Fistulas

Event	Management
Tracheoesophageal fistula, any grade	● Discontinue bevacizumab.
Fistula (non-tracheoesophageal), grade 4	● Discontinue bevacizumab.

Table 9 Management Guidelines for Wound Dehiscence

Event	Management
Wound dehiscence requiring medical or surgical intervention	● Discontinue bevacizumab.

Table 10 Management Guidelines for Posterior Reversible Encephalopathy Syndrome (PRES)

Event	Management
PRES or RPLS, any grade, confirmed by MRI	● Discontinue bevacizumab. ● Withold atezolizumab and tiragolumab. ● If the event improves, consider resuming atezolizumab and tiragolumab. If not, discontinue atezolizumab and tiragolumab.

PRES = posterior reversible encephalopathy syndrome; RPLS = reversible posterior leukoencephalopathy syndrome.